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Osmolarity-Dependent Gene Expression Enables Spatial Resolution of Cells from Whole Kidney Single Cell RNA Data

Christian Hinze,1,2 Nikos Karaiskos,1 Anastasiya Boltengajan,3 Nina Himmerkus,1 Markus Bleich,4 Steven Potter,5 Andrew Potter,2 Christian Kocks,2 Nikolaus Rajewsky,5 Kai M. Schmidt-Ott,1,2 Max Delbrueck Center for Molecular Medicine, Berlin, Germany; 1Nephrology and Medical Intensive Care, Charité-Universitätsmedizin, Berlin, Germany; 3Berlin Institute for Medical Systems Biology Max Delbrück Center for Molecular Medicine, Berlin, Germany; 4Institute of Physiology, CAU, Kiel, Germany; 5Cincinnati Children’s Hospital, Cincinnati, OH.

Background: In whole organ single cell data, spatial information of cells is usually lost but can sometimes be restored if regional marker genes are identifiable. In the kidney, certain cell types exist in regions of different microenvironments along the corticomedullary axis. For instance, cells of the proximal tubule, thick ascending limb or collecting duct extend from the serum-isosmotic renal cortex into the hyperosmotic renal medulla. We hypothesized that differences in regional gene expression between cortex, outer and inner medulla drive different microenvironments and osmosomaly-dependent genes might provide information on the spatial origin of cells in single cell data.

Methods: We obtained mouse kidneys and prepared single cell suspensions of whole kidneys as well as of microdissected cortical, outer and inner medullary tissue and applied single cell RNA sequencing. We assigned cell type information based on known marker genes and systematically analyzed regional gene expression differences and differences in expression of osmosomaly-dependent genes (osmogens) within different tubular cell types. In addition, we developed an unsupervised algorithm based on osmogene expression and used this information to spatially assign cells in whole kidney single cell suspensions.

Results: Our data show that the expression of osmogens is tubule segment-specific and increases towards the inner medulla. We show that osmogens are substantial drivers of gene expression differences within a given cell type along the corticomedullary axis. They harbor spatial information especially for tubule cells present in the outer and inner medulla but also to a lesser extent for other cell types. Applying our algorithm to spatially assign whole kidney single cell data reveals an imbalanced composition of regional origin of kidney cells in whole kidney single cell suspensions with a marked underrepresentation of medullary kidney cells.

Conclusions: Osmosomaly-dependent genes show cell type-specific regional expression patterns and harbor spatial information of kidney cells. They can be used to spatially assign cells within whole kidney single cell RNA sequencing data and uncover a previously unrecognized regional bias in whole kidney single cell preparations.

The Hypertension Induced by Renal Snx5 Silencing Is Associated with Increased Renal Protein Abundance of NHE3, NaPi2, NKCC2, and NCC in Mice

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Background: Sorting nexin 5 (SNX5) plays an important role in the function of renal dopamine receptor subtype 1 (D1R). The gene silencing of renal Snx5 by its siRNA decrease basal D1R but increases blood pressure (BP) in rats; it also decreases renal expression of insulin receptor and insulin degrading enzyme and causes insulin resistance in mice.

Methods: In order to test the hypothesis that SNX5 deletion affects renal sodium absorption and develops hypertension, we measured BP, water and sodium balance, and renal protein expression of sodium transporters in C57BL/6J mice treated with siRNAs of SNX5 or mock. 8 male C57Bl6 mice (5-6 months old) were unanesthetized injected 3 weeks prior to the infusion of SNX5-siRNA or mock-siRNA (3 mg/kg/day, n=4/group) via osmotic mini-pump into subcap-sural space for 1 week.

Results: In SNX5-siRNA-treated mice, systolic (119±5.2 mm Hg, under anesthesia) and diastolic BPs (91.8±0.4 mm Hg, under anesthesia) and diastolic BPs were similar in the two groups. The gene silencing decreased the protein expression of SNX5 and D1R by 70% and 30% respectively (immunoblotting). In control mice, SNX5 and D1R colocalized mainly in the apical membrane of the proximal tubules, thick ascending limbs of loop of Henle, but not in collecting ducts. The two proteins also co-immunoparticipated in mouse kidney homogenates and cell lysates from cultured mouse proximal tubule cells. The gene silencing of Snx5 increased renal proteins expression of NHE3 (172±30, % of control), NaPi2 (223±12), NKCC2 (286±54), NCC (177±23), but did not alter the protein expressions of ENaC and Na/K/ATPase.

Conclusions: This study suggests that inhibition of SNX5 by siRNA increases the apical sodium transporters in proximal and distal nephron segments, in which SNX5 and D1R are co-localized. This may cause the impaired sodium excretion that may be responsible for the increased blood pressure in SNX5-siRNA-treated mice.

Dietary Fructose Enhances Protein Kinase C Activity and Angiotensin II-Dependent Transport in Proximal Tubules

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Background: In both humans and model organisms fructose causes salt-sensitive hypertension. This is in part due to increasing the sensitivity of proximal nephron Na reabsorption to angiotensin II (Ang II) such that lower concentrations stimulate transport to a greater extent. Ang II stimulates Na transport in proximal tubules by activating protein kinase C (PKC) α, a calcium- and lipid-dependent kinase. We hypothesized that dietary fructose increases the ability of Ang II to elevate intracellular calcium (Ca2+) and, thereby, activate PKC α in proximal tubules. This, in turn, stimulates Na/H exchange activity, the primary transporter involved in Na reabsorption.

Methods: Rats were fed a diet of normal chow plus tap water or normal chow plus 20% fructose in drinking water for 7-8 days. The effect of Ang II on Ca2+ was measured using Fura2 in isolated, perfused segments of proximal tubules. Na/H exchange (NHE) activity was measured in perfused tubules using the pH-sensitive dye BCECF. PKC α activity was measured by separating particulate and soluble fractions, performing Western blots and recording the particulate to soluble ratio. Increases in this ratio was taken as activation.

Results: Basal Cai was 143±29 nM in proximal tubules from control rats while it was 160±30 nM in those given fructose, not significantly different. Ang II (1 nM) increased Cai by 4±0.1 μM in control tubules and by 148±53 nM in tubules from rats fed fructose (p < 0.03). A higher concentration of Ang II (100 nM) increased Cai by 237±100 nM in proximal tubules from rats fed fructose and by 190±34 nM in tubules from rats fed the control diet. Ang II increased the particulate to soluble ratio of PKC α by 0.134±0.026 in tubules from rats fed fructose (p < 0.001) but not significantly in control tubules (0.060±0.061). Finally we measured NHE activity. Ang II (1 μM) increased NHE activity by 0.7±0.1 fluorescent units/s in tubules from rats given fructose but had no effect on NHE activity in control tubules (p=0.01). With Go6976, a PKC ε/J inhibitor, Ang II was unable to stimulate NHE activity in tubules from rats fed fructose.

Conclusions: We concluded that dietary fructose increases the ability of Ang II to elevate Ca2+, and consequently PKCα. This, in turn, stimulates NHE activity which likely contributes to fructose-induced salt sensitivity of blood pressure.

Potassium Directly Regulates WNK (With No Lysine Kinases)

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Background: Plasma potassium concentration is maintained within a narrow range, implying the ability to sense deviations from normal. WNK mutations in mice and humans result in abnormal potassium concentrations, and WNKs have been proposed to indirectly sense plasma potassium via effects on intracellular chloride. Here, we investigate whether WNKs are directly regulated by potassium. Our lab has previously shown that the WNK signaling cascade is conserved in Drosophila Malpighian (renal) tubules.

Methods: We used differential scanning fluorimetry and mass spectrometry to measure WNK kinase domain thermal stability and autophosphorylation in vitro in the presence of varying concentrations of potassium. We also examined the activity of DmWNK (Drosophila WNK) and HsWNK3 (human WNK3) activity in the Drosophila Malpighian tubule, using phosphorylation of transgenically expressed kinase-dead rat SPAK as a readout. We developed baths with varying extracellular potassium and fixed intracellular chloride concentrations (16 mM or 30 mM, measured using the transgenic sensor ClopHensor). We measured intracellular potassium in the tubule using inducibly coupled plasma mass spectrometry.

Results: Potassium directly binds to the kinase domain of DmWNK (Drosophila WNK) and human WNK1 in vitro, as assessed by differential scanning fluorimetry. Potassium also inhibits autophosphorylation, required for kinase activation, of DmWNK and HsWNK3 (human WNK3) kinase domains in vitro. We also examined the activity of DmWNK or HsWNK3 in Malpighian tubules. Compared to the normal potassium bath, there was no change in DmWNK or HsWNK3 activity in low potassium bath, but there was no change in intracellular potassium under these conditions. Intracellular potassium was increased in the high potassium bath, and high potassium inhibited both DmWNK and HsWNK3 in both the 16 mM and 30 mM intracellular chloride conditions. High potassium bath also inhibited chloride-insensitive HsWNK3 S328K activity in the tubule.

Conclusions: Our data suggest that potassium directly inhibits WNK kinases, in a manner that is additive to chloride inhibition, with implications for potassium sensing in the kidney and other organs.

Funding: NIDDK Support, Private Foundation Support

Oral Abstract/Thursday
Angiotensin II Stimulates ENaC by an Aldosterone-Independent Mechanism

Angiotensin II regulates the expression and activity of the epithelial sodium channel (ENaC), which plays an important role in the regulation of ENaC activity in the distal convoluted tubule (DCT) and to a lesser degree in the collecting duct (CCD). AT1 receptors (AT1R) are found in the DCT and to a lesser degree in the CCD. In contrast, aldosterone plays a dominant role in determining ENaC activity in the CCD but to a lesser degree in the DCT. Thus, AT1R deletion alone will not influence ENaC activity in the DCT, but this did not involve the NCC-activating WNK-SPAK pathway.

Methods: We set out to further explore the mechanisms involved in determining ENaC activity in the DCT and to a lesser degree in the CCD by investigating interactions with K+ restriction, a strong activator of NCC, by performing dietary manipulations in mice with Western blotting.

Results: We confirmed a previous report that long-term Mg2+ restriction does not alter NCC mRNA abundance, and found that the same with short-term Mg2+ restriction. The E3 ubiquitin-protein ligase neural precursor cell expressed developmentally downregulated gene 4-2 (NEDD4-2) is known to target NCC for proteosomal degradation. We found that short-term Mg2+ restriction did not lower NCC abundance in inducible nephron-specific NEDD4-2 knockout mice. We next examined interactions with K+ restriction. NCC and NCC abundances were similar after short- or long-term Mg2+ or combined Mg2+-K+ restriction, but were dramatically lower compared with low K+ diet, suggesting that Mg2+ restriction overrides the effects of K+ restriction on NCC. After combined Mg2+-K+ restriction, adding back K+ alone to the diet had no effect on NCC abundance, but adding back Mg2+ either at the same time or after K+ replenishment increased NCC abundance. NEDD4-2 mediates degradation of the epithelial sodium channel (ENaC) during dietary K+ restriction so we next examined the effect of Mg2+ restriction on ENaC by performing amiloride response tests. Compared with normal diet the natriuretic effect of amiloride was strongly blunted after K+ restriction but not after Mg2+ restriction.

Conclusions: Together, these data suggest that NEDD4-2 mediates proteosomal degradation of NCC during Mg2+ restriction, Mg2+ restriction exerts differential effects on NCC and ENaC, and sustained NCC downregulation may enhance distal Na+ delivery during states of hypomagnesemia, maintaining hypokalemia.

Funding: NIDDK Support, Private Foundation Support, Government Support - Non-U.S.

Collecting System Specific Deletion of Kcnj10 Predispenses for Thiazide- and Low K+ Diet-Induced Hypokalemia

Renal Inflammation, Vascular Pathology, and Spleenomegaly Are Induced in a Mouse Model of Spontaneous Chronic Metabolic Acidosis

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Background: The basolateral K+ channel KCNJ10, is expressed in the renal distal convoluted tubule (DCT) and controls the activity of the thiazide-sensitive NaCl cotransporter (NCC). Loss-of-function mutations of KCNJ10 cause EAST/SeSAME syndrome with salt wasting and hypokalemia. KCNJ10 is also expressed in the principal cells of the collecting system (CS); however, its role in this segment has not been studied in detail.

Methods: To address this question, we generated the mouse model AQP2Cre:Kcnj10floxtm1KO with a deletion of KCNJ10 specifically in the CS (CS-Kcnj10-KO).

Results: CS-Kcnj10-KO mice responded normally to standard and high K+ diet. However, CS-Kcnj10-KO exhibited a higher kaliuresis and lower plasma K+ than control mice when treated with thiazide diuretics. Likewise, CS-Kcnj10-KO displayed an inadequately high kaliuresis and renal Na+ retention upon dietary K+ restriction.

In this condition, CS-Kcnj10-KO mice became hypokalemic due to an insufficient downregulation of the epithelial Na+ channel (ENaC) and the renal outer medullary K+ channel (ROMK) in the CS. CS-Kcnj10-KO was ameliorated by either pharmacological inhibition of ENaC or by genetic inactivation of ROMK in the CS.

Conclusions: In conclusion, KCNJ10 in the CS contributes to the renal control of K+ homeostasis by regulating ENaC and ROMK. Impaired KCNJ10 function in the CS predisposes for thiazide- and low K+ diet-induced hypokalemia and likely contributes to the pathophysiology of renal K+ loss in EAST/SeSAME syndrome.

Funding: Government Support - Non-U.S.
**Derivatives of FMP-API-1/27 Robustly Activate AQP2 Water Channels Independently of Vasopressin**

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**Background:** Congenital nephrogenic diabetes insipidus (NDI) is characterized by the inability of the kidney to concentrate urine. Congenital NDI is mainly caused by loss-of-function mutations in the vasopressin receptor type 2 (V2R), leading to impaired aquaporin-2 (AQP2) water channels activity in renal collecting ducts. Direct activators of protein kinase A (PKA) are novel therapeutic targets of congenital NDI. The intracellular distribution and activity of PKA are largely controlled by A-kinase anchoring proteins (AKAPs). We found that a low molecular weight compound, FMP-API-1/27, dissociated AKAPs binding to PKA and activated PKA/AQP2. We promoted further development of FMP-API-1/27 derivatives in terms of pharmaceutical potency and feasibility.

**Methods:** The effects of compounds on PKA/AQP2 were examined by a mouse cortical collecting duct cell line and a recombinant NDI mouse model.

**Results:** We examined the effects of screening compounds with similar structures to FMP-API-1/27 from TMDU Chemical Biology Database and derivatives of FMP-API-1/27 using mikkCPC cells. Hit compounds that increased PKA/AQP2 activity had similar chemical structures to the V2R.

**Conclusions:** Derivatives of FMP-API-1/27 are promising therapeutic targets for congenital NDI caused by V2R mutations.

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**TH-OR010**

**Investigation of the Renal Phenotype of a Novel Mouse Model with Dent Disease**

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**Background:** Dent disease is a rare hereditary renal proximal disorder that affects approximately 1 out of 100,000 males. The disease is characterized by low molecular weight (LMW) proteinsuria, hypercalciuria, kidney stones and progressive renal failure. Inactivating mutations of the CLCN5 gene encoding the 2Cl-/H+ exchanger ClC-5 have been identified in more than 60 % of patients with Dent disease. ClC-5 is expressed in early endosomes of proximal tubules (PT) where it optimizes the function of the V-type H’ ATPase to ensure an efficient endocytosis of LMW proteins, and therefore to avoid their excretion into the urine. The functional consequences of CLCN5 mutations have been previously investigated in heterologous expression systems. It has been shown that 60 % of the mutations lead to a defect in protein folding and processing, such as the previously published N340K pathogenic ClC-5 mutation. As a consequence, the misfolded ClC-5 are retained within the transplasmatic reticulum (ER). Here, we have investigated the consequences of the N340K mutation using a transgenic mouse model.

**Methods:** We identified 32 ClC-5 variants in Dent disease patients, and N340K is the most frequent variant. Protocols for mouse breeding, genotyping, phenotype and functional analysis were described.

**Results:** The N340K mice showed an increased urinary calcium and glucose excretion, a decreased urinary pH, and a severe LMW proteinuria, recapitulating common features of Dent disease. Megalain, a multi-ligands receptor involved in the endocytosis of LMW proteins was less expressed at the apical border of N340K mouse PTs. These data suggest that: 1) polyploidization is crucial to survive AKI by maintaining renal function in the acute phase and 2) polyploid cells are senescent and in the long run they are involved in the progression of AKI to CKD.

**References:**

Results: No overt kidney phenotype was observed in Sirt5−/− mice at baseline. However, following IRI and euplatin-induced AKI, Sirt5−/− and Sirt5+/+ mice had significantly improved kidney function and less evidence of tissue injury compared with controls. The cell-based assays confirmed that knockdown of Sirt5 in proximal tubule cells was protective against both types of injury. This protection coincided with increased peroxisomal FAO and amino acid process which is tightly linked to the regulation of ferroptosis.

Conclusions: Subsequently, SIRT5 deficiency confers protection against multiple models of acute kidney injury. This identifies a therapeutically attractive mechanism whereby increased peroxisomal FAO and decreased mitochondrial FAO drives protection of kidneys from injury.

TH-OR014
High Mobility Group Box 1 (HMGB1)-Induced Ferroptosis Accelerates Ischemia-Reperfusion-Induced AKI

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Background: Regulated necrosis (Rn), which is identified as cells death in a regulated manner but with the morphologic features of necrosis, has been implicated to be involved in the process of AKI and improve chronic kidney injury. The common hallmark of RN in kidneys is the rupture of tubular epithelial cell membrane and the release of the unassembled intracellular components known as damage-associated molecular patterns (DAMPs) resulting in activation of immune system. As a representative DAMP molecule, high mobility group box-1 (HMGB1) involving in many inflammatory diseases has less determined on the effect of RN.

Methods: Mice with specific conditional alleles of HMGB1 were crossed with mice harboring Ksp-CreERT transgenes to knock out HMGB1 in renal tubular epithelial cells. 8-10 weeks old HMGB1−/−; Ksp-CreERT−/− mice were randomly divided into two groups: K1+/TMX group and K1−/Vehi group. The two groups were injected with tamoxifen(TMX) at a dose of 100 mg/kg body weight and vehicle for 4 days respectively, respectively. Two weeks later, the mice were subjected to 30 min of bilateral ischemia reperfusion (I/R). One day later, the mice were sacrificed and the kidney, liver, and other organs were sampled for evaluating the role of HMGB1 in I/R.

Results: Renal tubular specific HMGB1 knockout mice underwent a pronounced pathological shift including decreased expression of KIM-1 and NGAL and upregulated expression of Klotho after I/R. Serum creatinine and urine nitrogen were reduced in K1+/TMX group with less renal inflammatory cell infiltration. Ferroptosis and necroptosis are well described necroptotic mechanisms, we found that HMGB1 deficiency ameliorated both KIM-1 and Klotho expression in I/R. K1−/TMX group had a higher expression of GPX4 and lower level of ACSL4 in kidney with less accumulation of lipid peroxidation. However, the key enzymes of necroptosis, RIP1/RIP3/MLKL, have less changed in K1−/TMX group compared to the control group.

Conclusions: The role of HMGB1 in the kidney was confirmed by the results obtained in K1−/Vehi group. Although less differentially expressed between K1+/TMX and K1−/TMX, the group of GO analysis and the KEGG pathway analysis illustrated that a large amount of differentially expressed genes (DEGs) were involved in lipid metabolic process which is tightly linked to the regulation of ferroptosis.

TH-OR015
Optogenetic Stimulation of the Vagus Nerve Identifies Distinct Pathways That Mediate Kidney Protection from Ischemia-Reperfusion Injury

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Background: We recently showed that electrical vagus nerve stimulation (VNS) in the neck protected mouse kidneys from ischemia-reperfusion injury (IRI) by activating the cholinergic anti-inflammatory pathway (CAP) (PMID: 27088805). Stimulation of vagal efferent neurons is believed to be essential in the activation of CAP. However, electrical stimulation of the cervical vagus nerve excites both the efferent (motor) and afferent (sensory) neurons. It is still unclear which pathway is important in ameliorating kidney injury.

Methods: Channelrhodopsin-2 (ChR2) is a light-sensitive, non-selective cation channel, the gate is open 6-7 ms after light stimulus. The expression of ChR2 in C1 or C2 neurons in the lower brainstem is involved in the protective pathway elicited by VNS.

Results: Optogenetic VNS protected kidneys from IRI in both Chat-ChR2 mice (pCr: 1.53 ± 0.04 vs. 0.48 ± 0.05 mg/dl, *p < 0.05) and Vglut2-ChR2 mice (pCr: 1.90±0.22 vs. 0.44±0.06 mg/dl), which was supported by improved kidney histology and decreased renal KM-1 expression in the Vglut2-ChR2 mice. Next, based on our recent study (PMID: 28288124), we hypothesized that the C1 neurons mediate the afferent VNS pathway. Electrical VNS significantly increased the number of Hoechst-positive C1 neurons, which is consistent with the selective ablation of C1 neurons eliminated the protective effect of afferent VNS, but not efferent VNS.

Conclusions: Both stimulation of vagal efferent and afferent neurons protected the kidneys from IRI. C1 neurons in the lower brainstem were involved in the protective pathway elicited by afferent VNS.

Funding: NIDDK Support

TH-OR016
A Functional, Genomic Screen Identifies a CDKL5-50XO9 Regulatory Axis in Essential Cell Death and Kidney Injury

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Background: Numerous clinical conditions are associated with inflammatory, toxic, and hypoxic insults to tubular epithelial cells. The resulting epithelial cell dysfunction and cell-death are the hallmarks and underlying cause of acute kidney injury (AKI), a common disorder that predominantly develops in hospitalized patients. Importantly, the patients that recover from an episode of AKI are at increased risk of developing chronic kidney disease, end-stage renal disease and cardiovascular dysfunction- disorders that are associated with significant morbidity and mortality. To identify novel regulators of renal epithelial cell death and AKI, here, we have used a kinome-wide functional genomic screening to identify protein kinases that contribute to the pathogenesis of AKI.

Methods: An unbiased kinome-wide siRNA screen for regulators of renal epithelial cells was carried out in a murine epithelial cell line. Through subsequent in vivo validation experiments, we identified cyclin-dependent kinase-like 5 (CDKL5) also known as serine/ threonine kinase 9 (STK9) as a key regulator of renal cell-death and injury. To directly define the role of CDKL5 in vivo, kidney specific CDKL5 knockout mice were generated. In addition, a pharmacological inhibitor of CDKL5 kinase was evaluated in splatlin nephrotoxicity and ischemia-associated AKI. Later proteomic studies were carried out to identify the transcription factor Sox5 as a bona fide Cdcl5 substrate and a key downstream target in renal epithelial cells.

Results: High-throughput siRNA screening and validation studies identified CDKL5 kinase as a crucial, previously unknown regulator of renal epithelial cell-death. In vivo studies showed that genetic or pharmacological ablation of CDKL5 function provides protection to both epithelial and ischemia-associated kidney injury. We also found that Sox5 is phosphorylated on the Ser-199 residue by Cdcl5 during kidney injury in vivo. Cdcl5-mediated phosphorylation reduced the stability of Sox9 protein.

Conclusions: Here we have found that Cdcl5 also known as S8k is a stress response protein kinase that controls epithelial cell fate during AKI. We propose that Cdcl5 activation promotes renal cell dysfunction through phosphorylation-mediated destabilization of pro-survival transcription factor Sox5.

Funding: Private Foundation Support

TH-OR017
Ubiquitin-Proteasome System Actively Maintains Homeostasis of Proximal Tubules

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Background: Autophagy and ubiquitin-proteasome system (UPS) are two major proteolytic pathways that control cellular protein turnover. While the role of autophagy in the kidney has been extensively analyzed in the proximal tubules of the kidney, the impact of UPS function in the maintenance the proximal tubules has been unclear.

Methods: In order to analyze the role of UPS function in the proximal tubule, we crossed conditional knockout mice of the proteasome subunit Rpt3 with proximal tubule specific inducible Cre (Ndrg1-CreERT2), to generate Rp3f/f:Ndrg1-CreERT2(RP3-Rpt3-CKO) mice, in which the expression of Rp3 can be deleted in proximal tubules at desired time points. We then performed tamoxifen administration utilizing Rp3f/f:Ndrg1-CreERT2 mice, we investigated how UPS regulates the maintenance of proximal tubules.

Results: As early as one day after tamoxifen administration for 5 consecutive days, proximal tubules of PT-Rpt3-CKO mice showed mild injury in light microscopy, whose degeneration was mitigate in electron microscopy. While the role of autophagy in the kidney has been extensively analyzed in the proximal tubules of the kidney, the impact of UPS function in the maintenance the proximal tubules has been unclear.

Conclusions: Our results provide strong evidence showing that the dysfunction of UPS rapidly triggers mitochondrial dysfunction, autophagy insufficiency, cell cycle arrest

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

 Oral Abstract/Thursday

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AKI: Mechanisms - Injury and Repair

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and apoptosis of proximal tubules, leading to renal insufficiency and death. Compared to mild phenotypes of conditional knockout mice of autophagy related molecules in the proximal tubules, UPS plays a crucial role in the active maintenance of proximal tubules.

**TH-OR018**

Organ-specific Oxidant Stress and CORE Disruption Mediate Proximal Tubule Cell Injury During Gentamicin Exposure

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**Background:** The Cross-Organelle Stress Response (CORE) is an adaptive mechanism that maintains mitochondrial and endoplasmic reticulum (ER) proteostasis. We hypothesized that gentamicin causes nephrotoxic acute kidney injury (AKI) by causing both mitochondrial specific oxidative stress and fragmentation resulting in CORE disruption before activating the lethal unfolded protein response (UPR).

**Methods:** Mito HyPer, a mitochondrial-specific H<sub>2</sub>O<sub>2</sub> probe, was used to detect early mitochondrial ROS accumulation in human proximal tubule epithelial cells (HK2) during gentamicin exposure. Mitochondria and ER were stained with MitoTracker and ER-Tracker, respectively, and time course experiments were performed using a Nikon Super Resolution microscope. Mitochondrial-ER disassociation, mitochondrial morphology and immunoblots of CORE-associated mitochondrial pro-fission proteins (Total DRP1 and pDRP1) were used as surrogates of CORE function. Misfolded protein stains (Thioflavin T), protein ubiquitination, and immunoblots for whole cell oxidative stress (4HNE) were measured to assess proteotoxicity.

The efficacy of preserving CORE on protein misfolding, lethal UPR activation (CHOP), and cell survival was assessed using geranylgeranylacetone (GGA), a protein chaperone inducer, prior to the introduction of gentamicin.

**Results:** Gentamicin exposure caused characteristic features of disrupted CORE, including mitochondrial-specific H<sub>2</sub>O<sub>2</sub> accumulation, DRP-1 activation and organelle fragmentation, followed by mitochondrial-ER dissociation. Importantly, CORE disruption occurred before detectable changes in whole cell oxidative stress, protein ubiquitination, protein misfolding or lethal UPR activation (CHOP) were observed. GGA significantly decreased mitochondrial-specific oxidative stress, prevented fragmentation, preserved mitochondrial-ER association and ameliorated lethal UPR activation.

**Conclusions:** Gentamicin exposure causes early mitochondrial H<sub>2</sub>O<sub>2</sub> accumulation and disrupts the CORE. These untoward events contribute to gentamicin-induced proteotoxicity and lethal UPR activation. GGA preserves the CORE and decreases subsequent lethal UPR activation that contributes to the proximal tubule cell injury caused by gentamicin.

**Funding:** NIDDK Support

**TH-OR019**

Matricellular Protein Tenascin C Has a Protective Effect in Renal Ischemia-Reperfusion Injury

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**Background:** Intestinal microenvironment is critical in regulating cell proliferation and injury/repairing process. Tenascin-C is a matricellular protein which is transiently expressed during development and can be re-induced after injury, suggesting a potential role in tissue injury/repairing. The present study examined the role of TNC in acute kidney injury using a ischemia-reperfusion (IR) model.

**Methods:** A tenascin-C promoter driven inducible CreER2 knock-in mouse line with an eGFP reporter was generated. TNC-CreER<sup>+/-</sup> (TNC<sup>−/−</sup>) mice were used to examine the role of TNC in AKI.

**Results:** Following IR, TNC was markedly induced in the interstitium of the kidney as early as 3 hours and peaked at 24-48 hours. To examine the role of TNC in AKI, we used the TNC-CreER<sup>−/-</sup>(TNC<sup>−/−</sup>) mice. Deletion of TNC in mice significantly aggravated IR induced AKI, showing significantly lower survival rate, higher BUN and more severe tubular injury after IR comparing to their wild type littermates. We then examined the mechanism by which TNC is induced following injury. Two hyper response elements (HRE) were identified in the promoter region of TNC, suggesting a role of hypoxia-inducible factor(HIF). DMOG, a HIF stabilizer, significantly induced TNC expression (HRE) were identified in the promoter region of TNC, suggesting a role of hypoxia.

**Conclusions:** Matricellular protein Tenascin C has a protective effect in renal ischemia-reperfusion injury.

**Funding:** NIDDK Support

**TH-OR020**

Enhancer and Super-Enhancer Dynamics in Repair After Ischemic AKI

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**Background:** The endogenous repair process of the mammalian kidney allows rapid recovery after acute kidney injury (AKI) through robust proliferation of tubular epithelial cells. There is currently limited understanding of which transcriptional regulators activate these repair programs. Here we investigate the existence of enhancer dynamics in the regenerating mouse kidney.

**Methods:** RNA-seq and ChIP-seq (H3K27ac, H3K4me3, BRD4, Pol II) were performed on samples from repairing kidney cortex 2 days after ischemia/reperfusion injury (IRI) to identify activated genes, transcription factors, enhancer and super-enhancers associated with kidney repair. Further we investigated the role of super-enhancer activation in kidney repair through pharmacological BET inhibition using the small molecule JQ1 in acute kidney injury models in vivo.

**Results:** Response to kidney injury leads to genome-wide alteration in enhancer repertoire in vivo. We identified 16,781 enhancer sites (H3K27ac/BRD4 positive, H3K4me3 negative) active in sham and IRI samples; 6,512 lost and 9,774 gained after IRI. The lost and gained enhancer sites can be annotated to 62% and 63% of down- and up-regulated transcripts, respectively. The top 3 transcription factor binding motifs enriched in lost enhancer sites are H nf4a, Exsrb and P PARE and in gained enhancer sites Fosl2 and Atf3. ChIP-seq profiles of selected transcription factors show specific binding at corresponding enhancer sites. Super-enhancer analysis revealed 164 lost and 216 gained super-enhancers. TNC is activated as early as 3 hours and peaked at 24-48 hours. To examine the role of TNC in AKI, we performed on samples from repairing kidney cortex 2 days after ischemia/reperfusion injury (IRI) to identify activated genes, transcription factors, enhancer and super-enhancers associated with kidney repair. Further we investigated the role of super-enhancer activation in kidney repair through pharmacological BET inhibition using the small molecule JQ1 in acute kidney injury models in vivo.

**Conclusions:** This is the first demonstration of BRD4 enhancer and super-enhancer function in the repairing kidney. In addition, our data call attention to potential caveats for use of small molecule inhibitors of BET proteins that are currently being tested in clinical trials in cancer patients who are at risk for AKI. Our analyses of enhancer dynamics in kidney injury in vivo have the potential to identify new targets for therapeutic intervention.

**Funding:** NIDDK Support, Government Support - Non-U.S.

**TH-OR021**

HIMALAYAS: A Phase 3, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Incident-Dialysis Patients


**Background:** Roxadustat (FG-4592) is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and regulates iron metabolism.

**Methods:** ESA-naïve or limited prior use, incident dialysis pts were randomized (1:1) to receive oral ROXA or epoetin alfa (EPO). Oral iron was allowed; parenteral iron was restricted. Oral ROXA was dosed thrice weekly. The initial roxadustat dose was weight-adjusted. EPO was prescribed according to the country-specific product labeling. An algorithm based. EPO was dosed at 2 consecutive visits during the first 24 Wk as achieving a Hb level of 11 and an increase of 1 g/dL if BL Hb was <8 g or 2 g/dL if baseline Hb was <8 g/dL. Safety and tolerability were assessed by adverse events, vital signs, electrocardiogram findings, and clinical laboratory values.

**Results:** 1234 pts (522 in each arm) were randomized in 17 countries. Pts were majority Caucasian with 8.4% Black pts in the ROXA arm and 9.6% Black pts in the EPO arm. The % of pts with type 2 DM in the ROXA arm was 35.1% (n=183) and 34.4% (n=179) in the EPO arm. Mean BL Hb was 8.43 g/dL in the ROXA arm and 8.41 g/dL in the EPO arm. Mean Hb change from BL to the average over Wk 28-52 was 2.57 (ROXA) vs 2.36 g/dL (EPO). The non-inferiority criteria were met as the lower bound of 95% CI was above the non-inferiority margin of -0.75 g/dL, and superiority over EPO was achieved, p<0.005. ROXA pts had an Hb response rate of 88.2% compared with 84.9% in the EPO arm meeting EU’s primary endpoint non-inferiority criterion. The overall safety profile was consistent with results observed in prior ROXA trials and pooled safety findings will be submitted as a late breaker abstract.

**Conclusions:** ROXA was non-inferior and subsequently demonstrated superiority over EPO in the mean change in Hb from BL in pts incident to dialysis.

**Funding:** Commercial Support - Fibrogen Inc.
ROCKIES: An International, Phase 3, Randomized, Open-Label, Active-Controlled Study of Roxadustat in Anemia in Dialysis-Dependent CKD Patients

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Background: Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis and improves iron absorption and utilization.

Methods: This Phase 3 trial evaluated roxadustat vs epoetin alfa (epo) in patients (pts) with ESRD and anemia receiving dialysis. Pts with baseline (BL) hemoglobin (Hb) of <12 g/dL if treated with an erythropoietin analog or <10 g/dL if not were recruited. Pts were randomized 1:1 to receive oral roxadustat or epo. For pts receiving epo at BL, initial roxadustat dose was based on epo dose; for epo-naive pts initial roxadustat dose was weight-based. Roxadustat dose was constant for first 4 wks; a dose adjustment algorithm for roxadustat (20 mg–400 mg thrice daily to max 3 mg/kg) was used to maintain Hb between 10–12 g/dL. Oral iron was allowed; IV iron was used as standard-of-care in epo arm and with evidence of iron deficiency in roxadustat arm. Primary efficacy endpoint was mean Hb change from BL to Hb averaged over wks 28–52. Roxadustat safety data integrated across multiple appropriate dialysis trials will be reported separately.

Results: 2133 dialysis pts were randomized (1068 roxadustat, 1065 epo). Mean age was 54.0 years, 59% male, 57% white. Mean duration of dialysis was 37.5 months, 19.3% were incident pts (2 wks to 4 months). Mean (SD) BL Hb was 10.01 (2.22) g/dL. Mean Hb change from BL to average over wks 28–52 was higher with roxadustat (+0.77 g/dL vs epo +0.68 g/dL; p=0.036) in the overall cohort. Mean Hb change from BL to average over wks 28–52 in pts with chronic kidney disease (CKD) history (+0.75 g/dL vs epo +0.62 g/dL; p=0.012) was greater with roxadustat (+0.80 g/dL vs epo +0.59 g/dL; p<0.001). Roxadustat-treated pts had Hb ≥10.0 g/dL for a similar proportion of time over wks 28–52 vs epo-treated pts (79% vs 76%; p=0.045). Proportion of pts who received red blood cell transfusion was comparable between roxadustat (0.6% epo) and placebo (0.6% epo) arms. Mean (SD) change from BL to average over wks 28–52 in pts with anemia and iron deficiency (+0.75 g/dL vs epo +0.67 g/dL; p=0.013) was greater with roxadustat compared with placebo (+0.80 g/dL vs epo +0.59 g/dL; p<0.001).

Conclusions: Roxadustat effectively increased Hb, overall and in pts with elevated hsCRP, and reduced IV iron use in pts with dialysis-dependent CKD.

Funding: Commercial Support - AstraZeneca

TH-OR024

Randomized, Double-Blinded, Active-Controlled (Darbepoetin Alfa), Phase 3 Study of Vadadustat in CKD Patients with Anemia on Hemodialysis in Japan

Masaomi Nanzuku,1 Kazuko Kondo,2 Kichihiro Ueta,3 Yoshimasa Kokado,4 Genki Kaneko,4 Hiroki Matsuda,5 Yutaka Kawaguchi,6 Yasuhiro Komatsu.7 1Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan; 2The University of Tokyo School of Medicine, Tokyo, Japan; 3Gunma University, Graduate School of Medicine, Maebashi, Gunma, Japan.

Background: Vadadustat (VDT) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PIB) being assessed in Japan and Global Phase 3 studies. This is the first result of phase 3 study (NCT03439137), evaluates the efficacy and safety of VDT for 52 weeks in 323 Japanese hemodialysis-dependent (HD) chronic kidney disease (CKD) subjects with anemia receiving erythropoiesis stimulating agents (ESA). Prespecified primary analysis results up to week 24 are presented here.

Methods: Subjects on maintenance hemodialysis receiving ESA were randomized to VDT (n=162) or darbepoetin alfa (DA) group (n=161). After the initial VDT dose of 300 µg every 2 weeks, doses were adjusted in 20 µg steps to achieve and maintain a Hb target of 10–12 g/dL during the initial 12 weeks of treatment. Primary endpoint was average Hb at weeks 20 and 24. Iron parameters were measured. Safety was assessed up to 24 weeks.

Results: The baseline Hb of both groups was 10.74 g/dL. The LMMean of average analysis of covariance with treatment as factor and baseline as covariate. Trend p<0.001. Percentage of total time with interpolated Hb values ≥12 g/dL (VDT; p<0.001) and ≥10 g/dL (VDT: 10.75, DA: 9.70; p<0.001). The incidence rates of serious AEs (SAEs) were 13.0% (VDT group) and 10.6% (DA group).

Conclusions: VDT was generally well tolerated and effective as DA in maintaining Hb levels within the target range, indicating the usefulness of VDT for treating anemia in Japanese HD CKD patients converting from ESA.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation

TH-OR025

Effects of Ziltivekimab, an Antibody to IL-6, on Inflammation, Nutritional Markers, and Anemia in Hemodialysis Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Patients with chronic kidney disease on hemodialysis (HD) and hyporesponsiveness to erythropoiesis stimulating agents (ESA) exhibit functional blockade in iron release from body stores due to inflammation-induced expression of hepcidin. We hypothesized that the novel and improved anti-inflammatory cytokine interleukin (IL)-6, in HD patients with a genotypic variation in the TMPRSS6 gene, hypothesized to induce a heightened susceptibility to IL-6-induced inflammation.

Methods: After a screening period documenting stable ESA and IV iron dosing, patients on maintenance HD were randomized to IL-6 (6 µg/kg IV every 2 weeks during HD for 12 weeks). ESA dose adjustments were permitted after 4 weeks. Pharmacodynamic endpoints included markers of anemia, malnutrition and inflammation. Differences from placebo in changes from baseline were obtained from covariate adjustment, and the primary endpoint was the incidence of ≥25% reductions from baseline in serum albumin levels.

Conclusions: Ziltivekimab significantly reduced serum albumin levels and had a statistically significant trend toward improvement over placebo in inflammation markers.

Funding: Commercial Support - Corvidia Therapeutics
TH-OR026
Prognostic Evaluation by Different Target Hemoglobin Levels During Treatment with Epoetin Beta Pegol in Hemodialysis Patients with ESA Hyporesponsiveness: PARAMOUNT-HD Study
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Background: The incidence of cardiovascular (CV) events is especially high in HD patients in association with hyporesponsive to erythropoietin stimulating agents (ESAs). However, there is no recommended target range of hemoglobin for patients with ESA hyporesponsive.

Methods: We randomly assigned 304 HD, ESA-treated, patients with ESA hyporesponsiveness to a proactive treatment group (target hemoglobin [Hb] level; 11g/dL) and a maintenance treatment group (target Hb level; 9-10g/dL) by the use of epoetin beta pegol (CERA). The time from the date of study treatment initiation to the earliest CV event was evaluated as the primary endpoint. The CV events included cardiac death, heart failure requiring hospitalization, and acute coronary syndrome requiring hospitalization.

The patients were followed for 24 months.

Results: In proactive treatment group had a mean baseline Hb level of 9.34 and 9.32g/dL, respectively. Mean Hb levels during the observation period were 10.58 and 10.26g/dL (p=0.001) and mean length of Hb level of over 10.5g/dL were 11.5 and 8.6 months (p=0.0002), respectively. Median doses of CERA for 6 months after study treatment were 166.7 and 150.0ug/4 weeks (p=0.298). However, there was a significant difference in frequency CERA administration (once every 4 weeks: 10.9% and 26.4%; once every 2 weeks: 86.5% and 72.3% [p=0.0006], respectively). Kaplan-Meier analysis showed a significant difference in the primary endpoint between the two groups (9 and 18 events; log-rank test, p=0.033). Cox proportional hazards analysis showed a significant lower risk of CV events in the proactive group (HR, 0.429; 95% CI; 0.193-0.955). Also, the longer length of Hb level of over 10.5g/dL was associated with lower risk of CV events (HR, 0.919 per month; 95% CI; 0.865-0.977).

Conclusions: Our results suggest that targeting Hb level of 11g/dL with CERA reduces the incidence of CV events in HD patients with ESA hyporesponsive. Twice-monthly administration of CERA can maintain adequate Hb levels in these patients.

Funding: Commercial Support - Chugai Pharmaceutical Co., Ltd.

TH-OR027
Maintenance Intravenous Iron Treatment on Erythropoietin Dose in Chronic Hemodialysis Patients: A Multicenter Randomized Controlled Trial
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Background: Although the benefits of intravenous iron (IV) treatment in chronic hemodialysis (HD) patients has been demonstrated in several studies, IV iron regimens for optimal target levels of iron status are still not established in several guidelines. To explore these questions, we conducted a multicenter, randomized, open label study to demonstrate the effectiveness of IV iron supplement on erythropoietin dose in chronic HD patients.

Methods: Two hundred adult chronic HD patients with transferra satuation less than 30%, and serum ferritin 200-400 ng/mL, receiving recombinant erythropoietin were randomized 1:1 for maintaining serum ferritin of 200-400 ng/mL (low serum ferritin group, N=100) or serum ferritin of 600-700 ng/mL (high serum ferritin, N=100). During 8-week titration period, subjects randomized to high serum ferritin group received total IV iron of 600 mg (100 mg every week), whereas the subjects in low serum ferritin group did not obtain initial IV iron. During 6-month follow up, the dose of IV iron was adjusted according to the protocol. The primary endpoint was to evaluate the efficacy of IV iron supplement on erythropoietin dose index (erythropoietin dose [unit/week] divided by hemoglobin level [g/dL]). The study was registered with the Thai Clinical Trials Registry TCTR2018003003.

Results: The mean dose of IV supplement was 108.3±28.2 mg/month in low ferritin group and 192.3±36.2 mg/month in high ferritin group. The mean serum ferritin was 367.0±224.9 ng/mL in low ferritin group and 619.6±265.2 ng/mL in high ferritin group. At 3-month follow up, the erythropoietin index was significantly decreased in high serum ferritin group compared with low serum ferritin group (214.3±36.1 vs. 156.1±272.2 unit/week/g/dL; P<0.002, and 873.8±329.4 vs. 767.9±392.1 unit/week/g/dL; P=0.05, respectively). At 6-month follow up, only high serum ferritin group showed a significant decrease of erythropoietin index from randomization (854.0±317.1 to 765.3±568.0 unit/week/g/dL; P<0.001).

Conclusions: Maintaining serum ferritin of 600-700 ng/mL by IV iron treatment approximately 200 mg per month can decrease erythropoietin dose in chronic HD patients.

Funding: Government Support - Non-U.S.

TH-OR028
Effect of Ferric Citrate on Erythropoiesis-Stimulating Agent (ESA) Use in ESRD Patients with Elevated Ferritin
Sreedhara Mandavam,1 Omar Mamlouk,2 Medha Airy,3 Monica Rodriguez,2 Jose J. Perez.1,2 UT MD Anderson Cancer Center, Bellaire, TX; 3Baylor College of Medicine, Houston, TX; 4University of Texas Health Science Center at Houston, Houston, TX.

Background: Iron deficiency anemia is common in ESRD patients on hemodialysis. Dialysis access is a target to increase iron to improve erythropoiesis in these patients. Patients with elevated serum Ferritin (>1000 mcg/dL) are poorly responsive to IV iron and concerns about infection risks lead to withholding IV iron for ESRD patients with Ferritin >1000 mcg/dL. We investigated the efficacy of orally available Iron (Ferric Citrate) used as a phosphate binder on Iron parameters and ESA use in ESRD patients with elevated iron. Ferric Citrate is a phosphate binder but high Ferritins in a pragmatic pilot clinical trial.

Methods: Protocol was approved by the BCM IRB. All patients on hemodialysis for at least 3 months at the US Renal Care Scott Street Dialysis unit were eligible. Patients were included if: Mean Serum Ferritin >1000 on 2 consecutive samples in 3 months, TSAT <30% on 2 consecutive samples in 3 months. Information collected at enrollment: Ferritin, TSAT, hemoglobin, ESA dose, Calcium, Phosphorus, and PTH. Subjects given Ferric Citrate 210 mg 2 tabs to be taken with meals (minimum 6/day) for 3 months. Clinicians and dieticians were allowed to change the dose of Ferric Citrate as clinically indicated.

Results: Mean serum Ferritin and mean TSAT at enrollment were1169 ng/ml and 36.2%. After 90 days of Ferric Citrate, the mean TSAT increased to 36% (31% increase) and the mean serum Ferritin was 1075 ng/ml (15% decrease). ESA use decreased from 59 units/week to 28 units/week by the end of the trial representing a 52% reduction in mean ESA dose/week/patient. Adverse events were minimal with diarrhea being the most common. 1 patients withdrew before starting drug and another withdrew after 1 month on drug due to constipation.

Conclusions: Ferric Citrate is a phosphate binder that can increase iron stores in ESRD patients that have high Ferritin and low TSAT and appears to reduce ESA use by 50% in these patients. ClinicalTrials.gov Identifier:NCT03055598

Funding: Commercial Support - Keryx Bio-Pharmaceuticals

Effect of Ferric Citrate on ESA and Iron Parameters

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TH-OR029
Effect of Ferric Citrate vs. Ferrous Sulfate on Iron, Hemoglobin, and Mineral Metabolism in CKD
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Background: Iron deficiency is common in CKD. Ferric citrate is a novel oral agent for treating iron deficiency anemia in CKD, but little is known about the efficacy of ferric citrate vs. ferrous sulfate (standard of care) in improving iron levels in CKD patients with iron deficiency.

Methods: 60 patients with stage 3b-4 CKD and iron deficiency (transferrin saturation [TSAT] <30% and ferritin <300 ng/mL) were randomized to ferric citrate (FC; n=30) or ferrous sulfate (FS; n=30) for 12 weeks. Primary outcomes were change in TSAT and ferritin. Secondary outcomes were change in hemoglobin, phosphorus, and FGF23.

Results: There were no significant differences in baseline characteristics by treatment arm except FGF23, which was higher in the FS arm compared to FC arm (19.4 vs. 12.3 pg/mL, p=0.004). Total FGF23 decreased 15% in the FC group but not in the FS group (Fig.1). Intact FGF23 decreased 19% in the FC arm (P<0.001) and 5% in the FS arm (P=0.33), and c-terminal FGF23 decreased 15% in the FC group.
High fibroblast growth factor 23 (FGF23) levels are associated with increased erythropoietin hyporesponsiveness among HD patients. FGF23 negatively regulates erythropoiesis. We hypothesized that higher FGF23 levels would be associated with increased erythropoietin hyporesponsiveness among HD patients. Among the pathogenic mechanisms of contrast-induced nephropathy (CIN), increased viscosity of concentrated contrast media (CM) in renal tubule can perturb renal hemodynamics and have a detrimental effect on tubular epithelial cells. However, the impacts of viscosity in CIN are still poorly understood. Conventional in vitro culture studies cannot reflect the rheological properties of CM. Therefore, we investigated the effects of CM viscosity on the renal tubule using kidney-on-a-chip and two different types of contrast media.

Methods: Renal proximal tubule epithelial cells (Ronenza) were cultured in Organoplate (Mimetas), applying time-averaged shear stress of 0.13 dyne/cm². We treated the cells with two types of CM, low-osmolar agent (iopromide, LOCM) and iso-osmolar agent (iodixanol, IOCM), varying iodine concentrations (50-250mgI/mL). We evaluated cell viability of each group with WST-8 assay. The results of cell viability in Organoplates were compared with those in static conditions. Further, we examined the effects of viscosity-induced renal damage, we increased time-averaged shear stress to 0.52 dyne/cm². Numerical simulations were also performed with different fluid viscosities.

Results: Overall, increased cell viability was observed under physiological shear stress compared to the static condition. While both LOCM and IOCM decreased cell viability compared with the negative control, LOCM was significantly less viable than IOCM at high concentrations. However, highly increased shear stress resulted in reduced viability in IOCM; no difference between IOCM and LOCM was found under the shear stress of 0.52 dyne/cm². Numerical simulations revealed that high viscosity slowed the flow rate and augmented fluid shear stress. Viscosity-mediated damage was prominent in high shear stress condition, which may represent CKD conditions with increased single kidney filtration rate. The lowest and highest levels of FGF23 were associated with increased ESA hyporesponsiveness among HD patients.

Conclusions: The lowest and highest levels of FGF23 were associated with increased ESA hyporesponsiveness in patients on maintenance HD.
TH-OR032
Modeling the Renal Epithelial-Microvascular Niche with Perfusable, Pericyte-Lined Capillary Networks In Vitro
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Background: Failed renal epithelial recovery after acute kidney injury is linked to decreased capillary density and expansion of pericyte-derived fibroblasts. How this altered microvascular niche contributes to epithelial regeneration is incompletely understood. Here we report an in vitro model to study how the microvascular niche alters the regeneration of renal epithelial cells.

Methods: Microvascular networks were generated from the self-assembly of human endothelial cells and fibroblasts under established vasogenic culture conditions. Perforated, non-perfused networks were then co-cultured with renal proximal tubular epithelial cells using Transwell inserts. Next, a culture device was developed to study effects from microvascular perfusion. The device housed multiple polydimethylsiloxane culture chambers to increase experimental throughput. Each chamber contained a perfusible microvascular network formed between gravity-fed 300 µm channels just below a porous membrane. Epithelial cells were seeded on the membrane after network formation. Microvascular network function was assessed by perfusion of 70 kDa fluorescent dextran and immunostaining. Markers of renal epithelial phenotype were measured using real time RT-PCR and immunostaining.

Results: Networks of interconnected, lumened endothelium developed in all models. Fibroblasts occupied the interstitial space and adopted a pericyte-like morphology around vessels. Co-culture of renal epithelial cells with non-perfused microvascular networks did not show a renal epithelial cell polarity but demonstrated expression of SLCE2A6, AQP1, and GGT1. In our custom culture device, microvascular networks had a vessel diameter of 18.6±1.7 µm and a density of 6.4±2.0 cm²/mm², spanned 0.33 cm², were perfusable in 76% of chambers seeded, and could form within ~10 µm of the epithelium. Epithelial cells seeded adjacent to the perfused capillary networks formed polarized monolayers.

Conclusions: Co-culture with non-perfused microvascular networks reduced expression of proximal tubular epithelial differentiation markers. A model with perfusible microvasculature containing capillary-scale, pericyte-lined vessels in co-culture with epithelial cells in a high-throughput perfusable culture platform was developed to better mimic the epithelial-microvascular niche in vivo.

Funding: NIDDK Support, Other NIH Support - R01-HL085339

TH-OR033
An Immunoprotected Bioreactor for Implanted Renal Cell Therapy
Rebecca C. Gologorsky,1 Eun jung Kim,1 Jarrett Moyer,1 Ana Santandreu,1 Charles Blaha,1 Nathan Wright,1 Benjamin W. Chui,1 Paul R. Brakeman,1 Shant M. Vartanian,1 H. David Humes,2 William H. Fissell,2 Shuyo Roy,1 University of California, San Francisco, San Francisco, CA; 2Vanderbilt University, Nashville, TN; 3University of Michigan Medical School, Ann Arbor, MI.

Background: An implantable bioartificial kidney without immunosuppression.

Methods: A bioreactor was designed, built, and tested in vivo. The bioreactor was tested in vivo to determine its efficacy. The bioreactor was implanted in a pig and the results were compared to those of a control group.

Results: The bioreactor successfully perfused and maintained renal epithelial cells in vivo. The results were comparable to those of the control group.

Conclusions: The bioreactor is a promising therapy for implantable bioartificial kidney.

Funding: Other NIH Support - NIH R25, Kidney U01

TH-OR034
Single Bioreactor Culture System for Mass Production of Kidney Organoids Takuya Matsumoto,1,2 Ryuji Morizane,1,2 1Harvard medical school, Boston, MA; 2Brigham and Women’s Hospital, Boston, MA; 3Wyss Institute, BOSTON, MA.

Background: Pluripotent stem cell (PSC)-derived kidney organoids have great potential to recapitulate multicellular relationships and microenvironments of native kidneys, which can be used for drug screening, toxicology assays, disease modeling, and regenerative medicine. Mass production of kidney organoids with a well-established quality control process could be readily scaled up to support development of cell-products for clinical use at industry levels in the future.

Methods: We used biotin-stained bioreactor system. Bioreactors were inoculated with single cell suspension of human PSCs at optimal cell density in StemFit® BasicII in a final 5 ml culture volume. Then, kidney organoids were differentiated by 6-step growth differentiation protocol which was modified from our previously reported protocol. Induction of nephrin progenitor cells (NPCs) and kidney organoids were validated using a combination of immunostaining and qPCR.

Results: 500-1000 organoids were generated in a 5-ml bioreactor. Kidney organoids cultured in this system contained proximal tubular cells (LTL+), podocytes (NEPHRIN+), distal tubular cells (LTL-ECADHERIN+), interstitial cells (MEIS1/2+/ PDGFBR+), and endothelial cells (CD31+). The sphere size at the beginning of differentiation was identified as a dominant factor which affected induction efficiency of NPCs and organoids. Optimization of CHIR concentration was also important for efficient NPC differentiation. Of note, higher expression of SIX2 at the NPC differentiation stage was positively correlated with more nephrin structures in organoids which were viable for a longer time (>35 days) without apoptosis.

Conclusions: We established a bioreactor culture system for manufacturing kidney organoids whose yield was 10 times more efficient than the conventional culture method (96 organoids in 96 well culture plates). Our results also indicated SIX2 expression in NPCs is a predictive marker for production of high-quality kidney organoids. This process could be readily scaled up to support development of cell-products for clinical use at industry levels in the future.

Funding: NIDDK Support, Commercial Support - Ajinomoto co.ltd.

TH-OR035
A High-Throughput Microfluidic Renal Proximal Tubule Model to Study CKD and CVD Risk Factors Erin M. Shaughnessy,1,2 Timothy J. Haggerty,1 Joseph L. Charest,1 Lauren D. Black,1 Else M. Vedula,1 Tufts University, Medford, MA; 2Draper, Cambridge, MA; 3Draper, Cambridge, MA.

Background: Chronic kidney disease (CKD) and cardiovascular disease (CVD) are highly interdependent conditions that share several risk factors, including hypertension. In the United States, hypertension affects nearly a third of CKD patients and is the second leading cause of kidney failure. However, the mechanisms contributing to the interdependence of CKD progression and hypertension are not fully understood, and platforms for studying the conditions in vitro are limited. An in vitro system capable of supporting kidney-specific function and mimicking vascular pathology in a reproducible format has the potential to increase understanding of the physiological interplay and to provide a tool for drug development.

Methods: Draper has developed a high-throughput microfluidic platform, PREDICT96, that controls fluid flow to 96 independent bilayer tissue replicates. Here, we report on the potential of the PREDICT96 platform for modeling renal proximal tubule responses to elevated flow rates with high fluid shear stress (5 dynes/cm²). Human renal proximal tubule epithelial cells (hRPTEC) and human microvascular endothelial cells (hMVEC) were cultured in adjacent channels under different medium perfusion rates mimicking normal and elevated blood pressure (BP) in the renal microvasculature.

Results: After 7 days, tissue was characterized based on barrier function indicated by trans-epithelial electrical resistance (TEER) and expression of proteins involved in BP regulation including luminal sodium-hydrogen exchanger 3 (NHE3) and basolateral Na+/K-ATPase, both previously found to be upregulated in hypertension. Preliminary data shows increased RPTEC barrier function, transporter expression and cell alignment with flow-induced shear stress in the renal and microvascular channels.

Conclusions: A high-throughput in vitro model of hypertension in the renal microvasculature will have powerful implications for studying interactions between CKD and CVD and for predicting toxicity responses of human tissue.

Funding: Other U.S. Government Support

TH-OR036
Kidney Proximal Tubule Engineering via Mel-Electrowriting Katia Jansen,1 Anne metje V. Gendener,2 Marleen Kristen,1 Joost van Duijn,4 Tina Vermonden,2 Jos Malda,2 Rosalinde Masereeuw,1 Miguel Castillo,3 1Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands; 2Utrecht University, Utrecht, Netherlands; 3UMC Utrecht, Utrecht, Netherlands; 4University Medical Center Utrecht, Utrecht, Netherlands.

Background: Tubular tissue engineering generally relies on large scaffolds (>1 mm) or smaller tubules within bulk hydrogels. However, for the engineering of kidney tubuli, these structures must preferably be both small-sized to increase surface area and freely

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TH-OR037

Matrix Elasticity Regulates Multiple Podocyte Functions
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Background: The extracellular matrix provides biomechanical signals to adherent cells. Chronic kidney disease is associated with changes in the structural and mechanical properties of the glomerular basement membrane (GBM) that may be relevant to disease progression. The aim of this work was to use polyacrylamide hydrogels as GBM analogs to determine how variations from physiological substrate stiffness regulate podocyte proliferation, migration, and traction force generation. In addition, YAP activation, an established regulator of cellular mechanotransduction was evaluated in podocytes grown on hydrogels with varying levels of stiffness.

Methods: Conditionally immortalized mouse podocytes were cultured on soft (0.5 kPa) and stiff (10-50 kPa) polyacrylamide hydrogels. Podocyte force generation was measured using traction force microscopy (TFM). Podocyte proliferation was evaluated based on nuclear EdU incorporation. Cell migration rates were measured by live-cell imaging. YAP nuclear localization was determined by quantitative immunofluorescence staining.

Results: TFM analysis showed that cell generated forces were orders of magnitude higher on stiff (10 kPa) compared to soft (0.5 kPa) hydrogels. Podocyte spreading was also significantly lower on soft gels. Tractions stresses were also higher on stiff hydrogel showing that increased force generation was not simply related to differences in cell spreading. Proliferation rate was nearly doubled on stiff gels compared to soft and the rate of podocyte migration was approximately 25 µm/hr on stiff substrates compared to <5 µm/hr on soft gels. Stiff substrates induced nuclear localization of YAP and resulted in up-regulation of gene expression for CTGF, Cyr61, Ankr1, and Birc5, all which are known downstream targets of YAP activation.

Conclusions: These data show that the elasticity of podocyte substrata is important in regulating multiple podocyte functions that may be relevant to maintenance of normal physiological function and/or progression of chronic kidney injury. Additional work is needed to understand the pathological significance of changes in GBM stiffness in different chronic kidney injuries and to elucidate the molecular mechanisms that regulate stiffness-induced changes in cell behavior.

Funding: NIDDK Support, Private Foundation Support

TH-OR038

Application of a Newly Engineered Podocyte Culture System to Study Intracellular Complement Production and Activation
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Background: Current technologies do not support long-term cell viability, differentiation and maintenance of podocytes. We developed a biophysical approach, termed macromolecular crowding(MMC), to create extracellular matrix(ECM)-rich tissue equivalents and decellularization. This approach generates decellularized grafts that scaffold podocytes to grow in an environment similar to native conditions. To show a potential application of this newly designed culture system we studied complement(C) activation in podocytes exposed to IgG from individuals with lupus nephritis(LN).

Methods: Human skin fibroblasts were cultured under MMC and then decellularized. Human immortalized podocytes were cultured on the decellularized matrix(DCM) at 33°C for 7 days and subsequently at 37°C for 14days. ECM deposition in the DCM-coated dishes was analyzed by SDS-PAGE, immunofluorescence(IF) and scanning EM and expression of podocyte markers by western blotting(WB) and IF. Podocytes were then exposed to IgG from patients with LN and C production and activation was studied.

Results: We found that DCM-coated dishes contained all major ECM molecules(laminin, fibronectin, collagen I & IV) and podocytes survived and differentiated on DCM-coated plates significantly better than on noncoated plates, as shown by development of interdigitating foot process (fig.a) and increased expression of nephrin and synaptopodin. Podocytes exposed to LN IgG displayed increased levels of C factors(C3, C4, C5, C5b9) and C3 activation products(fig.b).

Conclusions: Engineering in vitro microenvironment with DCM enhances podocyte viability, native physiology and morphology. This novel system enabled us to demonstrate increased C factor production by podocytes exposed to LN IgG and intracellular complement activation.

Funding: Other NIH Support - NIAID

TH-OR039

Hepatocyte Growth Factor-Producing Mesothelial Cell Sheets Reduce Apoptosis of Renal Tubular Epithelial Cells in Ischemia-Reperfusion Injury
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Background: Ischemia-reperfusion injury (IRI) is a model of acute kidney injury and chronic kidney disease which are clinically important problems to be solved. We have recently reported that renal subcapsular transplantation of hepatocyte growth factor (HGF)-producing cell sheets improved renal IRI in rats from acute to chronic phase. However, the mechanism is not well understood. Therefore, we assessed the apoptosis of the renal tubular epithelial cells after IRI with or without transplantation of the HGF-producing cell sheets.

Methods: HGF-transgenic human mesothelial cells (HGF-tg MC sheet) were cultured in temperature-responsive dishes for 4 days to prepare cell sheets. At day 7 after right nephrectomy a nude rat, two cell sheets were transplanted under the left renal capsule, and the left renal pedicle was clamped for 60 min. Reperfusion was performed after the ischemia, and the left kidney was harvested at day 2, 14, and 28 after IRI. Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) staining and caspase-3 staining were performed to evaluate apoptosis with paraffin-embedded sections of the kidney. HGF-tg MC sheet group was compared to other groups; a sham operation without IRI or treatment (Sham); IRI with no treatment (NT); IRI with intravenous administration of recombinant human HGF protein (IV HGF); or IRI with transplantation of non-transgenic MC sheets under the renal capsule (MC sheet).

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Underline represents presenting author.
Results: The number of caspase-3-positive cells was highest in the Sham group, lowest in the Western group, and somewhat higher in the other groups. With TUNEL staining, positive cells were significantly suppressed in the HGF-tg group, compared to WT and Sham groups. These results suggest that the suppression of apoptosis is one of the mechanisms to improve IRI by HGF-producing cells.

Funding: Government Support - Non-U.S.

TH-OR040

Transdermal Delivery of Kidney-Targeting Nanoparticles

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by cyst formation and kidney enlargement, resulting in end-stage renal failure. Most available therapies offer only controlling secondary consequences of ADPKD and are systemically administered via oral/intravenous routes in which drugs are eliminated by first pass metabolism, degraded by gastrointestinal tract, and cause off-target side effects. Herein, we aim to engineer a transdermal patch containing ADPKD treatment by combining 1) a dissolvable microneedle (DM) patch allowing controlled transdermal delivery of 2) kidney-targeted nanoparticles (KNP) with ADPKD-specific drugs. We hypothesize these KNP can deliver drugs specifically to diseased renal cells, thereby limiting systemic side effects while enhancing kidney bioavailability.

Methods: KNP synthesized DSPE-PEG(2000)-methoxy:DSPE-PEG(2000)-Folate:DSPE-PEG(2000)-FITC in 100:1:10 ratio and non-targeting NP consists of DSPE-PEG(2000)-methoxy:DSPE-PEG(2000)-FITC in 15:0:1 ratio. NP were synthesized by self-assembly of DSPE-PEG(2000)-methoxy:DSPE-PEG(2000)-Folate:DSPE-PEG(2000)-FITC. NP were characterized by cryogenic TEM, light scattering (DLS), and zeta potential. In vitro biocompatibility and binding were evaluated using MTS assay and confocal microscopy on human renal proximal tubule epithelial cells (RPTECs). The KNP incorporated DM (polyvinyl alcohol) patches were fabricated via micro-molding technique, evaluated for dissolution and NP release. Non-targeting and KNP exhibit a diameter of 15.0 ± 0.0 and 12.6 ± 1.2 nm as confirmed by TEM and DLS, and zeta potentials were found to be neutral (0.07 ± 0.02 and -0.32 ± 0.5 mV, respectively). When NP (1-100 µM) biocompatibility were assessed after 24 h on RPTECs, over 90% of cells were found to be viable and were comparable to the PBS-treated group. Additionally, KNP (100 µM) was found to be a more potent inhibitor of non-targeting NP after 30 min. KNP incorporated DM patches consists of uniform microneedles of 600 µm height and 300 µm width. These patches showed complete dissolution within 120 ± 30 seconds in PBS at physiological pH 7.4, indicating potential for rapid transdermal release of NP.

Conclusions: Our transdermal strategy delivery of KNP offer a promising drug delivery system for ADPKD. Future studies will incorporate a library of drugs to test therapeutic efficacy in vivo.

TH-OR041

High Fibroblast Growth Factor 23 Levels Induce Ventricular Arrhythmic-genesis via Intracellular Ca2+ Mishandling

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Background: Calciprotein Particles (CPP) are polydisperse colloidal nanoparticles composed of solid-phase calcium-phosphate (CaP) and protein serum-fetuin-A. Two types of CPP with different CaP properties exist: Primary CPP contain amorphous CaP, whereas secondary CPP contain crystalline CaP. We previously reported that CPP induced FGF23 expression/secretion in cultured osteoblastic cells (UMR106). We also reported that a single dose of phosphate gavage in mice increased plasma CPP levels followed by increase in FGF23 expression in the bone and FGF23 levels in the blood. However, the mechanism by which osteoblasts sense CPP remains unknown. In this study, we tested the hypothesis that Toll-like receptor-4 (TLR4) might function as a receptor for CPP. We also determined which CPP, primary or secondary, contribute to FGF23 induction.

Methods: In vitro experiments: CPP were generated in the culture medium of UMR106 by increasing concentrations of calcium (Ca) and phosphate (P). To inhibit formation of secondary CPP, we added betahydroxyapatite (BP) to the medium (BP inhibits transition of CaP from the amorphous phase to the crystal phase) and measured physical properties of CPP in the medium by small angle X-ray scattering (SAXS). FGF23 mRNA levels were determined by quantitative RT-PCR. In vivo experiments: To inhibit formation of secondary CPP, we injected BP in wild-type (WT) mice fed high P diet for 10 days. To test if FGF23 induction might depend on TLR4, we administrated a single dose of P by oral gavage in WT mice and mice lacking TLR4 (TLR4 KO).

Conclusions: Our study uncovers FGF23 as new target in the intracellular Ca2+ handling, able to induce contractile dysfunction and pro-arrhythmic phenotype in adult cardiomyocytes.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-OR042

A NPT2A-Selective Inhibitor Increases Phosphate Excretion in FGF23-Null and CKD Mice

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Background: The sodium-phosphate co-transporters NPT2a and NPT2c play key roles in reabsorbing filtered phosphate in proximal renal tubules thus contributing critically to phosphate (Pi) homeostasis. Expression of both transporters is regulated by parathyroid hormone (PTH) and Fibroblast Growth Factor 23 (FGF23). Consequently, inactivating mutations in FGF23, GALNT3, or KLOTHO lead to tumoral calcinosis because of increased tubular Pi reabsorption resulting in hyperphosphatemia. Increased plasma Pi levels have been associated to disorders in normal PTH synthesis or function, i.e. hypoparathyroidism and pseudohypoparathyroidism, respectively. Furthermore, acute and chronic kidney disease (CKD) typically leads to a significant elevation of plasma Pi and may be associated with exercise-induced disease progression and increased mortality.

Methods: A novel NPT2a-selective small molecule inhibitor, PF-06869206, which reduces phosphate uptake in human proximal tubular cells was given by oral gavage (10-500 mg/kg) to wild-type mice, to mice lacking Npt2a, Npt2c, or FGF23, and to mice with folic acid-induced AKI or adenine-induced CKD. Plasma Pi levels were measured at different time points after PF-06869206 administration, along with urinary Pi and creatinine.

Conclusions: Administration of PF-06869206 was well-tolerated and elicited a dose-dependent increase in fractional Pi excretion in wild-type mice that resulted in a reduction of plasma Pi levels by approximately 30%. This increase was indistinguishable in wild-type mice and in animals lacking Npt2c, while no changes were observed in Npt2a-null mice. Furthermore, in FGF23-null mice a single dose of the NPT2a inhibitor increased urinary Pi excretion by approximately 20% which reduced urinary Pi levels from 15.8 ± 1.2 mg/dl in WT and CKD mice maintained on PF-06869206 increased urinary Pi excretion thereby reducing plasma Pi levels.

Conclusions: The selective pharmacological inhibition of NPT2a holds promise as a novel therapeutic option for genetic and acquired hyperphosphatemic disorders.

Funding: NIDDK Support

TH-OR043

Calciprotein Particles Cause FGF23 Induction via TLR4 Stimulation in Osteoblasts

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Background: Calciprotein particles (CPP) are polydisperse colloidal nanoparticles composed of solid-phase calcium-phosphate (CaP) and protein serum-fetuin-A. Two types of CPP with different CaP properties exist: Primary CPP contain amorphous CaP, whereas secondary CPP contain crystalline CaP. We previously reported that CPP induced FGF23 expression/secretion in cultured osteoblastic cells (UMR106). We also reported that a single dose of phosphate gavage in mice increased plasma CPP levels followed by increase in FGF23 expression in the bone and FGF23 levels in the blood. However, the mechanism by which osteoblasts sense CPP remains unknown. In this study, we tested the hypothesis that Toll-like receptor-4 (TLR4) might function as a receptor for CPP. We also determined which CPP, primary or secondary, contribute to FGF23 induction.

Methods: In vitro experiments: CPP were generated in the culture medium of UMR106 by increasing concentrations of calcium (Ca) and phosphate (P). To inhibit formation of secondary CPP, we added betahydroxyapatite (BP) to the medium (BP inhibits transition of CaP from the amorphous phase to the crystal phase) and measured physical properties of CPP in the medium by small angle X-ray scattering (SAXS). FGF23 mRNA levels were determined by quantitative RT-PCR. In vivo experiments: To inhibit formation of secondary CPP, we injected BP in wild-type (WT) mice fed high P diet for 10 days. To test if FGF23 induction might depend on TLR4, we administrated a single dose of P by oral gavage in WT mice and mice lacking TLR4 (TLR4 KO). These mice were evaluated by measuring P, Ca, and FGF23 levels in the blood and FGF23 mRNA levels in the cranial bone.

Results: Secondary CPP with a hydrostatic diameter of approximately 35 nm were generated in the medium. In the presence of BP, these CPP disappeared and primary CPP with a diameter of around 9.2 nm were generated. FGF23 mRNA levels were much higher when BP was present in the medium. Administration of BP increased FGF23 mRNA levels in the blood, but suppressed FGF23 mRNA levels in the skull. A single dose of P ingestion increased FGF23 mRNA and circulating FGF23 levels in WT mice but not in TLR4 KO. These mice were evaluated by measuring P, Ca, and FGF23 levels in the blood and FGF23 mRNA levels in the cranial bone.

Conclusions: Primary CPP were a more potent inducer of FGF23 expression than secondary CPP. We also suggest that TLR4 is necessary for appropriate regulation of FGF23 expression/secretion.
Calciprotein Particle (CPP)-Inhibition Explains Magnesium-Mediated Protection Against Vascular Calcification
Jeroen H. De Baaij,1 Anique D. Ter Braake,1 Coby Eelderink,1 Lara W. Zeper,1 Andreas Pasch,2 Stephan J. Bakker,1 Martin H. De Borst,1 Joost Hoenderop.1 NIGRAM2+ consortium 1 Radboud University Medical Centre, Nijmegen, Netherlands; 2 University Hospital Bern, Bern, Switzerland; 3University Medical Center Groningen, Groningen, Netherlands.

Background: Phosphate (Pi) toxicity is a strong determinant of vascular calcification in chronic kidney disease (CKD). Pi induces the formation of calciprotein particles (CPP), which drive the calcification process. Magnesium (Mg2+) may prevent vascular calcification, but the mechanisms are poorly understood. Here, we investigated the role of Mg2+ in calcification and crystal maturation induced by Pi and secondary crystalline calciprotein particles (CPP).

Methods: Vascular smooth muscle cells were treated with high Pi or CPP2 and supplemented with Mg2+ and calcification was analyzed by medium absorbance, electron microscopy and energy dispersive spectroscopy. Effects of increased dietary Mg2+ intake on aortic calcification were assessed in Klotho knockout mice. The effects of Mg2+ on calcification propensity (Tm) were measured in sera from CKD patients and healthy controls.

Results: Mg2+ supplementation prevented Pi-induced calcification in vascular smooth muscle cells. In contrast, Mg2+ failed to inhibit CPP2-induced calcification, indicating that it acts before the formation of CPP2. Increased expression of the osteogenic genes osteopontin and alkaline phosphatase remained stable after Mg2+ supplementation. In CPP2 cultures, Mg2+ dose-dependently delayed the maturation of CPP2 by several days in vitro. Elemental analysis showed that CPP2 contain 37% oxygen, 19% Pi and 39% Ca2+, all remaining stable upon Mg2+ supplementation in already matured CPP2. Furthermore, in Klotho knockout mice, high dietary Mg2+ intake effectively prevented aortic calcification. In human serum, addition of 0.2 mmol/L Mg2+ increased Tm in healthy controls from 371 ± 16 minutes to 422 ± 20 minutes and in CKD patients from 323 ± 19 minutes to 367 ± 23 minutes (both P < 0.05). Each further 0.2 mmol/L addition of Mg2+ led to increases of ~40 minutes in both groups, resulting in a Tm of 566 ± 3 and 505 ± 21 minutes in healthy controls and CKD patients after addition of 1.0 mmol/L Mg2+, respectively.

Conclusions: Our results demonstrate CPP2 mediate Pi-induced calcification. Mg2+ prevents CPP2 formation and thereby prevents Pi toxicity leading to calcification. Mg2+ supplementation, even at low dosages, is a potential therapeutic strategy to reduce vascular calcification in CKD.

Funding: Government Support - Non-U.S.

Physiologic Regulation of Systemic Klotho Levels by Renal CaSR Signaling in Response to CaSR Ligands and Extracellular pH
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Background: Chronic kidney disease (CKD) progresses to end-stage renal disease accompanied by complications resembling the premature multi-organ failure akin to the Klotho-hypomorphic (+/-) mice (Kl/kl). The kidney is the source of soluble Klotho (sKlotho), and as renal disease progresses serum and urine sKlotho levels fail, and patients acquire characteristics resembling the of Kl/kl mice. Pharmacologic or dietary alkaline supplementation slows progression of CKD even in stages 3 and 4. The mechanism(s) by which HCO3 supplementation or alkaline diets work and physiologic mechanisms by which sKlotho levels might be regulated are unknown.

Methods: We measured: 1) urine and serum Klotho in mice treated with calciumimetics or alkalali: 2) Klotho release in medium from minced mouse kidneys, and 3) medium Klotho shedding from the kidney.

Results: In intact mice, minced kidneys, and cultured cells, (CaSR) activation with high Ca2+ or calciumimetics increases sKlotho levels via ADAM10-mediated shedding. Alkaline pH values increase, and acid pH values decrease CaSR signaling. Alkaline treatment increases serum and urine sKlotho in mice, Klotho shedding in mouse kidney homogenates and cultured cells in a CaSR-dependent manner. Oral K citrate for 72 hrs increases serum and urine Klotho in human volunteers. ADAM10-dependence was demonstrated using the ADAM10 inhibitor GI 254203X and siRNA. In HEK-293 cells the CaSR, Klotho, and ADAM10 form cell surface aggregates that disperse following CaSR activation, but not with ADAM10 inhibition.

Conclusions: We define a novel physiologic mechanism for regulation of sKlotho levels by the renal CaSR-ADAM10-Klotho pathway that can be modified by pH. We predict that acidosis accelerates, and alkalalinization slows the rate of loss of renal function in CKD partly because acid decreases, and alkaline increases renal CaSR-stimulated Klotho shedding from the kidney.

Funding: NIDDK Support, American Affairs Support, Private Foundation Support

Lipocalin 2 Regulates FGF23 Production in CKD
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Background: Phosphate (Pi) toxicity is a strong determinant of vascular calcification (VC) and elevated levels of FGF23. In a murine model of Alport disease, we show that CKD causes cardiac hypertrophy due to mechanisms independent of VC and FGF23 due to signaling through activin receptor type 2A (ActRIIA). We tested the hypothesis that decreased sKlotho levels due to cardiac activation of ActRIIA signaling and prevented by its inhibition in the absence of vascular stiffness and without change in FGF23 levels. We predicted that cardiac hypertrophy in 200 do Alport mice was due to decreased sKlotho levels.

Methods: Cardiac size and function were determined by heart weight/tibial length (HW/TL) and echocardiography in 200 day old (do) C57Bl6J genetic male mice on the C57Bl6J background. BUN, inulin clearance were used to measure kidney function. Aortic compliance was determined by pressure - diameter relationship. FGF23 levels were by Elisa. Mitochondrial morphology was by electron microscopy, and OXPHOS was by respiratory. ActRIIA signaling was inhibited by an ActRIIA-Fc ligand trap.

Results: 200 do Alport mice had BUNs of 50 -90 and 70-85 % reduction in renal function. Cardiac levels of psmd2 and inhibit βα were increased in Alport mice and cardiac FGF23 levels were decreased. These effects of CKD were reversed by ActRIIA signaling inhibition. Aortic compliance was unchanged compared to WT mice, and elevated FGF23 levels were not altered by the ActRII-Fc treatment. HW/TL was 6.2 mg/mm in 200 do Alport mice compared to 4.7 in WT control mice, and 4.9 in Alport mice treated Alport mice, p<0.01 (Fig.1). Cardiac hypertrophy was confirmed by echocardiography, but function was not significantly altered. Mitochondrial OXPHOS and morphology were significantly altered in 200 do Alport mice indicating a metabolic cause for the compensated hypertrophy.

Conclusions: Compensation cardiac hypertrophy in 200 do Alport mice was due in part to cardiac activation of ActRIIA signaling and prevented by its inhibition in the absence of vascular stiffness and without change in FGF23 levels.

Funding: NIDDK Support

Novel Mechanism of Cardiac Hypertrophy Within the CKD-MBD Syndrome
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Background: Cardiac Hypertrophy is a predecessor of cardiac morbidity associated with CKD and caused by factors that are components of the CKD-MBD syndrome: vascular calcification (VC) and elevated levels of FGF23. In a murine model of Alport disease, we show that CKD causes cardiac hypertrophy due to mechanisms independent of VC and FGF23 due to signaling through activin receptor type 2A (ActRIIA). We tested the hypothesis that decreased sKlotho levels due to cardiac activation of ActRIIA signaling and prevented by its inhibition in the absence of vascular stiffness and without change in FGF23 levels. We predicted that cardiac hypertrophy in 200 do Alport mice was due to decreased sKlotho levels.

Methods: Cardiac size and function were determined by heart weight/tibial length (HW/TL) and echocardiography in 200 day old (do) C57Bl6J genetic male mice on the C57Bl6J background. BUN, inulin clearance were used to measure kidney function. Aortic compliance was determined by pressure - diameter relationship. FGF23 levels were by Elisa. Mitochondrial morphology was by electron microscopy, and OXPHOS was by respiratory. ActRIIA signaling was inhibited by an ActRIIA-Fc ligand trap.

Results: 200 do Alport mice had BUNs of 50 -90 and 70-85 % reduction in renal function. Cardiac levels of psmd2 and inhibit βα were increased in Alport mice and cardiac FGF23 levels were decreased. These effects of CKD were reversed by ActRIIA signaling inhibition. Aortic compliance was unchanged compared to WT mice, and elevated FGF23 levels were not altered by the ActRII-Fc treatment. HW/TL was 6.2 mg/mm in 200 do Alport mice compared to 4.7 in WT control mice, and 4.9 in Alport mice treated Alport mice, p<0.01 (Fig.1). Cardiac hypertrophy was confirmed by echocardiography, but function was not significantly altered. Mitochondrial OXPHOS and morphology were significantly altered in 200 do Alport mice indicating a metabolic cause for the compensated hypertrophy.

Conclusions: Compensation cardiac hypertrophy in 200 do Alport mice was due in part to cardiac activation of ActRIIA signaling and prevented by its inhibition in the absence of vascular stiffness and without change in FGF23 levels.

Funding: NIDDK Support
TH-OR048

Identification of an Extracellular pH-Sensitive Residue in the Calcium-Sensing Receptor

Patricia Pacios centeno, Donald T. Ward. The University of Manchester, Manchester, United Kingdom.

Background: The calcium-sensing receptor (CaR) is the principal controller of parathyroid hormone (PTH) secretion. Mild acidosis (pH 7.2) inhibits CaR signalling in HEK-293 and bovine parathyroid cells, so permitting increased PTH secretion from human parathyroid cells.[1] Thus, acidosis could contribute to the CaR underactivation and secondary hyperparathyroidism of CKD but where the molecular site of the pH sensitivity remains unknown [1]. The crystal structure of the CaR reveals that CaR R66 and CaR S301 stabilize its active conformation. Therefore, here we investigated whether these residues mediate CaR pH sensitivity.

Methods: CaR activity was measured as Ca2+ mobilization (Fura-2) and extracellular signal-regulated kinase (ERK) phosphorylation in HEK-293 cells transfected with wild-type CaR or CaR R66A. CaR stimulated with HEPES buffer containing the EC50 concentration for Ca2+ (3.5nM CaR; 5 CaR+/s) at either pH 7.4 or 7.6.

Results: The CaR crystal structure predicts that following activation, CaR R66 creates a hydrogen bond with CaR S301 that is supported by a bound, negatively-charged bicarbonate ion (pKa 6.1). We hypothesize therefore that in pathophysiologic acidosis, the more neutral bicarbonates will no longer bind CaR R66, impairing the hydrogen bond and inhibiting CaR activity. Indeed we found that lowering pH from 7.4 to 7.6 inhibited CaR-induced Ca2+ mobilization in CaR+/s (−40 ± 5%, P = 0.001 ANOVA) whereas in CaR+/s there was no significant effect (−14 ± 9%, ns). Similarly, pH 7.0 inhibited CaR-induced ERK phosphorylation in CaR+/s (−86 ± 5%; P < 0.01) but not significantly in CaR+/s (−30 ± 12%, ns). Then in alkalosis, higher pH renders bicarbonate more negative which we hypothesize will better support the R66-S301 hydrogen bond, and thus enhance receptor activity. As predicted, raising pH from 7.4 to 7.6 stimulated CaR-induced Ca2+ mobilization in CaR+/s (125 ± 11%; P = 0.001) but not in CaR+/s (+3 ± 12%; ns). Similarly, pH 7.6 enhanced CaR-induced ERK phosphorylation in CaR+/s (24 ± 17%; P < 0.05) but not in CaR+/s (9 ± 12%; ns). Unlike for CaR+/s, the CaR R66A mutant retained its CaR+/s-like pH sensitivity.


Funding: Government Support - Non-U.S.

TH-OR049

In Vivo Deletion of Complex Genomic Enhancers Reveal a Kidney-Specific, Endocrine-Deficient Cyp27B1 Pseudonull Mouse and Loss of Reciprocally Regulated Cyp24a1 by FGF23 and PTH

Mark B. Meyer,1 Nancy A. Benkusky,1 Seong Min Lee,1 Glenviille Jones,2 J. W. Pike.3 1University of Wisconsin-Madison, Madison, WI; 2Queens University, Kingston, ON, Canada; 3University of Wisconsin-Madison, Madison, WI.

Background: Cyp27b1 and Cyp24a1 are reciprocally regulated in the kidney by the key hormones PTH, FGF23, and 1,25(OH)2D3. Our recent genomic studies in mice identified a complex kidney-specific enhancer module located within the introns of adjacent Mntl (M1) and Mnt21b (M21) genes that mediate basal and PTH induction of Cyp27b1 as well as suppression of FGF23 and 1,25(OH)2D3. The deletion of both M1 and M21 submodules fully eliminates basal Cyp27b1 expression and regulation in the kidney, leading to a systemic and skeletal phenotype similar to that of the Cyp27b1-KO mouse due to deletion of 1,25(OH)2D3 and high PTH. Cyp24a1 levels in the double KO mouse were low due to compensatory regulation by elevated PTH and reduced FGF23. However, expression of Cyp27b1 and its retention of its regulation by inflammation (LPS) in the NRTCs remained unperturbed. Importantly, dietary normalization of calcium, phosphate, PTH, and FGF23 rescues this aberrant phenotype and creates an ideal in vivo model with which to study NRTC production of 1,25(OH)2D3 and its potential impact on disease. Using a separate set of mouse enhancer deletions, we found that basal as well as PTH and FGF23 regulation of Cyp24a1 in the kidney was controlled by a set of downstream enhancers distinct from those that mediate 1,25(OH)2D3. Finally, we confirm the presence of a conserved chromatin landscape for both Cyp27b1 and Cyp24a1 in human similar to the mouse.

Methods: Using CRISPR-Cas9-mediated deletions of genomic enhancers (non-coding segments) in mice, we can separate tissue specific responses in both Cyp27b1 and Cyp24a1. We used ChIP-seq from adult human kidney cortex to explore conservation to mouse.

Results: Our current studies reveal a bimodal activity in the M1 intronic enhancer with components responsible for induction of Cyp27b1 by PTH and repression of 1,25(OH)2D3. The deletion of both M1 and M21 submodules fully eliminates basal Cyp27b1 expression and regulation in the kidney, leading to a systemic and skeletal phenotype similar to that of the Cyp27b1-KO mouse due to deletion of 1,25(OH)2D3 and high PTH. Cyp24a1 levels in the double KO mouse were low due to compensatory regulation by elevated PTH and reduced FGF23. However, expression of Cyp27b1 and its retention of its regulation by inflammation (LPS) in the NRTCs remained unperturbed. Importantly, dietary normalization of calcium, phosphate, PTH, and FGF23 rescues this aberrant phenotype and creates an ideal in vivo model with which to study NRTC production of 1,25(OH)2D3 and its potential impact on disease. Using a separate set of mouse enhancer deletions, we found that basal as well as PTH and FGF23 regulation of Cyp24a1 in the kidney was controlled by a set of downstream enhancers distinct from those that mediate 1,25(OH)2D3. Finally, we confirm the presence of a conserved chromatin landscape for both Cyp27b1 and Cyp24a1 in human similar to the mouse.

Conclusions: Collectively, these studies define a finely balanced homeostatic control mechanism employed by PTH and FGF23 with catastrophic toxicity protection from 1,25(OH)2D3 in the genomic regulation of vitamin D metabolism and its accompanied control of mineral maintenance.

Funding: NIDDK Support

TH-OR050

Nonanomalous Potency Inhibitors of SLC26A3 (DRA) Anion Exchanger as First-in-Class Treatment of Enteric Hyperoxaluria and Nephro lithiasis

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Background: Nephro lithiasis affects 9% of the US population in their lifetime. Two thirds of kidney stones are composed of calcium oxalate, for which hyperoxaluria is a major risk factor. Dietary oxalate is absorbed by intestine, and oxalate is also generated by liver as a metabolic end product. The majority of oxalate is excreted in urine with some excretion in stool. Gastrointestinal conditions such as bariatric surgery, inflammatory bowel disease and pancreatic insufficiency are associated with hyperabsorption of oxalate in colon (enteric hyperoxaluria). DRA (down-regulated in adenoma, SLC26A3) is an anion exchange protein in the intestine that functions in enteric oxalate excretion. It is prominently expressed in the colon and is in the main pathway for colonic oxalate absorption, with knock-out mice having 70% lower urine oxalate excretion. DRA is thus an attractive target for treating enteric and idiopathic hyperoxaluria, and calcium oxalate nephrolithiasis, by redirecting the majority of oxalate excretion through stool rather than urine.

Methods: We previously identified, by high-throughput screening, first-in-class DRA inhibitors (JCI Insight 2018; 3(14): 121370). The work herein includes the synthesis and characterization of a nanomolar potency (IC50 40 nM) inhibitor (DRA inh-A270), and demonstration of its efficacy in mouse models of hyperoxaluria and oxalate nephropathy.

Results: Single dose oral or intraperitoneal (ip) DRA inh-A270 (10 mg/kg) gave predicted therapeutic levels in serum for at least 72 h in mice. In a model of acute hyperoxaluria, bolus oral administration of sodium oxalate (2.5 micromol/kg) produced 3-fold increased urinary oxalate excretion that was largely prevented hyperoxaluria, renal failure (per serum creatinine), renal injury and calcium oxalate crystal deposition (per histology). In toxicity studies, one week high-dose DRA inh-A270 administration did not affect CBC or serum chemistry.

Conclusions: DRA inhibition by DRA inh-A270 represents a novel approach for treatment of enteric and idiopathic hyperoxaluria, and prevention of calcium oxalate nephrolithiasis.

Funding: NIDDK Support, Private Foundation Support

TH-OR051

Pragmatic Cluster-Randomized Trial of an Electronic Clinical Decision Support System (eCDSS) to Improve CKD Management in Primary Care

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Background: Whether eCDSS improves CKD management in primary care is not well known.

Methods: We conducted a 12-month, 3-arm, pragmatic, cluster-randomized trial to evaluate feasibility and preliminary effectiveness of two eCDSS strategies to improve CKD management in primary care. We used electronic health record to identify participants, deliver intervention, and ascertain outcomes. We randomized 524 adults with two or more GFR ≤60 mL/min/1.73 m2 in clustered primary care provider (PCP) to: (1) eCDSS; (2) eCDSS plus pharmacist; or (3) usual care. Intervention included risk Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
stratification with creatinine, cystatin C, albumin-to-creatinine ratio, followed by eCDSS embedded in EHR for individually tailored clinical guidance and patient education. eCDSS PLUS added a pharmacist follow up call. Primary clinical outcome was blood pressure (BP) change. Secondary outcomes were PCP CKD awareness, and appropriate use of ACEi/ARB and statin.

Results: All 81 eligible PCPs agreed to participate. Mean patient age was 70, 47% non-white, median eGFR$_{2009}$ 57.0 ± 0.6 mL/min/1.73 m$^2$. At baseline, there was high use of ACEi/ARB (61%), statin (67%) and BP control (71%). Among intervention patients (n=336), 178 (53%) completed triple-marker labs and 138 (41%) had labs and PCP visit with eCDSS deployed. eCDSS was opened by the PCP for 102/138 (76%) eligible encounters, with at least one suggested order or education material signed for 83/102 (81%). Among eCDSS PLUS 29/40 (73%) completed pharmacist call. After 12 months, BP change (SBP: -0.9 ± 0.9 mmHg; DBP: -0.2 ± 0.4 mmHg), PCP CKD awareness (50%) and use of ACEi/ARB (49%) and statin (56%) were similar across groups. In as-treated analyses, PCP CKD awareness was higher in eCDSS and eCDSS PLUS (73% and 69%) vs. usual care (47%) at study end, adjusted p=0.01.

Conclusions: This tailored, automated CKD eCDSS embedded in the EHR was highly utilized by participating PCPs. Due to insufficient uptake of testing and high baseline guidelines we cannot CKD care in the practice, we were unable to determine eCDSS effectiveness to improve CKD management. We did demonstrate increased PCP CKD awareness. This easily usable tool can be used in large pragmatic trials engaging PCPs to improve CKD management.

Funding: NIDDK Support

TH-OR052

Patiromer vs. Placebo to Enable Spirolonolactone in Patients with Resistant Hypertension and CKD According to Baseline Kidney Function (AMBER Trial)

Rajiv Agarwal,1 Patrick Rossignon,2 Dahlia Garza,3 Martha Mayo,3 Suzette Warren,1 Jia Ma,1 Ansarag Conrad,1 William B. White,2 Bryan Williams,3 1Indiana University School of Medicine, Indianapolis, IN; 2University of Lorraine and FCRIN INI-CRCT, Nancy, France; 3Relypsa, Inc., a Vifor Pharma Group Company, Redwood City, CA; 4University of Connecticut School of Medicine, Farmington, CT; 5University College London, London, United Kingdom.

Background: Spirolonolactone (SPIRO) is effective at reducing BP in patients (pts) with resistant hypertension (RHTN); however, its use in pts with CKD is often limited by hyperkalemia. In AMBER, patiromer (PAT) enabled more persistent use of SPIRO in pts with RHTN and eGFR 25 to 45 mL/min/1.73 m$^2$. We report results in prespecified subgroups with eGFR <30 and ≥30 mL/min/1.73 m$^2$.

Methods: This was a randomized, double-blind, placebo (PBO)-controlled RCT in adults with eGFR 25-45 mL/min/1.73 m$^2$ and uncontrolled RHTN. Pts were assigned (1:1) to receive PBO or PAT, and SPIRO 25 mg QD, with dose titrations permitted after 1 wk (PAT) and 3 wk (SPIRO). The primary endpoint (between-group difference at wk 12 in the % of pts on SPIRO) was assessed in prespecified subgroups with eGFR <30 and ≥30 mL/min/1.73 m$^2$.

Results: 295 pts were randomized, 66 (22.4%) and 229 (77.6%) with baseline (BL) eGFR <30 (median [Q1, Q3]; 27 [25, 29]) and ≥30 (median [Q1, Q3]; 38 [34, 42]) mL/min/1.73 m$^2$, respectively. BL mean (SD) automated office systolic BP (mmHg) was 143.7 (6.7) and 144.2 (6.8) and serum K$^+$ (mEq/L) was 4.8 (0.38) and 4.70 (0.36), respectively. Significantly more pts treated with PAT than with PBO remained on SPIRO at wk 12 in both subgroups (between treatment difference of 28.5% [P=0.0158] for pts with eGFR <30 mL/min/1.73 m$^2$ and 16% [P=0.0033] for pts with eGFR ≥30 mL/min/1.73 m$^2$) with P=0.46 for interaction between subgroups (Figure). (MEAN) CK cumulative SPIRO dose was higher with PAT than PBO, by 732 (274) mg and 274 (140) mg in pts with eGFR <30 and eGFR ≥30 mL/min/1.73 m$^2$, respectively. Adverse events occurred in 56% (PBO) and 63% (PAT) with eGFR <30 and 53% (PBO) and 54% (PAT) with eGFR ≥30. No pts had serum Mg <1.2 mg/dL; 1 PBO and 3 PAT pts (all with eGFR ≥30) had serum Mg 2.4 mg/dL.

Conclusions: PAT enabled more pts with advanced CKD and RHTN to continue treatment with SPIRO, regardless of whether eGFR is <30 or ≥30 mL/min/1.73 m$^2$.

Funding: Commercial Support - Funded by Relypsa, Inc., a Vifor Pharma Group Company

TH-OR053

Glomerular Hyperfiltration Predicts Cardiovascular Outcomes in Apparently Healthy Individuals

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Background: Glomerular hyperfiltration (GHF) is associated with increased risk of cardiovascular (CV) diseases in high risk conditions, but its significance in low risk individuals is uncertain. The aim of this study was to determine the CV risk associated with GHF in apparently healthy individuals.

Methods: 9,515 apparently healthy individuals without hypertension, diabetes, CV disease, stages 5-5 CKD and statin/aspirin with available follow-up data (governmental database) were identified from a large population study. From these, patients with GHF (eGFR > 95th percentile after stratification for sex/age) were compared to controls (eGFR 25th to 75th percentiles). Cardiovascular events (CVE) included CV mortality, myocardial infarction, unstable angina, heart failure, stroke and transient ischemic attack. CVE risk was assessed using Cox proportional hazard model and fractional polynomial regression.

Results: Baseline characteristics of individuals with GHF [eGFR 102 (95% CI 107, 115) mL/min/1.73m$^2$] and normal filtration [eGFR 92 (87, 97)] are presented in Table 1. During a median follow-up of 70 months, 245 CVEs occurred. GHF was associated with an increased risk of CVE [HR 1.78 (1.19, 2.64), p=0.005; Figure 1]. When evaluated continuously, only the highest eGFR percentiles were associated with increased CV risk (Figure 2).

Conclusions: GHF is independently associated with increased CVE risk in apparently healthy individuals. Whether this association is causal or not remains to be determined.

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GHF (n=997)</th>
<th>Normal (n=9505)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 (47, 57)</td>
<td>50 (44.5, 56)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>54%</td>
<td>53%</td>
<td>0.47</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.5 ± 4.5</td>
<td>28.7 ± 4.6</td>
<td>0.03</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>151 ± 15</td>
<td>143 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>87 ± 9</td>
<td>82 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.4 ± 1.0</td>
<td>5.2 ± 1.0</td>
<td>0.005</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.1 ± 0.8</td>
<td>3.1 ± 0.8</td>
<td>0.10</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.6 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67 ± 10</td>
<td>69 ± 10</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 1: Cumulative incidence of CVE with a Cox proportional hazard model adjusted for sex, age, body mass index, smoking, HDL cholesterol, LDL cholesterol, creatinine, proteinuria, and systolic blood pressure.

Figure 2: Fractional polynomial regression with 95% confidence intervals for linear and quadratic terms of GFR.

Funding: Private Foundation Support

TH-OR054

Acute Treatment Effects in Randomized Clinical Trials of CKD Progression

Lesley Inker, Hocine Tighiouart. Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration Tufts Medical Center, Boston, MA.

Background: Interventions in CKD trials often produce early short-term treatment effects on GFR slope (i.e. acute effect) that differ from its late long-term effects. The presence of acute effects complicates the design, interpretation and reduces statistical power of randomized clinical trials (RCT) with GFR slope as endpoint.

Methods: We computed the acute effect in past RCTs included in Chronic Kidney Disease Collaboration (CKD-EPI) using repeated measures models (N RCTs 57; N participants 60620). For the 30 studies with sufficient measurements prior to 18 months we truncated the follow-up time to 18 months to ensure that the long term trajectory did not overly influence the acute effect. We estimated GFR using the CKD-EPI 2009 creatinine equation. We included time since baseline, treatment, time by treatment interaction and baseline GFR as covariates and used an unstructured variance-covariance matrix to account for the correlated longitudinal measurements within each patient. We modeled time as a fixed effect using restricted cubic splines and then as a categorical variable with follow-up times fixed at each study specific schedule visits.

Results: In the total set of CKD-EPI RCTs, the overall mean (SD) acute effect of 0.19 (1.27) mL/min/1.73 m² over 3 months but both negative and positive acute effects were observed with 95% confidence intervals ranging from -2.3 to 2.7 mL/min/1.73 m² indicating large heterogeneity. The figure shows trajectories from baseline to 12 months for 6 example RCTs.

Conclusions: Acute effects are common but there is wide heterogeneity among RCTs. Understanding the timing, magnitude and nature of the acute effect of a specific intervention and population will inform optimal study design.

Funding: Private Foundation Support
Reduced Kidney Function Is Associated with a Greater Burden of Atrial Fibrillation: The KP-RHYTHM Study

Alan S. Go, Jingrong Yang, Kristi Reynolds, Nigel Gupta, Judith C. Lenane, Elisha Garcia, Sue hee Sung, Teresa N. Harrison, Matthew Solomon, Kaiser Permanente Northern California, Oakland, CA; Nephrology, University of California, San Francisco, San Francisco, CA; Kaiser Permanente Southern California, Pasadena, CA; Rhythm Technologies, Inc., San Francisco, CA.

Background: Atrial fibrillation (AF) is the most potent risk factor for ischemic stroke. Previous studies have reported that reduced kidney function is associated with a higher risk of developing AF. Having a greater burden of AF (i.e., amount of time spent in AF) is also an independent risk factor for stroke. However, whether kidney function influences the burden of AF is unclear.

Methods: The Kaiser Permanente (KP) RHYTHM Study included all adult members of KP Northern and Southern California integrated healthcare delivery systems who underwent 14-day continuous, beat-to-beat ambulatory ECG monitoring using the Zio XT Patch between October 2011-October 2016. We identified patients who had known estimated glomerular filtration rate (eGFR) by CKD-EPI within the year before monitoring, who were not receiving renal replacement therapy, and who had AF detected during the monitoring period. Patient demographic characteristics and stroke risk factors were obtained from electronic health records. We examined the multivariable association of log-transformed AF burden (% analyzable wear time spent in AF) per 10 mL/min/1.73 m² decrease in eGFR.

Results: Among 1069 eligible adults with detected AF on continuous ambulatory monitoring, mean age was 69.1 years, 45% were women, and 25% were persons of color. Overall, median AF burden was 4% (IQR:1% to 13%). After adjustment for proteinuria, age, gender, ethnicity, body mass index, hypertension, diabetes mellitus, and prior stroke/transient ischemic attack, every 10 mL/min/1.73 m² lower level of eGFR was independently associated with a 10% higher burden of AF (adjusted relative estimate 9.7%, 95% CI:1.1%-19.0%).

Conclusions: Among adults found to have AF on 14-day continuous ambulatory ECG monitoring, lower eGFR level was independently associated with a higher burden of AF. Reduced kidney function may contribute to excess risk of stroke through promoting both a higher incidence of developing AF as well as a greater burden of AF.

Funding: Commercial Support - Rhythm Technologies

igator: TH - Tuesday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Oral Abstract/Thursday

Th-Or057

ACEI/ARB Discontinuation and Adverse Outcomes in CKD

Carl P. Walther, Peter Richardson, Wolfgang C. Winkelmaier, Venkat Ramanathan, Salim S. Virani, Sankar D. Navaneethan. Baylor College of Medicine, Houston, TX.

Background: Treatment with ACEI/ARB is standard of care for CKD with albuminuria as it can slow disease progression. However, ACEI/ARB treatment can increase risk of hyperkalemia, hypotension, and acute kidney injury, especially in the setting of intercurrent illnesses. We investigated the association of ACEI/ARB discontinuation with patient characteristics and outcomes among VA patients with non-diabetic dependent CKD.

Methods: Patients followed at the VA who had eGFR <60mL/min/1.73 for >90 days, 2005-13, were identified; those with CKD G5 or ESKD were excluded. Patients entered the cohort at time of incident ACEI/ARB use, 2005-13; discontinuation (based on pharmacy fill data) was treated as a time-varying risk factor. Different durations of discontinuation (<90, 90-180, >180 days) were investigated, and death and incident dialysis were the outcomes. We used Cox regression, adjusting for demographic and clinical factors.

Results: We identified 238,615 people who met the inclusion criteria; 96.7% were male, and mean age was 71±10 years. 69,544 deaths and 6,100 dialysis initiations were observed. ACEI/ARB discontinuation was associated with more than doubling the risk of subsequent mortality, with a <90 day discontinuation having a hazard ratio for mortality (compared to no discontinuation) of 2.74 (95% CI 2.67-2.81) in adjusted analysis. Longer discontinuation intervals were also associated more than doubling of mortality risk (Table). ACEI/ARB discontinuation was also associated with more than two-fold increased risk for incident dialysis, with a <90 day discontinuation having a hazard ratio of 2.36 (95% CI 2.17-2.56) on adjusted analysis, and longer durations having similar risk.

Conclusions: ACEI/ARB discontinuation was associated with increased subsequent risk of death and incident dialysis in an elderly male VA cohort. Additional investigation, including causes of discontinuation and outcome circumstances, will elucidate relative contributions of ACEI/ARB discontinuation as a cause of the poor outcomes or a marker of worsening health.

Table. Associations of ACEI/ARB discontinuation with mortality and dialysis initiation, adjusted models (HR [95% CI])

<table>
<thead>
<tr>
<th>ACEI/ARB discontinuation</th>
<th>Mortality</th>
<th>Dialysis initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No discontinuation</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>&lt;90 days</td>
<td>2.74 (2.02-3.71)</td>
<td>2.36 (2.17-2.56)</td>
</tr>
<tr>
<td>90-180 days</td>
<td>2.63 (2.34-2.93)</td>
<td>2.70 (2.49-2.91)</td>
</tr>
<tr>
<td>&gt;180 days</td>
<td>2.62 (2.04-3.37)</td>
<td>2.70 (2.49-2.91)</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Autophagy Protects Podocytes from Diabetes-Related Glomerular Endothelial Dysfunction

Kosuke Yamahara,1 Mamoru Yoshiyabashi,1 Shinji Kume,2 Sho Sugahara,3 Mako Yamahara,4 Naoko Takeda,5 Norihisa Osawa,1 Masami Chinn-Kanasaki,2 Hideki Yoki,1 Masashi Mukuyama,6 Shin-ichi Araki,7 Hiroshi Maegawa,8 Shin’ichi University of Medical Science, Otsu, Shiga, Japan; 2Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; 3Kumamoto University Graduate School of Medicine, Kyoto City, Japan.

Background: In diabetic nephropathy, glomerular endothelial dysfunction is a primary event leading to albuminuria, and impaired podocyte autophagy is recently focused as a factor associated with progression to massive albuminuria. However, an interaction between these two events is still unclear. This study was designed to examine a nonprotective role of autophagy in podocyte injury during the development of diabetes-related glomerular endothelial dysfunction.

Methods: We generated tamoxifen (TM)-inducible podocyte-specific Atg5-deficient (TM-Atg5f/f) mice by crossbreeding with eNOS knockout mice, or an intravenous injection of saline and subsequent massive albuminuria via activation of ER stress during the development of diabetes-related glomerular endothelial dysfunction.

Results: In both TM-Atg5f/f and TM-Atg5f/f mice, HFD-feeding induced glomerular endothelial dysfunction, which was characterized by an increased urinary nitric oxide excretion, collapsed endothelial fenestrae, and decreased endothelial glyocalyx. HFD-fed TM-Atg5f/f mice showed slight albuminuria and nearly normal podocyte morphology. In contrast, HFD-fed TM-Atg5f/f mice developed massive albuminuria accompanied by severe podocyte injury. The severe podocyte damage in HFD-fed TM-Atg5f/f mice was observed in the podocytes adjacent to damaged endothelial cells. Interestingly, podocyte-specific autophagy deficiency did not exacerbate eNOS-deficiency-induced albuminuria, whereas it markedly exacerbated neprilysin-induced albuminuria along with severe podocyte injury. Finally, we found that ER stress was accelerated in the podocytes of TM-Atg5f/f mice stimulated with neprilysin, and that a treatment with molecular chaperone, TUDCA, was able to improve neprilysin-induced severe podocyte injury in the mouse.

Conclusions: Podocyte autophagy protects podocytes from diabetes-related glomerular endothelial dysfunction. Insufficient autophagy leads to severe podocyte injury and subsequent massive albuminuria via activation of ER stress during the development of endothelial dysfunction in diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-OR060

Gut Microbiome-Derived Phenyl Sulfate Contributes to Albuminuria in Diabetic Kidney Disease (Part 1)

Koichi Kikuchi,1 Daisuke Saigusa,2 Yoshitomi Kanemitsu,2 Yotaro Matsumoto,4 Eikan Mishima,2 Takafuli Toyohara,2 Takehiro Suzuki,2 Shizuko Nagao,3 Shinji Fukuda,3 Tomoyoshi Soga,2 Yoshitaka Tomiska,2 Takaaki Abe,2 Tohoku University Graduate School of Medicine, Aoba-ku, Sendai, Japan; 3Tohoku University Graduate School of Pharmaceutical Sciences, Niigata, Japan; 4Fujita Health University, Toyoake, Japan; 5Institute for Advanced Biosciences, Keio University, Tsuruoka, Japan.

Background: Diabetic kidney disease (DKD) is a major cause of renal failure in urgent of breakthrough in disease management. Type II diabetes causes significant changes in an array of plasma metabolites, and in humans, SLC41C1 is the only transporter capable of transporting into urine. We generated transgenic (Tg) rats overexpressing SLC41C1 in the proximal tubule, a typical human renal rexin model. Using this model, we characterize metabolites increased in diabetic wild type, but reduced in diabetic Tg rats.

Methods: Diabetes was induced by STZ. Untargeted metabolomics was performed by UPLC-QTOF/MS. Phenyl sulfate (PS) and other uremic toxins were measured by LC/MS/MS. Mitochondrial function was analysis by Flux analyzer. The fecal 16S rRNA were analyzed by MiSeq.

Results: PS was increase with the progression of diabetes and was decreased in Tg rats with limited proteinuria. In diabetic mouse models, PS administration induced albuminuria and podocyte damage due to mitochondrial damage. By DKD cohort analysis, the PS level is correlated with basal and 2-year progression of albuminuria. Phenol is synthesized from dietary tyrosine by gut bacterial-specific tyrosine phenol-lase (TPL) and absorbed phenol is metabolized into PS in the liver. Administration of TPL inhibitor reduced not only circulating PS level but also albuminuria in diabetic mice. Furthermore, TPL inhibitor ameliorated renal dysfunction in adenine-induced renal failure model. Because TPL inhibitor did not alter the major composition, the non-lethal inhibition of microbial-specific enzymes has a therapeutic advantage for the development of drug resistance.

Conclusions: PS is a modifiable cause and a target for the treatment of DKD. Chemical reduction of TPL should represent another aspect for developing drugs preventing DKD.

Funding: National Institutes of Health; National Institute of Diabetes and Digestive and Kidney Diseases.

TH-OR061

PLK1 Inhibitor Can Reverse the Diabetic Nephropathy in OVE26 Type 1 Diabetic Mice

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Background: Diabetic kidney disease (DKD) remains the leading cause of ESRD. However, treatment options are very limited. Since DKD is caused by multiple factors and its pathogenesis is complicated, it would be important to apply the systems biology to analyze the major gene signatures which are responsible for DKD and therefore, we could identify drugs which could reverse these gene signatures as potential treatment of DKD.

Methods: We analyzed public transcription data. SL1000 as a L1000 characteristic signature search engine has been applied widely in repurposing drugs for treatment of various diseases. Using this, we analyzed all public transcriptomic datasets related to DKD and GEO2EEnrich analysis to identify potential drugs, which reverse the gene signatures in DKD. We validated the findings by in vitro and in vivo studies.

Results: Gene expression datasets from 24 studies that compared DKD to normal kidney tissue were identified from GEO and Nephroseq. Differential expression was analyzed with GEO2EEnrich. We further performed meta-analysis of 27 DKD signatures from 24 studies using GEN3VA. Then L1000CDS2 was employed with each signature to prioritize matching above signatures created from over 20,000 drugs treatments of multiple human cell lines. We selected BI2536 from the top 5 most consistent drugs across the L1000CDS2 results, also considering their novelty and applications in other fields. BI2536 is a PLK1 inhibitor which
can lead to cell cycle arrest and has been studied broadly in tumor treatments. We found PLK1 to be an attractive target in the context of cancer, expressed on numerous gliomata and localized mostly on mesangial cells. In vivo, we found that treatment of BI2536 attenuated albuminuria and renal histological changes, and expression of renal fibrosis and inflammation markers. We further compared the gene and pathways regulated in DKD but reversed by BI2536, which revealed Snprad3 and Mrap3 significantly altered by BI2536. We confirmed that BI2536 inhibited Snprad3 and NF-kb phosphorylation in primary mesangial cells probably through direct interaction between PLK1 and these transcription factors.

**Conclusions:** Our data indicate that systems analysis could help to identify potential new targets for treatment of DKD. BI2536 could be a potential drug which could reverse the gene signatures in DKD and the renal protective effect of BI2536 is validated in vivo animal model of DKD.

**Funding:** NIDDK Support

**TH-OR062**

**High Glucose and High Osmolarity Modulate Function of FRMD3/ Protein 4.1O: A Candidate Gene of Diabetic Nephropathy**

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**Background:** FRMD3 has been proposed as a candidate gene for susceptibility of diabetic nephropathy (DN) in type 1 diabetes. FRMD3 encodes for protein 4.1O, which is a member of the 4.1 protein family. The molecular function of FRMD3/protein 4.1O is unknown. We aimed to analyse the earliest stages of DN and results from a defect in the glomerular filtration barrier. Linkage of the slit diaphragm protein nephrin to the actin cytoskeleton via adapter proteins are essential for the integrity of the glomerular slit diaphragm.

**Methods:** RNA was isolated from human podocytes and qPCR for FRMD3 was performed. Nephrin and protein 4.1O were stained in mouse glomeruli. In Cos7 cells, protein 4.1O and actin were visualized via immunofluorescence. Zebrafish larvae were treated with morpholinos against the orthologue of FRMD3 in zebrafish. Injection of fluorescently labeled FITC-dextran was monitored via eye fluorescence. A reduction of fluorescence was an indirect sign of glomerular tracer loss. Cells expressing protein 4.1O, its truncations and nephrin were subjected to cell lysis. Co-immunoprecipitation and Western blot analysis were performed. Kidney samples from patients with T1DN or T2DN were stained for protein 4.1O. Cells were treated with different glucose concentrations and mannitol for osmolarity control.

**Results:** Protein 4.1O is expressed in human podocytes. Protein 4.1O interacts with nephrin and actin vitro and in vivo. Injection of frmd3 morpholino morpholinos in zebrafish larvae leads to zebrafish yolk sac edema, slit diaphragm disruption and increase in glomerular permeability. The increase in glomerular permeability can be rescued by reconstitution of protein 4.1O AA 506-553, the nephrin binding domain. Protein 4.1O expression is increased in human T1 and T2DN. High glucose levels increase protein 4.1O expression while high osmolarity increases nephrin protein 4.1O interaction and protein 4.1O O-GlcNAcylation phenotype.

**Conclusions:** Protein 4.1O is a novel linker of nephrin to the actin cytoskeleton and essential for the glomerular filtration barrier. High glucose increases expression of protein 4.1O while high osmolarity leads to posttranslational modifications on protein 4.1O mediating an increased interaction with nephrin.

**TH-OR063**

**Short-Term Pulse Treatment with Nicotinamide Mononucleotide in Diabetic Nephropathy: Therapeutic Application of Metabolic Legacy Effect**

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**Background:** We previously demonstrated that the derangement of nicotinamide adenine dinucleotide (NAD+) metabolism and the inactivation of SirT1, an NAD+ dependent deacetylation enzyme, initiated diabetic nephropathy (DN) (Nat Med, 2013). SirT1 is activated by NAD+ precursor, nicotinamide mononucleotide (NMN). We tested short-term pulse treatment with NMN against DN.

**Methods:** We divided K562-old dd/bb and dd/m mice into five groups: dd/bb + saline (db/db); dd/bb + saline + (db/db); dd/bb + NMN 100 mg/kg (NM100); db/db + NMN 300 mg/kg (NM300); and dd/bb + NMN 500 mg/kg (NM500). Short-term pulse treatment with NMN was performed via i.p. injection for two weeks. We terminated the treatment at 10 weeks of age and evaluated remote effects of NMN therapy at 10, 24, and 30 weeks of age.

We also evaluated tissue NAD+ metabolite levels and the expressions of some enzymes of NAD+ metabolism, including Namp (convert nicotinamide (NAM) into NMN and Nmnat1 that converts NMN into NAD). We tested NMN or Nmnat1 that converts NMN into NAD.

**Results:** At 24 weeks, db/db exhibited higher levels of Hba1c and albuminuria, as well as more foot process effacement and reduced expression of SirT1 and Synaptotagmin in renal histology as compared to those in the db/db. Although the Hba1c levels in the NM500 and dd/bb were different, NMN treatment resulted in lower albuminuria at early stages in db/db mice. 10 weeks after the termination of therapy in a dose-dependent manner NMN treatment ameliorated foot process effacement and preserved SirT1 and Synaptotagmin expression. Renal NAD+ levels reduced with age in both db/db and dd/bb. In contrast, the NM500 maintained NAD+ levels at 24 weeks of age. Namp expression in the NM500 was higher than those in the db/db and dd/bb. Nmnat1 expression was lower in the dd/bb than those in these dd/m and NM500, although Nmnat1 expression between the db/db and NM500 was not different. These results indicated that the NMN treatment maintained renal NAD+ concentration by increasing Namp expression and maintaining Nmnat1 expression.

**Conclusions:** Short-term pulse treatment with NMN at the early phase of DN had long-lasting renoprotective effects via restoration of NAD+ and preservation of SirT1, Namp, and Nmnat1 expressions independently of glycolytic control. This intervention suggested the introduction of metabolic legacy effects during the course of DN.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
improves oxidative metabolism. Along with existing clinical approaches, enhancing "

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Department of Pathology, University of Helsinki, Helsinki, Finland; 3UC San "

Sara

PGC-1

TH-OR067

Murine Diabetic Nephropathy at Single Cell Resolution

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Background: Diabetic nephropathy (DN) is the most common cause of ESRD, but the transcriptional changes driving disease progression at the single cell level remain undefined. We hypothesized that single nucleus RNA-seq could provide insight into the cellular mechanisms of diabetic nephropathy.

Methods: We collected urine and kidney samples from control(n=2) and db/db(n=4) female mice at 17 weeks. We generated a total of 70,637 single nucleus transcriptsomes and performed a comprehensive bioinformatics analysis.

Results: db/db mice had 25±35 ug/mg urine Alt/creatinine ratio compared to 24±6 in control. On average we detected 2,940 unique genes/nucleus. By unbiased clustering, we could identify 18 major cell types representing all major cell types, including macula densa, with differential expression of hundreds of genes across all clusters. Diabetic kidney had higher leukocyte infiltration including T cells, dendritic cells and macrophages. Diabetic macrophages upregulated the receptor Ptx2, whose ligand PEDF ameliorates DN when administered exogenously. We generated a detailed diabetic glomerular intercellular communication map between podocytes, glomerular endothelium, mesangium and Cdhd6+ parietal epithelia. This revealed podocyte – parietal epithelial cell signaling via b-catenin suppressive Ijgpl4-Lppl signaling among others. We identified evidence for compensatory gene expression in the kidney as podocyte damage. We determined that protein kinase C epsilon and upregulation of type 1 adenylate cyclase, proteins known to mediate susceptibility to proteinuria. Other upregulated podocyte genes included angiogenic EphA6 and Shroom3, a GWAS hit for CKD. Unexpectedly, diabetic stroma cells showed the largest gene expression changes including genes related to integrin linked kinase, cell adhesion and calcium signaling.

Conclusions: This is the first comprehensive single nucleus transcriptional atlas of a mouse model of DN. We demonstrate the utility of this approach by revealing (1) activated macrophage recruitment, (2) detailed diabetic glomerular intercellular communication, (3) podocyte-specific expression of proteinuria susceptibility genes and (4) stromal cell activation.

Funding: Commercial Support - Janssen Pharmaceuticals

TH-OR068

Electrocardiographic Manifestations of Acute vs. Chronic Hyperkalemia

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Background: Hyperkalemia from kidney failure may cause life-threatening arrhythmia. Patients with end-stage renal disease (ESRD) have been thought to better tolerate high potassium levels than those with acute hyperkalemia. Thus, we postulated that patients with chronic hyperkalemia from ESRD have fewer electrocardiography (ECG) changes and less arrhythmias than patients with acute hyperkalemia from acute kidney injury. This study aims to determine the incidence of ECG changes in all patients presenting with hyperkalemia, and tests for differences in the incidence of hyperkalemic ECG changes between chronic and acute hyperkalemia groups.

Methods: We reviewed 256 adult admissions to William Beaumont Hospital Royal Oak Emergency Center with primary or secondary diagnoses of hyperkalemia in patients with chronic hyperkalemia from ESRD, and patients with acute hyperkalemia from acute kidney injury. Initial ECGs taken immediately after hyperkalemia diagnosis were evaluated by a blinded cardiologist. The overall incidence of ECG changes was measured, and differences between the two groups were assessed using unpaired t-tests, chi-square tests, and multivariate analysis with logistic regression.

Results: ECG changes attributed to hyperkalemia were seen in 32% of encounters. There was no difference in the incidence of ECG changes between chronic (ESRD) and acutely (non-ESRD) hyperkalemia patients. However, with univariate analysis, increased patient age (69±6 vs. 61.7 years, p=0.0003), increased serum potassium (7.05 ± 6.8 vs. 9.40±2.4, p=0.000) and history of ischemic heart disease (p=0.03) increased the risk of ECG changes. In the multivariate analysis, demonstrating that higher endogenous serum calcium levels were independently associated with less T-wave peaking (Odds ratio 0.68, p=0.0235).

Conclusions: This study demonstrated no difference in ECG changes between acute and chronic hyperkalemia groups, thus did not support the hypothesis that clinical arrhythmias are less prevalent with chronic hyperkalemia. As expected, increasing age, increasing potassium levels, and prior ischemic heart disease predisposed patients to ECG changes. Although pharmacologic calcium is known to protect against hyperkalemia-related arrhythmias, this study is underpowered finding less T-wave peaking with higher endogenous serum calcium levels, implying that higher nonpharmacologic calcium serum levels may be protective against arrhythmias.

TH-OR069

ECG12Net: A Deep Learning Algorithm Capable of Suprarehman Detection of Hypokalemia and Hyperkalemia by Electrocardiography

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Background: Detection of dyskalemia (hypo- and hyperkalemia), important causes of sudden cardiac death, currently depends on laboratory tests. Since cardiac tissue is very sensitive to dyskalemia, electrocardiography (ECG) may be able to uncover clinically important dyskalemias before laboratory results. Our study aimed to develop a deep learning model, ECG12Net, to detect dyskalemias based on ECG presentation and to evaluate its diagnostic logic and performance for this purpose.

Methods: Between May 2011 and December 2016, 66,321 ECG records with corresponding serum potassium (K+) concentrations were obtained from 40,180 patients admitted to the emergency department. ECG12Net is an 82-layer convolutional neural network, which estimates serum K+ concentration. Six clinicians (three emergency physicians and three cardiologists) participated a human-machine competition. We used sensitivity and specificity as evaluation measures to compare the performance of ECG12Net with these physicians.

Results: In a human-machine competition including 300 ECGs of different serum K+ concentrations, the area under curve in detecting hypo- and hyperkalemia by ECG12Net was 0.926 and 0.958, respectively, which was significantly better than that of our best clinicians. Moreover, the sensitivities and specificities of detecting hypokalemia and hyperkalemia were 97.8% and 83.3%, and 93.3% and 97.8%, respectively. In the test set including 13,222 ECGs, ECG12Net had the same performance with sensitivities for severe hypokalemia/hyperkalemia achieving 95.6% and 84.5%, respectively, with the mean absolute error of 0.531. The specificities of detecting hypokalemia and hyperkalemia were 81.6% and 96.0%, respectively.

Conclusions: A deep learning model based on 12-lead ECG may help physicians to promptly recognize severe dyskalemias and thereby reduce cardiac events.
and inflammation, have not been explored in man. The aim of this study was to investigate the associations of tissue sodium accumulation in a sample of healthy controls and CKD patients using noninvasive 23-sodium (23Na) magnetic resonance imaging (MRI).

Methods: Axial MR images of the lower leg were acquired in 10 controls and 35 CKD patients (eGFR 10-58 ml/min/1.73m2) on a 3T MRI. Proton images for anatomical reference and 23Na images for calculating mean tissue sodium concentration were acquired. Regions of interest included skin, pretibial tissue, bone, soleus, and gastrocnemius muscles (fig 1). Pearson correlation analysis between sodium concentration in different tissues and standard serum biomarkers was performed.

Results: Sodium concentration in all storage compartments was elevated in CKD patients relative to controls (data not shown), and significantly associated with serum albumin as a marker of malnutrition/inflammation complex (fig 2).

Conclusions: The negative association between serum albumin and tissue sodium concentration suggests that sodium accumulation may be a relevant factor driving systemic malnutrition/inflammation complex in the CKD population.
Increased Short-Term and Long-Term Mortality in Community- and Hospital-Acquired Hypernatremia and in Patients with Delayed Sodium Correction

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Background: This study examined short- and long-term mortality (i) in a large cohort of hospitalized hypernatremia patients with and without serum [Na+] correction and (ii) in hypernatremic patients with and without serum [Na+] correction within three days of hospital stay.

Methods: Adult patients admitted to Mayo Clinic Rochester in a three-year (2011-2013) period were examined. Patients were categorized into 3 groups based on serum [Na+] at admission and during hospitalization: 1) normal serum [Na+], 2) community-acquired hypernatremia, and 3) hospital-acquired hypernatremia. Normal serum [Na+] was defined as serum [Na+] at admission and during hospitalization within 138-142 mEq/L. Community-acquired hypernatremia was defined as serum [Na+] at admission ≥ 143 mEq/L, whereas hospital-acquired hypernatremia was defined as serum [Na+] at admission 138-142 mEq/L but any serum [Na+] during hospitalization ≥ 143 mEq/L. Outcomes included hospital and 1-year mortality.

Results: Of the total 25,781 patients, 44.7% (n=11,531) were normonatremic, 20.3% (n=5,229) were community-acquired hypernatremia and 35.0% were hospital-acquired hypernatremia. In fully adjusted models, ORs (95% CI) for hospital mortality and HRs (95% CIs) for one-year mortality were 4.93 (3.47-6.94) and 2.25 (2.01-2.53) for community-acquired and 4.11 (2.94-5.73) and 2.35 (2.12-2.60) for hospital-acquired hypernatremia. Hospital-acquired hypernatremia showed a higher hospital and not one-year mortality, than community-acquired hypernatremia. Among patients with community-acquired hypernatremia, 36.1% (n=1,893) remained hypernatremic by hospital day three ([Na+] >145 mEq/L). Fully adjusted hospital- and one-year mortality were significantly increased in patients without [Na+] correction, 3.01 (2.01-4.40), 1.51 (1.26-1.81), respectively, compared to those with [Na+] correction.

Conclusions: Hypernatremia, regardless of acquisition origin, is associated with elevated short-term and long-term mortality. Hospital-acquired hypernatremia was more common and had a higher short-term mortality than community-acquired hypernatremia. Failure to correct hypernatremia by hospital day three is associated with increased morbidity and mortality.

Potential Utility of Urine Estimated Ammonium-to-Creatinine Ratio in Patients with CKD

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Background: Renal ammonia ([NH₄⁺] excretion plays a critical role in the elimination of acid. Recent studies have reported that the impairment in urinary NH₄⁺ excretion is an important determinant of the development of metabolic acidosis and is an independent factor for predicting loss of renal function. However, urine ammonia measurements are not widely available in routine diagnostic laboratories, and its clinical significance is still unknown. We hypothesized that urine estimated ammonium-to-creatinine ratio (u-eNH₄⁺/u-Cr) as an indicator of urinary NH₄⁺ excretion, would be surrogates for early metabolic acidosis in patients with CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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Table 1. Time to resolution, blood gases and serum potassium between groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to resolution (h)</td>
<td>4.4 ± 1.0</td>
<td>19.1 ± 3.4</td>
<td>0.001</td>
</tr>
<tr>
<td>pH</td>
<td>7.30 ± 0.10</td>
<td>7.14 ± 0.32</td>
<td>0.001</td>
</tr>
<tr>
<td>pCO2</td>
<td>44.3 ± 5.7</td>
<td>47.1 ± 9.4</td>
<td>0.123</td>
</tr>
<tr>
<td>8.5</td>
<td>7.37 ± 0.25</td>
<td>7.35 ± 0.26</td>
<td>0.953</td>
</tr>
<tr>
<td>12.0</td>
<td>7.53 ± 0.37</td>
<td>7.53 ± 1.75</td>
<td>0.953</td>
</tr>
<tr>
<td>24.0</td>
<td>7.54 ± 1.32</td>
<td>7.61 ± 0.32</td>
<td>0.953</td>
</tr>
<tr>
<td>K+</td>
<td>1.96 ± 0.18</td>
<td>1.98 ± 0.08</td>
<td>0.123</td>
</tr>
<tr>
<td>Na+</td>
<td>132.2 ± 2.10</td>
<td>131.8 ± 0.16</td>
<td>0.123</td>
</tr>
<tr>
<td>HCO3-</td>
<td>29.5 ± 0.32</td>
<td>29.5 ± 0.32</td>
<td>0.123</td>
</tr>
<tr>
<td>P</td>
<td>9.84 ± 0.77</td>
<td>9.84 ± 0.77</td>
<td>0.123</td>
</tr>
<tr>
<td>CO2 (mmol/L)</td>
<td>31.6 ± 1.32</td>
<td>31.6 ± 1.32</td>
<td>0.123</td>
</tr>
</tbody>
</table>

Group A, Saline solution + Sodium Bicarbonate 100 mmol; Group B, Saline solution, K+, potassium.

TH-OR077
Development of a Novel Predictive Equation for Ionized Calcium in Hospitalized Subjects: Albumin-Corrected Calcium Equation Is Extremely Inaccurate
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Background: In clinical practice total serum Ca is often corrected according to albumin (0.8mg/dL per each 1g/L Alb<4 g/L). Recently, hidden Ca disorders have been associated to higher mortality in dialysis. Our objective was to develop a novel-specific correction equation for ionized Ca.

Methods: We reviewed electronic data from all hospitalized patients of a single tertiary-care center (2017-2018). Hidden hypocalcemia and hidden hypercalcemia were defined as: normal Alb corrected-Ca & ionized Ca <4.3 or >5.2 mmol/L respectively.

Results: We analyzed 7,158 Ca samples from 5,618 subjects (age 54±20 y, female 55%, 44% with AKI or CKD). Hypocalcemia and hypercalcemia according to ionized Ca occurred in 3.8% (275/7158) and 28.8% (2059/7158) respectively. Alb corrected-Ca had a poor correlation with ionized Ca (r=0.56, p<0.001). Hidden hypocalcemia and hidden hypercalcemia occurred in 2.2% (160/7158) and 5.7% (771/7158) respectively; 6% (375/7158) were erroneously diagnosed as hypocalcemia or hypercalcemia respectively when Alb corrected-Ca was employed. Agreement between Alb corrected-Ca for hypo, normo or hypercalcemia was poor (kappa 0.23).

A novel laboratory-specific prediction equation was developed: Ionized Ca (mg/dL), reference value 4.3±0.2 mg/dL; 0.04*total Ca - 0.27*Alb (g/L) - 0.06*P/ING/dL - 0.022*CO2 (mmol/L) + 2.16. This new equation substantially improved adjusted R² to 0.81 (95% CI 0.78-0.82, p<0.001) when compared with Alb corrected-Ca equation (R²=0.56). Area under ROC curve for hypercalcemia and hypocalcemia diagnosis with new equation was 0.98 (95% CI 0.97-0.99, p<0.001) and 0.86 (95% CI 0.84-0.87, p<0.001) respectively. In univariate models, Alb and eGFR were associated with Ca status misdiagnosis (OR:18.1, p<0.001) yet this association disappeared when multivariate analysis was performed.

Conclusions: We generated new expression and genotype information and conducted eQTL analysis on 121 microdissected human kidney glomerular and tubule samples. Bayesian colocalization method was performed to integrate the GWAS and eQTL data. We performed single cell RNA-seq on human healthy kidney samples. We generated new knockout mouse and confirmed the kidney disease by aging or by folate acid injection. We examined renal histology and gene expression. We analyzed lysosomes and autophagy in vivo and in cultured tubular epithelial cells in vitro.

Results: eQTL analysis indicated that in human kidney tissue samples with CKD risk variant, the expression of Manba was significantly lower when compared to the reference allele kidneys. Manba was mostly expressed in kidney tubule cells including proximal tubules and principal cells in the mouse kidney single cell dataset. Double immunofluorescence staining confirmed its expression pattern. Aging (at 70 weeks age) Manba-knockout mice exhibited an increase in numbers of lysosomes and autophagic vacuoles in tubular cells. In FA-induced kidney fibrosis model, Manba-knockout mice showed more severe fibrotic changes by histological analysis and an increase in proinflammatory genes by QRT-PCR. Manba-knockout mice and cultured Manba-knockout tubular cells demonstrated altered lysosomes and autophagy. As lysosomes play a key role in autophagy, Manba-knockout mice also showed lower autophagic flux.

Conclusions: Taken together, these findings indicate that Manba is a CKD risk gene. Manba deficiency exacerbates kidney fibrosis, likely via lysosomal alterations and an impaired autophagic clearance.

Funding: NIDDK Support

TH-OR079
Lysosomal β-Mannosidase (Manba) Is a CKD Risk Gene
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Background: Chronic kidney disease (CKD) is a complex gene-environmental disease affecting close to 10% of the population worldwide. Through the computational integration of CKD genome-wide association study (GWAS) variants and kidney function, we performed association-based expression identified trait (ABIT) analysis to identify newly discovered lysosomal β-Mannosidase (Manba) as a candidate CKD risk gene. Manba is a lysosomal glycosyl hydrolase. Here we studied mice with genetic manipulation of Manba to understand the role of Manba in CKD.

Methods: We generated gene expression and genotype information and conducted eQTL analysis on 121 microdissected human kidney glomerular and tubule samples. Bayesian colocalization method was performed to integrate the GWAS and eQTL data. We performed single cell RNA-seq on human healthy kidney samples. We generated new knockout mouse and confirmed the kidney disease by aging or by folate acid injection. We examined renal histology and gene expression. We analyzed lysosomes and autophagy in vivo and in cultured tubular epithelial cells in vitro.

Results: eQTL analysis indicated that in human kidney tissue samples with CKD risk variant, the expression of Manba was significantly lower when compared to the reference allele kidneys. Manba was mostly expressed in kidney tubule cells including proximal tubules and principal cells in the mouse kidney single cell dataset. Double immunofluorescence staining confirmed its expression pattern. Aging (at 70 weeks age) Manba-knockout mice exhibited an increase in numbers of lysosomes and autophagic vacuoles in tubular cells. In FA-induced kidney fibrosis model, Manba-knockout mice showed more severe fibrotic changes by histological analysis and an increase in proinflammatory genes by QRT-PCR. Manba-knockout mice and cultured Manba-knockout tubular cells demonstrated altered lysosomes and autophagy. As lysosomes play a key role in autophagy, Manba-knockout mice also showed lower autophagic flux.

Conclusions: Taken together, these findings indicate that Manba is a CKD risk gene. Manba deficiency exacerbates kidney fibrosis, likely via lysosomal alterations and an impaired autophagic clearance.

Funding: NIDDK Support

TH-OR080
Novel Neuroendocrine Features of Macula Dense Cells Suggest Their Chief Role in Glomerular Tissue Remodeling
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Background: Macula densa (MD) cells are strategically positioned at the glomerular entrance and traditionally known to regulate renal hemodynamics and renin release. The present study aimed to explore the emerging new neuron-like and secretory function of MD cells and their role in glomerular angiogenesis and tissue maintenance.

Methods: A newly developed MD cell research toolbox was applied including MD-GFP, MD-GCAMP5, Cdh5-Confetti mouse models for tracking MD and endothelial cell fate and (Ca²⁺) dynamics with intravital multiphoton imaging (MPM), freshly isolated single live MD cells, the newly established immortalized mouse MD cell line MDM, and MD gene profiling.

Results: Mice MD cell gene profile suggested axon guidance and growth as key MD cell functions, and high expression of secreted tissue remodeling and angiogenic factors Ccn1, Nov, Cclx14, Pappa2, Sema3e. MD-GFP mice enabled the visualization of single MD cells in vivo with high detail and confirmed the presence of a dense network of long (up to 100 μm) basal cell processes arborizing into the glomerular mesangium and vasculature, with highly dynamic features including rapid and extensive vesicular transport and outgrowth. MD⁺⁺/+ mouse showed high expression of nerve growth factor receptor (NGFR) and the regulation of nSOS and COX2 expression by NGF. In vivo AOM of MDM cells (Col4a3 cKO), revealed that unlike in other renal epithelia, MD cells show robust (5-fold compared to baseline), rapid, and propagating calcium transients (2-4 s spikes) that were due to several...
neuron-specific calcium entry, mobilization, and extrusion pathways. MD
is associated with ECM expansion. PEC-derived ECM proteins include Laminin
isoforms in focal segmental glomerulosclerosis (FSGS) and diabetic nephropathy is
not well defined. In activated parietal epithelial cells (PECs), upregulation of CD44
content. Interestingly, we also observed an additive effect on renal fibrosis when a
combination of EZ and RM was used compared to when either of the drugs was given
to AS mice.

Conclusions: Our study suggests that Col1-DDR1-mediated lipotoxicity may
represent a novel mechanism leading to podocyte injury in AS that is amenable to
therapeutic intervention through a repurposing strategy of EZ.

Funding: NIDDK Support

TH-OR082
Differential Expression of Parietal Epithelial Cell and Podocyte
Extracellular Matrix Proteins in Focal Segmental Glomerulosclerosis and
Diabetic Kidney Disease
Gek Cher Chan,1,2 Diana G. Eng,1 Jeffrey H. Miner,3 Charles E. Alpers,4 Kyle L. Hudkins,5 Antong Chen,1 Jeffrey W. Pippin,1 Stuart J. Shankland,1
1Division of Nephrology, University of Washington, Seattle, WA; 2Division of
Nephrology, National University Hospital, Singapore, Singapore; 3Division of
Nephrology, Washington University School of Medicine, St. Louis, MO; 4Department of Pathology, University of Washington, Seattle, WA; 5Department of Pathology, UChicago Medicine, Chicago, IL

Background: The differential expression of extracellular matrix (ECM) protein
isoforms in focal segmental glomerulosclerosis (FSGS) and diabetic nephropathy is
not well defined. In activated parietal epithelial cells (PECs), upregulation of CD44
is associated with ECM expansion. PEC-derived ECM proteins include Laminin (f1
(LAMB1), Perlecanchromat type IV (e2) (COL4A2). Podocyte-specific ECM proteins
include Laminin (β2 (LAMB2), Agrin and collagen type IV (e4) (COL4A4). This study
aimed to determine differential ECM protein expression by PECs in experimental and
human FSGS and diabetic nephropathy, and to determine if CD44 plays a role in
regulating ECM protein expression.

Methods: FSGS was induced in CD44 null (CD44−/−) and wild-type mice, using a
cytotoxic podocyte antibody. Kidney tissues were obtained at baseline and day 28 of
FSGS. Podocytes from TgBgal/βgal mice with low-penetrance in which mutagenization of
β-galactosidase was induced, in which severe hyperglycemia manifested resulting in advanced diabetic nephropathy at 24 weeks of
age, were used. BTBR non-diabetic wild-type mice of similar age acted as controls.

Human biopsies of normal kidney, FSGS and diabetic nephropathy were analyzed.

Results: In normal mouse and human glomeruli, PEC-derived ECM proteins were
found along the Bowman’s capsule while, podocyte-specific ECM proteins were found at
the glomerular basement membrane. However, in experimental FSGS, LAMB1, PerlecancellaneouswereincreasedinPECsandtherewasde novo
expressions of LAMB2 and Agrin along Bowman’s capsule. In diabetic ob/o mice, as well as in human biopsies with FSGS and diabetic nephropathy, similar findings were
observed. Because our previous results showed lower ECM expansion in CD44−/−
mice, we compared the difference of each ECM protein between CD44−/− and wild-type mice, to determine if ECM expansion was CD44-dependent. Perlecanc, COL4A2, LAMB2 and Agrin were significantly lower in CD44−/− mice, but not LAMB1 or COL4A4.

Conclusions: Therefore, CD44 plays a role in regulating ECM protein expression.
Activated PEC’s result in increased PEC-derived matrix production, and de novo
production of podocyte-specific ECM.

Funding: NIDDK Support

TH-OR083
CD44 Impacts Glomerular Parietal Epithelial Cell Changes in the Aged
Mouse Kidney
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Background: CD44, an activated parietal epithelial cell (PEC) marker, increases
with aging, and colocalizes with pERK to increase extracellular matrix and epithelial-
mesenchymal transition (EMT). The purpose of the current study was to determine the
effect of CD44 on PECs with aging.

Methods: CD44 knockout and wildtype control mice at 4 or 24 months were used
in this study. Immunohistochemistry and immunofluorescence staining were performed and
glomeruli were assessed as follows; outer cortex (OC) vs. juxta-medulla (JM), young vs.
aged, and wildtype (WT) vs. CD44 knockout (KO).

Results: Aged WT mice had an increase in segmental and global glomerulosclerosis
in JM glomeruli, whereas aged CD44KO mice did not develop either segmental or global
glomerulosclerosis. Bowman’s capsule length increased with age and was longer in JM
than in OC glomeruli. It was significantly less in aged CD44KO mice compared with WT
mice in both OC (212.4±11.7µm vs. WT, 252.4±16.5, µm, P<0.0001) and JM glomeruli
(325.1±24.0µm vs. 373.1±32.2, µm, P<0.0001). In WT mice, PEC number was higher in
JM versus OC glomeruli, and was increased with age in JM glomeruli, while knockout of
CD44 prevented this aged-related increase. PEC density was higher in JM than in
OC glomeruli, and was lower in aged mice than in young mice, however there was no
significant difference between WT and CD44KO mice. Glomerular tuft area was larger
in JM than in OC and was significantly less in aged CD44KO mice versus WT mice, in both
OC (241.2±24.1µm2 vs. 441.5±79.7µm2, P<0.0001) and JM glomeruli (601.1±82.2µm2
vs. 393.1±89.2µm2, P<0.0001). Podecyte number was higher in aged CD44KO mice
versus WT mice in JM glomeruli. Podocyte density was higher in aged CD44KO versus
WT mice in both OC and JM glomeruli. The expression of EMT markers, α-SMA and
vimentin, and activated form of ERK (pERK) and a downstream target of mTOR,
pS6RP was increased in aged WT mice especially in JM glomeruli, and was decreased
in CD44KO mice.

Conclusions: We showed that knockout of CD44 attenuated age-related increase of
glomerulosclerosis, Bowman’s capsule length, glomerular hypertrophy, pERK, pS6RP,
and EMT marker expression. Our data suggest that CD44 is involved in aged-related
changes of glomeruli and CD44 is associated with activation of ERK and mTOR signaling.

Funding: NIDDK Support

TH-OR084
MAD2B Contributes to Parietal Epithelial Cell Activation and Crescentic
Glomerulonephritis via Skp2
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Background: Mitotic spindle assembly checkpoint protein 2 (MAD2B), a well-
dedefined anaphase-promoting complex/cyclosome (APC/C) inhibitor and a small subunit
of DNA polymerase zeta, is critical for mitotic control and DNA repair. Previously, we
reported that upregulation of MAD2B is involved in several renal diseases. However, the
pathological role of MAD2B in crescentic glomerulonephritis (CGN) has not been fully
evaluated.

Methods: The objects of this study included patients with CGN, anti-glomerular
basement membrane antibody (anti-GBM) and in vitro cultured mouse PECs. In vivo,
the-anti-GBM model was established by intravenous injection of sheep anti-GBM serum
and intraperitoneal administration of recombinant human TNF receptor-Ig fusion protein
(TNFRI-Ig) in mice. MAD2B and prednisolone (PNS) were adopted to slow down crescent formation. In
vivo gene silence of MAD2B and Skp2 were carried out by small interfering (si) RNA.

Results: In the present study, we found an obvious MAD2B enhancement in
glomeruli of CGN patients and anti-GBM rats, which mainly originated from PECs.
Contrarily, MAD2B was increased in tumor necrosis factor-α (TNF-α)-treated PECs in
vitro, accompanied by cell activation, proliferation and extracellular matrix accumulation.
Importantly, knocking down MAD2B with siRNA dramatically attenuated
PECs activation. Furthermore, we found that the expression of Skp2, an APC/C-CDH1
substrate protein, was increased in glomeruli of anti-GBM rats and TNF-α-included PECs,
which could be suppressed by MAD2B depletion. Also, genetic deletion of Skp2 inhibited
TNF-α-induced PECs activation. Lastly, the administration of TNFRI-Fc and PNS in anti-GBM
rats reversed MAD2B and Skp2 accumulation, PEC activation, and subsequent crescent
formation.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Our data suggests a pivotal role of MAD2B in the pathogenesis of glomerulonephritis. Pharmacological and genetic clearance of MAD2B may provide a potential target for glomerular crescent formation interventions.

Funding: Government Support - Non-U.S.

TH-OR085
Fatty Acid Receptors GPR40/GPR84: Two Promising Targets in Kidney Fibrosis
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Background: Numerous clinical conditions can lead to organ fibrosis and functional failure. There is a great need for therapies that could effectively target pathophysiologically pathways involved in fibrosis. GPR40 and GPR84 are G protein-coupled receptors stimulated by free fatty acid ligands. Although both receptors have been associated with metabolic regulation and inflammation, they have not been previously linked to organ fibrosis. The dual GPR40 agonist/GPR84 antagonist PBI-4050 is a novel anti-fibrotic drug candidate entering phase III in idiopathic pulmonary fibrosis (IPF) and Alström syndrome. The aim of this study was to determine the role of GPR40 and GPR84 receptors and the effect of PBI-4050 treatment in models of acute kidney injury (AKI) and chronic kidney disease (CKD).

Methods: PBI-4050 was tested in cells involved in fibrosis (macrophages, fibroblasts and epithelial cells) and in various animal models of CKD (5/6 nephrectomized rat, db/db and db/db ONES1 mouse, adenine-induced CKD), AKI (IRI, LPS, UUO, doxorubicin) and in GPR40- and GPR84-knockout mice.

Results: PBI-4050 acts on cells involved in the fibrotic pathway: macrophages, fibroblasts and epithelial cells by regulating cytokines, fibrotil and remodeling markers. GPR40 is also expressed in proximal tubules and collecting duct while GPR84 is mainly expressed in podocytes. In experiments using either GPR40- or GPR84-knockout mice in models of kidney fibrosis (UUO, IRI, and adenine-induced CKD), GPR40 was found protective and GPR84 deleterious. Through binding to GPR40 and GPR84, PBI-4050 significantly attenuated fibrosis in other models of AKI (dextranurokinin, UUO and CKD/ DKD (5/6-nephrectomy, db/db mice). Moreover, in two phase II clinical trials (type 2 diabetes with metabolic syndrome, Alström syndrome) involving a total of 36 patients, PBI-4050 reduced kidney injury urinary biomarkers.

Conclusions: GPR40 and GPR84 may represent promising molecular targets in fibrosis pathways. We conclude that PBI-4050 is a first-in-class compound that may be effective for managing inflammatory and fibrosis-related kidney diseases.

Funding: Commercial Support - Prometic Life Sciences Inc.

TH-OR086
Endothelial Glycocalyx Hyaluronan Is Required for Glomerular Integrity and Is Determined by Shear Stress-Regulated Glycobiogenesis
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Background: Endothelial cells are covered by a glycocalyx envelop, both luminal and abluminal, which predominantly consists of proteoglycans and adhering proteins. Conditional EC loss of glomerular hyaluronan (HA) resulted in mesangiolysis and capillary ballooning and albuminuria. Over time this process develops into glomerular capillary rarefaction and glomerulosclerosis. Laminar shear stress is required to preserve glycocalyx expression, but how downstream cellular regulation of production and maintenance of glycocalyx hyaluronan occurs is unknown.

Methods: EC-HA production and expression were tested in vitro and in vivo using primary EC or conditional EC HAS2-KO mice by fluorescent staining for HA, CRISPR-CAS9 editing of the HAS2 gene and NMR of 13C labelled glucose to determine cellular glucose metabolism concentrations.

Results: Here, we show how biosynthesis of the major structural component of EC glycocalyx, hyaluronan, is regulated by shear. Both in vivo as well as in vivo, HA expression on the endothelial surface is increased upon laminar shear and reduced when exposed to oscillatory flow, which is regulated by KLF2. We demonstrated increased expression and translocation of HAS2 to the endothelial cell membrane during laminar shear. HA production by HAS2 was shown to be further driven by availability of the HA substrates UDP-glucuronic and UDP-glucuronic acid. KLF2 inhibits endothelial glycolysis and allows for glucose intermediates to shuttle into the hexosamine- and glucuronic acid biosynthesis pathways. In addition, we found that HA harbours a specific binding site for the key regulator of endothelial quiescence and maintenance in glomerular/endothelial barrier function, angiopoietin 1 (Ang1), and show that endothelial loss of HA resulted in disturbed Tie-2 kinase dependent glomerular endothelial stabilization.

Conclusions: These data demonstrate how endothelial glycocalyx function and functional adaptation to shear is coupled to KLF2 mediated regulation of endothelial glycosylation and HAS2 expression and HA is a critical growth factor signaling platform linking NO-mediated Ang II signaling. As such, glomerular endothelial hyaluronan is a hitherto unrecognized key ECM component required for glomerular structure and function, which is lost in diabetic nephropathy.

Funding: Commercial Support - DaVita Inc.

TH-OR087
Functional Intrarenal Alterations and Morphological Glomerular Basement Changes in Mice Deficient of the Angiotensinase Aminopeptidase A
Benedikt Maharenich,1,2 Arnd Schulze,1,2 Jan Wysocki,1 Minghao Ye,1 Yashpal S. Kanwar,3 Juan Carlos Q. Velez,3 Daniel Batlle.1 Northwestern University Feinberg School of Medicine, Chicago, IL; 2Charité University Medicine Berlin, Berlin, Germany; 3Ochsner Clinic Foundation, New Orleans, LA.

Background: Aminopeptidase A (APA) is an enzyme abundantly expressed in the kidney glomeruli and tubules which degrades both Angiotensin (Ang) I and Ang II and thereby potentially important for downregulating renal RAS overactivity. Our objective was to examine whether there is a kidney phenotype associated with APA deficiency.

Methods: Urinary albumin excretion rate (AER) and glomerular filtration rate (GFR) were evaluated in BALB/c mice with global APA deficiency (APA-/-) compared to wild-type (WT) mice. Kidneys harvested from 8-month-old mice were examined by light microscopy (LM) and electron microscopy (EM). Abundance of endogenous kidney Ang II and the ability of the kidneys to degrade exogenous Ang II ex vivo were evaluated. In addition, kidney Ang-converting enzyme (ACE) expression and activity were measured. Results: APA-/- mice had normal urinary AER and a GFR similar to that of wild-type (WT) littermates. By LM, kidneys from APA-/- mice showed mild mesangial expansion and mild to moderate thickening of the glomerular basement membrane (GBM). By EM, the APA-/- mice also exhibited mild increase of the mesangial matrix and moderate thickening of the GBM with a striking appearance of knob-like structures and sub-endothelial expansion. Kidney lysates of APA-/- showed a markedly slower degradation of exogenous Ang II (10 μM) compared to those of WT as shown by residual Ang II levels after 30 minutes (48.0 ± 4 vs 16.0 ± 5 %, respectively, p<0.001). Endogenous Ang II levels in APA-/-, however, were not different compared to WT kidneys (1.04 ± 0.2 vs 0.89 ± 0.3 femtol/ mg, p>ns). In addition, kidney lysates of APA-/- mice showed a profound decrease in ACE activity (2981 ± 374 vs 1002 ± 897 RfU/g, respectively, p<0.001), Endogenous Ang II levels in APA-/- mice were significantly decreased compared to APA+/- mice (4 vs 16.0 ± 5 %, respectively). mRNA (RT-real time PCR) and protein (Western blot) levels. The downregulation of ACE by decreasing Ang II formation likely counterbalances the impaired Ang II degradation due to APA deficiency.

Conclusions: Deficiency of APA results in glomerular morphological alterations in the mesangial stalk and the GBM and functional adaptations in intrarenal ACE expression and activity. These findings support a role of APA in maintenance of glomerular structure and intrarenal Ang homeostasis.

Funding: NIDDK Support

TH-OR088
Adoption of Home Remote Monitoring to Improve Outcomes in Peritoneal Dialysis (PD) Patients
Martin J. Schreiber, Mike Gonzales, Shannon Roepce, Kevin Cahill, Bram Van hout, Jodi Holly-Kestel, Patricia Herzog, Michelle Cassin. DaVita Inc, Denver, CO.

Background: The use of virtual health technologies has the potential to transform care of end-stage renal disease patients, allowing ongoing biometric data capture and virtual in-home interactions between patients and the healthcare team. Tracking biometric data through home remote monitoring (HRM) platforms, especially for high-risk patients, can promote a more proactive approach to care management and may improve outcomes.

Methods: We examined the acceptance and utilization of HRM by high-risk PD patients of a large dialysis organization (LDO); patient risk status was determined using a predictive clinical algorithm in conjunction with care team clinical judgement. Each home dialysis facility’s governing body approved the HRM protocol prior to use; patient consent and a physician’s order was required to place a patient on the HRM protocol. Alerts were designed for all biometric values tracked (blood pressure, weight, temperature). Patients could also engage via an iPad in Daily Health Sessions, which included questions about symptoms as well as educational content designed to reinforce training concepts.

Results: Since April 2017, over 12,000 patients have used HRM and over 4700 patients were actively using the platform in May 2019; more than 1 million data points have been collected to date. Metrics tracked during implementation included: patient enrollment rate, consistency of patient data transmission, and speed of alert resolution by the care team. Adoption metrics were assessed by program, along with hospitalization rates and mean time on therapy.

Conclusions: HRM was shown to be feasible among high-risk PD patients of an LDO. Uncontrolled blood pressure, treatment weight > target weight, and an increase in symptoms as well as educational content designed to reinforce training concepts.

Funding: DaVita Inc, Denver, CO.
A Transitional Start Unit (TSU) Improves Home Dialysis Adoption by Incident ESKD Patients

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Preparation: Pre-dialysis education remains inadequate for incident ESKD patients. This is important as the first 90 days of dialysis is a vulnerable time with a high risk of hospitalization and death. To address this problem, we designed a pilot quality improvement program, the TSU, to orient, educate and empower incident patients on key aspects of ESKD. Here, we report results through 26 months.

Methods: The TSU program provides 4-6 weeks of 1:1 dialysis education on nutrition, access, finances, modalities and transplant delivered by an interdisciplinary team following a set curriculum. Setting was two University of Virginia academic dialysis units. Only in-center incident patients were eligible for enrollment. Exclusion criteria included: prior selection of home therapy, permanent long-term care residency, hospice, unstable living arrangements or severe cognitive disability. Patients received four times weekly dialysis on M/T/TiH using NxStage S1 machines for 3-4 hours followed by the typical “long break”. Modest prescription changes by the primary nephrologist were allowed. Primary outcome was uptake of home therapies. Secondary outcomes included: comparison of weekend interdialytic weight gain (WE-IDWG) during TSU and after TSU program for patients who remained on in-center hemodialysis (ICHID) and other relevant quality metrics.

Results: 81 patients enrolled in the TSU. Patients were 52% male, 60.9% black with median age of 62. ESKD cause included 35% type 2 diabetes, 34% hypertension. After education in the TSU, 30.4% of patients chose home therapy (23% PD and 7.4% home HD). Overall prevalence of home therapy in our program is 14.3% with adoption among in-center new starts lower at 5-10%. The above result represents a significant increase in home therapy adoption. Average WE-IDWG was 32% less in the TSU (1.58 kg) versus subsequent thrice weekly ICHID (2.33 kg) (p-value < 0.01). There were two hospitalizations for volume overload during TSU program. Antihypertensive medications were reduced 12% at the end of the TSU period.

Conclusions: A TSU education program significantly increases home therapy adoption among incident ESKD patients and reduces IDWG over the long weekend break. Larger studies are required to determine the effect on hospitalizations.

Early Transitions from In-Center Hemodialysis to Home Dialysis

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Background: Most patients starting dialysis urgently and unplanned receive in-center hemodialysis (ICHID) but might prefer and have better outcomes on home dialysis. We identified those who transitioned from ICHID to home dialysis early following an unplanned dialysis start and determined whether those who transitioned early had a lower risk of death compared to those remaining on ICHID.

Methods: We identified adults in the USRDS who initiated ICHID from 2005-2013 with a central venous catheter and no maturing arteriovenous access who had no nephrology referral prior to dialysis. We used logistic regression to identify factors associated with an early transition to home dialysis (within 90 days of dialysis initiation). Among those who survived to day 90 of dialysis, we applied a Cox proportional hazards model to find the risk of death for those who transitioned compared to those who did not.

Results: Of 190,642 patients, 3923 (2%) transitioned to peritoneal dialysis (PD) and 7427 (4%) transitioned to home hemodialysis (HHD) with an average time on PD and HHD of 413 and 224 days, respectively. Younger age, white race, private insurance, rural neighborhoods, and initiating dialysis in a unit that has a PD program were associated with higher odds of an early PD transition. In contrast, older age, frailty, urban neighborhoods, and initiating dialysis in a unit that has a HHD program was associated with making an early HHD transition. Those who had transitioned to PD at any time during the first 90 days were less likely to die compared to those who had never transitioned to home dialysis [adjusted HR 0.86; 95%CI: 0.82-0.91]. In contrast, transition to HHD in the first 90 days was associated with a higher risk of death compared to those who had never transitioned (adjusted HR 1.31; 95%CI: 1.19-1.44).

Conclusions: Few patients who start ICHID urgently and unplanned make an early transition to home dialysis. Initiating dialysis in a center with home dialysis may help facilitate these transitions by increased exposure, awareness and education about home dialysis. The recent risk factors and demographics of patients transitioning to PD and HHD early suggest that these therapies may attract different types of patients and may explain the differences in outcomes between HHD and PD that we observed. However, further research is needed to understand the higher mortality among early transitions to HHD.

Training Duration Is Associated with Adverse Events in Home Hemodialysis Patients

Isabelle Gionest,1 Louis-Philippe Laurin,1 Jean-Philippe Lafrance,1 Annie-Claire Nadeau-Fredette,1 Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; 2Montreal University, Montreal, QC, Canada.

Background: Home hemodialysis (HHHD) training varies significantly at the center and patient-levels. This study aimed to explore the clinical outcomes associated with HHHD training length.

Methods: All HHHD patients successfully trained in a single-center dialysis center between January 2006 and July 2017 were included. Poisson models were built to assess hospitalization rate after start of HHHD in the home environment. Potential confounding were defined a priori and included age, sex, diabetes, cause of primary kidney disease and year of HHHD start. Time to first adverse event (hospitalization, definitive transfer to center hemodialysis [CHD] or death) was evaluated using a Kaplan-Meier curve and log-rank P.

Results: Forty-nine patients graduated from HHHD training in our program (1 patient was excluded due to delays related to dialysis machine unavailability). HHHD training was offered using a thrice weekly schedule with a median duration of 86 (67-108) days. Mean hospitalization rate was 0.33 (95% CI 0.24-0.44) episode per patient-year. Longer training duration was associated with a trend toward higher hospitalization rates (unadjusted incidence rate ratio [IRR] 1.12 per month, 95% CI 0.99-1.27, p=0.07) and a statistically significant increase in hospitalization rates when adjusted for confounding (adjusted IRR 1.20, 95% CI 1.01-1.41, p=0.03). During the total follow-up time of 131 patient-year, 4 patients died on HHHD, 9 were definitively transferred to HD, 18 received a kidney transplantation and 17 patients had a least 1 hospitalization. There was a trend toward lower event-free survival (hospitalization/definitive transfer to CHD/death) in the extended training group (4+ months of training, log-rank p=0.09).

Conclusions: In this small cohort, patients with longer HHHD training had more frequent hospitalizations. Enhanced home support could be offered to these more vulnerable patients once they graduate from HHHD training.
Illustrative Quotes

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**TH-OR093**

Dialysis Modality Choice Among Healthcare Workers: A UK Perspective

Jyoti B. Baharani,1 Karen J. Jenkins,1 Indranil Dasgupta,2 University of Sydney, Westmead, NSW, Australia; 3East Kent Hospitals NHS University Foundation Trust, Canterbury, United Kingdom

Results:

- 81 patients and 45 caregivers from 9 dialysis units in Australia, Hong Kong, and the US participated in 14 focus groups. Transcripts were analyzed thematically.

Conclusions:

- Recognizing and providing resources to cope with burnout are essential to ensuring the well-being of patients on PD and their caregivers. Further research is needed to develop tools to screen for burnout and interventions for improved care and outcomes in patients on PD.

Funding: NIDDK Support

**TH-OR095**

The Effect of Non-Visual Learning Preferences on Early Home Dialysis Adverse Events

Bourn L. Auguste,1 Michael Y. Ginsberger,2 Claire Kennedy,3 Thatsaphan Sritongkula,1 Margaret E. McGrath-Chong,1 Joanne M. Bargman,1 Christopher T. Chan,1 University of Toronto, Toronto, ON, Canada; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Toronto General Hospital, University Health Network, Toronto, ON, Canada

Background:

- Current approaches to home dialysis training are not individualized according to patients’ learning preference. We hypothesized that visual learning preferences were associated with fewer adverse events in both peritoneal dialysis (PD) and home hemodialysis (HHD) patients within 6 months of training completion.

Methods:

- We performed a retrospective single-centre cohort study at a large academic medical centre of prevalent HHD and PD patients. Patients received a VARK questionnaire at enrollment. VARK is a validated questionnaire that assesses a combination of individual visual learning preferences: visual (V), auditory (A), reading-writing (R) and kinesthetic (K).

Results:

- 118 PD and HD patients with an average age of 52.8 ± 13.5 years. 38% (44) of study participants were non-visual learners. Thirty patients had at least one adverse event within 6 months of training completion; 63% (19) of these patients were non-visual learners.

Conclusions:

- Visual learning preference is associated with fewer adverse events in home dialysis patients within the first 6 months of completing training. Individualization of home dialysis training by learning preference is warranted.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
TH-OR096
Short-Term Gaps in Insurance Lead to Long-Term Disparities in Peritoneal Dialysis Use
1Eugenia Kipers,1 John Meal,1 Jay Bhattacharya,1 Darius Lakdawalla,1 Byung C. Kipers,1 Lauren Fielding,1 Edward A. Wiener,1 Frank Bohmert,2 Jeffrey I. Silberzweig,2 The PEAK team "pulseData, New York, NY; 2The Rogosin Institute, New York, NY.

Background: Peritoneal dialysis (PD) offers improved quality of life over hemodialysis without compromising health outcomes. Uninsured patients do not become Medicare eligible until the first day of the fourth month of treatment. Using a quasi-experimental method, we studied whether short-term gaps in insurance were associated with long-term disparities in PD use.

Methods: Because Medicare eligibility starts on the first day of the fourth month of dialysis, patients starting dialysis at the end of the month have a shorter Medicare waiting period than patients starting dialysis at the beginning of the month. After identifying uninsured adults starting dialysis between 1/1/2006 and 12/31/2014 in the United States from a national registry, we studied whether starting dialysis at the end of the month was associated with higher PD use at day 360 than starting at the beginning of the month. Using two-stage least squares regression, we investigated whether gaps in insurance were associated with long-term disparities in PD use.

Results: The distribution of dialysis start day was distributed randomly (one-sample Kolmogorov-Smirnov, p>0.05). Patients starting dialysis in the first half of the month had a 10.7% (95% CI: 10.2-11.1%) probability of using PD at 360 days, while those starting in the last half of the month had an 11.8% (95% CI: 11.3-12.1%) probability (difference: 1.1% [0.5-1.7%]). Patients starting dialysis on the 31st had a 2.3% (95% CI: 1.1-3.5%) higher probability of PD use at day 360 than those starting on the 1st. Our two-stage regression showed that every 10 day gap without insurance was associated with a 1.0% (95% CI: 0.5-1.5%) absolute decrease in PD use at day 360. We projected that eliminating the Medicare waiting period entirely could increase the probability of long-term PD use in patients without insurance, from 11.2% to 19.8% (95% CI: 16.3, 23.3%).

Conclusions: Patients starting dialysis later in the month have shorter Medicare waiting periods and are more likely to use PD long-term. We exploited this difference to show that longer periods of time without insurance lead to persistent decreases in PD use. Extending Medicare coverage to the first three months of dialysis or earlier could substantially improve PD penetration.

Funding: NIDDK Support

TH-OR097
Use of Machine Learning to Inform Decision Making and Optimal Renal Replacement Therapy
Xiaoyan Wang,1 Ollie Fielding,1 Edward M. Lee,1 Jung Hoon Son,1 Chris Kipers,2 Lauren A. Wiener,1 Frank Liu,1 Andrew Bohmert,2 Jeffrey I. Silberzweig,2 The PEAK team "pulseData, New York, NY; 2The Rogosin Institute, New York, NY.

Background: We deployed a machine learning (ML) model to identify patients at risk of requiring RRT to support clinical care decision making in a multidisciplinary care (MDC) team. We compare the difference in optimal renal replacement therapy (RRT) starts pre and post implementation. To the knowledge of the authors, this is the first live application of ML to inform transition workflows.

Methods: An EHR database of 110,998 patients was used to create an ML model to predict progression to an eGFR <10 or RRT start in the next six months (see Kidney Week 2018 SA-P095)). The system calculates weekly risk scores for non-dialysis patients with an eGFR <55. For high risk patients an alert is sent to the patient’s nephrologist suggesting prompt referral to the PEAK MDC team. The team reviews high risk patients and provides education to inform their decision making. Optimal dialysis starts were defined as outpatient starts with access via AV fistula, AV graft, or peritoneal dialysis catheter.

Results: Since deployment of the ML model in October 2018, 54% of patients enrolled in PEAK had an optimal dialysis start. This is almost three times the national average of 20% (USRDS 2018 data) and 14% better than the 47.3% rate prior to use of the ML model. PEAK home dialysis rates have increased 20% vs. before deployment (24% vs 20%), and is now eight times the NYC average 24% vs 2.5%. PEAK members also received pre-emptive transplants at a rate five times the NYC average 12.5% vs 2.5%. PEAK patients with optimal starts had significantly greater provider interactions, as measured by unique appointment days prior to dialysis, than non-optimal starts (3.9 vs. 2.5 appointments, p<0.0001, unequal variances t-test). Optimal start patients are also associated with earlier enrollment, defined as the time from the first PEAK appointment to dialysis (329 vs. 179 days, p<0.02, unequal variances t-test).

Conclusions: The PEAK MDC-pulseData partnership has improved optimal dialysis starts and home dialysis modality rates by 14% and 22% respectively. Enrollment to the PEAK program has increased by 22% since Oct. 2018. Our results demonstrate that purpose-built AI tools used by an MDC team can increase optimal RRT outcomes.

Funding: Commercial Support - pulseData

TH-OR098
Efficacy and Safety of the Standard and Reduced Apixaban Dose Compared with No Anticoagulation in Dialysis Patients with Newly Diagnosed Atrial Fibrillation
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Background: The relative efficacy and safety of apixaban compared with no anticoagulation for atrial fibrillation (AF) has not been studied in dialysis patients.

Methods: This retrospective cohort study utilized 2012-2015 United States Renal Data System data. Dialysis patients with incident, non-valvular AF treated with apixaban (521 patients) were matched for relevant baseline characteristics with patients not treated with any anticoagulant agent (1561 patients). Competing risk survival models were used.

Results: Compared with no anticoagulation, apixaban was not associated with reduced risk of stroke or thromboembolism: HR 1.23, 95% CI 0.68-2.20, p=0.49. A significantly higher incidence of fatal or intracranial bleeding was observed with apixaban compared with no treatment: HR 2.48, 95% CI 1.25-4.90, p<0.009. A higher rate of stroke or systemic thromboembolism (Figure) and fatal or intracranial bleeding was seen in the subgroup of patients treated with the standard apixaban dose (5 mg twice daily) but not with the reduced apixaban dose (2.5 mg twice daily). A similar incidence of clinically significant bleeding events and major cardiovascular events was seen with apixaban compared with no treatment.

Conclusions: Randomized studies are needed to assess the efficacy of apixaban compared with no anticoagulation in chronic dialysis. Pending randomized data, prudence in prescribing apixaban to dialysis patients, especially at the standard dose, is warranted. The relative efficacy and safety of apixaban compared with no anticoagulation in chronic dialysis. Pending randomized data, prudence in prescribing apixaban to dialysis patients, especially at the standard dose, is warranted.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Rivaroxaban vs. Warfarin for Prevention of Ischemic Stroke/Systemic Embolism (ISSE) in Patients with Non-Valvular Atrial Fibrillation (NVAF) and Stage IV-5 CKD

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Background: There is limited evidence on the effectiveness and safety of direct-acting oral anticoagulants (DOACs) among patients with NVAF and advanced CKD. This study compared the risks of ISSE and major bleeding in patients with NVAF and stage IV-V CKD treated with rivaroxaban or warfarin.

Methods: Data from the Optum Deidentified Electronic Health Record (EHR) Database, we selected patients with NVAF and stage IV-V CKD who initiated therapy with rivaroxaban or warfarin from November 1, 2011 through June 30, 2018. Selected patients were required to both be diagnosed with CKD and have an estimated creatinine clearance <30 mL/min and/or evidence of dialysis. Propensity score (PS) matching was used to balance rivaroxaban and warfarin patients on 97 measured baseline covariates. Hospitalizations for ISSE and major bleeding over 2 years following treatment initiation were ascertained with validated endpoint definitions. Outcomes were analyzed as time-to-event data using Kaplan-Meier survival estimators and Cox regression.

Results: 781 rivaroxaban patients were PS-matched to 1,536 warfarin patients; after matching, all baseline covariates were well balanced (absolute standardized difference<0.1). The mean patient age was 80 years; 62% were female; 82% and 18% had CKD stage IV and V, respectively. The relative hazard (HR) of ISSE associated with rivaroxaban use compared to warfarin use was 0.93 (95% CI: 0.46, 1.90; p=0.85), and the corresponding HR for major bleeding was 0.91 (95% CI: 0.65, 1.28; p=0.91).

Conclusions: No statistically significant difference in the risk of ISSE or major bleeding was found between patients treated with rivaroxaban or warfarin. While further study is needed, rivaroxaban appears to be a reasonable alternative to warfarin for ISSE prevention in the setting of NVAF and stage IV-V CKD.

Funding: Commercial Support - Janssen Scientific Affairs

TH-OR102
Predictors to Identify Diuretic Resistance Early in Acute Decompensated Heart Failure (ADHF)
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Background: Resistance to loop-diuretics occurs frequently in patients hospitalized for ADHF, resulting in inadequate decongestion, readmission and poor outcomes. Early identification of diuretic resistance during the hospital course may aid in institution of appropriate therapies. We aimed to identify clinical biomarkers that predicted diuretic resistance in a study conducted to evaluate usefulness of high-dose spironolactone in loop-diuretic resistant ADHF patients.

Methods: The parent trial was a prospective, randomization trial in ADHF patients. Diuretic resistance was identified if subjects had weight loss≤1lb/day despite intravenous furosemide≥160mg/day (at least one dose of 80mg/day) or no change in dyspnea ≥3H after admission with usual care. Baseline clinical characteristics, blood chemistry including sodium, potassium and urine electrolytes were compared between diuretic-sensitive and resistant subjects.

Results: Twenty of 47 enrolled subjects met loop-diuretic resistance criteria. The mean age was 61+15 years, 66% were male, and 50% were Hispanic. There was no difference in age, gender and race, co-morbidities, admission for ADHF, EF, presence of pulmonary HTN between diuretic-responsive and resistant subjects. However, serum sodium was lower (137±134,139 vs. 139±137,141 mEq/L, p<0.03) and blood urea nitrogen was higher (11.42±7.63,18 vs. 7.68±5.71,8.23 mmol/L, p<0.009) in diuretic-resistant patients compared to the diuretic-sensitive group. Subjects with higher plasma renin activity (7.2±1.5,29.5 vs. 20.2±10.9 ng/ml/hr, p<0.03) and aldosterone (26.5±9, 56 vs. 5.2±3.7, 8.2 ng/ml, p<0.001), and lower urine sodium-potassium clearance were more likely to be resistant.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Incorporating Kidney Disease Measures into Cardiovascular Risk Prediction: Evaluation Using Electronic Health Record Data from 37 Health Care Organizations

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Background: Clinical guidelines for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) increasingly use absolute risk to guide decision-making, often relying on the AHA/ACC Pooled Cohort Equation (PCE) for risk estimation. Two kidney measures, estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (uACR), are CVD risk enhancers but they are not included in the PCE. We hypothesize that when eGFR and uACR data are available, their inclusion will mean a lower CVD risk assessment.

Methods: 836,047 patients in the OptumLabs® Data Warehouse’s EHR-derived data from 37 health care organizations (HCOs) were followed (mean (SD), 3.6 (2.4) years) from 37 health care organizations (HCOs) were followed (mean (SD), 3.6 (2.4) years) with no evidence of baseline ASCVD and data on PCE variables plus eGFR and uACR.

Results: Patients were age 59 (10) (mean (SD)) years, had total cholesterol 175 (35) mg/dL, HDL 45 (15) mg/dL, SBP 128 (16) mmHg, eGFR 81 (21) ml/min/1.73 m2, and uACR 10 (2-29) mg/g (median [IQR]), 51% were female, 74% had diabetes, and 4.5% were pregnant. The original PCE predicted a 5-year risk of 8.4%, and observed ASCVD was 4.2%. Adding eGFR and ACR to PCE improved the C-statistic by 0.022 (95% CI 0.0005-0.0453) overall, 97% of HCOs (36 of 37) improved by at least 0.3%. Over all, reclassification of 5-year ASCVD risk from low (< 3.75%) to intermediate (3.75%-9%) risk was by 47.9% (range by HCO: 30.8%–8.3%) and 61.7% (4.1 – 10.9%)

Conclusions: CKD measures (eGFR and uACR) are often available, and their integration into the PCE is feasible and results in meaningful risk reclassification across HCOs, particularly among higher risk CKD. Implementation in EHRs should include rigorous validation, attending to limitations, e.g., EHRs are blind to events occurring outside the HCO.


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Background: We examined temporal trends in hypertension (HTN) control overall and in those with and without CKD.

Methods: A total of 19,856 adults (≥20 years) with HTN from NHANES 1999-2000 to 2015-2016 were examined. HTN was defined as mean systolic blood pressure (BP) ≥140 or mean diastolic BP ≥90 mmHg. Analysis was limited to persons with CKD (eGFR <60 ml/min/1.73m2) and elevated albuminuria (ACR ≥30 mg/g), and further adjusting baseline logarithm transformed 24h-urinary protein and estimated glomerular filtration rate (eGFR) with a linear mixed model.

Results: HTN control improved overall between 1999-2000 and 2015-2016, from 9.1% to 25.2% (p<0.001). Greater improvement in HTN control was observed in the period from 1999-2000 to 2007-2008 (12.5%, p<0.01), than thereafter (3.5%, p=0.08). The temporal trend in HTN control differed by reduced eGFR status (p for interaction=0.02). HTN control was comparable in individuals with reduced and non-reduced eGFR until 2005-2006 and thereafter control improved more in those with reduced eGFR (Fig 1A). The difference in HTN control between those with and without reduced eGFR was -2% in 1999-2000 (p<0.01), 14% in 2007-2008 (p<0.04) and 7.0% in 2015-2016 (p=0.06). The temporal trend in HTN control by albuminuria status was similar to the overall trend (p for interaction=0.09). The HTN control was not associated with serum sodium or urea nitrogen. Urine sodium-potassium ratio at admission predicted loop-diuretic resistance with an AUC (95%CI) 0.69 (0.68, 0.71). A cutoff value of 2.96 had a sensitivity of 76% and specificity of 65% to identify loop-diuretic resistance (lower the value, more the resistance).

Conclusions: The admission urine sodium-potassium ratio may serve as a surrogate for high aldosterone activity, and is an inexpensive and rapidly available biomarker to recognize diuretic resistance in ADHF patients.

Funding: Commercial Support - Relypsy, Inc, a Vifor Pharma Group Company

White-Coat Hypertension Has a Predictive Role for Renal Outcome in Patients with Non-Dialysis CKD: Results from the C-STRIDE Study

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Background: Data on the predictive value of white-coat hypertension (WCH) for renal and cardiovascular (CV) outcomes in patients with chronic kidney disease (CKD) is controversial.

Methods: Totally, 1734 CKD stage 1-4 patients with both ambulatory BP (ABP) and clinic BP (CBP) data from the Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE) were enrolled in the present study. The BP pattern was categorized as normotension (NT), WCH, masked hypertension (MH) and sustained hypertension (SH) according to ABP and CBP values, respectively. The association of BP pattern with CKD outcomes, including initiation of renal replacement therapy and CV events, was evaluated by Cox regression model.

Results: The mean age of the cohort was 48.4±13.7 years with 43.2% females. The average value of ABP and CBP were 128±17/79±11 mmHg and 130±18/81±10 mmHg, respectively. And NT, WCH, MH and SH each had 678(39.1%), 834(8.4%), 538(31%) and 435(25.1%) patients. During a median follow-up of 4.7 years, 287 renal events and 128 CV events occurred, respectively. Compared with NT, the fully adjusted risk for renal events was significantly increased in WCH (hazard ratio [HR] 2.43; 95% confidence interval [CI] 1.34-4.31), MH (HR 2.42; 95%CI 1.66-3.50), and SH (HR 2.56; 95%CI 1.75-3.74), respectively. With regard to CV events, WCH, MH and SH also showed higher risk after adjusting for traditional CV risk factors (HR 2.53, 95%CI 1.21-5.29; HR 1.85, 95%CI 1.13-3.01; HR 2.63, 95%CI 1.63-4.25, respectively). After further adjusting baseline logarithm transformed 24h-urinary protein and estimated glomerular filtration rate, only SH showed a significantly increased risk for CV events (HR 1.81, 95%CI 1.10-2.99).

Conclusions: WCH is independently associated with an increased risk for renal events in non-dialysis CKD patients.

PRN Use of Antihypertensive Medications and Adverse Renal Outcomes: A Propensity Score-Matched Analysis

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Background: Despite absence of data demonstrating a clear benefit, hospitalized patients are often treated with PRN antihypertensive medications (PRNBPMeds) for symptomatic increases in blood pressure. We hypothesized that use of PRNBPMeds can be associated with abrupt lowering of blood pressures (BP) and worsening renal function.

Methods: Single center retrospective study of all adult patients admitted between Jan 2012 and April 2016 who received antihypertensive medications. We excluded those with possible hypertensive emergent, hypertensive emergency, renal disease and acute kidney injury (AKI) on admission. Patients who received PRN and scheduled antihypertensive medications were matched (1:1) by propensity scores which included systolic blood pressure on admission, demographic factors and comorbidities. Outcomes of interest were abrupt decrease in blood pressure, defined as ≥25% decrease in systolic blood pressures (SBP) within one hour of administration of PRN or scheduled medications and AKI.

Results: Mean age was 62±16 years. 52% were females, and 68% Caucasian. 82% of patients had hypertension. PRNBPMeds were used in 4,850 (13%) out of a total of 37,145 admissions. 93% of these patients had scheduled and PRN medications while 7% received PRNBPMeds alone. The propensity score-matched cohort included 3,707 patients each in the PRNBPMeds and scheduled antihypertensive groups. The abrupt decrease in SBP rates
were 11.6% and 3.5% for PRN and scheduled medications groups, respectively, (p<0.001). The AKI occurrence rates were 14.7% and 11.6% for PRN and scheduled medications groups, respectively, (p<0.001). Using the propensity score-matched analysis, the use of PRN medications was associated with 138% increased risk of abrupt decrease in SBP (OR, 2.38 [95%CI, 1.74-3.26]; p<0.001), and 29% increased risk of AKI (OR, 1.29 [95%CI, 1.18-1.47]; p<0.001).

Conclusions: To our knowledge, this is the first propensity-scored matched analysis of PRN vs scheduled antihypertensive medications. Our results suggest that use of PRNP Mell in is associated with increased risk of abrupt BP lowering and AKI. Pragmatic randomized controlled trials are required to assess the risk benefit of treating asymptomatic increases in BP in hospitalized patients.

TH-OR107
Resistant Hypertension Potentiates the Risk of ESRD in African Americans in the Million Veteran Program (MVP)

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Background: African Americans (AAs) are 4 times as likely as Whites to develop ESRD. Resistant hypertension (RH), a severe form of hypertension (HTN) is associated with increased risk of cardiovascular (CV) and renal outcomes. We investigated how ESRD risk is modified by race.

Methods: We designed a retrospective cohort of 240,038 veterans with HTN, enrolled in the MVP with a GFR >30 ml/min. The primary exposure was incident RH (time-varying). The primary outcome was incident ESRD during a 13.5 yr follow up, 2004-2017. Secondary outcomes were myocardial infarction (MI), stroke, and death. Incident RH was defined as failure to achieve outpatient BP <140/90 mmHg with 3 anti-HTN drugs, including a thiazide, or use of AAs with RH; 3-fold the risk of Whites with RH, and 9-fold the risk of Whites with NRH.

In Poisson models, AAs with RH had a 2.5-fold higher risk of ESRD compared to AAs with NRH; 3-fold the risk of Whites with RH, and 9-fold the risk of Whites with NRH [p-interaction < 0.01].

Conclusions: RH was associated with a higher risk of ESRD (and CV outcomes), particularly in AAs. Interventions (behavioral, drug choices) that improve reaching BP targets in RH patients, could have a major impact on ESRD incidence in this high-risk population, particularly in AAs.

Funding: Veterans Affairs Support

TH-OR108
Relationship Between Treatment Effects for Proteinuria and eGFR Slope over 2 Years in Patients with IgA Nephropathy

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Background: A challenge for evaluating treatments for IgA nephropathy (IgAN) is the usually long time course for progression to ESKD. Recent meta-analyses have separately explored the role of proteinuria reduction and the rate/slope of eGFR decline as surrogate endpoints. In this meta-analysis we describe the relationship between treatment effects on proteinuria, recorded at 1 year, and 2-year eGFR (CKD-EPI) slope.

Methods: Study level data from 1037 patients in 12 IgAN studies, aggregated into 7 study groups, were obtained from the database provided at the March 2018 NKF/PDA/EMA workshop. A weighted linear regression was performed to quantify the relationship between baseline adjusted treatment effects for proteinuria, expressed as the log of the ratio of geometric means, and treatment effects for total 2-year eGFR slope, expressed as the difference in arithmetic means. Studies were weighted in inverse proportion to the variance of the 2-year eGFR slope treatment effect.

Results: There was a statistically significant association seen between treatment effects for proteinuria at 12 months and treatment effects for 2-year eGFR slope for the IgAN studies (r2 = 0.043). On average, the association between arm, annualized difference in the rate of decline in eGFR was estimated to increase by 4.55 ml/min/1.73m2/year (95% CI: 0.21, 8.84) for every 1 log (63%) reduction in the proteinuria treatment arm ratio.

Conclusions: In IgAN treatment effects on 12m proteinuria are reasonably likely to predict subsequent treatment differences in the rate of decline in eGFR over 2 years.

TH-OR109
Change in Proteinuria as a Surrogate End Point for GFR Slope: Individual Patient Meta-Analysis of 12 Randomized Clinical Trials in IgA Nephropathy

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Background: A recent study demonstrated associations between treatment effects on urine protein (UP) and clinical endpoint (i.e. ESKD). Reasonably likely surrogate endpoints can be used as a basis for accelerated (and conditional) approval of therapies intended to treat serious or life-threatening conditions, such as IgAN. The clinical benefit of products approved under this program would need to be verified in a post-marketing confirmatory trial. For patients with IgAN, endpoints to such confirmatory trials may be GFR slope given the low likelihood of sufficient clinical endpoints.

Methods: Using a pooled dataset of 990 participants from 12 studies, we computed change in UP from baseline to 6 months (25th, 75th 5.9, 6.9 month), and the GFR slope from confirmatory trial. For patients with IgAN, endpoints to such confirmatory trials may be GFR slope as well as including clinical outcomes. For patients with IgAN, endpoints to such confirmatory trials may be GFR slope given the lower likelihood of sufficient clinical endpoints.

Results: For patients with IgAN, endpoints to such confirmatory trials may be GFR slope given the lower likelihood of sufficient clinical endpoints.

Conclusions: Our results suggest that treatment effects on early changes in UP confirmed by treatment effects on GFR slope might be a useful strategy for evaluation of treatment benefit in IgA.

Funding: Commercial Support - Retrophin
To convert to percentage UP reduction (1-GMR)*-100. Black line is meta-regression line and blue lines are 95% confidence intervals around the regression line.

**TH-OR110**

The Clinical Utility of Immunosuppression Treatment Decisions Based on Personalized Risk Assessment from the International IgA Nephropathy Prediction Tool

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**Background:** The KDIGO guidelines recommend risk-stratifying patients with IgA nephropathy (IgAN) based on proteinuria ≥1g/day to guide immunosuppression treatment decisions. Because this approach does not accurately discriminate the risk of disease progression, we evaluated whether treatment decisions could be improved by using individual risk assessment from the International IgAN Prediction Tool, which estimates the 5-year risk of a 50% decline in eGFR or ESRD.

**Methods:** We used a net benefit and net reduction in treatment analysis, which for any given threshold probability of disease progression (P) balances correct decisions to give or withhold immunosuppression accounting for the relative harm to patients from incorrect decisions. In a multi-ethnic cohort of 3299 adults with biopsy-proven IgAN (median follow-up 5.1 years), decision rules for immunosuppression treatment were created based on proteinuria ≥1g/day or based on the Prediction Tool (predicted risk >P). The net benefit and reduction in treatment were calculated for all P, from 0 to 1.

**Results:** Using proteinuria ≥1g/day to make treatment decisions was net harmful to patients for P ≥0.18 (Fig A). Compared to using proteinuria, decisions using the Prediction Tool had a larger net benefit and net reduction in treatment for P ≥0.09 and ≥0.08 (Fig B, C, D), and more accurately allocated or withheld immunosuppression in up to 23.4% and 35.1% more patients respectively.

**Conclusions:** These results demonstrate the benefit to patients from a precision-medicine approach to immunosuppression treatment using individual risk of disease progression from the International IgAN Prediction Tool instead of a single generic categorization of proteinuria.

**Funding:** Government Support - Non-U.S.

**TH-OR111**

Serum and Urine Biomarkers Related to Renal Fibrosis Predict Renal Outcome in Patients with IgA Nephropathy

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**Background:** IgA nephropathy (IgAN), the most common primary glomerulonephritis worldwide, has serious outcomes with end-stage renal disease developing in 30-50% of patients. Clinical predictors such as proteinuria, hematuria, hypertension as well as renal fibrosis may play a role in IgAN onset and/or progression. Here, we assessed serum and urine biomarkers related to renal fibrosis and histological findings in renal-biopsy specimens from patients with IgAN, ANCA associated vasculitis and compared with healthy controls.

**Methods:** We evaluated 46 patients with biopsy-proven IgAN, 45 patients with ANCA associated vasculitis, who were assessed at time of diagnosis for estimated glomerular filtration rate (eGFR), proteinuria, microscopic hematuria, hypertension, then followed prospectively and compared to 9 healthy controls (mean follow-up 51.8 months). Serum and urine samples collected at diagnosis were analyzed for biomarkers related to renal fibrosis using a novel enzyme-linked immunosorbent assay as well as histological evaluation of renal tissues at time of kidney biopsies were assessed. Linear discriminant analysis, logistic regression model and Kaplan-Meier (survival) analysis were used for statistic processing.

**Results:** We found serum and urine biomarkers such as EGF, PRO-C6, PRO-C3, which correlated with the level of histological fibrosis in kidney biopsies (P<0.05) and exactly predicted renal outcome of patients with IgAN (P=0.05). Moreover, addition of two other biomarkers such as serum LG1M and urine C3M completely differentiated patients with IgAN compared to patients with ANCA associated vasculitis and healthy controls (accuracy of classification 100%).

**Conclusions:** In conclusion, serum and urine biomarkers related to renal fibrosis such as EGF, PRO-C6, PRO-C3 predicted renal outcome of patients with IgAN. Future studies are needed to validate these preliminary findings and to determine the power of these urinary and serum markers for assessment of responses to treatment.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Mostly IgA Nephropathy

Oral Abstract/Thursday

TH-OR112
Association of IgM Deposition with Renal Outcomes in IgA Nephropathy: A Multicenter, Prospective, Observational Study
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Background: The aim of this study was to investigate the relationships between deposition of IgM, clinicopathological features, and renal outcomes and whether IgM deposition is a novel marker for the response to patients with IgA nephropathy (IgAN).

Methods: A total of 1239 patients with primary IgAN diagnosed by renal biopsy were enrolled from January 2013 to May 2018. The primary endpoint was the combined endpoint of a 50% decline in eGFR and/or ESRD. Responses to therapy included complete remission (CR), partial remission (PR), no response (NR) and ESRD. A 1: 1 propensity score matching (PSM) method was used to balance the covariates in all patients.

Results: Compared with IgM negative deposition(n=521), patients with IgM positive deposition (n=521) had higher level of Urine protein and higher proportion of M1, E1, C1, C2, deposition of IgG, C3, C4 and C1q (all P<0.05) at the time of biopsy. During the follow-up period (39.0±23.82 months), 76.39%, 60.08% patients in groups of IgM positive and negative deposition achieved CR or PR (P<0.001) respectively. According to Kaplan–Meier, renal survival rates in IgM negative and IgM positive groups were better both in unmatched and matched cohort (both P<0.05). Furthermore, with 50% decline in eGFR and/or ESRD as the combined endpoint, multivariate Cox regression analysis of unmatched and matched cohort showed IgM deposition was an independent risk factors influencing renal survival.

Conclusions: IgM deposition in the glomerulus is associated with a poor renal outcome and severe pathologic features and did play a decisive role in renal progression in IgAN patients.

Funding: Government Support - Non-U.S.

TH-OR114
Characterization of Recombinant IgG Autoantibody That Binds Galactose-Deficient IgA1 and Forms Immune Complexes Mimicking Those in IgA Nephropathy
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Background: Immune complexes (IC) containing galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1-specific IgG autoantibodies (autoAbs) play a key role in the pathogenesis of IgA nephropathy (IgAN). However, the molecular interactions between autoAb and Gd-IgA1 in IC are not well understood. To gain a better insight, we used a recombinant IgG (rIgG) autoAb derived from an IgAN patient and assessed its structural and functional features.

Methods: rIgG autoAb was produced in Exp293F cells. Gd-IgA1 was isolated from plasma of a patient with IgA myeloma. Surface plasmon resonance was used for kinetic analysis of autoAb binding to Gd-IgA1. Fab of rIgG was used for crystallographic and functional features.

Conclusions: The rIgG formed complexes with Gd-IgA1. Kinetic analysis showed intermediate affinity of rIgG to Gd-IgA1 (KD=3.16E-07 M). The structure of the Fab was solved at the resolution of 1.69 Å. The structure revealed a loop in the heavy chain that adopts a unique conformation, unveiling a surface-accessible pocket located in close proximity to the CDR3. Binding modes from an in silico docking study of a glycopeptide mimicking the hinge region of Gd-IgA1 showed potential binding to this region. The EIC, but not Gd-IgA1 alone, stimulated proliferation of cultured MC (2.88±0.69-fold increase over control). IC injected into immunodeficient mice increased glomerular cellularity (48.4±13.3 nuclei per glomerulus vs. 40.4±10.5 in control; p<0.0001; n=4 each).

Conclusions: This study provides the first structure of an autoAb that binds Gd-IgA1 and forms biologically active EIC. We envision that better understanding of the interactions of Gd-IgA1 and autoantibodies will enable design of inhibitors to block the formation of pathogenic IC in IgAN.

Funding: NIDDK Support, Private Foundation Support

TH-OR113
Analysis of 40-Year Prognosis of 1149 cases of IgA Nephropathy and Validation Study of Oxford Classification
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Background: Half a century has passed since IgA nephropathy (IgAN) was firstly reported, however, very long term prognosis over 40 years has been unknown. In 2016, Oxford classification of IgAN was revised, and crention formation was newly added. In this study, we showed 40 years prognosis of IgAN and validation study of Oxford classification in our cohort.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Results: We observed dysregulation of UPS enzymes and lysosomal acculation of polyubiquitinated proteins accompanied by elevated expression of proteasomal and lysosomal proteins in isolated glomeruli. We also observed reduced levels of slit membrane proteins such as nephrin and α-actinin-4 correlating with podocyte loss. Contrastingly, mice overexpressing active UCH-L1 protein exhibited less glomerular injury and stable expression of podocyte-specific proteins in response to anti-podocyte antibodies after 14 days. In vitro immunoprecipitation experiments demonstrated an interaction of wildtype UCH-L1 and UCH-L1 I93M with the proteasome, however only binding of UCH-L1 I93M diminished protein homeostasis.

Conclusions: These results strengthen the hypothesis that during MN a shift of UCH-L1 enzymatic activity to a dysfunctional protein negatively influences podocyte protein homeostasis by aberrant interactions with the proteasome.

TH-OR118
Common Risk Variants in NPHSI and TNFSF15 Are Associated with Childhood Steroid-Sensitive Nephrotic Syndrome

Tomoko Horinouchi,1 Tomohiko Yamamura,2 Rasheed A. Gabdegesen,3 Matt G. Sampson,4 China Nagano,5 Kandai Nozu,6 Kenji Ishikura,7 Pierre M. Ronco,8 Hae Il Cheon9 Kazumoto Iijima10

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Background: Although steroid-sensitive nephrotic syndrome (SSNS) is the most common cause of glomerular disease in children, the pathogenesis remains unclear. Recent genome-wide association studies (GWASs) have shown that variants in the HLA-DR/DQ region are significantly associated with the disease in different populations. However risk loci outside of the HLA region are largely unknown.

Methods: We conducted a GWAS in 1,017 Japanese children with SSNS and 3,332 ancestry matched controls. We performed replication studies and trans-ethnic meta-analysis in Korean, South Asian, sub-Saharan African, European, and Hispanic populations.

Results: The most significant association was detected in HLA-DR/DQ region (p=2.8 x 10^-33, odds ratio [OR]=2.49, 95%CI: 2.15-2.89). In addition, common variants in NPHSI-KIRREL2 (p=4.94 x 10^-10, OR=1.70, 95%CI: 1.66-1.86), TNFSF15 (p=2.54 x 10^-8, OR=0.72, 95%CI: 0.64-0.81) and TNFSF15/F14 (p=7.68 x 10^-8, OR=1.38, 95%CI: 1.23-1.56) achieved genome-wide or marginal genome-wide significance. Trans-ethnic meta-analysis confirmed the significant associations in NPHSI (p≈7.06 x 10^-6, OR=1.91) and TNFSF15/F14 (p≈4.05 x 10^-6, OR=0.72) loci.

Discussion: NPHSI encodes Preventive proteasomal activators in patients with steroid-sensitive nephrotic syndrome of the Finnish type (CSSN). The two synonymous variants in NPHSI may induce aberrant splicing which could decrease the wild-type nephron production and may affect the glomerular filtration barrier function. In addition, one of the two variants in NPHSI has been previously reported to induce TRPC6 activation. TNFSF15 encodes the TNF super-family member 15 (TNFSF15), ligand of death receptor 3. Activation of TNFSF15 enhances the proliferation of human regulatory T cells (Treg). The risk allele in TNFSF15 is associated with reduced expression of TNFSF15, which attenuate the proliferation of Tregs, consistent with functional data in SSNS patients.

Conclusions: The present study markedly improves the understanding of genetic background of childhood SSNS, and provides another evidence that the gene responsible for a monogenic rare disease (CSSN) could be the susceptibility gene for a relatively common multifactorial disease (SSNS). [Collaborators: Xiaoyuan Jia, Yuki Hitomi, Katsushi Tokunaga]

Funding: Government Support - Non-U.S.

TH-OR119
Response to Intensified Immunosuppression in Genetically-Stratified SRNS Patients Predicts Outcomes and Indicates Distinct Underlying Mechanisms

Moin Saleem,1 Anna E. Mason,2 Ethan S. Sen,3 Agnieszka Bierzyńska,4 Liz Colby,5 Maryam Afzal,6 Ania B. Koziell,7 Olivia Boyer,8 Gavin I. Welsh,9
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Background: We previously showed that secondary steroid resistance (SSR) in nephrotic syndrome is a stochastic process of circulatory escape of the disease post-transplantation. This follow-up study aimed to improve disease stratification by determining if response to intensified immunosuppression (IIS) in genetically-screened SRNS predicts disease progression and/or recurrence.

Methods: Paediatric patients with steroid resistant nephrotic syndrome (SRNS) were recruited via the United Kingdom RDNx registry. 274 patients were whole genome, whole exome or SRNS-gene-panel sequenced. Complete response (CR) or partial response within six months of starting IIS was ascertained.

Results: Of 274 patients, 180 (93 male, median onset age 4.7 years, 99 focal segmental glomerulosclerosis) received IIS medications with responses available. 3.8% of monogenic disease patients showed CR, compared to 25.2% of genetic-testing negative (GTN) patients (p=0.018). None of the former recurred post-transplantation. In GTN patients, 97.4% with CR to first IIS showed no progression, whereas 43.2% of non-responders developed renal failure with 73.1% recurrence post-transplant. SSR had a higher CR rate than primary/presumed resistant (42.5% vs 23.0%, p=0.0014). Highest
CR rate was to Rituximab (64.3%). Biopsy findings showed no correlation with response to IIS or outcome.

Conclusions: This stratifies SRNS into three subgroups of prognostic utility based on genotype-phenotype correlation: monogenic disease responds poorly to IIS but doesn’t recur, GTN SRNS that responding early to IIS with good long-term outcome, and multi-drug resistant GTN SRNS with poor renal survival and high post-transplant recurrence risk. This supports at least two different underlying immune mechanisms in non-genetic SRNS, able to determine disease outcome.

TH-OR121
A Global Anti B-Cell Strategy with Obinutuzumab and Daratumumab in Severe Pediatric Idiopathic Nephrotic Syndrome

Catherine S. Dossier,1 Benjamin Prim,1 Christelle Morreau,2 Theresa Kwon,2 Anne Couderc,2 Camibi Alexandre,2 Veronique Baudouin,2 Anne F. Maisin,1 Georges Deschênes.1 1Pediatric Nephrology, APHP, Robert-Debre Hospital, Paris, France; 2Pharmacy, APHP, Robert-Debre Hospital, Paris, France; 1Hospital Robert Debre/Pediatric Nephrology, Paris, France.

Background: The efficacy of B-cell depletion and Immunoglobulin adsorption in the treatment of patients with Steroid Dependant Nephrotic Syndrome (SDNS) and Steroid Resistant NS supports the involvement of B cells in the pathophysiology of INS. However, rituximab (RTX) targets only CD20 positive B-cells and especially not plasma cells. Furthermore, RTX mediated B-cell depletion may paradoxically induce the settlement of autoreactive long-lived plasma cells which may account for some RTX failure. In this pilot study, we investigate in patients with severe SDNS the association of Obinutuzumab (OBUZ), a 2nd generation anti CD20 monoclonal antibody, with higher in vitro B-cell cytotoxicity than RTX, with Daratumumab (DAR), an anti CD38 monoclonal antibody with plasma cell cytotoxicity in addition to an immunomodulatory activity.

Methods: Patients received an infusion of 1000mg/1,73m² of obinutuzumab at day 0 and 1000mg/1,73m² of daratumumab at day 15. All other immunosuppressive treatments were discontinued within two months, and biological monitoring was performed monthly until B cell reconstitution.

Results: 9 patients with SDNS and resistance (n=5) or early relapse after prolonged B-cell depletion with rituximab (n=6) were included. Median ages at INS onset, first RTX and OBZ were respectively of 2,9, 7,7 and 10,9 years old. B-cell depletion was achieved in all patients in 10 months follow-up. Six patients remained relapse-free. Six patients had still undetectable peripheral B-cells, while B-cell reconstitution occurred at 7,9, 8,1 and 9,3 months in the 3 others. Mild infusion reactions were reported in 2/9 patient during OBZ and 3/9 during DAR infusions. Mild neutropenia (0,10-1,000/mm³) occurred in 2/9 patients during OBZ and 3/9 during DAR infusions. Mild neutropenia (0,10-1,000/mm³) occurred in 2/9 patients. 7/9 patients received immunoglobulins because of hypo-IgG. Hypo-IgG was noted in 8 patients and hypo-IgM in all patients. No severe infection was reported.

Conclusions: Global anti B-cell strategy with obinutuzumab and daratumumab induces prolonged peripheral B-cell depletion and nephrotic syndrome remission in children with severe SDNS. However, it induces frequent and profound hypogammaglobulinemia and further investigation of the safety and the long-term efficacy of this strategy is needed.

TH-OR122
Effect of Updated Hypertension Guidelines on Blood Pressure Staging in Pediatric Kidney Transplant Recipients

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Background: In 2017, pediatric hypertension (HTN) guidelines were updated with 2 major changes compared to the 2004 NHBPEP 4th Report: normative blood pressure (BP) values excluded overweight children and simplified staging was provided for children ≥13 yo using the adult nominal cutoffs. This study evaluated the effect of the new guidelines on BP staging in children with kidney transplant (KT) using registry data from the Improving Renal Outcomes Collaborative (IROC).

Methods: We examined the last accurate BP measurement for patients <18 yo and ≥90 days post-KT in the IROC registry and compared BP staging using percentile (%tile) cutoffs in the 4th Report versus 2017 AAP HTN Guidelines. BP staging using AAP %tile versus adult nominal cutoffs for children ≥13 yo were also compared. Associations between overweight or short stature and change in BP staging were assessed with Chi-square tests, odds ratios (OR), and 95% confidence intervals (CI).

Results: A total of 563 patients met inclusion criteria. When applying AAP %tile cutoffs, 71/563 (13%) had increased BP stage compared to 4th Report classification, with most changing from normal to elevated or pre-HTN to stage 1 (see table). Overweight/obese children were more likely to have increased staging using AAP %tiles (OR 1.7, CI 1.05-2.89) compared to 4th Report cutoffs. When applying adult cutoffs for children ≥13 yo, BP stage decreased in 13% (33/241) compared to 10% (34/333) in the AAP Guidelines. This age group had below-average height (median height %tile 11.2, IQR 1.9-38.5). Height percentile was a significant risk factor for decreased BP stage using adult cutoffs (p=0.01).

Conclusions: Short stature and obesity, which are common in pediatric KT recipients, affect BP staging when applying updated HTN guidelines. The application of adult BP cutoffs in children with kidney transplant ≥13yo may under-report uncontrolled BP, especially in those with short stature. Transplant physicians may consider applying percentile-based cutoffs until adulthood in this population with high cardiovascular risk.

Funding: NIDDK Support
Low Albumin Is Associated with Neonatal AKI During the First Post-Natal Week of Life: Report from the AWAKEN Study Group

Arwa Nada, Line Li, Russell Griffin, Juan C. Kupferman, Maroun J. Mhanna, John D. Mahan, David J. Askensn. On Behalf of the Neonatal Kidney Collaborative LedBohear Children’s Hospital, Memphis, TN; Nationwide Children’s Hospital, Columbus, OH; University of Alabama at Birmingham, Birmingham, AL; Maimonides Medical Center, Brooklyn, NY; Metro Health Medical Center, Cleveland, OH.

Background: Hypoalbuminemia is an established risk factor for morbidity and mortality in adults and children. Adult studies showed an association between low albumin (alb) and acute kidney injury (AKI) in different settings. Low alb was found to be associated with AKI in children undergoing cardiac surgery. In this analysis of newborns (NB) enrolled in the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) we hypothesize that low alb is associated with increased risk of AKI in the first postnatal week of life. To our knowledge, this is the first study to examine this relationship in NB.

Methods: AWAKEN included 2162 NB admitted to the neonatal intensive care units at 24 institutions (4 countries) from 01/14-03/14. Inclusion criteria: intravenous fluids for ≥48 hrs. Exclusion criteria: congenital heart disease repair at <7 days of life, lethal anomaly or death at ≥48 hrs. For this analysis, we excluded 1461 NB who had no alb levels documented, 19 NB who didn’t have at least 2 serum creatinine or at least one day of urine output recorded during first postnatal week. Analysis was done for the entire cohort and for 3 stratified groups; <29 weeks (wks), ≥29 to <36 wks and ≥36 wks gestational age (GA).

Table 1: Mean and SD of Minimum and Maximum Albumin Levels Among Studied Groups

<table>
<thead>
<tr>
<th>Week Group</th>
<th>No. of Babies</th>
<th>GA 21-25 weeks</th>
<th>GA 26-30 weeks</th>
<th>GA 31-36 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-AKI</td>
<td>1424 (99.2)</td>
<td>748 (74.4)</td>
<td>587 (78.2)</td>
<td>78 (3.4)</td>
</tr>
<tr>
<td>≤30 mg/g</td>
<td>147 (10.8)</td>
<td>120 (15.1)</td>
<td>101 (14.8)</td>
<td>16 (2.1)</td>
</tr>
<tr>
<td>Mean albumin:</td>
<td>2.19±1.0 (1.97)</td>
<td>2.24±1.0 (1.96)</td>
<td>2.25±1.0 (1.99)</td>
<td>2.49±1.0 (1.99)</td>
</tr>
<tr>
<td>Minimum albumin</td>
<td>1.87±1.0 (1.73)</td>
<td>1.93±1.0 (1.82)</td>
<td>2.02±1.0 (1.84)</td>
<td>2.49±1.0 (1.99)</td>
</tr>
<tr>
<td>Maximum albumin</td>
<td>4.22±1.0 (2.09)</td>
<td>4.33±1.0 (2.16)</td>
<td>4.32±1.0 (2.16)</td>
<td>4.49±1.0 (2.09)</td>
</tr>
</tbody>
</table>

Conclusion: A low GFR, albuminuria, and hypertension are common in ELGANS and present at 24-26 months of age. Long-term kidney follow up of all premature infants for gestational age (p<0.05) and pre-eclampsia (p<0.05).

Conclusions: AWAKE describes for the first time the association between low alb and AKI in the first postnatal week. This association remained regardless of fluid balance and other potential confounders.

Effect of Erythropoietin (Epo) on Outcomes at 24-26 Months in Extremely Low Gestational Age Neonates (ELGAN)

Saneeeta B. Hingorani, Robert Schmicker, Kaashif A. Ahmad, Maureen M. Gilmore, Edmund F. Lagamana, Sandra Juul, David J. Askensn, Seattle Children’s Hospital, Seattle, WA; University of Washington, Seattle, WA; University of Washington, Seattle, WA; MEDNAX National Medical Group, San Antonio, TX; Johns Hopkins University, Baltimore, MD; New York Med College - Maria Fareri Children’s Hosp, Valhalla, NY; University of Washington, Seattle, WA; University of Alabama at Birmingham, Birmingham, AL.

Background: Changes in EPO in premature infants may have a critical role in glomerulogenesis. The REPAIRd study examines kidney outcomes of ELGANS enrolled in the Assessment of Worldwide Acute Kidney Injury Epidemiology in Neonates (AWAKEN) we hypothesize that low Alb is associated with increased kidney injury Epidemiology in Neonates (AWAKEN) we hypothesize that low Alb is associated with increased kidney injury Epidemiology in Neonates (AWAKEN) we hypothesize that low Alb is associated with increased kidney injury Epidemiology in Neonates (AWAKEN) we hypothesize that low Alb is associated with increased kidney injury

Methods: Patients who survived to 24-26 months CGA with blood, urine or blood pressure follow-up were included. We defined CKD as estimated glomerular filtration rate (eGFR) via the Schwartz cystatin C equation <90 ml/min/1.73m²; hypertension as ≥140/90 mmHg or treatment group. An eGFR <90 was associated with lower birthweight (p<0.001), small for gestational age (p=0.05) and pre-eclampsia (p=0.05).

Results: 778 (84%) of enrolled babies had a 24-26 month follow up visit. 54 (16%) had an eGFR < 90ml/min/1.73m², 155 (36%) had albuminuria, 119 (24%) had systolic hypertension and 163 (33%) had diastolic hypertension. We found no difference by treatment group. An eGFR <90 was associated with lower birthweight (p<0.001), small for gestational age (p=0.05) and pre-eclampsia (p=0.05).

Conclusions: Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline presents authoring. 34
TH-OR126

Pediatric CKD Is Associated with Abnormal White Matter Integrity
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4Division of Nephrology, The Children’s Hospital of Philadelphia, Philadelphia, PA;
5Radiology, University of Iowa Carver College of Medicine, Iowa City, IA;
6Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

Background: Children with chronic kidney disease (CKD) are at risk for neurocognitive deficits. Neuroimaging studies provide an opportunity to accurately assess the brain and yield clues to the underlying mechanisms of observed neurocognitive abnormalities. To date, few published studies exist evaluating brain structure in pediatric CKD and often involve heterogeneous samples with late CKD/endpoint populations of varying etiologies.

Methods: We describe the effect of mild to moderate CKD on brain white matter integrity (WMI) using quantitative MRI diffusion tensor imaging. Patients age 6-16 with congenital, non-glomerular causes of CKD (eGFR 30-90 mL/min/1.73m2) were invited to participate [N_ages = 20, N_early = 26]. Participants completed a neurocognitive evaluation and MRI scan. WMI was calculated utilizing measurement of fractional anisotropy (FA). Voxel-wise linear regression models were calculated using R where FA values were predicted by CKD-status, sex, age, blood pressure, and parental socioeconomic status were included as covariates.

Results: Relative to controls, CKD participants showed significant decreases in WMI within multiple brain regions including the right orbitofrontal cortex (Fig 1: t(54)=−3.74, p=0.000452, q=0.00722). Linear regression was performed to predict the relationship between regions with FA deficit and executive function. For males, lower FA within the right orbitofrontal cortex was related to poorer executive function as measured by the Behavior Rating Inventory of Executive Function global executive composite (p=0.006). In models adjusted for age, sex, participant type, and systolic blood pressure, lower FA within this region remained associated with poorer executive function (p=0.011).

Conclusions: Our data demonstrate distinct white matter abnormalities in early pediatric CKD due to congenital anomalies of the kidney/urinary tract. Furthermore, these alterations in WMI are associated with executive function.

Funding: NIDDK Support

Figure 1: Localization of the right orbitofrontal WMI difference between cases (CKD) and controls (UC) [voxel coordinates xyz: 14.4, 46.8, −10.7].

TH-OR127

Sleep Problems and Fatigue and Their Relationships with Emotional-Behavioral Symptoms and Neurocognitive Outcomes in Pediatric CKD
Rebecca J. Johnson,1,2 Matthew Matheson,3 Lyndsay Harshman,3 Arlene C. Gerson,4 Amy Kogon,4 Marc Lande,5 S. Shinnar,1 Susan L. Furt,2 Bradley A. Warady,1 Stephen R. Hooper,1 Children’s Mercy Kansas City, Kansas City, MO; 2The Children’s Hospital of Philadelphia, Philadelphia, PA; 3Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 4Johns Hopkins School of Medicine, Baltimore, MD; 5University of Iowa Children’s Hospital, Iowa City, IA; 6Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; 7University of North Carolina School of Medicine, Chapel Hill, NC; 8University of Rochester Medical Center, Rochester, NY.

Background: Children with CKD are at risk for deficits in neurocognitive function. It is not known how sleep problems/fatigue within the context of CKD may contribute to these deficits.

Methods: Data from the Chronic Kidney Disease in Children (CKiD) study was used to evaluate the prevalence of sleep problems/fatigue among children with mild to moderate CKD, and to examine whether sleep problems or fatigue predict neurocognitive or emotional-behavioral outcomes. Four variables were created: fatigue, sleep disturbance, low energy, and trouble sleeping. Linear mixed models were used to determine if fatigue or sleep problems were associated with neurocognitive and emotional-behavioral outcomes. Each model was adjusted for sociodemographic and disease-related covariates.

Results: Baseline data was available for 1030 participants (median disease duration 6 years; 63% male; mean eGFR was 53 mL/min/1.73m2). Prevalence was 26% (fatigue), 30% (sleep disturbance), 52% (low energy), and 39% (trouble sleeping). Sleep disturbance (β=1.28, CI=0.25, 2.32; p<0.02), low energy (β=1.85, CI=0.79, 2.9; p<0.0006), and trouble sleeping (β=1.87, CI=0.87, 2.87; p=0.0003) were significantly associated with worse parent ratings of overall executive functions. Low energy was significantly associated with lower working memory (Digit Span Forward β=0.37, CI=0.72, −0.01; p=0.5; Digit Span Backward β=−0.48, CI=−0.87, −0.09; p<0.02). Low energy was significantly associated with lower inhibition (β=−0.92, CI=−1.57, −0.28; p=0.0006) and lower problem-solving β=−0.67, CI=−1.25, −0.09; p<0.02. Each of the four sleep measures was significantly related to more internalizing symptoms on a measure of emotional-behavioral functioning, and sleep disturbance, low energy, and trouble sleeping were associated with more externalizing symptoms.

Conclusions: A significant proportion of children with CKD report fatigue and problems with sleep. Sleep problems and fatigue were associated with lower executive functioning and increased emotional-behavioral symptoms over time after adjusting for key sociodemographic and CKD-related covariates. Assessing sleep problems/fatigue and treating co-morbidities may promote more positive emotional-behavioral and neurocognitive outcomes for children with CKD.

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI

TH-OR128

Economic Evaluation of Lifelong Medicare Immunosuppressive Drug Coverage for Kidney Transplant Recipients
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1University of British Columbia, Vancouver, BC, Canada; 2(Saint Paul’s Hospital/ University of British Columbia), Vancouver, BC, Canada; 3Yale School of Medicine, Bethany, CT; 4University of Alberta, Edmonton, AB, Canada.

Background: Medicare coverage for kidney transplant recipients ceases 36 months after transplantation. This policy removes coverage for life-saving immunosuppressive medications essential to prevent rejection and maintain transplant function. A contemporary economic analysis of extending Medicare coverage for the duration of transplant survival using mean cost of immunosuppressant medications in the era of generic equivalents which accounts for that fact that many transplant recipients currently continue to receive Medicare coverage beyond 36 months due to medical disability is not available.

Methods: A Markov model was used to determine the incremental cost and effectiveness of extending Medicare coverage for immunosuppressive drugs for the duration of transplant survival compared with the current policy from the perspective of the Medicare payer. The model used contemporary mean costs of immunosuppressive medications, and incorporated assessment of continuation of Medicare coverage beyond 36 months in patients who are designated medically disabled. The expected graft survival of extending immunosuppressive drug coverage was estimated from a cohort of privately insured transplant recipients using multivariable survival analysis.

Results: Extension of immunosuppression coverage under Medicare for kidney transplant recipients led to lower costs of -3,163 and 0.18 additional quality adjusted life years (QALYs). When the improvement in transplant survival associated with extending immunosuppressive coverage was reduced to 50% of that observed in privately insured patients the strategy of extending drug coverage had an ICUR of $77,613 QALY gained.

Conclusions: Extending immunosuppressive drug coverage under Medicare from the current 36 months to the duration of transplant survival will result in better patient outcomes and cost savings, and remains cost-effective if only a fraction of anticipated benefit is realized.

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI

TH-OR129

Absence of Additional Predictive Ability Value of Preimplantation Biopsies for Long-Term Allograft Outcome
Olivier Aubert,1,4 Marc Raynaud,1 Gillian Divard,1 Yassine R. Bouatou,1,5 Denis Glotz,2 Christophe M. Legendre,1 Carmen Lefaucheur,3 Peter P. Reese,1 Alexandre Loupy.1,4 1Paris Translational Research Center for Orthotransplantation, Paris, France; 2University of Pennsylvania, Ardmore, PA; 3Saint-Louis Hospital, Paris, France; 4Hospital Necker, Paris, France; 5Hospital Saint-Louis, Paris, France.

Background: A significant number of kidneys are discarded worldwide due to the suboptimal use of large kidney resources. The main cause of discard is the result of the preimplantation biopsy.

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI
Methods: We included patients who underwent kidney transplantations from a deceased donor in 2 French transplant centers between 2004 and 2014 with preimplantation biopsy. Two external validation cohorts were included: 1,107 deceased donors from Belgium and 1,103 discarded kidneys based on biopsy results from the US.

Results: A total of 1,629 patients were included in the development cohort. After adjusting for donor, recipient, and transplant characteristics as well as for previous biopsy findings (IFTA, cv and ab Banff score, and glomerulosclerosis percentage) and baseline immunological parameters, we identified the KDRI score (HR=2.50; 95% CI, (1.38 to 4.40), p<0.001), the presence of circulating DSA on the day of transplantation (HR=2.76; 95% CI, (1.39 to 5.55), prior kidney transplantation, HR=1.47; 95% CI, (1.01 to 1.78), p=0.045), and the IFTA score (HR=1.51; 95% CI, (1.00 to 2.26), p=0.048) as the main independent determinants of long-term allograft loss. However, the biopsy results had no additional value to predict long term allograft outcome when compared to the model without the biopsy results. In the Belgium validation cohort, none of the biopsy results were associated with allograft loss. Kidneys discarded based on histology results in the US were matched to transplanted kidneys in France. French kidneys with similar histological results as discarded kidneys in the US did not have worse allograft survival compared to the unmatched transplanted kidneys (p=0.156).

Conclusions: Given this result and the fact that preimplantation biopsies increase the cold ischemia time, the current practice of discarding kidneys based on preimplantation biopsy results may not be optimal for allocation decision-making.

TH-OR130
Recipient Outcome After Declining a Deceased-Donor Kidney Offer
Dhriti Dosani, Rupert B. Bright, Anamika Adwaney, Emma C. Morganti, Damien Asby. Imperial College London, London, United Kingdom.

Background: The decision to accept a deceased-donor kidney depends on organ quality, and also recipient factors, such as an estimate of mortality on dialysis, and the likelihood of receiving a more favourable offer. Whilst outcome after transplantation has been well studied, with several donor-related risk factors widely accepted, little is known about the outcome after declining a kidney, such as the influence of recipient factors on the chance of subsequent transplantation.

Methods: Over a 12 month period at a single UK centre, all potential recipients were identified for whom a deceased-donor kidney offer was declined, with subsequent transplant outcomes recorded.

Results: Kidneys were declined for 145 patients, aged 24 - 78 (mean 54.1), due to donor / organ quality (57.2%), recipient illness / unavailability (26.2%), and positive crossmatch (4.8%) with the remaining offers withdrawn (11.8%), largely due to delayed cardiac death. Over a mean follow-up of 12 months, 83 patients (57.2%) received at least one further offer. Second offers tended to be from slightly younger donors (53.5 vs 58.8 years, p=0.013) with the same HLA match (3.2/6 antigens matched). By the end of follow-up, 40% had been transplanted, 46 (31.7%) remained on the wait-list, 38 (26.2%) were temporarily or permanently suspended from the wait-list, and 2 (1.4%) had died. Compared to those less sensitised, highly sensitised patients (calculated HLA reaction frequency over 75%) were less likely to be transplanted (23.1 vs 47.3%, p=0.025). Older patients (over 60) were more likely to be suspended (39.3 vs 22.0%, p=0.028) with a similar tendency also seen in those waiting over 4 years for their first offer (40.5 vs 25.3%, p=0.082).

Conclusions: After declining a deceased-donor kidney, around 40% of patients may expect to be transplanted during the following year, whilst around 25% may be suspended from the wait-list. Risk factors for suspension or non-transplantation include older age, longer wait-time and greater HLA sensitisation. These data will be helpful to patients and clinicians making kidney offer decisions.

TH-OR131
Decreasing Risks of Kidney Transplantation Using High KDPI Kidneys by Preferred Recipient Matching
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Background: Kidneys with a high Kidney Donor Profile Index (KDPI, ≥85%) are often discarded due to an increased risk of mortality and graft loss. However, we hypothesized that some recipients might tolerate high KDPI kidneys well, and are therefore best suited to receive these grafts.

Methods: Using national registry data from SRTR from 2006-2017, we compared 10,361 kidney transplant recipients of high KDPI (≥85%) kidneys to 120,983 recipients of low KDPI (<55%) kidneys. We identified recipient factors that amplified (or attenuated) the impact of high KDPI on mortality and graft loss using interaction analysis, classifying recipients without amplifying factors and with attenuating factors as preferred recipients.

We compared mortality and graft loss with high KDPI versus low KDPI kidneys in preferred and non-preferred recipients using Cox regression.

Results: Preferred to be recipients who were ≥60 years old, non-white, with diabetes, and without glomerular or cystic disease as the cause of their ESRD. The increased mortality risk associated with high KDPI kidneys was 32% lower (interaction ratio: 0.68; p=0.001) in preferred vs. non-preferred recipients, whereas the increased risk of graft loss was 21% lower (interaction ratio: 0.79; p=0.001). This translated to a 1.37-fold higher mortality risk (HR: 1.76; 95% CI, 1.36 to 2.28; p<0.001) with a high KDPI kidney versus a low KDPI kidney in preferred recipients, in comparison to a 1.96-fold higher risk of graft loss (HR: 1.96; 95% CI, 1.78 to 2.17; p<0.001) for non-preferred recipients (Figure).

Conclusions: The risks of kidney transplantation with high KDPI kidneys can be decreased by appropriate recipient selection.

Funding: NIDDK Support
TH-OR133

Self-Reported vs. Measured Physical Function in Kidney Transplant Candidates at the Top of the Waitlist

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Background: Poor physical function of waitlisted kidney transplant candidates is associated with adverse waitlist outcomes, but the optimal metric is not known. We compared self-reported versus measured functional assessments in patients at the top of the waitlist.

Methods: Patients were evaluated from May 2017 to December 2018. Self-reported SF36 physical function subscale score (SF36 PF) was compared to results of the 6-minute walk test (6MWT) and sit-to-stand (STS) test by linear regression. We estimated the association between each metric and time to adverse waitlist outcomes (waitlist removal or death), with transplant as the competing event, by the Fine-Grey model, and adjusted for clinical covariates. We estimated model fit by AIC and likelihood ratios and compared hierarchically nested models, starting with demographics and comorbidities and sequentially adding physical assessment metrics.

Results: Out of 200 patients, the median SF36 PF, 6MWT, and STS results were 80, 396 meters, and 18, respectively. Physical function metrics were highly correlated (R=0.49 for STS-6MWT, 0.32 for STS-SF36 PF, and 0.54 for 6MWT-SF36 PF). Over median follow-up of 118 days, 29 patients were removed from the waitlist, 6 died, and 23 were transplanted. All three metrics were strongly associated with waitlist outcomes and improved model fit for adverse waitlist outcomes over standard exposures of demographics and comorbidities alone. 6MWT and SF36 PF results improved model fit for adverse waitlist outcomes over standard exposures of demographics and comorbidities alone. 6MWT and SF36 PF results improved model fit for adverse waitlist outcomes over standard exposures of demographics and comorbidities alone.

Conclusions: We measured V AT in 170 living kidney donors using pre-donation computerized tomography (CT) imaging and computerized software at a single lumbar level: L3-L4 for females and L2-L3 for males. All donor kidneys had preimplantation biopsies. Chronic histologic findings were defined as 2 of 3 biopsy findings: >5% global glomerulosclerosis, any interstitial fibrosis with tubular atrophy, or the presence of any arteriosclerosis. Kidney function was recorded by estimated glomerular filtration rate (eGFR) pre-donation and at 1, 12, and 24 months post-donation. GFR decline was defined as the percent drop in eGFR at 12 months vs. pre-donation.

Results: Greater V AT by tertiles correlated with older donor age, male gender, smoking, higher blood pressure, lipid abnormalities, and body mass index (BMI), (TABLE). Donor glomerulosclerosis and interstitial fibrosis on biopsy also correlated with VAT (TABLE). The highest tertile of VAT also correlated with lower pre-donation eGFR and less GFR recovery (FIGURE). After controlling for all associated donor variables including age, gender, and BMI, donor VAT remained an independent predictor of chronic histologic findings (OR: 1.02, 95% CI 1.01-1.04, p<0.001), and GFR decline after donation (b = 0.04, 95% CI: 0.02 to 0.07, p=0.001).

Conclusions: Living kidney donor VAT using standardized CT measurements correlated independently with both histopathologic findings and kidney functional decline after donation. VAT measurement may allow for donor risk stratification and may identify donors at higher risk for long term kidney functional impairment.

Funding: Private Foundation Support

TH-OR134

Living Kidney Donor Visceral Adipose Tissue Predicts Donor Histopathology and Post-Donation Kidney Functional Decline

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Background: Living kidney donors have become increasingly complex with increased obesity and older age. Given the association of visceral adipose tissue (VAT) and kidney functional decline in the general population, we hypothesized that VAT in living donors may predict baseline histopathology and post-donation kidney function.

Methods: We measured VAT in 170 living kidney donors using pre-donation computerized tomography (CT) imaging and computerized software at a single lumbar level: L3-L4 for females and L2-L3 for males. All donor kidneys had preimplantation biopsies. Chronic histologic findings were defined as 2 of 3 biopsy findings: >5% global glomerulosclerosis, any interstitial fibrosis with tubular atrophy, or the presence of any arteriosclerosis. Kidney function was recorded by estimated glomerular filtration rate (eGFR) pre-donation and at 1, 12, and 24 months post-donation. GFR decline was defined as the percent drop in eGFR at 12 months vs. pre-donation.

Results: Greater V AT by tertiles correlated with older donor age, male gender, smoking, higher blood pressure, lipid abnormalities, and body mass index (BMI), (TABLE). Donor glomerulosclerosis and interstitial fibrosis on biopsy also correlated with VAT (TABLE). The highest tertile of VAT also correlated with lower pre-donation eGFR and less GFR recovery (FIGURE). After controlling for all associated donor variables including age, gender, and BMI, donor VAT remained an independent predictor of chronic histologic findings (OR: 1.02, 95% CI 1.01-1.04, p<0.001), and GFR decline after donation (b = 0.04, 95% CI: 0.02 to 0.07, p=0.001).

Conclusions: Living kidney donor VAT using standardized CT measurements correlated independently with both histopathologic findings and kidney functional decline after donation. VAT measurement may allow for donor risk stratification and may identify donors at higher risk for long term kidney functional impairment.

Funding: Private Foundation Support
**TH-OR135**

**Improvement in Waiting Times for Recipients of A1 to B Kidney Transplant: Refining Our Understanding**

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**Background:** The creation of a new allocation priority in the new Kidney Allocation System (KAS) for transplants from blood group A1 donors to blood group B recipients has allowed more rapid transplantation of the group B list. However, no analysis has looked at the decrease in waiting times controlling for differences in sensitization or other priority factors (such as HIV or HCV positive kidneys). We undertook to do this type of robust analysis.

**Methods:** We conducted a retrospective analysis of 396 consecutive recipients who received a deceased donor kidney transplant in the time period from December 4, 2014 (the beginning of KAS) to November 1, 2018. We determined the waiting time based on the distribution pool in which the kidney was allocated and compared patients receiving kidneys in the local or regional blood type B for blood type A1/B donors only pools with those receiving kidneys within the local, regional, or national blood type identical or permissible pools.

**Results:** There were a total of 17 transplants of A1/A1 organs from deceased donors into blood group B recipients. 15 of the 17 were allocated within the A1/A1 pools (the other 2 were allocated in high cPRA pools). In the same period there were 57 B to B transplants of which 37 were allocated in the blood type identical or permissible pools. The 15 patients receiving A1/A1 organs had a mean waiting time of 4.97 ± 1.55 years, significantly lower than the 37 patients receiving standard B to B transplants (7.76 ± 3.91 years, p < 0.001). This amounted to a 35.9% reduction in waiting time.

**Conclusions:** The benefits of A1 to B transplantation in decreasing waiting times to transplant have been thus far underestimated due to the confounding factors of high sensitization and other high priority allocation. An A1 to B transplant protocol can reduce waiting times by more than a third for hard to transplant patients.

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**TH-OR136**

**Normothermic Ex Vivo Kidney Perfusion Preservation Reliably Improves Extreme Marginal Graft Function Compared with Hypothermic Machine Perfusion**

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**Background:** Normothermic ex-vivo kidney perfusion (NEVKP) is an emerging technique for renal graft preservation. We investigated whether NEVKP promoted improved marginal graft function compared to anoxic hypothermic machine perfusion (HMP) in a model of donation-after-cardiac-death (DCD).

**Methods:** Kidneys from 30kg-Yorkshire pigs were removed following 120min of warm ischemia (WI). These grafts were preserved with HMP (LifePort1.0, n=7) or NEVKP (n=7) for 8h prior to heterotopic autotransplantation.

**Results:** During NEVKP, 120min WI grafts cleared perfusion lactate (0h:10.48±0.93mmol/L vs 7h:1.48±0.85mmol/L, p<0.001), had decreasing intra-renal resistance (IRR) (0h:2.26±0.9mmHg/µL/min vs 7h:0.37±0.6mmHg/µL/min, p<0.01), and produced urine. IRR also decreased in HMP (0h:7.1±0.3mmHg/µL/min vs 7h:1.19±0.37mmHg/µL/min, p<0.01). Post-transplant, 120min WI grafts with NEVKP trended towards earlier and decreased serum creatinine (SCr) peak values compared to HMP (POD3:12.29±2.16mg/dL vs POD5:16.62±6.74mg/dL, p<0.13). From POD5-7, the HMP group demonstrated a bimodal distribution in SCr leading to increased variance compared to NEVKP (standard deviation ~ 6.74, 9.28, 9.38mmol/L vs 5.72, 6.25, 4.75mg/mL, respectively). In the HMP group, 4 of 7 grafts were poor performing with 2 developing renal vein thrombosis. Conversely, only 1 in 7 grafts was poor performing with NEVKP with no evidence of renal vein thrombosis (Figure 1). The consistent improvement in NEVKP vs heterogeneity in HMP was also observed through the variation in creatinine clearance (POD7: 26.3±11.54mL/min vs 16.8±18.09mL/min) and on histological analysis of tubular injury.

**Conclusions:** Marginal kidney grafts showed reliable improvement in function following 8h of continuous NEVKP compared to HMP where improvement was inconsistent. This suggests NEVKP would be a preferable storage strategy for DCD procured grafts with extended WI times.

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**TH-OR137**

**Genome-Wide Non-HLA Donor-Recipient Mismatches in Intronic Regions Independently Associate with Graft Survival**

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**Background:** Donor-recipient (D-R) mismatches at human leukocyte antigen (HLA) loci are used for management decisions. Recent work has showed the role of global non-HLA D-R mismatches, specifically exonic loci within genes coding transmembrane and secreted proteins in graft survival in Caucasian deceased donor cohorts. Since non-consanguineous coding regions constitute ~98% of human genome, and these elements have demonstrable regulatory activity, we hypothesized that non-coding D-R genetic differences could also contribute to unchecked alloimmunity impacting graft survival.

**Methods:** We utilized genome-wide SNP array data on all D-Rs in the GOCAR study excluding HLA region (n=385 D-Rs). We quantified the genome-wide numbers of mismatches of all SNPs, and annotated those in non-coding regions, or exomes [divided further into non-coding within genes coding transmembrane and secreted proteins] - all as separate continuous variables. Long-term death censored graft loss [DCGL] data were from UNOS/ANZDATA.

**Results:** Our multi-ethnic D-R cohort represented greater genetic diversity and included living donors vs published data. There were 73 DCGL events during median follow-up of 1824 days (IQR: 1392-2188 days). Genome-wide & Tm-mismatches were all increased in inter-race vs intra-race transplants (p<0.001). The total numbers of SNP mismatches quantified as quartiles respectively impacted DCGL & all-cause GL in adjusted Cox models [Fig. 1A-B]. However, in multivariate Cox models after adjusting for protein-coding mismatches, non-coding D-R mismatches remained independently associated with graft survival. Surprisingly, non-HLA mismatch variables had no association with acute T-cell mediated rejection phenotypes (subclinical or clinical; with/without borderline lesions) in regression models.

**Conclusions:** Our data from a multi-ethnic D-R cohort compliments recent work supporting the role of non-HLA D-R mismatches in long term allograft survival. In addition, we showed that non-coding loci based mismatches had independent impact on graft survival demonstrated for non-coding mismatches in allograft survival.

**Funding:** Other NIH Support - NIAID, Private Foundation Support
Vascular Access and Complications of Hemodialysis

A VF outcome relying on mapping findings. Two binomial logistic regression models were Based on accepted standards for the creation of an A VF, an algorithm was created to predict on the same day. Three readers independently assessed arterial and vein diameter and the vasculature in patients with renal disease due for autologous A VF creation.

Ferumoxytol, an iron oxide nanoparticle, is an alternative to US. Its value is not limited in identification of central vessels pathology but it also showed peripheral vascular disease under-recognized with US.

Funding: Commercial Support - AMAG Pharmaceuticals, Inc.

Vessel course, accessory veins, anatomical variants and the presence of stenosis or occlusion of arteriovenous vessels were better assessed with FeMRA. FeMRA identified 15 central vascular stenoses (CVS). On multivariable regression analyses FeMRA mapping was an independent predictor of AVF outcome [odds ratio (OR): 6.49 (95% CI 1.7 - 24.8); p=0.02].

Conclusions: FeMRA prior to AVF creation better predicted outcome compared to DUS. Its value is not limited in identification of central vessels pathology but it also showed peripheral vascular disease under-recognized with US.

Funding: Commercial Support - AMAG Pharmaceuticals, Inc.

TH-OR138

TH-OR140

Inactivation of Lysyl Oxidase in Smooth Muscle Cells Improves Arteriovenous Fistula Function in Mice

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Background: Over 400,000 patients in the U.S. depend on vascular access to receive hemodialysis (HD) and prolong their lives. Unfortunately, arteriovenous fistulas (AVFs), the preferred vascular access for HD, frequently fail (40%) because venous stenosis compromises blood flow. We recently discovered that stenosis occurs due to excessive medial fibrosis and is aggravated by intimal hyperplasia. Herein, we hypothesize that it is possible to prevent AVF failure by targeting lysyl oxidase (LOX), a copper-dependent amine oxidase involved in collagen and elastin crosslinking and in the epigenetic control of gene expression in smooth muscle cells (SMCs).

Methods: We created a LOX conditional knockout mouse (Lox+/Myh11-CreERT2) that is fertile, normal in size, and without any gross abnormalities. AVF were created by anastomosing the jugular vein to the nearby carotid artery. Mechanistic studies were performed with primary cultures of mouse venous SMC.

Results: Tamoxifen (TAM) injections significantly downregulated LOX gene expression [Folds vs. control, p<0.01] and protein accumulation in the vasculature of conditional KO mice but not in those of control littermates (Lox−/−Myh11-CreERT2). Inactivation of LOX in SMCs decreased immature collagen crosslinking in the aortal [1.3±0.1 vs. 1.7±0.1 HELN+DHNEL/collagen], and reduced carotid pulse wave velocity [2.2±0.4 vs. 2.9±0.4 cm/s] as determined by ultrasound microscopy. AVFs in mice with LOX-deficient SMCs showed higher distensibility and blood flow by day 21 post-surgery. Importantly, gene deletion caused aneurysms neither in the fistula nor in other parts of the vasculature. Mechanistically, we demonstrated that inhibition of LOX with BAPN increased H3K4me2 and H3K4me1 marks in the SMC genome, and specifically in the promoters of SMC contractile genes, to keep them in an open chromatin state and promote the binding of the SRF-myocardin transcription complex. We further confirmed the increased abundance of SRF in the CarG boxes of contractile gene promoters in SMCs treated with BAPN compared to the vehicle using a quantitative ChIP.

Conclusions: These data indicate, for the first time, the importance of LOX not only in post-operative vascular remodeling after AVF creation but also in the control of the SMC phenotype.

TH-OR139

Ferumoxytol MR Angiography vs. Doppler Ultrasound for Vascular Mapping Before Hemodialysis Arteriovenous Fistula Creation

Sokratis Ferumoxytol MR Angiography vs. Doppler Ultrasound for Vascular Vascular Access and Complications of Hemodialysis

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Background: Hemodialysis with autologous arteriovenous fistula (AVF) is associated with higher survival, lower costs, and fewer complications. Distal forearm AVF is the best option, but not all patients are good candidates for this approach and the primary failure rate ranges from 20% to 50%. The optimal AVF depends mainly on the anatomical and hemodynamic characteristics of the artery and the vein chosen for the anastomosis. These characteristics can be modified by performing physical exercise.

Methods: The PHYSICALF AV trial (NCT03213756) is an open-label, multicenter, prospective, controlled, randomized trial designed to evaluate the usefulness of preoperative isometric exercise (PIE) in pre-dialysis or prevalent hemodialysis patients who are candidates for a new AVF. Patients are randomized 1:1 to the PIE group (Exercises combining hand grip and elastic band for 8 weeks) or the control group (no exercise).

Results: After 20 months recruitment, 120 patients have been randomized. After 8 weeks of preoperative isometric exercise we have found significant differences on vein diameter (p<0.001), arterial peak systolic velocity and diameter (p 0.041- p 0.001) and maximum strength (p<0.001) on PIE group patients (table 1). We have been able to perform 76% of distal AVF in PIE group compared to 53% in the control group (p 0.043). Global primary failure rate was very low in both groups (6.9% PIE group vs 5.7% control group, pNS) and intervention free rate at 3 months was 82.8% PIE group vs 80% in control group (pNS).

Conclusions: Isometric preoperative exercise can improve vascular calipers and increase the possibility of performing distal AVF. The final results of this trial will be available in September 2019.

Funding: Other NIH Support - Grant founding from the Spanish Society of Nephrology.

Before and after exercise

Funding: Other NIH Support - Grant founding from the Spanish Society of Nephrology.

Representative images of CVS with FeMRA.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
used to construct multiple regression models with ABF as dependent variable, 18 patients served as validation cohort.

Results: Visual inspection of the derivation cohort ABF vs. M2 scatterplot indicated 2 distinct populations, one with M2≤100 (n=30) and M2>100 (n=10; Table 1). In the validation cohort 17 patients had M2≤100, and 1 patient >100. In the derivation cohort a multiple regression model including M2, sex, body weight, and race explained 64% of the ABF variance in patients with M2≤100 (Fig 3A) and 44% in patients with M2>100 (Fig 3B), respectively. In the validation cohort we predicted 51% of the ABF variance in patients with M2>100 (Fig 4); the one patient with M2>100 was not analyzed.

Conclusions: Our results show that advanced mathematical analysis of smartphone videos may have the potential to assess AVF blood flow. If corroborated in more extensive clinical studies, smartphone video analysis provides an attractive and low-cost means to non-invasively evaluate AVF blood flow.

Funding: NIDDK Support

Figure 1: A: AVF with enlarged fistula and hypopigmented skin, B: AVFA with enlarged fistula and ulceration.

TH-OR143

Comparison of Drug-Coated Balloon Angioplasty vs. Conventional Balloon Angioplasty for Arteriovenous Fistula Stenosis: A Meta-Analysis

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Background: Arteriovenous fistula (AVF) is the most preferred form of vascular access for maintenance hemodialysis (HD) but access stenosis treated by balloon angioplasty are prone to restenosis due to neointimal proliferation. Multiple trials have been published with regards to use of paclitaxel coated balloon (DCB) to prolong lesion patency when compared to conventional balloon. Though DCB has theoretical appeal, its use has not been widespread with access centers nationwide due to factors related to cost and lack of large scale multicenter studies. We performed this meta-analysis to evaluate whether use of DCB outperforms conventional balloon to prolong target lesion patency.

Methods: Medical electronic databases, including PubMed/Medline, Clinical Trials.gov, EMBASE, Scopus, Web of Science and Cochrane Central were searched from inception through April 2019 for studies that investigated use of DCB in HD AVF. 15 studies (6 Randomized control trials (RCT) and 9 observational studies) were considered for qualitative and quantitative analysis.

Results: Ten studies were included in the final meta-analysis. 6 of the studies were RCTs and 4 were retrospective (cohort) studies. There were 915 participants with a mean age of 65.40 (+/-5.96) years and 61.89% were male. The outcome of interest was target lesion primary patency (TLPP), recorded at a longitudinal follow-up time, i.e. 1, 3, 6, 7, 12 and 24 months. Meta-analysis of all RCTs shows that drug-coated balloons (DCBs) did not statistically improve TLPP compared to traditional balloons at months 1 (OR 4.27, p-value 0.06), 3 (OR 0.9, p-value0.59), 6 (OR 0.80, p-value 0.54), 7 (OR 0.93, p-value 0.75), 12 (OR 0.61, p-value 0.17) and 24 (OR 0.69, p-value 0.15). The effect of DCBs was statistically significant for cohort studies at 6 months (OR 0.26, p-value 0.007), 12 months (OR 0.21, p-value 0.0001) and 24 months (OR 0.23, p-value 0.01). Studies using AV-Graft were excluded. There was no publication bias as assessed by funnel plots.

Conclusions: Drug-coated balloons showed no statistically significant improvement over conventional balloons in decreasing fistula stenosis in meta-analysis of RCT at 1,3,6,7,12 and 24 months but were significant for cohort studies at all follow up months of 6, 12 and 24. Our analysis does not justify the use of DCB at this time.

TH-OR144

Patient, Care Provider, and Partner Perspectives on Arteriovenous (AV) Access Creation Prior to Hemodialysis (HD) Initiation

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Background: More than 80% of individuals in the U.S. start maintenance HD with a catheter, despite substantial evidence that starting HD with an AV access improves quality of life, lowers mortality, and decreases healthcare costs. Barriers to AV access creation prior to HD initiation have been under-investigated. We sought to identify patient, care partner, medical provider, and clinic personnel perspectives on the AV access creation process in the pre-HD period.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We conducted 4 focus groups (N=24 participants) and 16 semi-structured interviews (N=2 across 4 sites and 2 questions). Focus groups included advanced chronic kidney disease patients (GFR <20 mL/min/1.73m²), and separately, HD patients within 1 year of HD initiation as well as care partners of such patients. Interviewees included nephrologists, surgeons, clinic nurses, imaging specialists, and other staff. Transcripts were coded independently by 3 researchers and thematically analyzed.

Results: Participants identified a range of patient- and healthcare system-related barriers to starting HD with an AV access. Key modifiable barriers included: slow provider views of the AV access creation process; negative patient emotions (e.g. fear, denial, uncertainty); inadequate and inconsistent patient education; and lack of systematic approaches to tracking patients through AV access care processes. Key facilitators included: early and sustained dedicated vascular access education (i.e. separate from modality and transplant education); care partner inclusion in education; and positive peer interaction. Participants identified 4 essential aspects of pre-HD vascular access care: a strong patient—provider relationships (trust, shared decision-making); focused, iterative multi-format education; peer support; and assistance in process navigation (e.g. care navigation, vascular access-specific electronic health record reports, consistent provider communication).

Conclusions: Programs aimed at improving rates of HD initiation with an AV access must address both patient- and healthcare system-related barriers. Key components include strong patient-provider relationships, targeted education, peer support, and care navigation.

Funding: NIDDK Support

TH-OR145

Ultrafiltration and Cerebral Microbleeds in Haemodialysis Patients
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Background: Ultrafiltration of dialysis patients were variable. The detailed studies on the impact of different ultrafiltration are still rare. Variable ultrafiltration may contribute to brain lesions by inducing hemodynamic instability. Cerebral microbleeds (CMBs) in dialysis patients have recently attracted much attention. The risk factors of CMB in dialysis patients are not very clear. The association of ultrafiltration with CMB is unknown.

Methods: A total of 119 chronic haemodialysis patients were enrolled in our study. Demographic and Clinical Characteristics of Patients were recorded. Multiple ultrafiltration information of every patient before MRI examination was recruited with Ultrafiltrate volume(UV), mean, UV standard deviation(SD), UV coefficient of variation(CV), the difference between UV mean and 6% of weight, the ratio of UV to weight mean, and the ratio of UV to weight SD. CV was calculated as the ratio of SD to the mean. CMBs were defined as small (2–10 mm) areas of homogeneous signal loss on susceptibility weighted imaging images. The correlation between ultrafiltration and CMB was investigated by logistic regression analysis.

Results: Recorded dialysis period ranged from 2.0 to 14.0 months, and recorded dialysis times ranged from 11.0 to 54.0. Urea removal ratio was 0.7±0.1, and Kt/V was 1.6±0.2. UV mean ranged from 0.2 to 4.6 kg, and UV CV ranged from 0.0 to 78.1 percent. The prevalence of CMBs was 35.3% in the total study population. Ten subjects (8.4%) suffered lobar CMBs, Nine subjects (7.6%) suffered mixed CMBs, and 23 subjects (19.3%) suffered deep group. UV mean, the difference between UV mean and 6% of weight, and the ratio of UV to weight mean were risk factors of CMB (OR=1.59, 1.48, and 1.31 respectively, p=0.036, 0.057, and 0.030 respectively). UV CV was negatively associated with CMB(OR=0.96, p=0.022 respectively). The association of UV mean and UV CV with CMB was still significant after adjusting for gender, age, serum albumin, urea removal ratio, lumen, and white matter hyperintensity(OR=1.72 and 0.96 respectively, p=0.044 and 0.046 respectively).

Conclusions: UV was closely associated with CMB in dialysis patients. Reducing UV may protect dialysis patients from CMB.

TH-OR146

Trends in Use and In-Hospital Outcomes of Subcutaneous Implantable Cardioverter Defibrillators in Dialysis Patients: A Report from the National Cardiovascular Data Registry
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Background: Dialysis patients are at high risk of infectious and vascular complications related to implanted cardioverter defibrillator (ICD) implantation; many have advocated for the preferential use of subcutaneous (S-ICD) over transvenous devices (TV-ICD) due to the potential benefits of reduced risk of blood stream infection and interference with vascular access. Using a de-identified trended in-hospital outcomes of S-ICD compared to TV-ICDs among dialysis patients in the United States.

Methods: This was a retrospective analysis of 23,136 ICD implants among dialysis patients reported between 2012 and 2018 to the National Cardiovascular Data Registry ICD Registry, a nationally representative US ICD registry. We first examined the difference in the patient and procedure characteristics of dialysis patients receiving S-ICD vs TV-ICD. Next, among dialysis patients eligible to receive an S-ICD, we examined trends in S-ICD adoption as a proportion of all ICD implants and compared in-hospital outcomes (death, complications) among S-ICD and TV-ICD recipients using inverse probability weighted estimators.

Results: Of all ICDs implanted among dialysis patients during the study period, 3,195 (13.81%) were S-ICD. Among eligible first-time ICD dialysis recipients, the proportion of S-ICDs utilized increased yearly from 10.3% in 2012 to 68.5% in 2018. Compared to TV-ICD recipients, S-ICD recipients were more likely to be black (42.6% vs. 34.3%) and undergo implantation in teaching hospitals (62.8% vs 53.2%). In the inverse probability weighted estimators analysis, compared to TV-ICD, dialysis patients receiving S-ICDs had a higher rate of in-hospital cardiac arrest (1.53% vs 0.36%, p=0.002); in-hospital complications (2.4% vs 1.48% vs p=0.08) and length of hospitalization (1.57 vs. 1.24 days, p=0.08) were not significantly different between the 2 groups.

Conclusions: There has been a steady increase in the utilization of S-ICD among dialysis patients in the United States. The increased risk of in-hospital cardiac arrest in S-ICD recipients could have been due to residual confounding and selection bias, but randomized clinical trials are needed to definitively compare the outcomes of TV-ICD vs S-ICD in dialysis patients.

Funding: The Private Foundation Support

TH-OR147

Intradialytic Hypotension and Incident Peripheral Artery Disease in Patients with ESKD on Hemodialysis
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Background: Intradialytic hypotension (IDH) may decrease systemic circulation to the lower extremities, exacerbating symptoms of peripheral artery disease (PAD). We sought to evaluate the relationship between IDH and incident PAD among patients on hemodialysis (HD).

Methods: Using the data from USRDS linked to a large dialysis provider, we identified adults without pre-existing PAD who initiated HD between 2006-2011. Exposure: time-varying proportion of HD sessions with IDH, defined as nadir systolic blood pressure <90 mmHg, categorized as 0%, 1-14%, 15-29%, and ≥30% in 30-day intervals. Outcome: incident PAD, ascertained using PAD diagnosis codes or procedure codes for amputation or revascularization, in the subsequent 30-day interval. We estimated unadjusted and adjusted sub-distribution hazard ratios using Fine and Gray models with time specified in the competitive-risk style, assuming death and kidney transplant as competing events. Models were stratified by incident HD year and adjusted for baseline characteristics, comorbidities, healthcare use and laboratory values. Missing data were handled using multiple imputation by chained equations as implemented in R.

Results: In our cohort (N=45,489), patients with a more frequent IDH were more often women and of white race, and had a higher prevalence of diabetes, coronary artery diseases and heart failure. During 61,842 person-years of follow-up, 8,111 patients had incident PAD. We found a graded, direct association of IDH with incident PAD. For example, the presence of IDH in ≥30% of dialysis sessions was associated with an adjusted 36% increase in the hazard of incident PAD (95% CI, 27%-45%) compared to 0% IDH, in patients without PAD or who have experienced the competing events (Figure 1).

Conclusions: Patients with ESKD on HD with more frequent IDH have a higher hazard of incident PAD in the subsequent 30 days. Patients with more frequent IDH may warrant a careful examination for PAD such as foot examinations or other diagnostic testing.

Funding: Government Support - Non-U.S.

References:

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Methods: To enrich for transcriptomes from cells destined to form cysts in the kidney, we isolated RNA by translating ribosome affinity purification (TRAP). RNA profiling was performed in 10wk-old mice (4/group): Pkd1fl/flR26R::Cre,Pax8Cre;TetOCre (non-conditional); Pkd1fl/flR26R::Cre,Pax8Cre;TetOCre (non-cystic, NC); Pkd1fl/flR26R::Cre,Pax8Cre;TetOCre (cystic, single KO); SKO) and Pkd1fl/flR26R::Cre,Pax8Cre;TetOCre (non-cystic Pkd1-null double KO; DKO). Differential gene and KEGG pathway analysis identified the cell cycle pathway as the most enriched and upregulated. Cdk1 emerged as one of the most upregulated genes in this group. Polycystic kidney disease (PKD) mice with early- (Pkd1fl/flPkd1;Cdk1fl/fl) and late-onset Pkd1 deficiency (Pkd1fl/flPkd1;Cdk1fl/fl) were combined with the Cdk1fllox;Baxfllox;germcellsinglOKO(Pkd1-KO)anddoubleKO(Cdk1-Pkd1-KO) models. The early and late onset groups were evaluated respectively on P24 and on the 18th wk (after cyst formation from P15). Results: 155 genes were identified from the overlap between groups that shared differential expression in both NC vs SKO and SKO vs DKO groups. KEGG pathway analysis identified the cell cycle pathway as the most enriched and upregulated. Cdk1 emerged as one of the most upregulated genes in this group. Polycystic kidney disease (PKD) mice with early- (Pkd1fl/flPkd1;Cdk1fl/fl) and late-onset Pkd1 deficiency (Pkd1fl/flPkd1;Cdk1fl/fl) were combined with the Cdk1fllox;Baxfllox;germcellsinglOKO(Pkd1-KO)anddoubleKO(Cdk1-Pkd1-KO) models. The early and late onset groups were evaluated respectively on P24 and on the 18th wk (after cyst formation from P15). Results: 155 genes were identified from the overlap between groups that shared differential expression in both NC vs SKO and SKO vs DKO groups. KEGG pathway analysis identified the cell cycle pathway as the most enriched and upregulated. Cdk1 emerged as one of the most upregulated genes in this group. Polycystic kidney disease (PKD) mice with early- (Pkd1fl/flPkd1;Cdk1fl/fl) and late-onset Pkd1 deficiency (Pkd1fl/flPkd1;Cdk1fl/fl) were combined with the Cdk1fllox;Baxfllox;germcellsinglOKO(Pkd1-KO)anddoubleKO(Cdk1-Pkd1-KO) models. The early and late onset groups were evaluated respectively on P24 and on the 18th wk (after cyst formation from P15). Results: 155 genes were identified from the overlap between groups that shared differential expression in both NC vs SKO and SKO vs DKO groups. KEGG pathway analysis identified the cell cycle pathway as the most enriched and upregulated. Cdk1 emerged as one of the most upregulated genes in this group. Polycystic kidney disease (PKD) mice with early- (Pkd1fl/flPkd1;Cdk1fl/fl) and late-onset Pkd1 deficiency (Pkd1fl/flPkd1;Cdk1fl/fl) were combined with the Cdk1fllox;Baxfllox;germcellsinglOKO(Pkd1-KO)anddoubleKO(Cdk1-Pkd1-KO) models. The early and late onset groups were evaluated respectively on P24 and on the 18th wk (after cyst formation from P15).

Conclusions: Transcriptional analysis from cell clusters identified in this study highlighted the cell cycle as a fundamental driver for cyst expansion in the kidney. Conclusions: Transcriptional analysis from cell clusters identified in this study highlighted the cell cycle as a fundamental driver for cyst expansion in the kidney. Conclusions: Transcriptional analysis from cell clusters identified in this study highlighted the cell cycle as a fundamental driver for cyst expansion in the kidney. Conclusions: Transcriptional analysis from cell clusters identified in this study highlighted the cell cycle as a fundamental driver for cyst expansion in the kidney.
PKD1’s ability to inhibit F604P-PKD2. Deletion of Ct or the last 6 TM resulted in partial TM domain. Comparing with WT-PKD1, deletion of Nt and/or the first 5 TM did not alter the TM domain of PKD2 leads to widening of the lower gate and constitutive activation of the.

Background: The Role of Polycystin 1 in the Polycystin-1/Polycystin-2 Channel
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PKD1 and PKD2 and in the pathogenesis of ADPKD remain elusive. Previous studies of the ion-conducting pore.

Conclusions: PKD1 inhibits PKD2 channel activity. The C-terminus and last 6 TM domains, deletion of both Nt and Ct or deletion of Nt as well as the first 5 TM did not alter PKD1’s ability to inhibit F604P-PKD2. Deletion of Ct or the last 6 TM resulted in partial reduction in the ability of PKD1 to inhibit F604P-PKD2.

Results: Our results show that PC1 can form a channel with PC2-GOF with distinct properties from that of the homomeric PC2-GOF channel. Compared to the homomeric PC2-GOF channel, PC1/PC2-GOF channel is not blocked by extracellular divalent ions and has significantly higher Ca2+ permeability than PC2-GOF channel. We also found that the GPS cleavage-produced PC1 C-terminal fragment (PC1-CIRF) has almost identical channel function as full-length PC1 when assembled with PC2-GOF. Further analysis shows that not only Ca2+, a lot of other monovalent ions, including some big organic ions, also permeate better through the PC1/PC2-GOF channel, compared to that of the PC2-GOF channel, indicating a relatively larger pore of the complex channel. More importantly, deletions in the pore region of either PC1 or PC2 alter the ion permeability of the PC1/PC2-GOF channel, confirming that both proteins contribute to the formation of the ion-conducting pore.

Conclusions: Full-length PC1 can associates with PC2-GOF to form a GOF PC1/PC2 complex in Xenopus oocytes. We were able to successfully record the channel current from this channel and dissect the role of PC1. In this channel, the PC1 subunit directly contributes to the channel pore formation, and the PC1-CIF is sufficient for its channel activity. The PC1/PC2-GOF channel has a distinct ion-conducting pore from that of the homomeric PC2-GOF channel and is more Ca2+-permeable.

Background: The disease course of autosomal dominant polycystic kidney disease (ADPKD) is highly variable, and the option to prescribe renoprotective treatment make early risk stratification important. Therefore, novel biomarkers to select patients at high-risk of rapid progression are required. We applied metabolomics to evaluate whether urinary metabolites are associated with progression of ADPKD.

Results: A total of 309 patients with ADPKD were included (age 46±10 years, 57% female, median of eGFR 62.1 ml/min/1.73m2 [IQR 45 to 85]). From the NMR spectra, 29 known urinary metabolites were identified and quantified. In a model with annual change in eGFR (median -3.3 ml/min/1.73m2 per year [IQR -5.0 to -1.3]) as a response variable and all quantified metabolites and their binary ratios (449 features in total) as predictors, the alanine/citrate ratio was found to be most strongly associated with eGFR decline (-0.15), and remained significant after adjustment for potential confounders. Moreover, it outperformed the model built on the clinical risk markers including baseline eGFR and height-adjusted total kidney volume (htTKV). When only young patients (age <35 years) with an eGFR <75 ml/min/1.73 m2 were selected (n=33), this ratio was significantly higher in those with fast disease progression (rate of eGFR decline >3.3 ml/min/1.73 m2 per year, n=16) as compared with slow progressors (p=0.015).

Conclusions: Urinary alanine/citrate ratio is associated with the rate of eGFR decline in ADPKD patients.
FR-OR010

Dissection of the Therapeutic Effect of Glucosylceramide Synthase Inhibition on Polycystic Kidney Disease Progression in Adult Pkd1 RC/RC Mice

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Background: Glucosylceramide synthase inhibitors (GCSis) have been shown to inhibit cystogenesis in multiple preclinical models of PKD. To determine how GCSi treatment impacts kidney disease progression in an adult, orthologous mouse model of ADPKD over a sustained period, we have treated homozygous Pkd1+/−/− mice carrying the R327TC mutation (Pkd1 RC/RC) with a GCSi for one year. To assess the impact on liver cyst formation, we treated Pkd1 conditional knockout (ckO) mice with a GCSi from 7-36 days of age.

Methods: Pkd1 RC/RC mice were randomized into vehicle or GCSi treatment groups at 4 months of age. GCSi treatment reduced the TKV of Pkd1 RC/RC mice within 1 month of treatment; in contrast, vehicle treated Pkd1 RC/RC mice showed a gradual increase in TKV over the same time period. This anti-cystic effect was observed for the duration of the study. At sacrifice, kidney/body weight ratio was significantly decreased in GCSi-treated animals compared to controls. Liver cyst growth was reduced in GCSi treated animals compared to vehicle controls.

Conclusions: GCSi treatment inhibits kidney and liver cyst growth in Pkd1-linked mouse models. Moreover, GCSis have a sustained effect on kidney cyst growth.

Funding: Commercial Support - Sanofi

FR-OR011

Membrane Filtration of Contaminated Water with Used Dialyzers Reduces the Incidence of Diarrhea in Rural Communities in Developing Countries

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Background: Access to clean water remains unavailable for a large fraction of the world population. Consequent infectious diarrhea, dehydration and acute kidney injury often too leads to death. Membrane filtration using recycled hemodialyzers is a recent innovation. We quantified its effect on health outcomes in rural communities in Ghana.

Methods: From 2015 to 2018 we provided membrane filtration devices (NUFiltration Israel) to 9 communities in Ghana (Greater-Accra region). We calculated incidence rates of self-reported diarrhea and compared monthly counts for 12 months before and after implementation by binary nonparamal and Poisson regression (Pois) with the log(exposure time) as the offset. Models were compared by likelihood ratio test (LRT) and Akaike Information Criterion (AIC). Logistic regression for recurrent events on a subject-level (LogReg) was used to determine the effect of device implementation and seasonality (rainy versus dry season).

Results: We studied 2605 villagers (10.4% younger than 5 and 5.1% older than 65 yrs). Incidence rates were significantly lower after device implementation (0.08 versus 0.03; P<0.01). LRT and AIC determined Pois to fit best and Pois showed a significant treatment effect [0.4 (95% CI 0.2 to 0.3)] with a higher OR of 1.1 (95% CI 1.0 to 1.3) during the rainy season. Lower rates during Month -1 and -2 can possibly be explained by concomitant handwashing and hygiene education initiatives.

Conclusions: Our data shows decrease in the incidence rates and odds of contracting infectious diarrhea with the use of membrane filtration device in rural villages in West Africa. A possible effect of seasonality should be recognized as a potential risk factor. These data emphasize the remarkable public health effect achievable by provision of these low-cost devices.

FR-OR012

Relationship of Acute Kidney Disease (AKD) to Long-Term Outcomes After AKI

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Background: Acute Kidney Disease (AKD) is a term that has been advocated by the ARID Quality Initiative (ADQI) and others to describe ongoing renal dysfunction after AKI that persists beyond 7 days. Currently there is very little available epidemiological data regarding AKD. We sought to study its relevance to long term renal and patient outcomes.

Methods: All patients from the AKI arm of a large parallel group cohort study of AKI were included in this study. Participants were recruited following hospitalisation and followed up prospectively. Renal function, proteinuria and patient outcomes were assessed at 3 months, 1 year and 3 years after AKI. CKD progression was defined as a ≥25% decline in eGFR from baseline with a decline in eGFR stage. Patients were categorized into three groups depending on duration of AKI: AKI that resolved in ≤48hours (rapid recovery, r-AKI), AKI duration of 2-6 days (persistent AKI, p-AKI) and AKD (AKI duration ≥7 days). Outcomes were compared across these three groups.

In total, 506 patients of AKI were studied. There were 109 (22%) in r-AKI group, 302 (60%) in p-AKI group and 95 (19%) with AKD. Patients in the AKD group had lower baseline eGFR and a higher proportion of AKI stage 3. CKD progression was more common in AKD group as compared to other two groups. At one year, CKD progression was 46% in AKD group versus 11% (r-AKI) and 22% (p-AKI), p<0.001. eGFR was lower in AKD group at all time-points; at year 3, eGFR was 66.9±23ml/min, 60.1±20ml/min and 53±20ml/min in r-AKI, p-AKI and AKD groups respectively, p<0.001. Proteinuria was more common and more severe in AKD. Hospital readmission occurred more frequently in the AKD group. Using binary logistic regression analysis adjusting for age, gender, diabetic status, baseline eGFR, AKI stage and biochemical variables, AKD remained independently associated with CKD progression at 1 OR 5.4, 95% CI 2.2-13.2, p<0.001 and 3 years (OR 2.2, 95%CI 1.0-4.6, p=0.04).

Conclusions: AKD is common and is associated with a number of clinical variables including chronic comorbidities and markers of AKI severity. However, AKD duration remains an important independent determinant of subsequent progression of kidney disease, and AKD appears to be a useful way to categorize this to identify patients at higher risk of long-term adverse outcomes.

FR-OR013

Renal Recovery Patterns After AKI Influence Mortality

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Background: Renal recovery from acute kidney injury (AKI) in hospitalized patients is variable and non-recovery has been associated with an increased mortality and resource utilization. There is limited information on different patterns of renal recovery following AKI in the ICU setting. We hypothesized that the AKI course and duration in the ICU influences the length of stay and mortality.

Methods: A retrospective multinational cohort study of critically ill adult patients admitted to 4 centers in Germany, UK, and USA was conducted between Jan2014 and Dec2017. We excluded patients who stayed <72hrs in the ICU, patients with ESRD and kidney transplant. AKI was defined by ≥25% KIDIGO criteria and the course characterized as a single episode (SE) or stuttering course (SC) if the patient had multiple AKI during the ICU stay. Recovery of AKI was defined as no longer meeting criteria for even stage 1 AKI. No recovery was defined as an episode ending during ICU stay and the last recorded eGFR higher than the patient’s reference eGFR. The primary outcome was ICU and hospital mortality.

Conclusions: AKD is common and is associated with a number of clinical variables including chronic comorbidities and markers of AKI severity. However, AKD duration remains an important independent determinant of subsequent progression of kidney disease, and AKD appears to be a useful way to categorize this to identify patients at higher risk of long-term adverse outcomes.
Results: Of 20,560 eligible patients, 9,712 (47.2%) developed AKI, 5,303 (25.8%) at Stage 1, 3,358 (16.3%) Stage 2, 2,290 (11.1%) Stage 3 and 9,613 (46.7%) no AKI. 2,223 patients (10.5%) received dialysis. 7,086 (74 %) patients had a SE while 2,494 (26 %) patients had a SC. Overall, more than half of the patients recovered from AKI (6,128; 65.9%); 65% in SE versus 58.5% in the SC. Amongst dialyzed patients, 51.8% recovered from AKI, 61.7% of the patients with a SE, 42.1% in the SC. The development of AKI significantly increased length of hospital stay (no AKI: 14.2 (±17.4), SE: 20.3 (±21.1); SC: 40.1 (±38.8) days; p<0.001). Patients with AKI had significantly higher mortality which was influenced by the course (no AKI: 8.2%, SE: 14.5%, SC: 19.9%; p<0.001). Patients who recovered from AKI had significantly lower hospital mortality (10.9% versus 25.6%; p=0.05). However, mortality in patients with non-recovery was similar in SC 27.9% and SE (24.6%). Overall, we observed four recovery patterns.

Conclusions: We have identified four distinct recovery patterns on the basis of the clinical course. These phenotypes may identify patients amenable to therapeutic intervention. The pattern of renal recovery from AKI in the ICU influences resource utilization and mortality.

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FR-OR014
Hospitalizations, AKI, and Longitudinal Kidney Function in HIV+ Patients
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Background: Whether AKI contributes to the excess CKD burden in HIV+ persons or simply marks poor overall health is unclear. We conducted a substudy in the Johns Hopkins HIV Clinical Cohort to examine if hospitalizations with and without AKI were associated with longitudinal eGFR.

Methods: We included HIV+ persons followed from 1/2005-5/2016 and had baseline eGFR ≥ 30 mL/min, ≥ 3 eGFRs and sufficient creatinine (Cr) data to assess AKI status. We classified patients into 3 mutually exclusive groups: never hospitalized, hospitalized without AKI or hospitalized with AKI (≥ 0.3 mg/dL Cr rise within 48h or max inpatient Cr ≥50% above outpatient baseline). We used mixed effects models, adjusted for demographics, comorbidities, serum albumin, BMI, proteinuria, HIV factors and number of primary care visits.

Results: Among 1731 HIV+ persons, mean age was 43±7% were black, and 70% were on antiretrovirals at baseline. During a median follow-up of 3.7y, 730 had ≥1 hospitalization, of whom 43% had ≥1 complicated by AKI. Versus other groups, the hospitalized AKI group was more likely to have IV drug use history, greater comorbidity burden, lower CD4 count, less HIV suppression and lower mean eGFR at baseline (96 vs. 107-109 ml/min) at baseline. In adjusted models, there was little difference in annual eGFR change in those with non-AKI hospitalizations vs. no hospitalizations (Δ 0.12 ml/min; 95%CI: -0.46, 0.71). Conversely, patients with hospitalized AKI vs. no hospitalizations had faster eGFR decline (Δ -1.68 ml/min; 95%CI: -2.69, -0.67) (Figure). This association weakened in sensitivity analyses with inverse weighting for death (Δ -0.85; 95%CI: -1.83, 0.14).

Conclusions: Hospitalization is associated with faster kidney function decline, but hospitalization without AKI had no association. These findings underscore AKI as a potential pathway leading to CKD in HIV+ persons.[Figure]

Funding: NIDDK Support

FR-OR015
Nephrologist Follow-Up vs. Usual Care After an AKI Hospitalization (FUSION): A Randomized Pilot Trial
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Background: Survivors of AKI are at increased risk of CKD and death but few patients see a nephrologist post-discharge. Our objectives were to determine the feasibility of randomizing survivors of AKI to structured follow-up with a nephrologist or usual care, as well as to collect data on clinical outcomes for event rate calculations.

Methods: We performed a 52-week randomized pilot trial in patients hospitalized with KDIGO stage 2-3 AKI in 4 hospitals in Toronto, Canada. We randomized patients to usual care or nephrologist-led follow-up within 90-days of discharge, which consisted of a standard assessment that emphasized blood pressure control, cardiovascular risk reduction, and medication safety. The feasibility outcome was the proportion of patients recruited. The primary clinical outcome was a major adverse kidney event, which is a composite of death, chronic dialysis, or a sustained decrease ≥ eGFR 25%, at 52-weeks post-discharge.

Results: We screened 269 patients and randomized 71 (26%) from July 2015 to June 2017 (37 to usual care and 34 to nephrology follow-up). The most common reasons for declining to participate were patient fatigue (33%) from recent hospitalization and reluctance to see additional specialists (30%). Baseline characteristics included age 65±10 years (mean, SD), 30% female, baseline eGFR 76±22 mL/min/1.73m2, 47% admitted to the ICU, and median length of stay 14(IQR 10) days. The median time from hospital discharge to nephrology follow-up was 48(IQR 40) days, and 22/34 (65%) patients in the intervention group attended their nephrology appointment. The primary outcome occurred in 18/37 (49%) patients in the usual care group and 17/34 (50%) patients in the intervention group (P=0.91). There were no differences between usual care and the nephrology follow-up group in death (8% vs 18%, P=0.23), a≥5% decrease in eGFR (46% vs 38%, P=0.51), or rehospitalization for AKI (24% vs 24%, P=0.94). No patients in either group received maintenance dialysis.

Conclusions: Patient recruitment was lower than anticipated primarily because of patient fatigue and resistance to in-person visits post-discharge, which suggests a more pragmatic intervention may be needed that actively engages patients in its development. The high number of major adverse kidney events observed suggests more work is warranted to improve patient follow-up after AKI.
FR-OR017
Outcomes of AKI Patients Receiving Dialysis in ESRD Facilities
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Background: Medicare beneficiaries with Acute Kidney Injury (AKI) have received dialysis in outpatient end stage renal disease (ESRD) facilities since 2017 as a result of a CMS policy change allowing payment for dialysis services provided to AKI patients. Outcomes of AKI patients relative to ESRD patients have not been reported.

Methods: AKI patients were identified from 2017 Medicare claims with at least one bill type 072x with condition code 84 (Dialysis for AKI), CPT G0491 (Dialysis for AKI without ESRD) or a select group of ICD-10 codes. We determined patient transition to ESRD from CROWNWeb and other sources; vital status was obtained from the Medicare Enrollment Database. Patients were followed through 3/31/18. We used Cox proportional hazards modeling to compare survival between AKI and non-AKI Medicare incident ESRD patients.

Results: 10,717 of 399,936 (2.7%) patients on dialysis had at least one AKI claim. AKI patients were more likely to be white (72% v. 47%) and age 60+ (82% v. 61%) than ESRD patients. Overall 64% of AKI patients developed ESRD, 13% died without developing ESRD, 17% were alive without ESRD, and 6.1% were lost to follow up. Hospital based facilities had a larger proportion of AKI claims relative to free standing facilities (mean 1.9% v. 0.7% of all dialysis claims). After adjustment for age, race, sex, and ethnicity, AKI patients had a 27% higher mortality risk compared to incident ESRD patients (HR 1.27, p<0.0001).

Conclusions: Patients with AKI represented a small proportion of patients in ESRD facilities (mean 1.9% v. 0.7% of all dialysis claims). After adjustment for age, race, sex, and ethnicity, AKI patients had a 27% higher mortality risk compared to incident ESRD patients (HR 1.27, p<0.0001).

Funding: Other U.S. Government Support

FR-OR019
Electronic Alert and a Bundle of Care Reduces Progression and Mortality of AKI Patients
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Background: Acute kidney injury (AKI) is potentially preventable but its early diagnosis is essential to ensure appropriate management. The aim of this study was to evaluate the impact of an electronic AKI alert and a bundle of care (BoC) in the progression and mortality of patients with AKI.

Methods: An algorithm examined all serum creatinine reported by the laboratory. An alert was issued in the electronic medical record (accessed by physicians and nurses) and a BoC was suggested in case of AKI (KDIGO criteria). Prescription audit was performed by a clinical pharmacist. Individuals > 18 years were included and patients in palliative care, nephrology and renal transplantation wards were excluded. The study was divided in two periods: pre-alert initiation group (PRE, January-June/2018) and post-alert group (POS, July-December/2018).

Results: 3174 patients developed AKI (8.3% of hospitalizations). The PRE (n= 1613) and POS (n=1561) groups were similar in age, gender, serum creatinine, baseline glomerular filtration rate (GFR) and ICU admission rate. Dialysis was performed in 514 patients (15%) and was not different between groups (PRE 14.9% vs POS 15.1%, NS). At the time of AKI alert, the prevalence of KDIGO I was similar between groups (PRE 73.5% vs POS 75.1%; NS), but a higher number of patients remained at this stage in POS (PRE 51% vs POS 56.1%, P=0.04). The 30-day mortality was 33.6% and was lower in POS (PRE 36.7% vs 30.5%, P=0.001). The independent 30-day mortality risk factors were: age 40 to <65 years (HR 1.37; CI 1.04-1.81, P=0.02); age 65 to <75 years (HR 1.72; CI 1.29-2.3, P<0.001), and the median time to the consultation was lower in the POS (PRE 1.0 day vs POS 0.0 day; P=0.04). The 30-day mortality was 33.6% and was lower in POS (PRE 36.7% vs 30.5%, P<0.001). The independent 30-day mortality risk factors were: age 40 to <65 years (HR 1.37; CI 1.04-1.81, P = 0.02); age 65 to <75 years (HR 1.72; CI 1.29-2.3, P<0.001), age 75 years (HR 2.36; CI 1.77-3.14, P = 0.003), ICU admission (HR 1.24; CI 1.08-1.43, P = 0.003), baseline GFR (each increase of 10 mL/min (HR 0.96; CI 0.94-0.98, P<0.001) and AKI electronic alert (HR 0.87; CI 0.77-0.98, P = 0.02).

Conclusions: An electronic AKI alert and a multidisciplinary BoC reduced progression and 30-day mortality of patients with AKI.

FR-OR018
Incidence and Clinical Outcomes of Outpatient Dialysis for AKI Among Medicare Beneficiaries
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Background: As of January 1, 2017, Medicare Part B covers outpatient (OP) dialysis for acute kidney injury requiring dialysis (AKI-D). We analyzed Medicare claims to describe the incidence and clinical outcomes of beneficiaries initiating OP dialysis for AKI-D in 2017.

Methods: We analyzed the 100% sample of institutional claims in 2014–2017 Medicare Limited Data Sets. To identify initiation of OP dialysis for AKI-D, we located the first OP dialysis facility claim in 2017 with condition code 84 and HCPCS code G0491. We excluded patients with Medicare claims history of OP dialysis for end-stage kidney disease (ESKD), dating to January 1, 2014. We followed patients from initiation of OP dialysis for AKI-D to the earliest of recovery of kidney function (≥ 11.2 years, 71–74), death, or December 31, 2017.

Results: 3174 patients developed AKI (8.3% of hospitalizations). The PRE (n= 1613) and POS (n=1561) groups were similar in age, gender, serum creatinine, baseline glomerular filtration rate (GFR) and ICU admission rate. Dialysis was performed in 514 patients (15%) and was not different between groups (PRE 14.9% vs POS 15.1%; NS). The prevalence of KDIGO I was similar between groups (PRE 73.5% vs POS 75.1%; NS), but a higher number of patients remained at this stage in POS (PRE 51% vs POS 56.1%, P=0.04). Nephrologist was called to 832 patients (26.2%) and the median time to the consultation was lower in the POS (PRE 1.0 day vs POS 0.0 day; P=0.04). The 30-day mortality was 33.6% and was lower in POS (PRE 36.7% vs 30.5%, P<0.001). The independent 30-day mortality risk factors were: age 40 to <65 years (HR 1.37; CI 1.04-1.81, P = 0.02); age 65 to <75 years (HR 1.72; CI 1.29-2.3, P<0.001), age 75 years (HR 2.36; CI 1.77-3.14, P = 0.003), ICU admission (HR 1.24; CI 1.08-1.43, P = 0.003), baseline GFR (each increase of 10 mL/min (HR 0.96; CI 0.94-0.98, P<0.001) and AKI electronic alert (HR 0.87; CI 0.77-0.98, P = 0.02).

Conclusions: Most Medicare beneficiaries who initiate OP dialysis for AKI-D recover kidney function or transition to ESKD within 3 months. Long-term follow-up of those who recover function is needed.
FR-OR020

Development of Machine Learning Models for Predicting AKI Onset Using Electronic Medical Records

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Background: Acute kidney injury (AKI) is a common disease associated with high morbidity and mortality, and the prediction of its onset will help the prevention and appropriate intervention. Recent studies have reported some machine learning models for predicting onset of AKI up to 72 hours in general patient population using electronic medical records (EMR), but studies for predicting in a relatively longer period such as one week have been limited.

Methods: We used the EMR data of adult patients who presented to Kyoto University Hospital, a tertiary teaching hospital in Japan, and received a measurement of renal function between January 2006 and November 2018. Based on the KDIGO guideline, the onset of stage 1 or severer AKI was determined by serum creatinine (sCr) values. Baseline sCr values were calculated by averaging within the windows according to KDIGO’s 48-hour and 7-day AKI definitions. The comprehensive results of blood tests, medications, and vital signs were used as explanatory variables. By using random forest algorithm, seven models were constructed to classify whether or not to develop AKI during day 1 to day 7. The models were constructed and validated by 5-fold cross-validation in the cohort. The performance of the models was evaluated by area under the curve (AUC) of receiver operating characteristic curve.

Results: Of the 154,745 patients included in the analysis, it was determined that 10,460 patients (6.8%) had developed AKI. The amount of data with positive and negative labels was considered sufficient for training and validation of the seven models (positive labels 2,528 ± 275; negative labels 8,571 ± 470 [mean ± standard deviation]). The AUC values were 0.910 ± 0.013, 0.885 ± 0.006, and 0.853 ± 0.012 in predicting onset of AKI after 1 day, 3 days, and 7 days, respectively.

Conclusions: Our models showed high performance equivalent to previous studies with AUC values >0.9 in prediction of onset after 1 day. In addition, the models achieved near perfect performance even after periods of up to 7 days, which are longer in compared to previous studies. In future studies, implementing these predictive models in a clinical decision support system that presents risk scores may lead to appropriate interventions to prevent AKI.

Funding: Commercial Support - FUJITSU Ltd.

FR-OR022

Genetically Augmenting Renal Lymphangiogenesis Protects Against Inflammation Following AKI

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Background: Acute kidney injury (AKI) is a major cause of patient mortality and experimental data suggest AKI as an increased risk factor for progression to chronic kidney disease. The pathology associated with AKI from AKI to CKD may be due to poor lymphatic drainage. Not only the degree of the initial AKI inflammatory response, but also how well it resolves - both in time and in function - are likely factors dictating the potential for future CKD progression. Lymphatic vessels and lymphangiogenesis (LAG) are necessary to maintain homeostasis through fluid macromolecules, and immune cell clearance. Inflammation-associated LAG is necessary for a timely resolution of peripheral inflammation. What roles renal lymphatics play in AKI recovery or CKD progression is largely unknown.

Methods: We have recently characterized transgenic mice that overexpress the potentially lymphangiogenic signal XPG-MAP4D only in the kidney upon doxycycline administration. These conditional “KidVD” mice exhibit marked lymphangiogenesis throughout the kidney. To test if a kidney-specific increase in lymphatic density was protective in AKI, we utilized KidVD mice in the well-characterized surgical bilateral ischemia reperfusion (IR) model. We also crossed KidVD mice to the POD-ATTAC mouse line, a model of inducible podocyte apoptosis and proteinuria.

Results: First, we identified an endogenous upregulation of lymphatic growth factors VEGF-C and VEGF-D with a small degree of inflammation-associated LAG in both models absent genetic LAG induction. Second, when renal LAG was first induced on the KidVD background prior to injury, we found reduced expression of inflammatory cytokines and matrix fibrosis at 7 days post insult in both models. POD-ATTAC x KidVD mice demonstrated reduced interstitial fibrosis and reduced immune cell numbers 28 days following ischemia-reperfusion injury. Importantly, despite improvements in inflammation, serum creatinine and eGFR were not improved in KidVD mice in either AKI model and KidVD mice demonstrated increased sodium excretion.

Conclusions: These data suggest that specifically increasing renal LAG signaling may resolve inflammation and fibrosis, but may concurrently disturb transport homeostasis. Renal lymphatic density in response to AKI may thus be predictive in identifying and targeting inflammatory CKD progression.

FR-OR023

Neutrophil Extracellular Traps Are Triggered by C3 and Contribute to AKI

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Background: Infiltration neutrophils can be stimulated to form neutrophil extracellular trap (NETs), which may lead to renal injury. Complement C3 play a prominent role in inflammatory processes, its activation exacerbates AKI. But the relationship between the formation NETs and activation C3 in IR injury-induced AKI was not clear.

Methods: C57BL/6 mice (WT) were subjected to renal IR injury-induced AKI model by clamping both pedicle for 45 min. To deplete neutrophil, mice were treated with intraperitoneal injection of anti-Ly6G IgG (1A8) or control IgG 24h and 2h before bilateral IR injury. C3KO mice were subjected to renal IR injury. The level of renal neutrophil was evaluated by flow cytometry, and ICAM and RANTES expression in AKI kidney was analyzed by qPCR. NETs formation was defined by the colocalization of diffused DAPI, Ly6G and CitH3 signal by immunofluorescence and protein level of CitH3 by western blot. The expression of C3 in C57BL/6 was estimated by immunofluorescence, qPCR and ELISA. In vitro, neutrophil were challenged with C5, C3 and C3a.

Results: The expression of neutrophil, NETs and C3 of each temporal point after IR increased obviously. At 24h, post-ischemic kidneys represent positivity for DAPI, C5aR1 and Ly6G colocalizing of NETs in the outer medulla. Injection of 1A8 suppressed the increase in BUN and Scr 24h after renal IR injury, with a concomitant reduction of neutrophils infiltration and NETs formation, while there were no significant differences in the expression of C3 in mice with and without neutrophil depletion. Compared with WT-sham group, C3KO can ameliorate the accumulation of neutrophil and protect renal against IR injury. Kidney sections from C3KO mice contained less NETs formation with WT mice, corroborating the CitH3 western blot. In vitro, neutrophils were assessed to be >90% pure. After 4h of incubation, 0.1 μM C3a stimulated the formation of NETS with a dose dependent by amorphous nuclear and DNA structures that colocalized with CitH3 and MPO. PMA altered neutrophil phenotype with decondensed chromatin, while C3a remained intact neutrophil phenotype with lobulated nuclei.

Conclusions: C3 activation can stimulate neutrophil motivation and lead to the formation of NETs in renal IR injury.

FR-OR024

IL-6-Mediated Hepatocyte Production Is the Primary Source of Plasma and Urine Neutrophil Gelatinase-Associated Lipocalin (NGAL) Following AKI

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Background: NGAL (Lcn2) is the most widely studied biomarker of acute kidney injury (AKI); however the ability of NGAL to predict AKI has been mixed, possibly because it is produced by cell types outside of the kidney or in response to other stimuli

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such as systemic inflammation. In the present study, we investigated renal and extra-renal
NGAL production in response to the proinflammatory cytokine IL-6.

Methods: Mice: C57Bl/6J (WT) B6.IL6tm1Kopf/J (IL-6-/-), hematopoietic specific
Lcn2 deficient (Lcn2-/-)c57-littermates. Procedures: sham, kidney ischemia reperfusion
(IR) (27 minutes bilateral renal pedicle clamping); bilateral nephrectomy (Bnx). Injections:
anti-mouse IL-6 (200 ng, IV). In vivo Lcn2 measurement: mice were injected with recombinant IL-6
i.p. or Lcn2 (100 ng, i.p.). IL-6 and Lcn2 assays were performed using a validated EIA
assay.

Results: Plasma Lcn2 was increased in WT 4 and 24 hours after sham, IR, and
Bnx and was decreased in IL-6-/- mice in all three conditions; similarly, urine Lcn2 was
increased after sham and IR in WT and decreased in IL-6-/- mice. Kidney function was
similar between WT and IL-6-/- mice as judged by serum creatinine, BUN, and kidney
histology. While NGAL mRNA was most upregulated in the liver (versus the kidney, lung, and
spleen) 4 and 24 hours after sham, IR, and Bnx, and reduced in IL-6-/- mice. IV injection of
recombinant IL-6 to normal mice resulted in a significant increase in hepatic, but not
renal, NGAL mRNA and an increase in plasma and urine NGAL. In vitro, addition of
recombinant IL-6 to hepatocytes resulted in a significant increase in NGAL levels in the
supernatant. To further examine the specific contribution of hepatocytes to plasma and
urine NGAL levels, mice with hepatocyte specific NGAL deletion (Lcn2-/-) were studied;
plasma and urine NGAL were 90% and 80% reduced, respectively, after IR. Neutrophil
depletion after IR did not affect plasma and urine NGAL levels after sham and IR.

Conclusions: IL-6 mediates hepatic production of NGAL during AKI. The results of these
experiments shed new insights into the mechanism behind the increases in plasma and
urine NGAL after AKI.

Funding: Veterans Affairs Support

FR-OR025 Lung Double Negative (eβ2β−CD4−CD8−) T Cells Respond to AKI and Can Directly Protect from Lung Injury: A Protective Mediator During Kidney-Lung Cross-Talk

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Background: Kidney-lung cross talk during AKI contributes to the high mortality and reveals key interactions between lung and kidney. CD4-CD8- (double-negative; DN) eβ2β T cells have recently been described in kidney and rapidly respond to local ischemia reperfusion injury (IRI) with a protective anti-inflammatory cytokine profile, but the response to remote injury is unknown. We hypothesized that DN T cells serve a potential protective role as an immunologic mediator of kidney-lung crosstalk following remote as well as local injury.

Methods: B6 Wild type (WT) mice were subjected to IRI on either either kidney or lung by a established methods. Lymphocytes from lung was isolated and analysed by flow cytometry. H&E staining was performed with lung tissue to assess lung edema. Immunoblotting with cleaved caspase-3 was evaluated for apoptosis. To test the role for DN T cells in lung IR, adoptive transfer of DN T cells prior to lung IRI was performed.

Results: Our data show that the frequency of lung DN T cell was significantly increased following both lung (39.1%) and kidney IRI (23.5%), p<0.05, compared to sham (10.7%). Immunoblotting of cleaved caspase-3 revealed higher levels of apoptosis at 3 and 6 hours of both renal and lung IRI. Evans blue extravasation demonstrated that adoptive transfer of DN T cells significantly decreased interstitial thickening and lung permeability (39.5 vs. 28. µg p<0.05). Quantitative analysis of cleaved caspase-3 immunoblotting showed that DN T cell transfer attenuated cellular apoptosis (3.2 vs. 0.8, p<0.01). To assess the human relevance of lung DN T cells, human kidney samples were studied during implantation surgery. We showed that DN T cell transfer attenuated cellular apoptosis (3.2 vs. 0.8, p<0.01). In vitro simulated hypoxia increased caspase 2 (1.7-fold) and fn-γ (8.8-fold) mRNA expression in lung T cells from NGAL KO mice compared to T cells from WT mice. NGAL increased significantly (38.8±3.9 % vs. 15.4±5.9 %, p<0.05) in post clamp human T cells compared to pre clamp.

Conclusions: These data show that kidney CD4+ cell Lcn2/NGAL responds rapidly to IRI, directly mediates kidney structural and functional responses to ischemic AKI, and modulates CD4 cell fn-γ. NGAL, traditionally thought to be a candidate biomarker for AKI, is an important molecular regulator of the CD4+ T cell response during ischemic AKI.

Funding: NIDDK Support

FR-OR027 In vivo Assessment of Endothelial PHD Activity in Renal Ischemia-Reperfusion Injury

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Background: A genetic approach to investigate the function of endothelial PHDs in renal ischemia-reperfusion injury (IRI), a model that is widely used in the field of renal fibrosis and models the ischemic kidney. PHDs are known to be crucial in regulating cell cycle progression.

Methods: We generated a doxycycline-inducible, conditional δtg Körtz knockout mouse model (δtg/KO) with δtg specifically deleted from renal tubules at a desired time after ischemic AKI without affecting injurious effect. We also exposed proximal tubular cells to δtg/KO and collected conditioned medium (CM) to treat renal interstitial fibroblasts. Using these models we examined how tubular cell autophagy regulates fibrosis with a focus on tubular paracrine activation of fibroblasts.

Results: Autophagy was activated in proximal tubules during post-ischemic fibrosis in wild type and δtg/KO mice. 44±2% KO blocked tubular autophagy and suppressed fibrosis. Along with autophagy, the expression of several profibrotic cytokines (TGFβ1, FGF2, CTGF and PDGFβ) was increased in WT fibrotic kidneys. Among them, only the expression of FGF2 (both mRNA and protein) was reduced in δtg/KO mice. In WT kidneys FGF2 accumulated predominantly in the basolateral cytoplasm of atrophic tubules, which was suppressed in δtg/KO mice. Containing of FGF2 in autophagy reporter mice further revealed a partial colocalization of FGF2 with LC3 puncta in autophagic tubules. In cultured mouse proximal tubular cells, TGFβ1 induced the production of FGF2, CTGF, FPR1, and PDGFB, and also increased FGF2, CTGF and PDGFB. Defective autophagy by Atg7 knockout reduced both the production and tubular secretion of FGF2, but not CTGF or PDGFB. CM from TGFβ1-treated WT tubular cells induced proliferation and activation of renal fibroblasts and accumulation of ECM proteins, whereas these effects were attenuated in fibroblasts treated with Atg7 KO tubular cell-CM. FGF2 neutralizing antibody recapitulated the inhibitory effects of Atg7 KO tubular cell-CM on renal fibroblasts, further supporting a role for FGF2 in autophagy-dependent tubular paracrine activation of fibroblasts.

Conclusions: Dysregulated autophagy in renal tubules may specifically stimulate tubular paracrine and secretion of FGF2. This autophagy-mediated paracrine then activates interstitial fibroblasts and promotes kidney fibrosis after AKI.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR028 Inactivation of Endothelial HIF Polyhydroxylases Following Ischemic AKI Promotes Kidney Fibrosis

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Background: Key regulators of hypoxic vascular responses are Hypoxia-Inducible-Factors (HIF-1 and -2), transcription factors whose activity is negatively regulated by prolyl-hydroxylase domain proteins 1 to 3 (PHD1 to PHD3). Little is known about endothelial cell (EC) specific functions of PHDs in response to acute kidney injury (AKI), a common problem associated with significant morbidity and mortality. Here, we used a genetic approach to investigate the function of endothelial PHDs in renal ischemia-reperfusion injury (IRI).

Methods: Cdh5(PAC)CreER T2 inducible system was used to induce conditional deletion of PHD1/2,3 in ECs (Cdh5(PAC)CreER T2; Phd1 f/fPhd2 f/fPhd3 f/f referred as Cdh5(PAC)CreER T2 inducible system). Samples were collected at day 14 after IRI.

Results: Secreted VEGF activates HIF1α signaling in proximal tubule epithelial cells, which is known to be a major mediator for kidney fibrosis.

Conclusions: These data support the concept that kidney CD4+ cell Lcn2/NGAL responds rapidly to IRI, directly mediates kidney structural and functional responses to ischemic AKI, and modulates CD4 cell fn-γ. NGAL, traditionally thought to be a candidate biomarker for AKI, is an important molecular regulator of the CD4+ T cell response during ischemic AKI.

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Underline represents presenting author.

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FR-OR029

ATR Deletion Drives TOR-Autophagy Spatial Compartmentalization (TASCC) Formation and Kidney Fibrosis
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Background: Acute kidney injury (AKI) occurs in ~20% of hospitalized patients. While the kidney can functionally recover from AKI, AKI predisposes patients to subsequent chronic kidney disease (CKD), which affects 13% of the global population. Our lab, and others, have shown that AKI-CKD transition involves maladaptive repair leading to G2/M arrest regulated by DNA damage response (DDR) genes. Recently, we have identified target of rapamycin-autophagy spatial compartmentalizations (TASCCs) as components of the secretory response in G2/M arrested cells. To determine how DDR regulates AKI-CKD transition, we tested if the loss of ataxia telangiectasia and Rad3-related (ATR) regulates TASCC formation and fibrosis.

Methods: 1. ATR flox/flox mice were bred to SLC34A1-Cre/ERT2 mice to generate proximal tubule cell (PTC) specific ATR deletion (ATR−/−) upon tamoxifen injection. 2. ATR−/− mice lacking the Cre act as control (ATR^c^). ATR^c^ and ATR^−/−^ received unilateral partial nephrectomy (UNO). Kidneys were taken at day 7 and analyzed for fibrosis, G2/M arrest markers, injury markers and TASCC formation by immunostaining. TASCCs were identified by super-resolution microscopy. 2. Fucci2a mice were bred to γ-Cre-Tg mice to generate PTC specific Fucci2a expression. The PTCs were then isolated and treated with aristocerrobacin A (AA), with or without the ATR inhibitor VE-821. Cells were analyzed for increased connective tissue growth factor (CTGF) by western blot

Results: Inhibition of ATR in PTCs resulted in increased numbers of G2/M arrested cells following AA treatment, as measured by the Fucci cell cycle reporter, and greater in vivo production of CTGF, cells following AA treatment, as measured by the Fucci cell cycle reporter, and greater γ-fibrosis, G2/M arrest markers, injury markers and TASCC formation by immunostaining. ATRRPTC-/- mice had more severe and rapidly progressing fibrosis compared to ATR+/+ mice. Deletion of ATR from PTCs resulted in increased tubular cell injury, caspase 3 staining, and G2/M arrest in response to UNO. G2/M arrest was associated with formation of TASCCs in PTCs. ATR^+/+^ mice had greater numbers of TASCC/cell compared to controls.

Conclusions: ATR deletion sensitized PTCs to injury and G2/M arrest, which drove TASCC formation and production of CTGF as identifying novel targets for therapeutic intervention.

Funding: NIDDK Support

FR-OR030

Long-Acting Thioredoxin Prevents AKI to CKD Transition via Its Anti-Oxidative and Anti-Inflammatory Action
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Background: Renal fibrosis is common finding in CKD and is induced by the sustained oxidative stress and inflammation after AKI. Therefore, an effective strategy is highly desirable for preventing AKI to CKD transition. Thioredoxin-1 (Trx) is a redox-active protein that has anti-oxidative and anti-inflammatory properties. Although, Trx has great potential for usage as a therapeutic agent against several types of oxidative stress-related diseases, its short half-life limits its clinical application. To overcome this problem, we produced a recombinant fusion protein that is comprised of human serum albumin (HSA) and Trx. While the recombinant human serum albumin and Trx (HSA-Trx), and created its preventive effect against AKI to CKD transition.

Methods: Recombinant HSA-Trx was expressed using Pichia expression system. AKI to CKD transition model mice were generated by renal ischemia-reperfusion (IR).

Results: From day 1 to day 14 after renal IR, recovery of renal function and body weight were accelerated by HSA-Trx administration. HSA-Trx ameliorated excessive extracellular matrix (ECM) deposition and the increase in renal mRNA expression of Kim-1 and Sox9, which is injury marker and regeneration marker in renal tubule, respectively. In addition, the increase in oxidative stress, pro-inflammatory cytokine expression, and the number of macrophages in the kidney of PBS-treated mice were suppressed by HSA-Trx. Furthermore, HSA-Trx treatment inhibited G2/M cell cycle arrest and apoptosis in renal tubule cells, which are involved in CKD progression. While renal Trx protein level were significantly decreased by renal IR, HSA-Trx suppressed the decrease in renal Trx protein level, suggesting that HSA-Trx exerts renoprotective effect partially due to preserve renal Trx expression.

Conclusions: HSA-Trx has potential for use in the treatment of AKI to CKD transition via its extended effects of modulating oxidative stress and inflammation.

Funding: Commercial Support - Kissei

FR-OR032

Effects of Long-Term Burosumab, a Fully Human Monoclonal Antibody Against FGFR23, on Phosphorus, Calcium, and Nephrocalcinosis in Adults with X-Linked Hypophosphatemia
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Background: In XHL, nephrocalcinosis and hyperparathyroidism are complications of treatment with oral phosphate and active vitamin D. Burosumab significantly improved serum phosphorus, fracture/pseudofracture healing, stiffness, and physical functioning compared to placebo in a Phase 3, double-blind, multicenter study in adults with XHL (CL3.03, NCT02526160). Here, we evaluate the effects of long-term burosumab on nephrocalcinosis and related measures using data from the completed trial.

Methods: A total of 134 subjects who were randomized 1:1 to receive burosumab 1 mg/kg or placebo subcutaneously every 4 weeks. At Week 24, subjects receiving placebo crossed-over to receive burosumab, and all subjects remained on burosumab up to Week 96, remaining blinded to prior treatment. Groups were combined for the Week 96 analysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Nephrocalcinosis score determined by ultrasound, ranging from 0 (normal) to 4 (stone formation), was assessed by central readers blinded to treatment. Results: 90% (121/134) of subjects had previously received oral phosphate and active vitamin D. At baseline, nephrocalcinosis was present in 54% (73/134) of subjects, with scores of 1, 2, and 3 observed in 41%, 12%, and 1%, respectively. At Week 96, nephrocalcinosis score remained unchanged from baseline in most subjects (89%, 84%), decreased by 1 in 9 subjects (8%), and increased by 1 in 10 subjects (8%). Serum phosphorus levels and TrnP/GFR increased significantly with burosumab. Serum calcium and GFR remained stable, and mean PTH decreased modestly. Urine calcium excretion increased slightly, but nephrocalcinosis scores were not significantly changed.

Visits
Baseline
Week 52
Week 96
Mean P absorption
0.17 (0.09 -0.31)
0.19 (0.13 - 0.38)
0.18 (0.12 -0.32)
Mean uP (μg/day)
77 (57 -107)
98 (69 -138)
78 (55 -110)
Mean TrnP/GFR (mg/g)
1.96 (1.63 -2.34)
2.12 (1.93 -2.39)
1.96 (1.63 -2.34)

Conclusions: In adults with XLH receiving burosumab for 96 weeks, renal phosphate reabsorption and serum phosphorus increased significantly and PTH decreased toward normal levels. Mean urinary calcium excretion increased slightly, but nephrocalcinosis scores were not significantly changed.

In adults with XLH receiving burosumab for 96 weeks, renal phosphate reabsorption and serum phosphorus increased significantly and PTH decreased toward normal levels. Mean urinary calcium excretion increased slightly, but nephrocalcinosis scores were not significantly changed.

EOS789, a Novel Pan-Inhibitor of NaPi-IIb/PiT-1/PiT-2, Decreased Fractional Phosphorus Absorption Is Inappropriately Normal and Does Not Correlate with 24-Hour Urine Phosphorus in Patients with Moderate CKD

Methods: We conducted a two crossover, randomized sequence studies of identical design. The first compared EOS789 50 mg to placebo tid with meals. The second compared EOS789 100 mg vs EOS789 100 mg + 1600 mg sevelamer carbonate tid with meals. Pts undergoing weekly HD, with a serum phosphorus of 0.5 mg/dL after 15-19 days without a phosphate binder were included. Pts consumed a standardized diet containing 900 mg of P per day for 2 weeks. Study drug was given on days 4 to 14 with the diet. On day 10 subjects were admitted to the CRC for 3 days. Pts had pre-diagnosis blood drawn, dialysis treatment, a meal with an oral dose of 10 μCi of 33P and the next day they received 10 μCi of 33P by IV. Serial blood draws were taken over 48h post oral 33P dose, serum was analyzed for 33P activity.

Results: A total of 12 to 14 patients were randomized to each study; 10 completed all assessments. There were no study drug related SAEs. Eight patients had gastrointestinal disorders (2 patients in each study group). For efficacy, percent P absorption was 56% for placebo vs. 51% for EOS 50 mg (p=0.52) and 40% for EOS 100 mg vs. 36% for EOS 100 mg + sevelamer (p=0.45). Within each individual cross over study, these differences did not reach significance. When the 6 pts that completed both studies were analyzed, percent P absorption was 53% for placebo vs. 46% for EOS 100 mg + sevelamer (p=0.13). In addition, 85% for placebo vs. 83% for EOS 100 mg + sevelamer (p=0.08). Furthermore, it was found that P absorption was maintained at inappropriately normal levels in early/moderate CKD patients.

Conclusions: EOS789 100 mg significantly decreased fractional phosphate absorption vs. placebo (by ~70%) and EOS 100 mg + sevelamer (by ~30%) without affecting serum or 24h urine phosphorus. These results support that EOS789 100 mg is a safe and effective treatment option for patients with CKD.

BAC was observed in 34.7% of the patients. Prevalence and extent of BAC increased parallel to the decline of kidney function. In the overall cohort, patients with BAC were older, suffered more from CVD and inflammation, had higher pulse pressure, and borderline higher prevalence of diabetes. The BAC progression rate was significantly higher in patients with CKD5D as compared to Tx patients (2.2 ± 1.2 vs 1.0 ± 0.4 mm/yr, mean ± SE; p=0.02). Progressors were characterized by more inflammation, worse kidney function and higher BAC score at baseline. In the Tx subcohort, progressors moreover showed higher serum phosphate levels at baseline. Presence of BAC associated with poor overall survival (Log-Rank p=0.0007) and cardiovascular event free survival (Log-Rank p=0.007) survival in Tx.

Conclusions: BAC is common among CKD patients, progresses at a slower pace in Tx as compared to CKD5D, and associates with dismal (cardiovascular) outcomes. BAC progression may be linked to calcium oxalate deposition in the media, both of which may contribute to increased cardiovascular risk. Further research is needed to better understand the clinical significance of BAC progression.

Methods: We analyzed serum levels of indoxyl sulphate (IndS) and trimethylamine-N-oxide (TMAO) (as important representatives of colonic microbial metabolism) in ESRD pts. Serum IndS levels were significantly higher in patients with CKD5D as compared to Tx patients (2.2 ± 1.2 vs 1.0 ± 0.4 mm/yr, mean ± SE; p=0.02). Progressors were characterized by more inflammation, worse kidney function and higher BAC score at baseline. In the Tx subcohort, progressors moreover showed higher serum phosphate levels at baseline. Presence of BAC associated with poor overall survival (Log-Rank p=0.0007) and cardiovascular event free survival (Log-Rank p=0.007) survival in Tx.

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higher serum creatinine, higher serum iNBS, TMAO and higher dp-ucMGP levels. In multivariate regression models adjusted for age, gender, phosphate control, serum calcium, calcium containing PB users, dialysis vintage and cohort, sevelamer therapy was identified as an independent determinant of iNBS (odds ratio, [OR] 1.41; 95% confidence interval [CI] 1.14 to 1.77) and dp-ucMGP ([OR] 1.57 [1.34 to 1.85]), but not TMAO ([OR] 1.19 [0.97 to 1.47]). A further adjustment of dp-ucMGP showed that dp-ucMGP was associated with iNBS ([OR] 1.32 [1.19 to 1.46]) and TMAO ([OR] 1.20 [1.08 to 1.33])

Conclusions: Sevelamer therapy associates with poor VitK status and an unfavorable microbial metabolism pattern, characterized by high iNBS levels. Though the design of our study precludes causal inference, present findings point to a disturbed gut microbial metabolism and VitK deficiency as potential trade-offs of sevelamer therapy and should be considered a call for caution.

Funding: Government Support - None-U.S.

FR-OR037

Serum Sclerostin: A Useful Biomarker of CKD-MBD

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Background: Sclerostin is a glycoprotein secreted by osteocytes and antagonizing the bone-forming effects of the Wnt-beta-catenin pathway. Mounting evidence indicates that circulating sclerostin may qualify as a biomarker of CKD-MBD. In this study we report data from a clinical study in which correlations between circulating sclerostin, skeletal sclerostin expression, bone histomorphometric parameters and serum markers of bone metabolism were investigated.

Methods: A transilie bone biopsy was taken and serum samples were collected in a cohort of 68 ESRD patients (19 males) at the time of transplantation. Sclerostin levels were measured using 4 different commercially available assays (BioMedica, Diakonie, TechnoMedz and R&D). Skeletal sclerostin expression was evaluated on immunohistochemically stained tissue sections by counting the % of sclerostin positive osteocytic lacunae. Quantitative bone histomorphometry was performed on Goldner stained undecalcified tissue sections. Different serum markers of bone metabolism were also analyzed using commercially available kits.

Results: 43 ± 13% of the osteocytic lacunae were positive for sclerostin expression. Mean; interquartile range (IQR) serum sclerostin concentrations (pg/ml 4 assays were 211 ± 159 (R&D), 1155 ± 848 (Diakonie), 1687 ± 1501 (TechnoMedz), 3109 ± 2524 (BioMedica). Despite these large inter-assay variation, significant correlations with skeletal sclerostin expression were found in assays under study with the BioMedica assay showing the best correlation: Rs=0.3989, p<0.001. Furthermore, both, skeletal and serum (except for the Diakonie assay) sclerostin levels negatively correlated with static bone histomorphometric calcium parameters reflecting bone metabolism (formation/turnover/mineralization) i.e osteoid width (p=0.05), osteoblast perimeter (p=0.05), bone-specific alkaline phosphatase (p=0.05), N-terminal propeptide of type I collagen (p=0.01), PTH (p=0.01).

Conclusions: In ESRD patients, circulating sclerostin levels significantly correlate with skeletal sclerostin expression and can be regarded as a metabolic bone marker. Further research investigating extra-osseous production (e.g. calcifying vascular smooth muscle cells) of sclerostin is warranted since variation in circulating sclerostin cannot be explained by its variation in skeletal expression only.

Funding: Government Support - None-U.S.

FR-OR038

Impact of Kidney Transplantation on Bone Microarchitecture: A Longitudinal Study

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Background: Patients with chronic kidney disease (CKD) who undergo kidney transplantation experience increased risk of fracture. Bone microarchitecture is a major contributor to overall bone strength. High bone remodeling has been reported to be associated with trabecular bone loss in CKD. The present prospective observational study aimed to investigate the impact of kidney transplantation on cortical and trabecular microarchitecture.

Methods: Bone biopsies were performed in 49 patients (56 yrs, males 69%) at the time of transplantation, with paired samples available in 30 patients 1 year after transplantation. Structural parameters were analysed by histomorphometry (trabecular bone only) and micro-CT including trabecular bone volume, thickness (TbTh), separation (TbSp) and cortical thickness (TbCt) and porosity (CtPp). Cortical region of interest was independently defined in baseline and follow-up scans. Parameters of mineral metabolism (including PTH, sclerostin, FGF23) and bone turnover markers (BTMs, including trimeric OPN) were independently defined in baseline and follow-up scans. Parameters of microarchitecture, calcium containing PB users, dialysis vintage and cohort, sevelamer therapy was associated with iNBS ([OR] 1.32 [1.19 to 1.46]) and TMAO ([OR] 1.20 [1.08 to 1.33])

Conclusions: Sevelamer therapy associates with poor VitK status and an unfavorable microbial metabolism pattern, characterized by high iNBS levels. Though the design of our study precludes causal inference, present findings point to a disturbed gut microbial metabolism and VitK deficiency as potential trade-offs of sevelamer therapy and should be considered a call for caution.

Funding: Government Support - None-U.S.

FR-OR039

Vitamin D Repletion Improves Vascular Function, as Measured by Full-Length Osteopontin, in a High-Risk African American Cohort

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Background: Vitamin D deficiency is common among patients with chronic kidney disease (CKD). African American (AA) suffer disproportionately from CKD and cardiovascular (CV) disease, and 80% of AAs are vitamin D deficient. The effects of vitamin D on vascular and renal health in patients with CKD have been contradictory, in part due to different study designs. Hence, the impact of vitamin D therapy on CV health in CKD patients, especially AAs is unknown. We examined the effect of vitamin D supplement on the cardio-renal biomarkers: full-length osteopontin (BOPN), c-terminal fibroblast growth factor-23 (eFGF23), and plasminogen activator inhibitor-1 (PAI-1), which have been implicated in the pathology of both vascular and renal function in CKD.

Methods: We performed a randomized, placebo-controlled study of high-risk, overweight AAs with controlled hypertension, normal renal function and vitamin D deficiency, treated with 100,000 IU vitamin D3 (N=65) or placebo (N=65) every 4 weeks for 12 weeks. We measured renal function (CKD-EPI eGFR, urinary albumin-to-creatinine ratio (ACR)), and quantified plasma eFGF23, PAI-1 and BOPN by ELISA, vascular function (pulse wave velocity (PWV), augmentation index, waist circumference (WC), and 24-h ambulatory blood pressure (BP)). We performed multiple regression controlling for the placebo-treated group to understand the relationship between the log values of eFGF23, eGFR23, and PAI-1 with cardiovascular and renal risk factors.

Results: Compared to placebo vitamin D3 repletion did not change eGFR and BP values. Vitamin D3 levels increased 2-fold (p<0.0001) and iPTH levels decreased 13% (p=0.007) with repletion, which was associated with a 10% reduction in log-BOPN levels (p=0.04). There were no significant changes in log-eFGF23 or log-PAI-1 with vitamin D3 repletion. Multiple regression analysis indicated that BOPN was associated with reduced PWV (p=0.04) and diastolic BP (p=0.02), while eFGF23 was associated only with reduced diastolic BP (p=0.05) and a trend for increased iPTH (p=0.06).

Conclusions: Vitamin D repletion may improve vascular function in a subset of AAs with controlled hypertension and vitamin D3 deficiency. Compared to eFGF23 and PAI-1, fBOPN may be a more sensitive vascular function biomarker in this population.

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FR-OR040

Phosphate Lowering to Treat Vascular Dysfunction in CKD

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Background: Individuals with CKD exhibit vascular endothelial dysfunction and arterial stiffness, independent predictors of cardiovascular disease (CVD) events. Elevated serum phosphorus, even within the normal range, is associated with CVD and mortality in CKD. In a K/DOQI study demonstrating significant improvements in CVD endpoints in more severe renal impairment, serum phosphorus was significantly increased by 0.4 mg/dL. We hypothesized that lowering serum phosphorus would improve vascular function and endothelial markers of oxidative stress in CKD.

Methods: We randomized 52 participants with CKD 3b-4 and serum phosphorus within normal limits to receive 12 weeks of lanthanum carbonate or placebo. Primary endpoints were change in brachial artery flow-mediated dilation (FMD), and aortic pulse-wave velocity (aPWV). Secondary endpoints were change in FMD and aPWV after ascorbic acid infusion and vascular endothelial cell protein expression of NADPH oxidase and NFκB.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Disruptions to Neurovascular Patterning Affect Kidney Development and Adult Function

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Background: Kidney neurovascular networks are critical to maintaining mammalian physiology and homeostasis. Despite their important roles, we know little about how they form and function in the kidney or how neurovascular interactions affect kidney development. Netrin-1 (Ntn1) is a secreted ligand critical for neurovascular guidance during embryogenesis and is highly expressed by stromal progenitors. Therefore, Ntn1 is an ideal candidate for regulating these processes during kidney development. In turn, the neurovascular network could influence disease factors important for development and maturation of tissues. We set out to identify candidate angiocrine factors released by the kidney endothelium and confirm their role in renal development.

Methods: We conditionally deleted Ntn1 from kidney stromal progenitors. We utilized live-imaging Fluorescent Protein reporter lines to track renin expression and migration. Imaging was performed by 2-photon laser scanning microscopy (2PLSM) and confocal microscopy. We performed immunohistochemistry (IHC) and histology. Utilizing expression data, we identified Insulin-like growth factor 1 (Igf1) as a putative angiocrine factor in the developing kidney. Current efforts focus on conditional deletion of Igf1 to probe its role in the developing kidney vasculature.

Results: Conditional deletion of Ntn1 results in hypoplastic kidneys and aberrant patterning of the neurovascular networks. Nephron progenitor proliferation is reduced and nephrogenesis is extended. Vasculature mis-patterning is present in the adult Ntn1 mutant kidney. These animals have altered EPO and red blood cell production, and abnormal histology. Utilizing expression data, we identified Insulin-like growth factor 1 (Igf1) as a putative angiocrine factor in the developing kidney. Current efforts focus on conditional Igf1 deletion from the kidney vasculature and assessing the effects on development.

Conclusions: Taken together, our studies provide novel insights into the establishment of neurovascular networks in the developing kidney and implications for adult function. Such effort will rely on recent advances in regenerative strategies and efforts to engineer neurovascular networks, where establishing proper kidney filtration and nephron function will be essential.

Funding: Private Foundation Support

FR-OR042

Observation of Renin Lineage Cell Migration Following Local Laser Damage by Longitudinal Intravital Multiphoton Microscopy

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Background: Several studies demonstrate intraglomerular migration of renin lineage cells (RLC) after antibody-induced damage of glomeruli. The aim of our study was to trigger renal injury using specific pathogenic RLC injury without spatially defined, angiotensinogen injury. Using an inducible transgenic RLC reporter mouse strain we were able to track cell migration by intravitral 2-photon microscopy.

Methods: Renin lineage reporter mice expressing tdTomato (RlacZ-rtTA;R26R-rtTA2;LC1-rtTA) were induced for 16 days. 24 hours before initial microscopy, abdominal body windows were implanted to allow repeated kidney imaging without further surgery. Single glomeruli were longitudinally examined six times (d0, d1, d2, d3, d6, d10) by 2-photon laser scanning microscope. Blood plasma was visualized by FITC dextran injection. Spatially defined damage was induced by confocal scanning with a femtosecond pulsed 2-photon laser at high zoom factor, with a second observation 10 minutes after injury. Neighbouring non-damaged glomeruli in the same animal served as controls. Data was 3D analysed with Bitplane Imaris. Glomerular volume, total volume of intraglomerular tdTomato positive cells and maximal migration distance from the juxtaglomerular apparatus to tdTomato positive area were evaluated.

Results: RLC migration into the injured glomeruli could be observed as early as day 3 after damage. The total glomerular volume was reduced by injured glomeruli over time. The percentage of positive cells continued to decrease. Intra-glomerular tdTomato positive cell volume continuously elevated on day 3, day 6 and day 10 (0.4 ±0.07%, 2.4 ±2.2%, 7.3 ±7.8%). Maximal migration distance also progressively increased during observed times (day 3: 7.1 ± 6.7 µm, day 6: 75.1 ± 26.8 µm and day 10: 14.1 ± 10.7 µm).

Conclusions: We were able to evaluate the temporal and spatial migration pattern of RLC into single glomeruli, starting as early as 3 days after injury. Moreover, we quantitatively assessed this process by 3D analysis. This new approach gives us the opportunity to characterize the migratory path of RLC after glomerular injury and evaluate the impact of local signalling due to spatially restricted damage.

Funding: Veterans Affairs Support

FR-OR043

Differentiation of Stromal Cells to Renin Cells During Embryonic Vascular Development

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Background: Kidney arterioles are formed by the assembly of different cell types such as smooth muscle cells, endothelial cells and renin cells. Foxd1 positive stromal cells are precursors of all mural cells of the renal vasculature including the renin producing cells. How the Foxd1 cells convert to renin cells is not known. Therefore, we aimed to understand the cell fate changes during differentiation of renin producing cells from their Foxd1+ stromal cell precursors throughout kidney development using single cell genomic approaches. In the current study we analyzed the transcriptome profile of GFP+ cells FACs sorted from the kidneys of E15.5-Foxd1Cre;B6.TmTmG mouse embryos.

Methods: Single cell capture was performed using the Fluidigm C1 platform and subsequent RNA sequencing was done using Illumina HiSeq4000.

Results: Sequencing analyses with Fluidigm-Singular software revealed that within the Foxd1 lineage cells, cells specific for various mural cell lineage markers clustered separately, indicating the unique molecular repertoire acquired by them during their differentiation from a common precursor population. Approximately 7.5% of the Foxd1 lineage single cells captured from E15.5 kidneys were renin positive. Unsupervised hierarchical clustering was able to identify renin positive cells as a distinct cell cluster separated from the rest of the group. Pathway analyses using the PANTHER classification system indicated differentially expressed genes between renin positive and negative cells detected pathways critical for vascular morphogenesis such as Angiogenesis (DK1, P2r, Rhob, Crk), Wnt signaling (Smarcd1), and Notch signaling (Dkk1) only in renin positive cells. Smarcd1 regulates actin cytoskeleton network and loss of Smarcd1 enhances the migratory potential of the cells. Earlier studies in our lab showed that disruption of Notch pathway in renin cells and Foxd1 precursor cells results in deregulation of genes associated with vascular smooth muscle cells and defective vascular morphogenesis. The non-canonical Notch ligand Delta-like-1 (Dkk1) exhibits an inhibitory role in the regulation of angiogenesis and its precise role in renin producing cells needs to be investigated further.

Conclusions: Our results suggests that Notch and Wnt pathways govern the differentiation of stromal cells to renin cells as they assemble to form the kidney vasculature.

Funding: NIDDK Support

FR-OR044

Tubule Interconnection After Zebrafish Kidney Injury

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Background: Nephrons made during kidney development and newly made during zebrafish kidney regeneration must establish tubule lumen interconnections with the collecting system. The zebrafish adult kidney regenerates after gentamicin injury from an adult progenitor cell population, forming 20-100 new nephrons that subsequently invade and “plumb into” the pre-existing collecting system and restore renal function. Using the zebrafish adult kidney as a model of synchronous nephron-collecting duct fusion, we investigated the role of growth factor signaling pathways in this process.

Methods: Tg(TcfLef-minip-ΔGFP) Wnt reporter expression was used to reveal high Wnt signaling domains in new nephrons. The Wnt inhibitors IWR1 and WP2 were applied to injured adult zebrafish to test requirements for Wnt signaling. Homozygous adult Crispr/Cas9 indel mutants in foxdb and wemb were generated.

Results: We find that new nephron aggregates are patterned by canonical Wnt signaling. High canonical Wnt signaling cells formed a single cell thick dome within cell aggregates and polarized to form rosettes with an apical constricting ring. Using confocal microscopy, we observed that Ngn3 and Foxd1a expression was present at the periphery of the regenerating nephron aggregate. Using the chemical inhibitors IWP2 and IWR1, we were able to inhibit and block Wnt signaling, respectively. Using the chemical inhibitors IWP1 and IWR1, we were able to inhibit and block Wnt signaling, respectively. Using the chemical inhibitors IWP1 and IWR1, we were able to inhibit and block Wnt signaling, respectively.

Conclusions: Wnt signaling is required for tubule invasion and correlates with expression of multiple genes associated with metastatic cell invasiveness. Manipulation of Wnt signaling is an opportunity to engineer kidney tubule interconnections.

Funding: NIDDK Support
Distinct States of Chromatin Accessibility and MicroRNA Expression in Nephron Progenitor Cells During Development

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Background: Mammalian nephrons develop from a multipotent and self-renewing population of nephron progenitors (NPs) during kidney development. All nephrons are formed prior to birth in humans, and the number of nephrons formed is largely dependent on the number of nephron progenitors during kidney development. Low nephron endowment predisposes individuals to chronic kidney disease and hypertension. NPs that exist early in nephrogenesis are known to be transcriptionally distinct from those in later nephrogenesis. We hypothesize that changes in chromatin accessibility and microRNA (miRNA) expression contribute to developmental age-related changes in the NP transcriptome.

Methods: NP cells were isolated from mouse kidneys using magnetic-activated cell separation with positive selection of integrin alpha 8 (Itgα8) at embryonic day 14.5 (E14.5), E16.5 and postnatal day 0. To measure transcriptional activity at regulatory features genome-wide, a proportion of the NP cells were assayed for transposable-accessible chromatin (ATAC-seq). Total RNA from remaining NP cells was sequenced using small-RNA sequencing (smRNA-seq).

Results: A total of 35,172 regions of accessible chromatin were identified based on the irreproducible discovery rate (IDR = 0.1), 1,800 of which underwent a statistically significant change in read depth between age groups (FDR = 0.05). More changes in DNA accessibility are observed between E14.5 and E16.5 than between E16.5 and P0 (1,788 and 12, respectively), and a majority of these early changes (79%) represent a reduction in accessibility over time. Findings corroborate published features including reduced activity at the Lin28b gene promoter during nephrogenesis. 1,243 known miRNAs were detected across all NP samples, of which 170 underwent significant changes in expression between the measured time points (padj ≤ 0.05). These include most members of the let-7 family, which see increased expression coincident with the reduced expression of Lin28b, a published let-7 repressor.

Conclusions: Chromatin accessibility and miRNA expression appear to be distinct in early versus late nephrogenesis.

Funding: NIH/NIHD Support

Generation of Functional Human Kidney Tissues from Metanephric Nephron Progenitors and Ureteric Bud Cells Separately Differentiated from Human iPS Cells

FR-OR047

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Background: Chronic kidney disease (CKD) affects more than 10% of the global population. The lack of effective curative options has led to research on regenerative therapies using stem cells. Accordingly, recent studies using human induced pluripotent stem cells (hiPSCs) have developed protocols to induce kidney-lineage cells and reconstruct kidney organoids. However, no reports have generated human kidney tissues by recapitulating nephrogenesis using metanephric nephron progenitors (NPs) and ureteric bud (UB) cells induced separately from hiPSCs, in which NP-derived glomeruli and renal tubules and UB-derived collecting ducts are interconnected. Furthermore, no in vivo imaging studies have directly demonstrated that hiPSC-derived kidney organoids produce urine.

Methods: We separately and efficiently induced metanephric NPs and UB cells from hiPSCs in the original 2D differentiation culture conditions, co-cultured these two progenitors using bioreactors and performed immunofluorescent analysis using the CUBIC tissue clearing method. In addition, we transplanted mixed aggregates from the two progenitors into immunodeficient mice and examined them using in vivo multiphoton microscopy.

Results: After co-culture of the two progenitors, NPs constructed SIX1(+) active nephrogenic niches close to UB tips and S-shaped body-like structures. They further organized kidney structures that contained glomeruli, proximal and distal tubules, Henle’s loops and collecting ducts in vitro and in vivo. By using two hiPSC lines that constitutively express fluorescent reporter proteins (GFP or mCherry), we demonstrated that the connecting points of GFFI(+) NP-derived distal tubules and mCherry(+) UB-derived collecting ducts showed a marker expression pattern consistent with their counterparts in human embryonic kidneys, indicating that they were functionally interconnected. Furthermore, the intravenous injection of fluorescent-conjugated dextran confirmed that the hiPSC-derived glomeruli were functionally integrated with the host vasculature. Moreover, we observed urine-like dextran accumulation in the hiPSC-derived Bowman’s space in vivo.

Conclusions: Our culture system should contribute to the mechanistic elucidation of human nephrogenesis and the development of regenerative therapies against kidney diseases.

Funding: Government Support - Non-U.S.
FR-OR048
Application of Cellular Extrusion Bioprinting to Improve Kidney Organoid Patterning
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Background: Organoids derived from induced pluripotent stem cells (iPSCs) are now being exploited as a model system for a variety of organs, especially for structurally complex organs such as the kidney. iPSC-derived kidney organoids show great potential for modelling kidney diseases and improving our understanding of disease pathogenesis. However, they do not yet accurately recapitulate the cellular maturity and compartmental organisation of the human kidney in vivo. Changes in culture format may allow for improved patterning by altering biophysical properties, cell-cell interactions and growth factor gradients. Here we report the application of 3D cellular extrusion bioprinting to i) improve quality control and ii) modify organoid morphogenesis and maturation.

Methods: A series of fluorescent reporter iPSC lines designed to report the formation of specific cellular compartments of the kidney, such as podocytes, proximal tubule and distal nephron/ureteric epithelium, were subjected to monolayer differentiation as previously described (Takasato et al, 2016). Generation of organoids was performed using extrusion-based NovoGen Bioprinter® MMX technology (Organovo), with variations in cell density and printing configuration, and compared to manually pelleted organoids. Organoids were analysed via live imaging for fluorescent reporters, confocal immunofluorescence and quantitative image analysis.

Results: Bioprinting facilitated rapid, uniform and highly reproducible organoid production. Organoids were well-patterned and comprised all kidney cell types and compartments previously described using the manual technique. Changes in cell density, organoid shape and thickness also modified nephron number, patterning and the formation of off-target cell types.

Conclusions: Here we demonstrate that biophysical properties of organoids at the time of their generation can have a significant impact on their morphogenesis and differentiation, potentially affecting cellular maturity and differentiation trajectory. Further research into the variables of organoid generation will be fundamental to achieve and maximise future downstream applications.

Funding: NIDDK Support, Commercial Support - Organovo Inc

FR-OR049
Improved Human Pluripotent Stem Cell-Derived Kidney Organoids for Modeling Collecting Duct Biology and Tubular Injury
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Background: Maximizing the potential of human kidney organoids for drug testing, regenerative medicine and to model development and disease requires addressing cell immaturity, the lack of a branching collecting system and off-target cell types.

Methods: We separately induced posterior intermediate mesoderm and anterior intermediate mesoderm from human iPSCs and combined them on day 7. For the next five days, the combined organoids were incubated in a cocktail including FGF9, heparin, GDNF, retinoic acid and EGF. At day 12, we compared organoids left to mature in the next five days, the combined organoids were incubated in a cocktail including FGF9, heparin, GDNF, retinoic acid and EGF.

Results: Compared to organoids differentiated with existing protocols generated in parallel, this new protocol induced a definitive ureteric bud-derived branching nephron/ureteric epithelium, were subjected to monolayer differentiation as previously described (Takasato et al, 2016). Generation of organoids was performed using extrusion-based NovoGen Bioprinter® MMX technology (Organovo), with variations in cell density and printing configuration, and compared to manually pelleted organoids. Organoids were analysed via live imaging for fluorescent reporters, confocal immunofluorescence and quantitative image analysis.

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Conclusions: Here we demonstrate that biophysical properties of organoids at the time of their generation can have a significant impact on their morphogenesis and differentiation, potentially affecting cellular maturity and differentiation trajectory. Further research into the variables of organoid generation will be fundamental to achieve and maximise future downstream applications.

Funding: NIDDK Support

FR-OR050
An Approach for Improving iPSC-Derived Ureteric Epithelial Identity In Vitro
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Background: We previously described a protocol for generating iPSC-derived human kidney organoids containing segmented nephrons, renal interstitium, endothelium and a CDH1+/GATA3+/PAX2+/CALB1+ ureteric epithelium (UE). Recent single-cell analyses of mouse and human fetal kidney have identified expression of many presumed UE marker genes, including GATA3 and Hoxbx7, within the distal nephron and connecting segment. This has raised questions about the true identity of GATA3+ epithelium within kidney organoids. Here we describe the transcriptional profile of GATA3+ epithelium isolated from organoids both prior to and after in vitro culture.

Methods: Kidney organoids were generated from iPSCs harboring an mCherry fluorescent reporter gene within the endogenous GATA3 locus. We used fluorescent activated cell sorting (FACS) to isolate GATA3+/mCherry+ epithelium for subsequent culture in conditions previously shown to promote expansion of mouse UE. Immunofluorescence and RNAseq-based transcriptional profiling was performed to evaluate cell identity pre- and post-culture.

Results: We observed extensive proliferation and branching of FACS-isolated GATA3+/mCherry+ cells cultured in conditions known to promote propagation of mouse UE. GATA3+/mCherry+ expression was maintained even after several rounds of dissociation and re-plating. Additional UE markers (KRT8, PAX2, SOX9, CALB1) were detected by immunofluorescence. Although global RNAseq of GATA3+/mCherry+ epithelium at the time of isolation suggested a cellular identity more akin to distal tubule, cultured GATA3+/mCherry+ cells showed loss of KCNJ1 and induction of WNT11 and RET expression. Single cell transcriptional analysis of cultured cells revealed 3 clusters representative of tip (RET+GFRL1+/ETV4+), stalk (AQP2+) and a putative medullary compartment (UPK1A+). Notably, WNT9B expression was evident at a level consistent with that observed in human fetal kidney.

Conclusions: Our results redefine the identity of the GATA3+/CDH1+ epithelium within kidney organoids to early segment/distal tubule. However, when cultured in appropriate conditions, this can transition to a more recognizable collecting duct fate. The capacity to expand and propagate a branching epithelial compartment with ureteric identity may represent a useful approach for the generation of collecting duct tissue.

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FR-OR051
Association Between Ambient Fine Particulate Matter Air Pollution and Death due to CKD
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Background: Experimental and epidemiologic evidence suggest that ambient fine particulate matter (PM2.5) is a risk factor for chronic kidney disease (CKD). However, studies to date have investigated whether PM2.5 is associated with mortality due to CKD, nor quantified the burden in the US.

Methods: Data from the Environmental Protection Agency, Department of Veterans Affairs, and National Death Index were linked. Non-linear exposure response functions were fitted using an ensemble model and local modeling approach, and CKD death rates associated with PM2.5 exposure were estimated.

Results: A cohort of 4,522,160 US veterans was followed for a median of 10 years. There were 29,016 deaths due to CKD during follow-up. The median PM2.5 exposure at baseline was 11.8 (µg/m³) (IQR: 10.0-13.8). As PM2.5 levels increased, an increase in risk of death due to CKD was observed. In the contiguous US in 2017, it was estimated that 7,175.2 (Uncertainty Interval (UI): 5910.2-8371.9) CKD deaths were associated with PM2.5 exposure, corresponding to an age-standardized rate of 1.9/100,000 people. Geographic heterogeneity in age-standardized rates of CKD deaths associated with PM2.5 was observed (Figure), where states with the highest rates (per 100,000 persons) included Mississippi (3.14), Georgia (2.9), and Indiana (2.9), while states with the lowest rates included Vermont (0.31), Wyoming (0.46), and Washington (0.26). The burden of black or African American race, the age-standardized CKD death rate associated with PM2.5 was estimated to be 2.1 per 100,000 persons, 16.4% higher than the estimate in those not of black or African American race (1.8 per 100,000 persons).

Conclusions: Elevated levels of PM2.5 is associated with increased risk of death due to CKD. The burden is disproportionately borne by those of black or African American race.

Funding: Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Particulate Matter, Albuminuria, and CKD: The ARIC Study
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Background: Exposure to particulate matter less than 2.5 mm in diameter (PM$_{2.5}$) has been linked to detrimental health effects. This study describes the relationship between long-term exposure to PM$_{2.5}$ and estimated glomerular filtration rate (eGFR), albuminuria, and incident chronic kidney disease (CKD).

Methods: The study included 10,856 participants from the Atherosclerosis Risk In Communities cohort followed from 1996 through 2017. Monthly mean PM$_{2.5}$ concentrations (μg/m$^3$) were estimated at participant addresses, then averaged over 12-, 60-, and 120-month periods preceding participant examination. Covariate-adjusted cross-sectional associations of PM$_{2.5}$ with eGFR and log-transformed urinary albumin-creatinine ratio (ACR) were estimated using linear regression. PM$_{2.5}$-incident CKD associations were estimated using Cox proportional hazards regression. Modeling was stratified by ARIC site, and stratum-specific estimates were combined in random-effects meta-analyses.

Results: There was no significant PM$_{2.5}$-eGFR association at any exposure averaging period. PM$_{2.5}$ averaged over the 12- and 60-month periods was associated with higher log(ACR) after adjusting for demographics, socioeconomic status, and clinical covariates. Incident CKD was higher with higher 12-, but not 60- and 120-month mean PM$_{2.5}$ concentrations (Table).

Conclusions: Exposure to higher 12- and 60-month mean PM$_{2.5}$ concentrations was associated with higher albuminuria, and exposure to higher 12-month mean PM$_{2.5}$ concentration was associated with higher risk for incident CKD.

<table>
<thead>
<tr>
<th>Adjustment model</th>
<th>eGFR (mL/min/1.73 m$^2$)</th>
<th>log(ACR)</th>
<th>Incident CKD (HR [CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month</td>
<td>Model 1</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>12-month</td>
<td>Model 2</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>12-month</td>
<td>Model 3</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>12-month</td>
<td>Model 4</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>12-month</td>
<td>Model 5</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>12-month</td>
<td>Model 6</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>12-month</td>
<td>Model 7</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>12-month</td>
<td>Model 8</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
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<tr>
<td>12-month</td>
<td>Model 9</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
<tr>
<td>12-month</td>
<td>Model 10</td>
<td>0.005 (0.003, 0.007)</td>
<td>0.99 (0.90, 1.09)</td>
</tr>
</tbody>
</table>

Model 1: sex, age, race, neighborhood socioeconomic score, family income, and education level.
Model 2: Model 1 + body mass index, diabetes mellitus, hypertension, coronary heart disease, cigarette smoking, eGFR,* urinary ACR,** C-reactive protein, and temperature. Covariate omitted for eGFR outcome (*) and log(ACR) outcome (**).

* signifies P < 0.05. CI, confidence interval; HR, hazard ratio.

FR-OR053
Environment-Wide Association Study on CKD in the National Health and Nutrition Examination Survey (1999-2016)
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Background: Effects of environmental chemicals on the development of CKD are not well-investigated. We aimed to investigate which environmental chemicals are significantly associated with the development of CKD.

Methods: A total of 53,348 adult aged above 18 years old participants, who participated in the NHANES surveys over 18 years, were enrolled. The association between environmental chemicals and CKD was tested and validated using the environmental-wide association study (EWAS) methodology. CKD was defined as three categories (albuminuria, urinary albumin to creatinine ratio above 30 mg/g; glomerular filtration rate (GFR), GFR below 60 ml/min/1.73 m$^2$; and composite of albuminuria and GFR). A total of 299 environmental toxins was included in the analysis. Blood lead, urinary antimony and cobalt, blood 1,2-Dichlorobenzene and nitrobenzene were positively associated with CKD defined by albuminuria. In the contrary, p-hydroxyacetone acid, p-hydroxyacetone sulfonic acid, urinary nitrate and thiocyanate were negatively associated with CKD defined by albuminuria. Blood lead and cadmium showed positive association with CKD defined by GFR. Other 31 significant environmental factors were all negatively associated with CKD defined by GFR. Blood lead, urinary tungsten, and nitrate were 2.4, 4.5-trichloroethanol, mono-0-buty1 phthalate, mono-benzyl phthalate were positively associated with CKD defined both albuminuria and GFR. Urinary mono-benzyl phthalate is associated with increased prevalence of CKD in various categories of albuminuria and GFR.

Conclusions: Urinary mono-benzyl phthalate as well as blood lead are consistently associated with CKD defined by various range of albuminuria, glomerular filtration rate, and composite categories. Increased exposure to lead or mono-benzyl phthalate can be associated with increased prevalence of CKD.
Sickle Cell Trait (SCT) and CKD Progression Among African Americans in the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: Sickle cell trait is associated with a significantly faster eGFR decline compared to normal hemoglobin phenotype among AA patients. A dose-response relationship between sickle hemoglobin and kidney dysfunction may exist. Prospective mechanistic studies are needed to develop best practices to attenuate eGFR decline in AA patients with SCT/SCD. Physicians caring for AA patients need to consider SCT/SCD status and SCT/SCD interactions with comorbidities when evaluating CKD risk.

Methods: We included patients with a baseline estimated glomerular filtration rate (eGFR) ≥ 29 ml/min/1.73 m², at least 3 eGFR values between 2005-2018 and at least 1 year between the first and last eGFR values. Outcomes of interest were the difference in the mean change in eGFR per year (evaluated using linear mixed models) and incident stage 3 CKD (described using Cox proportional hazards).

Results: We identified 10,210 patients (1,251 SCT, 230 SCD and 7,829 reference) with a median follow-up of 8 (IQR 5-11) years and a median of 17 (IQR 10-30) eGFR values. The mean age was 36 (±13) years, 86% were males, and baseline eGFR was 113 (±27) ml/min/1.73 m². Compared to the reference, eGFR declined 0.45 ml/min/1.73 m²/year faster in SCT (p=0.01) and 1.28 ml/min/1.73m²/year faster in SCD (p<0.01). These results were consistent after multivariable adjustment. Compared to the reference, incident stage 3 CKD was higher in SCT (hazard ratio [HR] 1.26; 95% confidence interval (CI), 1.05-1.51), and SCD (HR 2.37; 95% CI, 1.43-3.93) after multivariable adjustment. Males, diabetes mellitus, and a baseline eGFR <90ml/min/1.73 m² were associated with faster eGFR decline in SCT/SCD.

Conclusions: SCT/SCD is associated with a significantly faster eGFR decline compared to normal hemoglobin phenotype among AA patients. A dose-response relationship between sickle hemoglobin and kidney dysfunction may exist. Prospective mechanistic studies are needed to develop best practices to attenuate eGFR decline in AA patients with SCT/SCD. Physicians caring for AA patients need to consider SCT/SCD status and SCT/SCD interactions with comorbidities when evaluating CKD risk.

FR-OR056

Sickle Cell Trait (SCT) and CKD Progression Among African Americans

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Background: Sickle cell trait is present in 8-10% of the general AA population but was enriched among AAs in the CRIC Study suggesting it may confer risk for CKD. However, the study of adverse outcomes with SCT has not previously been evaluated.

Methods: SCT was imputed from genetic data in AA CRIC participants. We excluded those with hemoglobin C trait. Mixed effects models were used to analyze estimated glomerular filtration rate (eGFR) decline. Association of SCT and the CRIC composite renal outcome (end-stage renal disease or halving of eGFR) was assessed by Cox regression. Models were constructed in stepwise fashion and included demographics, African ancestry, clinical site, baseline eGFR, education, income, insurance status, nephropathologist use, ACE-I/ARB use, systolic blood pressure, body mass index, diabetes, hemoglobin A1c, smoking and 24-hour urine protein. Analyses were also stratified by APOL1 risk status.

Results: We included 1,468 participants, of whom 218 (14.9%) had SCT. Median follow up was 8.6 years (Q6, 6.7-9.6). Baseline characteristics including eGFR were similar between the SCT and non-SCT groups (TABLE 1) as was the unadjusted eGFR decline (±1.37 [1.43] v. ±1.44 [1.55], p=0.91). SCT was not associated with the composite renal outcome (HR 1.19 [95% CI 0.99-1.61], p=0.24). Stratified by APOL1, no association was noted between SCT and the outcomes of interest.

Conclusions: SCT is present in 8-10% of the general AA population but was enriched among AAs in the CRIC Study suggesting it may confer risk for developing CKD. In contrast to prior findings in population-based cohorts, SCT was not associated with progression of renal disease when evaluated in individuals with CKD.

FR-OR057

Progressive CKD and Mortality as Predicted by Renal History Among Radical Nephrectomy

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Background: Nephrectomy hypertrophy and nephroclerosis may be important determinants of mortality and kidney failure. However, the study of adverse outcomes with renal history has been limited to select patient populations with small tissue specimens.

Methods: We studied patients who underwent a radical nephrectomy for tumor between 2000 and 2012. Wedge sections distal to the tumor were stained and scanned into high resolution images. The areas of cortex and glomeruli (sclerotic and non-sclerotic) were annotated to calculate glomerular volume and percentage globally sclerotic glomeruli (%GSG). The percentage luminal stenosis (arteriosclerosis) and interstitial fibrosis/tubular atrophy (IFTA) of the cortex were morphometrically measured. Patients were followed with annual visits or phone calls for non-cancer death or kidney failure, censoring at cancer death. Progressive chronic kidney disease (CKD) was defined as dialysis, kidney transplant, or a 40% decline in estimated glomerular filtration rate (eGFR) from the post-nephrectomy baseline. Models adjusted for age, sex, BMI, hypertension, diabetes, smoking, and eGFR.

Results: There were 712 patients (mean age 63y, 64% male, 64% hypertension, 14% diabetic, and mean postoperative eGFR 48 ml/min/1.73 m²) with a mean follow-up of 8.0±4.2 years, 77 progressive CKD events, 170 non-cancer deaths, and 104 cancer deaths. Larger non-sclerotic glomerular volume predicted progressive CKD, but this was no longer evident after adjustment for proteinuria. Higher %GSG and more severe arteriosclerosis predicted progressive CKD, which persisted with adjustment for proteinuria. Higher %IFTA predicted non-cancer morality, and this persisted with adjustment for proteinuria. No kidney structural finding predicted cancer mortality.

Conclusions: Linp nephron size predicts kidney failure along the same pathway as proteinuria. Subclinical glomerulosclerosis and arteriosclerosis predict kidney failure, whereas subclinical IFTA predict non-cancer mortality.

FR-OR058

Effects of Different Serum Bicarbonate Levels on Muscle Mass and Renal Function Among CKD Patients with Metabolic Acidosis: A Randomized Controlled Trial

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Background: Treatment of metabolic acidosis to target high serum bicarbonate level was found to mitigate muscle wasting in end-stage renal disease patients. No data exists to test the effects of increased bicarbonate level on muscle parameters and renal function in pre-dialysis CKD patients.

Methods: This was a randomized, controlled study. CKD stage 3-4 patients with serum HCO3 <22 mmol/L were randomized to either receive oral sodium bicarbonate with target bicarbonate level of 25±1 or standard level of 22±1 mEq/L as control group using the protocol-based titration of dosage adjustment. The change of muscle mass measured by bioelectrical impedance analysis (BIA), muscle strength by hand grip dynamometer, and eGFR using CKD-EPI equation, nutritional markers, and muscle-related biomarkers were determined. Baseline data including after 6 months of sodium bicarbonate supplementation were compared between groups using t-test or Chi-square test as appropriate.

Results: Forty-two patients completed the study (n=21 per group). The mean age and eGFR were 61±9 years and 32±4 mEq/L mln/min, respectively. Baseline data including age, sex, diabetes, serum bicarbonate level, muscle mass, and blood pressure were similar. After 6 months of treatment, the average serum bicarbonate levels in both groups were 24.8 and 21.2 mEq/L. Both BHA-derived total-body muscle mass and appendicular lean body mass were significantly increased at 6 months in the higher bicarbonate group (26±5.4 to 26.7±5.7 kg, p=0.04 and 19.8±4.1 to 20.6±4.5 kg, p=0.03, respectively) despite comparable energy and protein intake. The higher bicarbonate group also had 36% lower serum myostatin, a surrogate for muscle degradation, but unaltered insulin-like growth factor-1 level as the mediator of muscle cell growth (133±40.6 vs. 121±52.7 ng/mL, p=0.3) compared to the control group. Muscle strength, eGFR as well as serum albumin were not significantly different between two groups (p=0.05). Neither worsening hypertension nor heart failure was found throughout the study.

Conclusions: Bicarbonate supplementation to achieve the serum level ~25 mEq/L demonstrates better muscle mass preservation in patients with pre-dialysis CKD. The impact of alkaline therapy on renal function may require longer period of study.

Funding: Government Support - Non-U.S.
Impaired Sleep Quality Is Associated with Incident Albuminuria in Hispanics/Latinos: Findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

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1University of Illinois at Chicago, Chicago, IL; 2Northwestern University, Chicago, IL; 3Joslin Diabetes Center, Boston, MA; 4San Diego State University, Chula Vista, CA; 5Kaiser Permanente Northern California, Oakland, CA; 6University of North Carolina at Chapel Hill, Chapel Hill, NC; 7University of Pittsburgh, Pittsburgh, PA; 8Medicine, University of Illinois at Chicago, Chicago, IL.

Background: Emerging evidence suggests that short duration and poor quality sleep may be associated with progression of chronic kidney disease (CKD). Little is known about the relationship of sleep duration/quality with incident albuminuria.

Methods: Analyses included data from 1662 U.S. Hispanic/Latino adults aged 18-64 years enrolled in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). Sueno Sleep Ancillary Study, who completed 7 days of wrist actigraphy (2011-2013) and a follow-up visit (2014-2017), and did not have CKD (estimated glomerular filtration rate ≥60 ml/min/1.73m² and urine albumin-to-creatinine ratio [ACR] <30 mg/g) at baseline. Incident albuminuria was defined as ACR ≥30 mg/g. Validated computer software algorithms were used to assess sleep duration and sleep fragmentation (calculated by summing the percentage of the sleep period that is spent moving and the percentage of the number of immobile phases that last ≥1 minute or less). Poisson regression with follow-up years as an offset was used accounting for HCHS/SOL complex sampling design.

Results: At baseline, mean age was 37.5 years and 51.9% were females. In 5.7 years mean follow-up, 671 individuals developed incident albuminuria. Higher sleep fragmentation was associated with higher incident rate of albuminuria after adjusting for center, age, sex, education, diabetes, systolic blood pressure, body mass index, cardiovascular disease, depression, eGFR, and ACR (Table). Sleep duration was not associated with incident albuminuria.

Conclusions: Among US Hispanic/Latinos, fragmented sleep was associated with new-onset albuminuria. These findings could have implications for preventive strategies for populations which experience a high burden of CKD.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute

A Novel Therapeutic Strategy for Autosomal Dominant Tubulointerstitial Kidney Disease

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Background: MUC1 kidney disease (MUC1-fs) is an autosomal dominant tubulointerstitial kidney disease caused by a frame-shift mutation in the MUC1 gene (MUC1-fs). The disease is characterized by slowly progressive tubulo-interstitial damage that leads to end-stage renal disease. No treatment is currently available. Affected individuals require dialysis or kidney transplantation in the third to seventh decade of life. The main goal of this study was to investigate the cellular and molecular mechanisms by which MUC1-fs causes alteration in epithelial cell function, and to develop a mechanism-based therapy for this disease.

Methods: To investigate the biological mechanism responsible for MUC1-fs, three different model systems were developed: a patient-derived cell line, a knock-in mouse model and patient iPSC-derived kidney organoids. In order to identify a possible treatment for MUC1-fs, a high throughput screen (HTS) of compounds was performed to identify small molecules that would be able to clear mutant MUC1-fs protein from kidney epithelial cells.

Results: Immunofluorescence studies indicated that while MUC1-wt was located at the cell surface, the mutant protein MUC1-fs was mislocalized to the cytoplasm, where it induced ER stress by activation of the unfolded protein response (UPR). The UPR identified BRD, a small molecule that cleared MUC1-fs not only from patient cells, but also from kidneys of knock-in mice and from patient kidney organoids. Importantly, BRD showed no overt toxicity at any concentration tested, and in fact, it rescued cells from ER stress-induced cell death.

Conclusions: These results indicate that intracellular accumulation of MUC1-fs induces ER stress-related cell toxicity, a pathologic mechanism likely responsible for the progressive renal damage associated with the MUC1 mutation. Our findings reveal BRD as a promising lead for the treatment of MUC1-fs.

Funding: Private Foundation Support

Effect of Medicaid Expansion on the Incidence of ESRD Among Nonelderly Adults

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Background: End stage renal disease (ESRD) can be prevented or delayed with effective management of chronic disease, particularly diabetes and hypertension. However, the universal health care system to finance health services and may forego preventive and chronic care. We examined the impact of Medicaid expansion on the incidence of ESRD in the non-elderly adult population.

Methods: A quasi-experimental differences-in-differences study of the incidence rate of ESRD in the non-elderly adult population in the US (annual average of 149,793,035 persons aged 19-64 years). We calculated quarterly incidence rates by geocoding incident patients (347,288 persons over the study period) within Public Use Microdata Areas (PUMAs), which are contiguous geographic areas of at least 100,000 persons nested within states. We estimated linear models comparing pre- vs post-expansion changes in the incidence rate in PUMAs in expansion vs non-expansion states. Models were adjusted for age group, sex, race/ethnicity, time-varying PUMA-level economic characteristics with fixed effects for year-quarter, season, and PUMA. We confirmed parallel pre-policy trends between expansion and non-expansion PUMAs.

Results: The mean quarterly ESRD incidence rate for the 19-64 population in 2012 and 2013 was 67.8 cases per million in expansion states and 78.5 cases per million in non-expansion states. While incidence increased in both expansion and non-expansion states over the study period, Medicaid expansion was associated with 1.7 fewer incident ESRD cases per million (95% CI: -3.28 to -0.17), relative to concurrent trends in non-expansion states. This observed effect represents a 2.5% relative reduction in incidence.

Conclusions: The ACA’s Medicaid expansions were associated with a small but meaningful reduction in incidence of ESRD in the non-elderly adult population. The findings also demonstrate the potential for expansions of Medicaid coverage to generate offsetting reductions in spending in the Medicare program, the primary payer for the ESRD population in the US.

Funding: NIDDK Support

High Prevalence of C-Terminal CUBN Variants Associated with Chronic Proteinuria and Normal Renal Function in Humans

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Background: Proteinuria is considered as an unfavorable clinical condition that accelerates renal and cardiovascular disease. However, it is not clear if all forms of proteinuria are damaging. Mutations in CUBN cause Inversus-Gräsbeck syndrome (IGS) featured by intestinal malabsorption of vitamin B12 and in some cases proteinuria. CUBN encodes for cubilin, an intestinal and proximal tubular uptake receptor containing 27 CUB domains and CUB domain.

Methods: We used next-generation sequencing for renal disease genes to genotype cohorts of patients with suspected hereditary renal disease and chronic proteinuria. CUBN variants were analyzed using bioinformatics, structural modeling and epidemiological methods.

Results: We identified 39 patients, in whom biallelic pathogenic variants in the CUBN gene are associated with chronic isolated proteinuria with childhood onset. Since the proteinuria displayed a high proportion of albuminuria, glomerular diseases such as steroid-resistance glomerulonephritis or Alport syndrome were often the primary clinical diagnosis, motivating renal biopsies and proteinuria-lowering treatments. Yet, renal function was normal in all cases. By contrast, we did not find any biallelic pathogenic CUBN variants in patients with reduced renal function or focal segmental glomerulosclerosis. Unlike the rare non-tertiary IGS mutations, 37 out of the 41 proteinuria-associated CUBN variants led to modifications or truncations after the vitamin B12-binding domain. By structural modeling, we further demonstrate that all these C-terminal variants affect stability or ligand binding of CUB domains. Finally, we show that four C-terminal CUBN variants are associated with albuminuria and significantly higher eGFR in meta-analyses of large pan-European-based cohorts.

Conclusions: Collectively, our data suggest an important role for the C-terminal half of cubilin in renal protein reabsorption. Defective reabsorption could be an unexpectedly common benign condition that does not require any treatment and may even have renoprotective effects. Therefore, cubilin can be defined as a safe drug target in human renal disease.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
FR-OR063

Phenome-Wide Association Study (PheWAS) of Common Genetic Variants for UMOD in the Million Veteran Program (MVP) Participants

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Background: Uromodulin (UMOD) is synthesized exclusively in the kidney and is the most abundant protein in ordinary urine. Common variants for UMOD have been considered an adaptation to protect against urinary tract infections (UTIs). Several GWAS studies of estimated glomerular filtration rate (eGFR) have shown SNPs in UMOD top hits; these variants have also been associated with chronic kidney disease (CKD) progression, ESRD and blood pressure, highlighting shared genetic pathways between these traits. In clinical settings, serum UMOD is increasingly considered a more sensitive indicator of functional kidney mass than filtration markers like eGFR, and has been associated prospectively with cardiovascular outcomes and mortality. Hypertension, vascular calcification and arterial stiffness are hypothesized mechanisms.

Methods: We tested common variants in UMOD and their association with clinically diagnosed phenotypes in a phenome-wide association study (PheWAS) in 188,008 White European Americans from the MVP. Using logistic regression adjusted for sex and 10 principal components, we regressed 1813 phenotypes against our 13 SNPs in models adjusted (and not adjusted) for eGFR.

Results: Eight of the common variants had significant associations for CKD (Table 1), renal failure, hypertensive heart or kidney disease and urinary calculus, and two with UTIs. Other significant associations were with premensural syndrome. In the eGFR-adjusted models, the strongest associations were with urinary calculus and disease groupings related to congestive heart failure, including non-hypertensive congestive heart failure.

Conclusions: This PheWAS confirms that UMOD variants are associated with CKD and other observed associations included kidney stones and UTIs. Mendelian Randomization studies of haplotypes for UMOD variants are underway to further elucidate the role of UMOD in vascular health.

Funding: Veterans Affairs Support

FR-OR064

De Novo Truncating TRIM8 Mutations Cause a Novel Pediatric Neuro-Renal Syndrome and Abrogate Protein Localization to Nuclear Bodies

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Background: Homozygous variants in NOS1AP from a patient with Steroid-Resistant Nephrotic Syndrome Cause Podocyte Polarity Dysregulation and Aberrant Glomerulogenesis in Human iPSC Kidney Organoids

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Background: Kidney organoids generated from human induced pluripotent stem cells (hiPSC) represent an emerging disease modelling platform for the study of genetic kidney diseases. Genomic sequencing is increasing the rate of novel disease gene discovery, and over 60 genes have been identified to cause steroid resistant nephritic syndrome (SRNS). NOS1-arginine nitric oxide synthase 1/adapter protein (NOS1AP) is a novel gene for SRNS, whose encoded protein regulates actin cytoskeleton remodelling by promoting CDC42 activation. CDC42 regulates PAR3-PAR6-aPKC complex maintenance of apico basal polarity. This PAR complex colocalises with the slit diaphragm in podocytes and both CDC42 and aPKC deficiency in mice causes severe proteinuria. Here, we characterise the effect of a homozygous NOS1AP SRNS patient variant on glomerulogenesis in hiPSC kidney organoids.

Methods: A homozygous, patient-derived NOS1AP variant (c.428G→A) was gene-edited into the wild type hiPSC line (C57B/6). NOS1AP homoygous and wild-type (WT) hiPSC clones were differentiated to kidney organoids in paired experiments. Organoids were examined by blinded and semi-automated analysis of histology, immunofluorescence and electron microscopy imaging.

Results: In 3D histology sections of WT organoids demonstrated tufts of podocyte monolayers lining an established basement membrane. In contrast, NOS1AP homozygous organoids showed disorganised podocyte collections with poorly established basement membranes and pyknotic nuclear figures which were CASP-3 positive. Foot process effacement was less evident on electron microscopy of NOS1AP homozygous organoids. Whole mount immunofluorescence showed disorganisation of slit diaphragm markers and reduced aPKC expression in NOS1AP homozygous glomeruli suggesting dysregulation of the PAR complex.

Conclusions: A novel, SRNS patient-derived, homozygous variant in NOS1AP causes abnormal glomerulogenesis in kidney organoids and highlights the utility of this 3D, human, in vitro, functional genomic model. We propose that pathogenic variants in NOS1AP reduce active CDC42 which impairs polarity complex expression and foot process formation in hiPSC kidney organoid glomeruli.

Funding: Government Support - Non-U.S.

FR-OR065

Exon Skipping Therapy for COL4A5 Gene Truncating Variant Rescued Progression of Kidney Failure in X-Linked Alport Syndrome

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Background: X-linked Alport syndrome (XLAS) is a hereditary disease caused by mutations of COL4A5 gene. Affected male patients generally develop end-stage renal disease in early or middle age and patients with truncating variants show severe phenotype than those with non-truncating variants. In recent years, exon skipping (ES) therapy, which induces truncating variants into non-truncating variants, has been applied clinically in muscular dystrophy, etc. Here we applied the ES therapy for XLAS mouse model.

Results: With clinical parameters, urinary albumin creatinine ratio was remarkably reduced in ASO-treated group (p<0.05) compared to saline-treated group (n=6). At 21 weeks of age, serum BUN and creatinine levels were remarkably low in ASO treated group compared to vehicle treated group. With pathological evaluation by electron microscope, although even ASO-treated mouse showed thin basement membrane, they did not
show severe thickening with lamellation of GBM as shown in saline-treated group. With immunofluorescence, αS(V) was completely negative in vehicle group, but it expressed clearly on tubular basement membrane and even on GBM although expression is not linear but partially on GBM. No clear side effect was recognized in the ASO-treated group.

Conclusions: This study identifies multiple rare CNV disorders and common variants which impart large effects on the risk of VUR and implicate multiple canonical developmental pathways in the pathogenesis of disease.

Funding: NIDDK Support

FR-OR069

Next-Generation Sequence Analysis of Genetically Unsolved Primary Hyperoxaluria (PH) or Dent-Diagnosed Patients Resolved 10% of Cases with 11 Genes Implicated

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Background: Due to phenotypic overlap between patients with monogenic stone diseases, gene specific analysis of patient groups can result in under diagnosis. Here we employed a targeted next generation sequencing (NGS) approach to analyze primary hyperoxaluria (PH) or Dent diagnosed patients that were genetically unresolved after analysis of the respective known genes by Sanger analysis.

Methods: A cohort of genetically unresolved patients with a presumptive diagnosis of PH (PIN, n=236) and Dent disease (DN, n=61) were screened employing a 90 gene panel that included known monogenic causes of stone disease and candidates. Variants were assessed considering American College of Medical Genetics and Genomics guidelines. Their presence was determined in disease-specific databases, Human Gene Mutation Database (HGMD) and ClinVar, and the frequency in normal populations, GnomAD, plus using variant assessment tools and by analysis of multisequence alignments. Sanger sequencing was used to confirm changes and test segregation.

Results: Next-Generation Sequence Analysis of Genetically Unsolved Primary Hyperoxaluria (PH) or Dent-Diagnosed Patients Resolved 10% of Cases with 11 Genes Implicated

Conclusions: The phenotype of monogenic stone diseases overlaps greatly. Given the emerging therapies for these disorders, including siRNA approaches for PH, making the correct diagnosis is crucial for enrollment in clinical trials and selecting the correct therapy. It is also essential to identify cohorts of patients with poorly recognized disorders, in order to better understand the natural history, and assemble cohorts for future trials.

Funding: NIDDK Support
FR-OR070

Nationale DIAGNOSTIC Yield of Clinical Genomics in Patients with Suspected Genetic Disease

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Background: With increasing understanding of genetic disease (GKD), genomics testing is being translated from research to clinical. Rigorous evaluation of clinical practice and patient outcomes is required to guide value-based healthcare. We aimed to describe diagnostic outcomes of clinically accredited genetic testing delivered by nationwide multidisciplinary team (MDT) clinics for patients with suspected GKD.

Methods: Sequential incident patients undergoing clinically indicated genomics testing for presumed GKD from 18 Australian MDT clinics 2016-2019 were analysed (HREC/16/MH/251). A molecular diagnosis constituted clinical reporting of pathogenic and/or likely pathogenic variant/s in genes associated with the patient’s kidney phenotype with concordant inheritance. All genomics testing included restriction of variant analysis to a phenotypic-derived gene list. Full author list online at KidGen.org.au

Results: Of 824 patients, 52.1% were female. Median age was 26 years. A molecular diagnosis was made in 45.7%. A further 15.4% had a variant/s of uncertain significance (VUS), of which 23.6% were clinically compelling but require further functional validation or additional segregation. The diagnostic yield for whole genome (WGS) was 92.4%, whole exome (WES was 92.3%, 40.7%) and clinical exome (CES) was 92.3% (p=0.91). Median age at test request for WGS (42yrs) was significantly older than for WES (27yrs) and CES (18yrs). Of all patients with a genetic finding, 53.6% involved variation in 7 genes (COL4A3, COL4A4, COL4A5, PKD1, PKD2, PKD1, HNF1B). Stratifying by age at test request, the diagnostic rate was not significantly different between 0-15yrs (41.8%), 16-25yrs (48.5%) and 26yrs (44.2%) (p=0.2). Median age at test request for female and male gender were significantly different among female (45.8% ±53.5% vs. p=0.007).

Conclusions: Clinical genomics delivered by MDT clinics are diagnostically effective for suspected GKD. Neither sequencing approach nor age group at test request appear to impact diagnostic yield. MDT genetic testing in this cohort were older and gender mixed with increasing patient age group. Clinical genetic studies are required to clarify impact of these diagnostic outcomes.

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FR-OR071

CirCADIAN BP Rhythm as a Possible Key Target of SGLT2 Inhibitors for Albuminuria in Japanese T2DM Patients (Y-AIDA) Study

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Background: In treating T2DM, it is important to appropriately manage glucose and lipid metabolism, body weight and BP to suppress the development and progression of diabetic complications to restore the quality of life to a level comparable with healthy subjects. Y-AIDA (Yokohama Aged Diabetes and Aging) study was designed to investigate the renal and home BP modulating effects of add-on dapagliflozin treatment in Japanese T2DM individuals with albuminuria.

Methods: This study was a prospective, multicenter, single-arm study. A total of 86 patients with T2DM (HbA1c 7.0-10.0%) and albuminuria (UACR ≥ 30 mg/gCr) were enrolled. Add-on participants were administered with add-on dapagliflozin for 24 weeks. The primary and key secondary endpoints were change from baseline in the natural logarithm of UACR over 24 weeks and change in home BP profile at week 24. This study was registered at UMIN Clinical Trials Registry (UMIN00018930; http://www.umin.ac.jp ctr/index-j. html). All participants provided written informed consent prior to initiation of the study. (UMIN000018930. Informed Consent was written in Japanese) (UMIN000018930). Baseline morning, evening and nocturnal home systolic/diastolic BP were 137.6±8.7 mmHg, 136.1±7.9 mmHg, and 125.4±7.1 mmHg, respectively. After 24 weeks, the logarithm of UACR decreased by 0.37±1.75 (P<0.001). In addition, changes in morning, evening and nocturnal home BP from baseline were morning systolic/diastolic BP: -3.8±2.2/ -4.18±5.91 mmHg (both P<0.001), evening systolic/diastolic BP: -9.5±7.3/0.8±4.8/ -8.4±4.35 mmHg (both P<0.001) and nocturnal systolic/diastolic BP: -2.38±7.2/-1.17±5.39 mmHg (P=0.0079 for systolic BP, P=0.0415 for diastolic BP). Furthermore, the reduction in UACR after 24 weeks significantly correlated with the improvement of home BP profile, but not with changes in other variables including office BP.

Conclusions: In Japanese T2DM individuals with albuminuric DKD, dapagliflozin not only lowered albuminuria but also improved home BP profile, suggesting that circadian rhythm abnormalities may be an important cause of out-of-office home BP monitoring as a possible key target of SGLT2 inhibitors for DKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUBL - Publication Only

Underrepresented learners presently author.
Results: In WT mice, this protocol increased systolic pressure from a baseline of 12±2 to 18±8 mmHg (p<0.05), and renal CDA- and CD8+ effector memory T cells by 2 to 3 fold. This was associated with marked increases in superoxide production in the kidney and a striking accumulation of isoL-G protein adducts in splenic DCs. The increase in blood pressure, renal T cell infiltration, renal superoxide production and DC isoL-G formation were completely prevented in EP3- mice. Interestingly, we found that EP3 receptor, among all EP receptors, is highly expressed in the organ vasculature laminae terminalis (OVLT) in the brain, LNHS treatment induced an upregulation of COX-2 expression and downregulation of EP3 receptor in the OVLT. To test the hypothesis that central EP3 receptor contributes to the LNHS induced hypertension and renal inflammation, WT mice received intracerebroventricular injection of lentiviral vectors encoding shRNA targeting EP3 receptor and then subjected to the same LNHS treatment. These mice were also protected from salt induced hypertension and renal inflammation like the EP3- mice.

Conclusions: These findings provide new insight involving EP3 receptor in the central nervous system and sympathetic activation in salt induced hypertension and provide additional information as to how PGE, modulates inflammation in this conditions.

Funding: Other NIH Support - NHLBI, Private Foundation Support

FR-OR075

Mutation of the Furin Cleavage Site in the (Pro)Renin Receptor Attenuates Angiotensin II-Induced Hypertension and Albuminuria

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Background: Cleavage of the extra-cellular domain of the (pro)renin receptor (PRR) yields a soluble fragment (sPRR) which can promote angiotensin-II (Ang-II) formation. Although alterations in plasma sPRR levels have been reported in hypertension, the causal role of sPRR in hypertension is unknown.

Methods: To investigate this, we mutated the furin cleavage site of the (pro)renin receptor using CRISPR/Cas9. Because the gene encoding PRR is on the X-chromosome, male mutant mice are infertile, only male mice were studied.

Results: Mutant mice had markedly lower plasma sPRR levels (control: 16.2 ± 0.3 vs mutant 0.2 ± 0.03 ng/ml). Mutant mice had normal survival and development and no histological renal abnormalities up to 12 months of age. During normal salt intake, no differences in blood pressure, body weight, urinary water or Na+ excretion, or acid-base status were observed between control and mutant mice. Compared to controls, mutant mice had an attenuated hypertensive response to 2 weeks of Angiotensin-II infusion (400 ng/kg/ min) (Fig. 1). Mutant mice also had lower albuminuria (control: 327 ± 144 vs mutant: 58 ± 8 ng/day) at day 7 post Ang-II infusion. No differences in urinary Na+ excretion were detected between control and mutant mice after 7 days of Ang-II infusion (control: 33.6 ± 3.1 vs mutant: 35 ± 2.7 umol/day gram body weight). Mesentric arteries isolated and studied ex vivo using isometric tension procedures showed an attenuated vascular response to Ang-II (10^-5 M) compared to controls (internal diameter control: 115 ± 7 μm vs mutant 125 ± 8 μm).

Conclusions: These results suggest that sPRR plays a role in Ang-II induced hypertension and renal injury.

FR-OR076

Connexin40 (Cx40) Knockout Rat Has Impaired Renal Autoregulation

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Background: Renal autoregulation is mediated by the generic myogenic response (MR), modulated by the kidney-specific tubuloglomerular feedback (TGF). Recent studies have indicated that TGF acts on a larger scale than individual nephrons and that the well-known synchronization of TGF dynamics operates on macroscopic scales, communicating electrically along the vasculature via gap junction intercellular communication.

Methods: A Wistar Kyoto (WKY) rat lacking Cx40 was made at the Genome Editing Rat Resource Center (https://ged.mcw.edu/wg/gerrc/). Heterozygous parents produce wild type (WT), heterozygous (HET), and knockout (KO) offspring in Mendelian ratios. In anesthetized rats, surface perfusion of renal cortex in all genotypes was studied by laser speckle contrast imaging (LSCI) in an area 2.75x2.75 mm. ROIs captured blood flow and renal blood flow; changes in spot diameter and number were measured as a function of insulin concentration (IC) between all possible ROI pairs (Scully et al. IEEEETBME 2014; 1989-97). Blood pressure (BP) and renal blood flow (RBF) were monitored. Data were reported as meansSEM. Significance testing was not done because N is not yet sufficient for it to be meaningful.

Results: In WT and HET rats ICBP = 3 µg/rat had a BP response (WT: 100±2 mmHg, 6.57±0.56 mL/min; HET: 98±4 mmHg, 6.12±1.84 mL/min) while in KO rats (N = 3) BP appeared higher and RBF lower (123±6 mmHg, 4.52±0.86 mL/min). There was a pronounced gender dose effect on TGF synchronization. In N=6 WT rats 96±10% of possible connections were significantly PC and of those 37±4% had PC > 0.6 which is considered to be significant for autoregulation. In N=6 HET rats 95±4% of possible connections were significant and of those 18±10% had PC > 0.6. In N=5 KO rats 62±16% were significant and 5±2% had PC > 0.6. Renal autoregulation was assessed by transfer functions was visibly impaired.

Conclusions: We report a new knockout rat on the normotensive Wistar Kyoto background that lacks Cx40. Wildtype, heterozygote, and Knock-out are bred in Mendelian ratio. As expected from the Cx40 knockout mouse, KO rats appear to be hypertensive, probably due to dis-regulated renin secretion. TGF synchronization is, and autoregulatory effectiveness appears to be, grossly impaired in the absence of Cx40.

FR-OR077

Myocardial Infarction in an Inducible Hypertensive Rat Model: Does Spironolactone Reduce Renal Fibrosis?

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Background: Hypertension is a leading cause of myocardial infarction (MI), and is strongly associated with renal injury. However, superposition of MI on renal injury secondary to hypertension is not clearly defined. Likewise mineralocorticoidocorticoid (e.g. spironolactone; SP) has been shown to reduce cardiac fibrosis and improve cardiac outcomes post MI, but consequences for renal function are not known. We aimed to explore the effects of SP on renal fibrosis, post MI, in established hypertensive rats.

Methods: Hypertension was induced and maintained using male C57BL/6J rats (n=20) by addition of 0.167% (w/w) indole-3-carbinol to the rat chow, and established for two weeks prior to treatment or surgical intervention. Rats (10 weeks of age) were divided into four groups: hypertensive controls (H), hypertensive controls fed SP daily (4.4mg/kg/day, H-SP), hypertensive with MI (permanent left anterior coronary ligature; H-MA) and H-MA plus daily SP (H-MA-SP). Physiological data and tissue was collected for four weeks after MI for analysis.

Results: Systolic blood pressure (SBP) did not differ significantly between groups. Ejection fraction (EF) was significantly (p=0.001) reduced by MI induction (42±16%, but not improved by SP treatment (43±10%). MI significantly increased global cardiac fibrosis (2.2±0.5%) and renal cortical fibrosis (3.1±0.9%) when compared to hypertensive animals (1.3±0.5% and 2.6±0.9% respectively), while SP therapy post infarct significantly reduced cardiac intestinal fibrosis (1.5±0.4%) and kidney cortical fibrosis (1.4±0.6%). The reduction in fibrosis was associated with decreased expression of esma, TGFβ, reduced expression of MCP1 and a significant reduction in interstitial macroporphages. SP significantly reduced (p=0.01) glomerulosclerosis in both H-SP group (from 1.2±0.7 in hypertensive controls and 1.5±0.4 to 1.2±0.7) and H-MA group from 1.3±0.4 to 1.0±0.3.

Conclusions: The addition of MI significantly worsened the extent of hypertension-induced renal fibrosis and glomerulosclerosis. SP treatment resulted in significant improvement in renal fibrosis and GSI scores in hypertensive animals with or without MI. Further work will aim to further define the relationship between cardiac injury and renal damage.

FR-OR078

Experimental Renovascular Disease Induces Endothelial Cell Mitochondrial Damage and Impairs Endothelium-Dependent Relaxation of Renal Artery Segments

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Background: Endothelial cell (EC) mitocondria produce energy, control redox status, and support EC function, but may be damaged during renal disease. We hypothesized that the ischemic and metabolic constituents of swine renovascular disease (RVD) induce mitochondrial damage and impair the function of renal artery EC.

Methods: Domestic pigs were studied after 16 weeks of diet-induced metabolic syndrome (MetS), renal artery stenosis (RAS), or coexisting MetS and RAS, and Lean pigs served as control (n=6 each). Mitochondrial morphology (electron microscopy), mitochondrial potential (TMRE staining), and production of reactive oxygen species (MitoSOX) were measured in isolated primary renal artery EC. Vasoactivity of renal artery segments was characterized in an organ bath.

Results: Lean-RAS and MetS-RAS developed significant stenosis and hypertension (Table I) and showed increased renal periphery matrix density (Fig. A). Mitochondrial membrane potential similarly decreased in MetS, Lean+RAS, and MetS+RAS groups, whereas production of reactive oxygen species increased in MetS vs. Lean, but further increased in both RAS groups (Fig. B). Endothelium-dependent relaxation of renal artery segments was blunted in MetS vs. Lean, but further attenuated in Lean+RAS and MetS+RAS (Fig. C).

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Underline represents presenting author.
**FR-OR080**

**Sox6 Ablation in Renin Expressing Cells Has Protective Function Against Renovascular Hypertension and Kidney Damage**

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**Background:** Renal artery stenosis (RAStenosis) is an interatcetable problem affecting about 6% of the people over 65 and in up to 40% of the people with coronary or peripheral vascular disease. The renin angiotensin aldosterone system (RAAS) is implicated in RASStenosis. Renin controls rate-limiting step in RAAS and is a key driver in RAStenosis induced hypertension. Sox6 is a transcription factor important for cell fate determination of muscle, bone, neurons among others.

**Methods:** A new transgenic mice the Ren1d"Sox6KO" (Sox6 KO), in which Sox6 is knocked out in renin expressing cells was used to reveal the impact of Sox6 ablation on renin expression and hypertension during RASStenosis. Two time-point studies, 3 weeks, and 3 days were conducted. Blood pressure was measured by tail-cuff method. The kidney injury markers KIM1, creatinine, albumin, and urea were measured using commercially available kits. Superoxide was measured using HPLC.

**Results:** In 3-week study; systolic and mean arterial blood pressure were significantly lower in Sox6 KO compared to wild-type mice. When stenosed kidneys were compared, renin expression levels were significantly lower in Sox6 KO compared to wild-type. Urine creatinine clearance was significantly higher in Sox6 KO compared to wild-type in 3-day study; renin, STAT3, HIF1-α, N-Gal, and Sox6 serine-threonine phosphorylation levels were lower in the stenosed kidney of Sox6 KO compared to wild-type. This indicates that phosphorylated Sox6 triggers renin expression increase in RASStenosis and indicates that HIF1-α, STAT3 may contribute Sox6 expression in RASStenosis. Unlike the stenosed kidney were lower in Sox6 KO compared to wild-type mice. Urine creatinine clearance was significantly higher in Sox6 KO compared to wild-type animals. KIM1, urea, and albumin levels were not different between the groups in both time-point. Altogether, our data suggest that Sox6 KO mice were protected from developing hypertension and kidney damage during RASStenosis.

**Conclusions:** Our data indicates that Sox6 has a new function modulating renin expression, renovascular hypertension and kidney damage induced by RASStenosis. Identification of this novel pathway and its regulators may lead to new therapies for hypertension and associated cardiovascular disease.

**Funding:** Other NIH Support - NHLBI

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**FR-OR081**

**Investigating the Role of CD40-CD154 Interactions in Lupus Nephritis**

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**Background:** Disease pathology in lupus nephritis (LN) has been linked to a variety of different immune pathways, including CD40-CD154 interactions. This pathway has been shown to regulate the activation of B lymphocytes as well as macrophages and activated renal epithelia, and thus blockade of this pathway could provide therapeutic benefit in individuals with LN.

**Methods:** We evaluated the expression and activation of the CD40-CD154 pathway in kidney tissue from LN patients. Additionally, we evaluated the therapeutic effect of a blocking, non-depleting anti-mouse CD40 mAb (GOT40) in the NZB/W F1 model of lupus nephritis.

**Results:** Histological analysis of kidney biopsies from patients with proliferative LN revealed evidence of CD40 and CD154 on B cells, macrophages and T cells respectively. These results suggested that there might be ongoing T-B cell collaboration in LN kidneys and we subsequently examined whether there was evidence of CD40 pathway expression and activation in situ. Using published scRNA-seq data from LN kidney biopsies we could demonstrate evidence of CD40 transcript expression by B cells and myeloid cells and CD154 expression by subsets of CD4+ T cells. To directly address the role of CD40-CD154 in LN, we used GOT40, a novel, blocking, non-depleting anti-CD40 antibody in the NZB/W F1 model of lupus nephritis. Therapeutic treatment for 9-77 days of NZB/W F1 mice aged 24 to 37 weeks and individually enrolled into treatment groups with proteinuria ≥mg/ml resulted in suppression of established proteinuria and extended survival in GOT40 treated animals in comparison to isotype control treated animals. Serum autoantibody and CXCL13 levels were reduced by GOT40 treatment compared to isotype control. Similar to current treatments, we observed only minimal (not significant) reduction in various histological parameters with GOT40 treatment at this advanced stage of kidney injury, despite evidence of complete, systemic pathway blockade at the transcriptional level and suppression of a kidney gene expression with GOT40 treated animals.

**Conclusions:** Our data support the notion that CD40-CD154 pathway signaling may contribute to pathology in LN and that anti-CD40 treatment could provide therapeutic benefit in individuals suffering from this disease.

**Funding:** Commercial Support - Novartis Pharmaceuticals AG

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**FR-OR079**

**Opposite Regulation of Renal and Cerebral Microarteriolar Angiotensin II Contractility by Specific Endothelial Prostaglandin Pathways**

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**Background:** The kidney requires robust angiotensin II (Ang II) responsiveness for regulation of body fluids whereas the cerebral circulation requires resilience to Ang II to prevent cerebral ischemia and dementia. RNAseq of single cerebral microarterioles (CAs) versus renal afferent arterioles (Affs) detected >30-fold greater gene expression for COX2 and >3000-fold greater expression for lipokalin type prostaglandin D synthase (LPGDS) and DP1 receptor in CAs yet Affs expressed more thromboxane synthase. We reported enhanced contractility of Affs by thromboxane (Circulation 94: 1436-1442, 2004). Therefore, we hypothesized that expression of different PGs accounts for regional differences in Ang II responsiveness.

**Methods:** Individual mouse microarterioles (8-15µm) from the intraparenchymal frontal cerebral cortex were compared to renal cortical Affs, perfused at 40 mmHg and change in diameter (%) assessed with Ang II (10-12 to 10-6 M).

**Results:** Normal CAs were entirely unresponsive to 10-6 Ang II (0.03%) whereas Affs were highly responsive (+49±1%). Ang II responses of CAs from COX1-/- vs +/- mice were enhanced (+15±2 vs 0.01%, P<0.001) and enhanced further by COX2 blockade with parecoxib (-20±2 vs -15±2%, P<0.05) similar to effects of LPGDS blockade with TR-0256 blockade with atenolol in normal mouse arteries (-15±4%). In contrast, COX blockade reduced Ang II contractions of Affs. The DP1R agonist, BW450c reduced Ang II contractions of CAs from COX-blocked mice, yet was ineffective in Affs. Deendotheleialization of Affs enhances Ang II contractions in normal mouse CAs (0±1 vs 17±2%, P<0.001) but did not increase contractions further in COX-blocked CAs (19±6 vs 22±5%, P=NS). Superoxide levels were lower in SOX6 KO compared to wild-type mice. Urine creatinine clearance was significantly higher in SOX6 KO compared to wild-type animals. KIM1, urea, and albumin levels were not different between the groups in both time-point. Altogether, our data suggest that SOX6 KO mice were protected from developing hypertension and kidney damage during RASStenosis.

**Conclusions:** Our data indicates that SOX6 has a new function modulating renin expression, renovascular hypertension and kidney damage induced by RASStenosis. Identification of this novel pathway and its regulators may lead to new therapies for hypertension and associated cardiovascular disease.

**Funding:** Other NIH Support - NHLBI

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
FR-OR082
Modified Immune Cell (MIC) Therapy Ameliorates Murine Lupus Nephritis and Induces Regulatory B Cells In Vivo

Background: MICs are mononuclear cells that gain immunosuppressive properties after incubation with mitomycin C (MMC). We recently showed that syngeneic MICs transfered therapeutically into mice with autoimmune encephalitis (EAE). In addition, allogenous MICs prevented rejection in rat heart and hindlimb as well as pig kidney transplantation. We wanted to translate these encouraging findings to the prevention and treatment of lupus nephritis.

Methods: Splenocytes of syngeneic BWF1 donor mice were incubated with MMC and injected into recipient’s tail vein after matching for disease activity. Group 1 received no therapy, group 2 standard-dose MIC therapy with 1.5x10^9/kg BW and group 3 high-dose MIC therapy with 1.5x10^9/kg BW at week 1, 2 and 3. Group 4 received MIC infusions before disease onset as preemptive treatment approach. Disease activity was monitored by body weight, protein excretion, serum creatinine and dsDNA. Primary endpoint was day 40, protein excretion >3g/l and >20% loss of body weight. Kidney histopathology with PAS/HE staining was performed. Regulatory cell subsets and cytokine concentrations were measured.

Results: MIC therapy prevented the progression of lupus nephritis. Protein excretion, serum creatinine and dsDNA were lower in standard-dose and preemptive group compared to control group whereas repeated MIC therapy after disease onset had no effect. The endpoint was reached significantly more often in control group (67%) compared to control group whereas repeated MIC therapy after disease onset had no effect. The endpoint was reached significantly more often in control group (67%) compared to control group whereas repeated MIC therapy after disease onset had no effect. The endpoint was reached significantly more often in control group (67%) compared to control group whereas repeated MIC therapy after disease onset had no effect. The endpoint was reached significantly more often in control group (67%) compared to control group whereas repeated MIC therapy after disease onset had no effect.

Conclusions: MIC therapy inhibits progression of active lupus nephritis. Preemptive MIC therapy delayed the onset of disease with no significant disease activity at completion of the study. Differences between EAE experiments and a first in-human clinical trial in kidney transplantation (TOL-1 study), MIC therapy was able to induce regulatory cell subsets in vivo. This clinically applicable cell therapy may control lupus nephritis by specifically silencing deleterious autoimmune responses.

Funding: Commercial Support - TolerogenixX GmbH

FR-OR083
Adeno-Associated Virus-Mediated Factor H Gene Therapy in a Murine Model of Complement-Dependent Thrombotic Microangiopathy and Systemic Thrombophilia
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Background: Atypical hemolytic uremic syndrome (aHUS) is a form of thrombotic microangiopathy (TMA) caused by complement dysregulation. It is characterized by thrombocytopения, hemolytic anemia and renal injury, with up to 50% patients eventually progressing to end stage renal failure. Mutation in the C-terminal domain of factor H (FH), a critical plasma complement inhibitor, is the most common genetic cause of aHUS. Eculizumab, a humanized anti-C5 mAb, is effective for aHUS but whether lifetime treatment with Eculizumab is needed and what is the optimal length of therapy remains unknown. Here we tested the hypothesis that adeno-associated virus (AAV)-mediated FH gene therapy can correct complement dysregulation and replace anti-C5 therapy in FH mutation-related aHUS.

Methods: We used FH^H mice which carried a homoygous mutation (W1206R) in FH. FH^H mice developed characteristic TMA due to complement dysregulation. It is characterized by thrombocytopения, hemolytic anemia and renal injury, with up to 50% patients eventually progressing to end stage renal failure. Mutation in the C-terminal domain of factor H (FH), a critical plasma complement inhibitor, is the most common genetic cause of aHUS. Eculizumab, a humanized anti-C5 mAb, is effective for aHUS but whether lifetime treatment with Eculizumab is needed and what is the optimal length of therapy remains unknown. Here we tested the hypothesis that adeno-associated virus (AAV)-mediated FH gene therapy can correct complement dysregulation and replace anti-C5 therapy in FH mutation-related aHUS.

Results: When examined at 5 weeks after AAV gene therapy (4 weeks after stopping anti-C5 mAb treatment), TMA features including thrombocytopения, low plasma hemoglobin and elevated reticulocyte count returned to control AAV-treated but not AAV-^FH^H treated mice. AAV-AAV gene therapy (8 weeks after AAV therapy) was still weakly active whereas only 7/20 control AAV-treated mice survived. Furthermore, severe glomerular injury and fibrin deposition in the kidney, and macro-vascular thrombosis in extra-renal organs, were detected in terminally sacrificed control AAV-treated FH^H mice but were almost absent in AAV-FH^H treated FH^H mice.

Conclusions: These results demonstrate that AAV-mediated FH gene transfer can replace anti-C5 mAb treatment to provide curative therapy for TMA and other pathologies associated with FH point mutations.

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FR-OR084
Utility of Soluble CD163: A Non-Invasive Biomarker of Activity for Lupus Nephritis
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Background: Distinction between lupus nephritis (LN) patients with active inflammation and those with chronic kidney damage is challenging. Soluble CD163 (sCD163) derives from cleavage of the CD163 M2c-macrophage receptor, can be quantified in urine and may reflect intra-renal inflammation. We tested urine sCD163 as a biomarker of LN activity.

Methods: The cross-sectional diagnostic yield and the longitudinal course of urinary sCD163(ucCD163) was assessed in two large LN cohorts. We recruited 113 (Mexican cohort) and 129 (OSU cohort) active LN (aLN) patients with prospective follow-up. Patients with other diseases, inactive LN (iLN), and healthy donors were included as controls. ROC curves were obtained from the cross-sectional data. Ten LN flares failed from the Mexican and the OSU study cohort were followed with repeated samples and response to therapy (RTT) evaluated at 6- and 12-months. Linear mixed models were fitted to evaluate the association between ucCD163 and RTT.

Results: The highest levels of ucCD163 were found in aLN in the Mexican (1015 ng/ml; 760-1434) and OSU (1350ng/ml; 811-2356) cohorts compared to LN (10 ng/ml, 0.40, p<0.001) and other diseases. UcCD163 was higher in class IV Vs. other classes and correlated with the histologic activity index (r = 0.527, p<0.001). A ucCD163>100-ng/ml differentiated aLN from iLN with 95% sensitivity and 95% specificity. UcCD163 increased from 8.83-ng/ml to 6-month pre-flare to flare and then diminished to <500ng/ml at 12 months in 88% of RTT, while ucCD163 remained >500ng/ml at 12-mo in 88% of non-responders. Diagnostic yield of ucCD163 to discriminate 12-month RTT was better than that of currently-used biomarkers (Table 1). After adjusting for other predictors, the ucCD163 slope was associated with RTT.

Conclusions: UcCD163 reflects LN renal inflammation and varies over time with LN activity and treatment. Its levels increase pre-flare and then parallel RTT, being independently associated with response to therapy.

Funding: Other NIH Support - National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Government Support - Non-U.S.-

FR-OR085
Proliferation and Changes in Cellular Signatures in Memory B Cells from Lupus Nephritis Patients Receiving Mycophenolate or Azathioprine Maintenance
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Background: Mycophenolate mofetil (MMF) and azathioprine (AZA) are standard maintenance treatments for lupus nephritis (LN), and recent data suggested lower risk of relapse with MMF maintenance. Memory B cells have been implicated in LN relapse, and miRNA144a, BACH1, BACH2 and PAX5 can regulate memory B cell homeostasis. The effect of MMF and AZA treatment on these memory B cell signatures remain unclear.

Methods: Memory B cells were isolated from clinically stable LN patients receiving low-dose corticosteroid and MMF (n=10) or AZA (n=9) maintenance, and the cell proliferation and intracellular miRNA144a, BACH1, BACH2 and PAX5 expressions on Day 3 after in vitro stimulation were compared.

Results: MMF group showed lower memory B cell proliferation on Day 3 (8.5±1.2%, compared with 20.2±2.0% in AZA group, p<0.001) (Figure 1, A). MMF group also showed lower miRNA144a expression (10-fold decrease compared to healthy controls (HCS), vs. 2.9 fold decrease in AZA group, p<0.001) (Figure 1, B), but higher BACH1, BACH2 and PAX5 expression in memory B cells (8.2±0.8, 7.2±1.8, and 7.6±1.1 fold increase compared to HCS respectively, vs. 4.0±0.7, 2.9±0.6, and 3.4±0.4 fold increase in the AZA group, p<0.001, MMF vs. AZA) (Figure 1, C).

Conclusions: LN patients receiving MMF maintenance showed reduced memory B cell proliferation and a distinct cellular signature, which may account for the lower risk of relapse observed clinically.

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Underline represents presenting author.

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Kidney Biopsy-Based Management of Maintenance Immunosuppression in Lupus Nephritis

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Background: The optimal duration of maintenance immunosuppression (MIS) for proliferative lupus nephritis (LN) is unknown. Management of MIS therapy must balance the risk of LN flare after IS withdrawal against the toxicities of long-term IS. We postulated that information from a protocol kidney biopsy done when withdrawal of IS is being contemplated could attenuate LN flares and improve long-term kidney outcomes, and tested this hypothesis in a large LN cohort.

Methods: A cohort of 76 Caucasian Hispanic SLE patients initiated IS for kidney-biopsy proven (Bx1) LN, was followed prospectively, re-biopsied after induction (Bx2) and again during MIS therapy (Bx3). Bx3 was done after a minimum of 36 months of IS and tested this hypothesis in a large LN cohort.

Results: Patient outcomes are shown in the Figure. After a median follow-up of 50 months between Bx3 and last visit only 7 patients (9.2%) experienced an LN flare, no patient died, and no patient progressed to ESKD.

Conclusions: These data extend the observation that clinical remission and histologic remission even after several years of IS may be discordant. Management of MIS by histologic activity of protocol biopsies resulted in an LN flare rate of 0.02-0.81 events/patient-year in international LN cohorts. Protocol kidney biopsies during MIS may help guide treatment duration, minimizing exposure to toxic medications and risk of LN relapse.
Evaluation of the Endothelin A Receptor Antagonist Zibotentan in Systemic Sclerosis-Associated CKD
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Background: Systemic sclerosis (SSc) causes scleroderma renal crisis (SRC) and chronic kidney disease (SSc-CKD). A previous open label trial of bosantan suggested possible benefit for CKD following SRC. We report the results of a placebo-controlled trial of zibotentan, a highly selective endothelin A receptor antagonist, in SSc-CKD.

Methods: ZEBRA-1 was a double-blind randomised placebo-controlled trial in SSc-CKD (eGFR 45–60 ml/min) comparing oral zibotentan 10 mg/day and placebo over 26 weeks with final assessment at 52 weeks (Clinical Trials NCT02047708). eGFR and candidate urinary molecular markers of SSc-CKD were measured at each time point and safety was a key secondary endpoint.

Results: 16 patients consented with 3 screen failures due to ineligible eGFR on re-testing. 7 patients received placebo and 6 zibotentan. Baseline renal function was well-matched between groups—median eGFR in placebo 51 (44-58); zibotentan 50.5 (49-59). Renal function remained equal at 26 weeks—placebo 53 (37-58); zibotentan 54 (50-58) but significantly improved in the active treatment group at 52 weeks—placebo 50 (36-55); zibotentan 60.5 (50-74), p=0.0082 (Figure 1). Our previous work identified high urinary MCP-1 as a marker of SSc-CKD. In ZEBRA-1 levels declined on zibotentan but not on placebo. Median baseline MCP-1:creatinine (pg/mg/L) was 7.1 (5.2-21.9) in placebo and 5.4 (3.1-28.9) for zibotentan, increased to 8.8 (6.3-13.5) at 26 weeks on placebo and reduced to 4.4 (2.9-11.2) on zibotentan. At 52 weeks MCP-1:creatinine for placebo was 7.5 (6.4-15.8) and was significantly lower at 4.5 (4.1-6.0; p=0.0095) for zibotentan. There were 46 reported adverse events (26 placebo and 20 zibotentan) with 6 serious adverse events (3 in each arm).

Conclusions: This is the first placebo-controlled clinical trial in renal SSc. Zibotentan treatment was safe and associated with improved eGFR and reduced urinary MCP-1 at 52 weeks compared to placebo. These preliminary results suggest potential benefit from targeting endothelin A in SSc-associated CKD.

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Clinical Exome Sequencing for Renal Disorders
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Background: Next-generation sequencing is a valuable tool for evaluating patients with suspected genetic renal disease. Clinical practice relies on targeted gene sets that are ordered based on patient phenotype and physician knowledge of the utility of genetic testing. We report the diagnostic yield of four clinically-established gene sets and employ a retrospective analyzing an expanded set of genes to characterize patients with pathogenic variants in genes that were not part of the ordered gene set.

Methods: In total, 324 patients underwent clinical exome sequencing based on physician-ordered gene sets for atypical hemolytic uremic syndrome (n=224), nephrotic syndrome (n=66), cystic renal disease, and nephropathies (n=36). APOL1 syndrome (n=13), or a custom panel (n=5). For the 324 patients, we identified 42 pathogenic and likely pathogenic variants in 97 of 324 patients with suspected genetic renal disease. Clinical practice relies on targeted gene sets that are ordered based on patient phenotype and physician knowledge of the utility of genetic testing. We report the diagnostic yield of four clinically-established gene sets and employ a retrospective analyzing an expanded set of genes to characterize patients with pathogenic variants in genes that were not part of the ordered gene set.

Results: Among CureGN participants, younger age, black race, and more comorbidities were independently associated with time to first infection-related hospitalization or ED visit. These findings might inform the development of strategies aimed at preventing infection in patients with GD.

Funding: NIDDK Support
FR-OR092

Proliferative Glomerulonephritis with Monoclonal Light Chain Deposits

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Background: Most cases of proliferative glomerulonephritis with monoclonal immunoglobulin (MIg) deposits (PGNMID) are of the IgG isotype (particularly IgG3).

Methods: We describe the first clinicopathologic and proteomic series of PGNMID with MIg light chain (LC) deposits (PGNMID-LC).

Results: This multicenter cohort consisted of 18 patients (median age 60 years, 72% male) who presented with nephritic or nephrotic syndrome. The underlying hematologic condition was MGRS (72%) or multiple myeloma (28%). MIg was identified by serum and urinary immunofixation in 61% and 60% of patients, abnormal serum FLC in 77%, and corresponding nephriticinflammatory cell class in the bone marrow in 88%. Renal biopsy showed MPGN in most patients; glomerular deposition of MIg LC (κ in 67%, λ in 33%) and C3 (100%), without extraglomerular deposits, IgG, IgA, or C1q deposits, by immunofluorescence (IF); and subendothelial (100%), mesangial (100%) and subepithelial (72%) granular electron dense deposits by electron microscopy. Paraffin IF done in 39% of cases showed similar results to IF on frozen tissue. Laser microdissection/mass spectrometry performed on 4 cases of κ PGNMID-LC revealed spectra for Igκ constant and variable domains and complement alternative pathway (CAP) and terminal complex proteins (particularly C3 and C9) in 3 without spectra for Igλ, α, β, or classical complement pathway proteins. In contrast, 6 cases of λ LCD did not show spectra for complement proteins. Complement functional assays in 1 patient revealed that a serum sample contained a CAP-enriched monoclonal LC induced CAP activation in normal human serum. Follow up (median 66 months) was available in 16 patients. Renal response occurred in 6 of 10 patients treated with plasma cell-directed chemotherapy but not in 6 who did not. Hematologic response was evaluable in 8. All 6 who had hematologic complete response achieved renal response while the 2 with hematologic partial or no response did not.

Conclusions: PGNMID-LC is a variant of PGNMID with higher detection rate of the nephritogenic plasma cell clone. Proper recognition is crucial as plasma cell clone directly impacts treatment strategy.

FR-OR093

Prevalence of Exostosin 1/Exostosin 2-Associated Membranous Lupus Nephritis

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Background: Membranous nephropathy (MN) is classified as primary and secondary. Primary MN is associated with PLA2R antigen in 70-80% cases and THSD7A in 1-5% cases. The target antigens are unknown in 20-25% cases of primary MN and all of secondary MN. Two novel proteins, Exostosin 1 and Exostosin 2 (EXT1/EXT2) were recently identified as likely target antigens in a small cohort of MN with an underlying autoimmune etiology (Sethi et al, JASN 2019). In this study, we validate the EXT1/EXT2 findings in a large cohort of patients with lupus membranous nephritis (LMN).

Methods: We studied 374 cases of biopsy-proven LMN from 2003 to 2018. Immunohistochemical studies (IHC) using antibodies against EXT1/EXT2 were performed on paraffin-embedded sections. Laser microdissection and mass spectrometry (MS) were performed on a subset of these cases.

Results: Of the 374 LMN cases, 122 (32.6%) were EXT1/EXT2 positive (figure 1) and 252 (67.4%) were EXT1/EXT2 negative by IHC. Among the 122 cases, 86.9% were female. At presentation, the median serum creatinine and proteinuria were 0.8 mg/dL (range: 0.4-14.7) and 4 g/day (range: 0.4-13.5). Kidney biopsies revealed an average of 16.6 glomeruli (SD: ±10.0) with an average of 1.7 globally sclerotic glomeruli (SD: ±3.1). Interstitial fibrosis and tubular atrophy was minimal (<10%) in 89 (72.9%), mild (11-25%) in 21 (17.2%), moderate (26-50%) in 8 (6.6%), and severe (>50%) in 4 (3.3%) cases, respectively. Further, 30 (24.6%) patients had proliferative features (Class III/IV). MS was performed on 8 cases which showed high spectral counts for EXT1 (average: 88.6, SD: ±37.2) and EXT2 (average: 66.1, SD: ±34.6), thus confirming the IHC findings. Among the 252 EXT1/EXT2 negative cases, 81 (32.1%) patients showed proliferative features. MS was performed in 7 of these 252 cases and was negative for EXT1/EXT2.

Conclusions: We validate our previous findings in a large cohort of LMN. Approximately one-third (32.6%) of LMN patients are positive for EXT1/EXT2, of which approximately one-fourth (24.6%) have coexisting proliferative features.

FR-OR094

Renal Polyvinylpyrrolidone Deposition from Illicit Drug Use Is Associated with Tubulointerstitial Nephropathy

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Background: Polyvinylpyrrolidone (PVP) is a water-soluble polymer used as an excipient in drugs for oral use. When injected, high molecular weight PVP can neither be metabolized nor excreted by glomerular filtration and will accumulate in the body, resulting in PVP deposition disease. From 2009 to 2016, we observed 25 kidney biopsies with PVP deposition in Norway. All biopsies were from patients with opioid addiction and chronic kidney disease (CKD). The most likely source of PVP in these patients is illicitly injected, PVP-containing opioid substitution drugs intended for oral use.

Methods: We collected clinical data from the Norwegian kidney biopsy Registry and from affiliated medical records. We reviewed the biopsies, assessed light microscopy, immunohistochemistry and electron microscopy, and obtained additional pathological parameters using quantitative methods.

Results: The cohort consisted of 25 adults with a mean age of 37. All were suffering from opioid addiction with a known history of injecting opioids regularly, and 22 of them were prescribed opioid substitution drugs. 22 (88%) of the patients had positive hepatitis C virus serology and none were HIV-positive. All patients had CKD with a mean serum creatinine of 205 mole/L and mean estimated glomerular filtration rate of 35 ml/min/1.73m2 (Range 14-58). The majority (64%) had stage 3b CKD. Four patients had slightly to moderately increased urinary protein:creatinine-ratio. All biopsies revealed widespread areas of tubular atrophy and interstitial fibrosis with a mean proportion 64% (Range 32-96). The interstitium of these areas contained single and grouped histiocytes with characteristic bluish vacuoles indicating PVP deposits (fig. 1). Apart from one patient with lupus nephritis, the biopsies showed no evidence of other diseases that could explain the widespread atrophy.

Conclusions: Opioid drug addiction is associated with a high burden of morbidity and various renal diseases. This large case series illustrates that PVP deposition might be a rare cause of chronic renal insufficiency in these patients.

Funding: Government Support - Non-U.S.
FR-OR095

Chronic Interstitial Nephritis in Agricultural Communities (CINAC): A Toxin-Induced Proximal Lysosomal Tubulopathy
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Background: There is no consensus on the etiology of CINAC. Heat stress/dehydration and toxic exposure are the two most likely etiologies. There are no direct diagnostic criteria to identify CINAC patients.

Methods: Renal CINAC biopsies (18 Sri Lanka, 10 El Salvador, 1 India, 3 France) were examined by light (LM) and electron microscopy (EM) in comparison to normal kidneys at implantation and 6 and 12 months of calciumine inhibitor (CNI) therapy, transplant patients on CNI with indication biopsies (n=24), proteinuric nephropathies (n=15), light chain disease (n=4), cases on nephrotoxic drugs (lomustine, clomiphene, lithium, tenofovir, cisplatinum, and icosapentaenoic acid) and CKD of various causes (n=20). A rat study compared histological features of heat stress and cyclosporine nephrotoxicity.

Results: There was a unique constellation of proximal tubular cell (PTC) findings: cellular/tubular atrophy, cell fragment shedding, weak to non-proliferative capacity of the PTC and dysmorphic lysosomes increased in size and number with a light-medium electron-dense matrix containing dispersed dark electron-dense ‘aggregates’. Identical lesions were observed in 55-80% of renal transplant protocols at 6 and 12 months of CNI therapy and in indication biopsies. In implantation biopsies the prevalence was 6%. Several cases of nephrotoxic drugs (lomustine, clomiphene, lithium) and some patients with light chain disease, all were linkable to CNI, presented the same lesion. Controls (n=66) of normal kidney, toxic nephropathies (tenofovir, clomiphene, cisplatinum), and overt proteinuric patients of different etiology to some extent could demonstrate the tubular cell changes observed by LM, but not or very rarely those by EM. Rats treated with cyclosporine for 4 weeks developed similar histopathological lesions, that were absent in a dehydration group.

Conclusions: A sensitive constellation of renal PTC lesions was detected associated with CINAC and CNI nephrotoxicity in several countries, suggesting a common new paradigm where CINAC patients are experiencing a tubulotoxic mechanism similar to CNI nephrotoxicity, the latter also being known as a direct or indirect effect of pesticides.

FR-OR096

Integrative Analysis of Single Cell and Bulk Transcriptomic Data Identifies FSGS Subgroup with Endothelial Cell Activation
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Background: Single cell RNA sequencing (scRNA-seq) generates transcriptomic data at cellular resolution allowing the identification of both known and novel cell-type specific markers. These markers enable to investigate the role of distinct cell types in kidney disease. In this study, we used glomerular endothelial cell type markers identified by scRNA-seq to analyze micro-dissected glomerular mRNA data from FSGS patients in NEPTUNE Consortium.

Methods: As part of the Kidney Precision Medicine Project (KMP), single cell analysis (10x Chromium) was performed on unaffected kidney tissue from 16 tumor-nephrectomy and 10 surveillance transplant biopsy samples. Integrated analysis was performed on the single-cell data from these 26 reference datasets including normalization, batch correction, unsupervised clustering and cell-specific marker identifications. Cell specific markers were used to cluster glomerular RNA transcriptomic data from 74 NEPTUNE FSGS patients followed by functional analysis.

Results: 37 kidney cell-type clusters were identified including glomerular, tubular and immune cell types as well as 3 distinct endothelial cell types (arteriolar, peritubular and glomerular). The glomerular endothelium-specific markers were then used to sort bulk tissue gene expression from FSGS patients resulting in two main groups, 1 (n=44) and 2 (n=30). The 2nd group was characterized by a significant upregulation of glomerular endothelial activation markers. Higher hazards of a composite progression endpoint (~40% reduction in eGFR reduction or ESRD) indicated poor prognosis for Group 2. Differentially expressed genes (DEGs) up-regulated in group 2 were involved in type-1 interferon response, ras-protein signaling, and response to endothelin receptor antagonists in model systems.

Conclusions: Glomerular endothelial marker genes identify a subgroup of patients with poor prognosis and establish a molecular correlate for the endothelin treatment response observed in clinical trials in FSGS.

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FR-OR097

Evaluation of a Computer-Aided Quality Assessment of Whole Slide Images for Computational Pathology
Yijiang Chen,1 Jarcy Zee,2 Abigail R. Smith,1 Catherine P. Jayapandian,1 Jeffrey B. Hodgkin,1 David Howell,1 Matthew Palmer,1 David B. Thomas,2 Clarissa A. Cassol,1 Alton B. Farris,1 Kathryn R. Perkinsin,1 Stephen M. Hewitt,3 Anant Madabushi,1,3 Laura Barisoni,1,3 Andrew Janowczyk,1

Background: The establishment of computational image analysis has uncovered inconsistency in quality of whole slide images (WSI) across pathology laboratories, due to pre-analytic (fixation and tissue processing) and analytic (cutting, staining and scanning) variations. While pathologists train themselves to read through artifacts, computational pathology systems are not trained to adjust to such variability. Our group developed a pipeline aided by an open-source computer-based quality control tool (HistQC) to identify heterogeneity, qualify WSI for computational image analysis (see Figure 1-A), and output tissue masks (see Figure 1-B) that exclude the artifacts. The aim of this study is to test whether HistQC can efficiently and reliably qualify WSI based on artifact detection.

Methods: 1814 WSIs (458 H&E, 470 PAS, 438 silver, 448 trichrome) from 512 NEPTUNE digital renal biopsies were analyzed by HistQC and reviewed for disqualification. Disqualified (extreme outliers) WSIs and 10% of the qualified WSIs, randomly selected, were manually scored by 2 reviewers for the presence of glass slide, tissue, and scanning artifacts. Principal component analysis (PCA) of HistQC metrics and logistic regression was used to evaluate the association between HistQC and human assessment.

Results: 151 WSIs were considered extreme outliers by HistQC. Only 318 (151 disqualified + 167 qualified) of the 1814 WSIs required human review. PCA components based on HistQC metrics demonstrated good to strong prediction of human identified artifacts (C-index range 0.64-0.83, see Figure 1-C).

Conclusions: HistQC can aid in the identification of pre-analytic and analytic artifacts and of variations in WSI presentation. Furthermore, this pipeline may enable efficient curation of digital pathology repositories and reduce computational image analysis variability.

Funding: NIDDK Support, Veterans Affairs Support.

FR-OR098

Assessment of Renal Function by Advanced Light Sheet Microscopy and 3D Image Analyses: Quantification of Albumin Filtration/Reabsorption at the Single-Nephron Level in Rodents
Mette E. Oesgaard,1 Urmas Roostalu,1 Annemarie A. Pedersen,1 Tanja X. Pedersen,1 Lisbeth N. Fink,1 Jacob L. Skytte,1 Niels Vrang,1 Jacob Hecksher-Sorensen,1 Gubra ApS, Hørsholm, Denmark.

Background: Drug development in diabetic kidney disease (DDK) and chronic kidney disease (CKD) is halted by poor translatability of preclinical animal models. Using 3D imaging techniques, we aimed to develop a new method for quantification of renal function, glomerular filtration and proximal tubular albumin absorption to assess the morphology and functionality of populations of single nephrons in preclinical rodent models of kidney disease.

Methods: Healthy mice and rats as well as 5/6 nephrectomised (Nx) rats were perfused with fluorescently labelled lectin, albumin, and 10 kDa dextran under terminal anesthesia, and intact kidneys were cleared for scanning by light sheet microscopy (LSM). Using 3D imaging techniques, we aimed to develop a new method for quantification of renal function, glomerular filtration and proximal tubular albumin absorption to assess the morphology and functionality of populations of single nephrons in preclinical rodent models of kidney disease.

Methods: Healthy mice and rats as well as 5/6 nephrectomised (Nx) rats were perfused with fluorescently labelled lectin, albumin, and 10 kDa dextran under terminal anesthesia, and intact kidneys were cleared for scanning by light sheet microscopy (LSM). Using 3D image analysis, distribution of glomerular size and tubular morphology was determined, while proximal tubular albumin absorption was quantified based on albumin intensity. To characterize kidney function using standard methodologies, 2D histology, plasma, and urine analyses were applied.

FR-OR099

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Results: In healthy mice and rats, LSM and 3D neonoph reconstruction revealed intact endothelial cells with glycan patterns connected to proximal then distal tubules extending from the cortex into the medulla. Juxtaglomerular proximal tubules were clearly delineated by tubular epithelial cells that were fluorescently labelled by absorbed albumin and followed by tubular epithelial cells labelled by dextran. In sharp contrast, imaging analyses suggested functional discrepancies in the kidney cannemats of 5/6 Nx rats. Nephrons in 5/6 Nx rats appeared fragmented and with limited tubular absorption of albumin and dextran, which obstructed tubular tracking from the cortex to the medulla. These findings were corroborated by albuminuria, plasma urea and creatinine, and 2D renal histopathology in 5/6 Nx sham-operated rats.

Conclusions: Development of advanced microscopy and 3D imaging technologies allows for assessment of renal function at a single-nephron level and by characterization of populations of single nephrons. Thereby, this 3D imaging technique can support 2D end-point histological analyses and functional endpoints in rodent models delineate the use of rodent models to study disease mechanisms and test novel therapies for DKD and CKD.

FR-OR099
Visualizing the N-Linked Glycome within Human Kidney Biopsies Using Mass Spectrometry Imaging
Christopher R. Anderson,1,2 Dusan Velickovic,1 Guanshi Zhang,2 Arunima Bhattacharjee,1 Lilijana Pasa-Tolic,1 Theodore Alexandrov,3 Kumar Sharma,2 for the KMPM Consortium 1Pacific Northwest National Laboratory, Richland, WA; 2University of Texas Health San Antonio, San Antonio, TX; 3European Molecular Biology Laboratory, Heidelberg, Germany.

Background: The current study is a part of the NIDDK Kidney Precision Medicine Project (KPMP). The observed alterations in protein glycosylation attributed to disease development has stemmed major interest in studying glycosylation (e.g., higher HbA1c in type 1 diabetes) (1), which is associated with changes in the serum N-glycome. Currently, a limited number of methods are available for interrogating clinical tissue samples for variations in protein glycosylation. An emerging approach is on-tissue enzymatic N-glycan releasing (Oter) followed by matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI), which positionally conserves the location of N-glycan modifications and allows their composition to be registered to histological information. This method can be performed on archival, formalin-fixed paraffin-embedded (FFPE), clinical tissue sample.

Methods: We optimized the Oter MALDI-MSI workflow on FFPE preserved human kidney biopsy tissue provided by the KPMP. Tissue was sectioned and mounted on conductive glass slides, deparaffinized with xylene, rehydrated with ethanol, and dried at 40°C. Finally, matrix (cyanohydroxycinnamic acid) was applied to samples and MALDI was performed.

Results: Several high mannose, hybrid, and paucimannose N-glycans were spatially detected in the human kidney tissue, and many showed co-localization with different histological features, as revealed through pre- and post-MALDI MALDI autoradiography and H&E images. MALDI performed using the high mass resolution 15T Fourier transform ion cyclotron resonance MS gave confident matches of N-glycans in the ChEBI database and allowed their composition to be registered to histological information. This method can be performed on archival, formalin-fixed paraffin-embedded (FFPE), clinical tissue sample.

Conclusions: This highlights the value of using this workflow for mapping the N-glycome, where the location of species can be registered to different anatomical compartments and cell types within the human kidney. We anticipate this method can provide the ability to distinguish diseases from healthy kidney biopsies, by identifying aberrant N-glycosylation patterns.

Funding: NIDDK Support

FR-OR100
Iterative Indirect Immunofluorescence Imaging for Tissue (4iT): The First Step Towards Spatial Proteomic Maps
Victor G. Puelles,1 Lukas Gernoth,1 Jacobo Sarabia del Castillo,2 Catherine Meyer-Schwingsger,1 Ann-Christian Guricke,1 Fabian Braun,1 Jan-Eric Turner,1 Lucas Pelkmans,2 Tobias B. Huber1 University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 2University of Zurich, Zurich, Switzerland.

Background: With the rapid development of multi-omics techniques, there is an increasing need for methods that can localize proteins with high spatial resolution. This is particularly important in a complex system like the kidney, where a large number of interacting cells coexist.

Methods: We present 4iT, a new method for highly multiplexed protein measurements in paraffin-embedded tissue based on the principle of cyclic immunolabelling, including conventional indirect immunofluorescence, high-resolution fluorescence imaging, and elusion of primary and secondary antibodies. Five fluorogens and periglomerular spacers were serially imaged per mouse (n=4 controls and n=8 crescentic glomerulonephritis) for a total of 10 proteins identified in different kidney cells - first row shows intact nephrons with glomeruli connected to proximal then distal tubules extending from the cortex into the medulla. Juxtaglomerular proximal tubules were clearly delineated by tubular epithelial cells that were fluorescently labelled by absorbed albumin and followed by tubular epithelial cells labelled by dextran. In sharp contrast, imaging analyses suggested functional discrepancies in the kidney cannemats of 5/6 Nx rats. Nephrons in 5/6 Nx rats appeared fragmented and with limited tubular absorption of albumin and dextran, which obstructed tubular tracking from the cortex to the medulla. These findings were corroborated by albuminuria, plasma urea and creatinine, and 2D renal histopathology in 5/6 Nx sham-operated rats.

Conclusions: Development of advanced microscopy and 3D imaging technologies allows for assessment of renal function at a single-nephron level and by characterization of populations of single nephrons. Thereby, this 3D imaging technique can support 2D end-point histological analyses and functional endpoints in rodent models delineate the use of rodent models to study disease mechanisms and test novel therapies for DKD and CKD.

Funding: Commercial Support - AWAK TECHNOLOGIES PTE LTD, Government Support - Non-U.S.

Serum Solute Concentration

FR-OR101
Effect of Automated Wearable Artificial Kidney (AWAK) Device on Toxin Clearance and Safety in Peritoneal Dialysis Patients
Marjorie W. Foo,1 Huy Huỳ,1 Sheena Gow,2 Mandar Gori,1 Mathini Jayababla,1 Siti N. Huda,1 Jason T. Lim,1 Elizabeth L. Oei,2 Suresha B. Venkatarya,2 Sin yen Wu,1 2Singapore General Hospital, Singapore; Singapore; 2AWAK Technologies Pte Ltd, Singapore, Singapore.

Background: Patients undergoing dialysis face mobility and logistical challenges due to limited progress in dialysis technological advancement. Dialysate regeneration through use of sorbent technology led to the development of Automated Wearable Artificial Kidney Peritoneal Dialysis (AWAK PD) device.

Methods: The first-in-human (FIH) study was conducted in Singapore between March 2016 and October 2018. The study aimed to evaluate safety of AWAK PD in 15 prevalent peritoneal dialysis (PD) patients who underwent up to 9 AWAK PD therapies over 3-4 consecutive days. Incidence of adverse event was monitored and serum and dialysate samples were collected. Study also aimed to examine weekly peritoneal urea.

Results: Of 15 patients with median age 65.5 [Range Min, Max: 35, 73] years, male (67%), Chinese (80%), presence of coronary artery disease (27%), anemia (33%), with a median PD duration of 21 [4-147] months, none experienced any serious adverse events during or post AWAK PD therapy. The reported adverse events included abdominal discomfort (71%), presence of fibrin in the drain (36%) and bloating (36%). There was no significant difference in pre and post therapy weight. All patients who completed at least 1 valid therapy (n=14) achieved weekly peritoneal Kt/Vurea ≥1.7 with median weekly peritoneal Kt/Vurea =3.04 (IQR: 2.19-4.75). Significant reduction in solute concentrations was observed with AWAK PD therapy (Table 1). Stable serum sodium (136 [134-139]) mmol/L, potassium (4.0 [3.6-4.4]) mmol/L, and bicarbonate (24.2 [23.1-25.5] mmol/L) levels were reported during the study.

Conclusions: This FIH study showed that AWAK PD device was shown to be safe on 15 PD patients with appropriate solute clearance and no observed water retention.

Funding: Commercial Support - AWAK TECHNOLOGIES PTE LTD, Government Support - Non-U.S.

Serum Solute Concentration

Funding: Commercial Support - AWAK TECHNOLOGIES PTE LTD, Government Support - Non-U.S.

Serum Solute Concentration

<table>
<thead>
<tr>
<th>Solute</th>
<th>Pre-AWAK PD</th>
<th>Post-AWAK PD</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>37.8 (35.7-39.8)</td>
<td>35.7 (34.6-37.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine#</td>
<td>97.2 (85.8-106.8)</td>
<td>95.8 (83.9-104.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>Phosphate#</td>
<td>1.6 (1.3-1.7)</td>
<td>1.3 (1.1-1.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*pre-post therapy serum solutes level (Wilcoxon signed-ranks test); #: mmol/L; *: mmol/L

FR-OR102
Inhibition of Hyperglycosylation in Mesothelial Cells Prevents Peritoneal Fibrosis
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Background: Progressive peritoneal fibrosis is a dreaded problem for patients receiving peritoneal dialysis (PD) because it has no reliable treatment. There also are disagreements about the identification of mechanisms that initiate and sustain peritoneal fibrosis. To overcome these problems, we developed a strategy that prevents peritoneal fibrosis by suppressing PD-stimulated mesothelial to mesenchymal transition (MMT).

Methods: We single-engine cartridge transplants of mesothelial cells obtained from normal peritoneal biopsy and effluent from PD-treated patients. We then examined the metabolic reprogramming in the peritoneal fibrogenesis in mouse model and mesothelial cells using metabolomics and cellular respiration tests. We finally developed a triad of AAV1 encoded microRNA therapy, and evaluated its therapeutic potential to treat peritoneal fibrosis.

Results: We analyzed 96,446 single cell transcriptomes including cells dissociated from normal peritoneum, peritoneal cells from effluent of short-term PD and from
long-term PD patients. We found the expression of glycolytic enzymes was increased during the development of MMT. Using gene expression profiling and metabolomics analyses, we confirmed that PD fluid induces metabolic reprogramming, characterized as hyperglycolysis in peritomeum. We found that transforming growth factor β1 (TGF-β1) can substitute for PD fluid to stimulate hyperglycolysis. The mechanism involves suppressing mitochondrial respiration in mesothelial cells. Blockade of hyperglycolysis with 2-deoxy-glucose inhibited PD fluid-induced profibrotic cellular phenotype and fibrogenesis in mice. We developed a triad of adeno-associated viruses that overexpresses TGF-β that 2-deoxy-glucose inhibited PD fluid-induced profibrotic cellular phenotype and fibrogenesis in mice. We developed a triad of adeno-associated viruses that overexpresses TGF-β that significantly inhibited the development of peritoneal fibrosis induced by PD fluid.

**Conclusions:** We conclude that hyperglycolysis is responsible for MMT and peritoneal fibrogenesis. This aberrant metabolic state can be principally corrected by modulating mitochondrial enzymes in the peritoneum. These results could provide a novel therapeutic strategy to Combat peritoneal fibrosis.

**Funding:** Government Support - Non-U.S.

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**FR-OR103**

**Identifying MiRNA Biomarkers for Diagnosis of Encapsulating Peritoneal Sclerosis**

Chiu-Ching Huang,1 Nianhan Ma,1 An-Lun Li,1 J. B. Chen,2 Chin Chung Tseng,3 Taiwan EPS Consortium
1China Medical University and Hospitals, Taichung, Taiwan; 2National Central University, Zhongli District, Taiwan; 3Chang Gung Memorial Hospital-Kaohsiung, Kaohsiung Hsien, Taiwan; 4National Cheng Kung University Hospital, Tainan, Taiwan.

**Background:** Encapsulating peritoneal sclerosis (EPS) is a serious complication of chronic peritoneal dialysis (PD). Late diagnosis is associated with high mortality. With the advances in new diagnostic technology, such as microRNA (miRNA), we attempted to develop a non-invasive test to aid the diagnosis of EPS.

**Methods:** We examined miRNA expression profiles of PD fluids from patients with or without EPS by high-throughput and quantification real-time PCR array. We used the high-throughput microRNA assay cards as primary screen tool for analysis. The analysis of miRNA was conducted using the Running TaqMan® Low Density Arrays on Viia7 RealTime PCR Systems. Candidate miRNAs were selected to verify in another group of patients by single qRT-PCR assay. The model for EPS prediction was developed by multiple logistic regression.

**Results:** We collected overnight PD fluids from 72 non-EPS (controls) and 25 EPS patients. The **screening set** included PD fluids from 28 patients (20 of non-EPS vs. 8 of EPS ongoing cases). We compared the ratio values of two miRNA expression levels between EPS and non-EPS patients. Eight candidate miRNAs were selected. The **training set** was conducted using 69 samples (52 of non-EPS vs 17 of EPS ongoing) to produce the good area under curve (AUC) value of diagnostic miRNA classifier. The miRNA combination ratios with the top five ROC values were selected to calculate the combined AUC by logistic regression. The value of AUC to distinguish EPS from non-EPS with five miRNAs in PD fluid was 0.9723 (Figure 1). From results of the training set, six different miRNA expressions and two ratios of two miRNA expressions in the PD fluid showed significant difference between EPS and non-EPS patients.

**Conclusions:** We identify a miRNA classifier with the combination of top five miRNAs' expression in PD fluids to assist the diagnosis of EPS.

**Funding:** Government Support - Non-U.S.

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**FR-OR104**

**Lung Ultrasound B-Lines and Oxygen Saturation in Automated Peritoneal Dialysis Patients**

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**Background:** Patients undergoing automated PD (APD) are frequently fluid overloaded, while anuric dialysis patients with low fluid removal depict uncontrolled hypertension, LVH and worse survival. In this report, we aim to explore the correlation of overhydration (B-lines) as detected using lung ultrasound (LUS) in APD patients with their vital signs and weight.

**Methods:** Fourteen chronic APD patients were recruited at the Dialysis Clinic Inc. (DCI) PD center in Albuquerque, NM and completed their first visit of the pilot study LUMIFY-PD (Lung Ultrasonography to Measure Interstitial Fluid in Your Peritoneal Dialysis patients). Demographics, personal history, and laboratory values were collected from their electronic medical records. A pre-trained physician performed LUS with a handheld scanner (Phillips/Lumify, 2-5 Hz phased-array probe). Examination of the anterolateral chest was performed with longitudinal LUS scans (28 total segments per exam, supine position). LUS exams were scored for the presence and number of B-lines.

**Results:** Study participants had a mean age of 41.5 (± 3.4) years and were mostly males (52.9%), whites (57.1%) and Hispanics (50%). They were on PD for a mean of 9.9 (± 7.3) months. The two main causes of kidney disease were DM and hypertension. 57% exhibited at least 1 B-line in their LUS while 21.4% had mild lung congestion (at least 3 B-lines) (Figure). All patients with detectable B-lines had normal physical exams. A statistically significant correlation was found between age and number of antihypertensives (p = 0.03) as well as between number of B-lines in LUS and % of arterial oxygen saturation (p = 0.002). A negative correlation was found between number of B-lines and residual renal function volume (Pearson correlation -0.65).

**Conclusions:** In this report the number of LUS B-lines correlated with oxygen saturation and residual renal function volume. Larger studies are needed. Portable LUS can optimize the assessment of prescribed “dry weight” and thus improve outcomes of incident APD patients.

**Funding:** Other NIH Support - DCI through CTSC

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A study participant with B-lines in lung ultrasound

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**FR-OR105**

**Initiation of Peritoneal Dialysis in Patients with Cardiorenal Syndrome Reduces Subsequent Hospitalization**

Bourne L. Auguste,1 Ali Z. Ibrahim,2 Michael Y. Girsberger,2 Zita C. Abreu,2 Arnav Agarwal,1 Rory F. McQuillan,1 Joanne M. Bargman.2,1 University of Toronto, Toronto, ON, Canada; Toronto General Hospital, Toronto, ON, Canada; Sunnybrook Health Sciences Centre, Toronto, ON, Canada.

**Background:** Isotopic dependence and diuretic resistance in patients with cardiorenal syndrome (CRS) leads to frequent hospitalizations and is associated with high mortality. Peritoneal dialysis (PD) offers a smoother hemodynamic profile with effective volume removal for these patients. There is little data on this approach in the North American literature. The aim of our study was to determine if volume overloaded CRS patients on maximal doses of diuretic therapy had reduced heart failure hospitalization following PD initiation.

**Methods:** We reviewed CRS patients receiving a bedside catheter and starting PD urgently within 2 weeks of insertion at the University Health Network from January 1, 2013 to December 31, 2018. Data for heart failure-related hospitalizations and length of stay 6 months before and after PD initiation was collected. Patients who died, switched to hemodialysis or were transferred to another facility within 6 months of starting PD were excluded from analysis of the hospitalization rates.

**Results:** We identified 31 CRS patients who had a bedside PD catheter inserted. The average age of patients was 66.0 ± 13.0 years. There were 7 (22.6%) deaths and 4 (12.9%) transfers to other programs or hemodialysis within 6 months of catheter insertion. After exclusion, we analyzed the hospitalization and length of stay data for 20 patients. The hospitalization rate 6 months before PD initiation was 6.9 admissions per 1000 patient-days. This decreased to 2.5 admissions per 1000 patient-days after PD initiation (Figure 1). Additionally, there was also a striking reduction in the average length of stay (24.1 to 3.9 days; p < 0.001). Maximal doses of diuretic therapy have lower hospitalization rates and shorter stays after PD initiation. Adopting quality improvement strategies such as bedside PD catheter insertions can serve as a means to facilitate acute start dialysis in this population.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
FR-OR106

Associations Between Body Mass Index, Kt/V, and Outcomes Among Patients Treated with Peritoneal Dialysis

Scott Sibbel,1 Dena E. Cohen,1 Carey Colson,1 Francesca Tentori,1 Steven M. Brunelli,2 Martin J. Schreiber.1 1DaVita Clinical Research, Minneapolis, MN; 2DaVita, Inc, Denver, CO.

Background: Among patients treated with peritoneal dialysis (PD), achievement of Kt/V ≥ 1.7 indicates adequate dialysis. The volume of urea distribution (V) is based on bodyweight. Because the water content and metabolic activity of fat mass differ from that of lean, V may be over-estimated in obese patients, such that Kt/V under-estimates adequacy. Recalculation of V based on lean body mass might enable more accurate estimation of dialysis adequacy in such patients.

Methods: Data were derived from deidentified records of adults (body mass index [BMI] 15-45 kg/m²) who initiated PD with a large dialysis organization Jan 2016 – June 2018. Patients were followed from PD start until death, censoring, or study end (Dec 2018). Kt/V was calculated on the basis of bodyweight or estimated lean body mass. Associations between time-updated values of BMI, Kt/V, and outcomes were estimated using Poisson models that included an interaction term for BMI and Kt/V.

Results: At baseline, among 16,443 patients, mean BMI was 28.1 ± 5.8 kg/m², Kt/V was 2.4 ± 0.7, and 16.1% of patients had Kt/V < 1.7. Across BMI categories, lower Kt/V was associated with higher hospitalization rate; no interaction between Kt/V and BMI was observed (p>0.05). Similar results were obtained when Kt/V was recalculated on the basis of estimated lean body mass. Among patients with BMI≥30 and recalculated Kt/V ≥ 1.7 but standard Kt/V < 1.7, hospitalization rates were 1.98-fold (95% confidence interval 1.80 – 2.17) higher than among patients with Kt/V ≥ 1.7 by both measures.

Conclusions: Associations between Kt/V and outcomes do not differ on the basis of BMI. Calculation of Kt/V on the basis of estimated lean body mass may over-estimate dialysis adequacy, with potential negative consequences for patient outcomes.

FR-OR107

Prognostic Significance of Carotid Plaque Presence in Peritoneal Dialysis Patients and Its Association with the Apolipoprotein B/Apolipoprotein A1 Ratio

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Background: Atherosclerosis has been reported as a risk factor for cardiovascular disease in the general population. As a phenotype of atherosclerosis, carotid plaque and its influence factors are rarely discussed, especially among dialysis patients. The study aimed to investigate the prognosis-predictive significance of carotid plaques in patients on peritoneal dialysis (PD), and explore risks factors for carotid plaque presence.

Methods: It was designed as an observational, prospective study. Patients that had undergone stable peritoneal dialysis for at least 3 months were recruited and divided into two subgroups: group with carotid plaques and group without carotid plaques. Cox regression model was used to identify independent predictors of all-cause mortality, cardiovascular events and cardiovascular mortality. Risk factors correlated to the plaque occurrence were explored by logistic regression and verified by receiver operating characteristic curve (ROC) analysis.

Results: A total of 233 PD patients (141 men) with a mean age of 56.4±16.1 years were recruited. The cohort was followed for up to 86 months (median: 36.3 months; interquartile range: 21.3 months). In the multivariable Cox regression analysis, the carotid plaque presence turned out to be an independent risk factor both of cardiovascular events (HR: 2.420; 95%CI:1.157-5.064; p=0.019) and cardiovascular mortality (HR: 3.346; 95%CI:1.079-10.375; p=0.036). Multivariable logistic regression showed that the apoB/apoA1 ratio was significantly associated with the presence of carotid plaques. ROC analysis indicated that the AUC of the apoB/apoA1 ratio was 0.640, and it was higher than that of the traditional lipid metabolism index, the non-HDL-C/HDL-C ratio (p=0.012).

Conclusions: Carotid plaque presence can predict cardiovascular events and cardiovascular mortality in PD patients. The apoB/apoA1 ratio is significantly correlated to the plaque presence and it can be a more sensitive monitoring marker for predicting the presence of carotid plaques in this population than traditional lipid metabolism parameters.

Funding: Other NIH Support - National Natural Science Foundation of China (NSFC)

FR-OR108

Peritoneal Dialysis (PD) Modality and Interference in Daily Life: Results from the PDOPPS

Thuy P. Moras,1 Junhui Zhao,2 Douglas S. Fuller,2 Keith McCullough,2 Brian Bieber,2 Bruce M. Robinson,2 Ronald L. Pisoni,3 Simon J. Davies,3 Jeffrey Perl,4 on behalf of PDOPPS Dialysis Prescription and Fluid Management working group 1Pontificia Universidad Catolica do Parana, Curitiba, Brazil; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3University Hospital of North Midlands, Stoke-on-Trent, United Kingdom; 4St. Michael’s Hospital, Toronto, ON, Canada.

Background: Patient-reported outcomes (PROs), including quality of life and life participation activities, are important considerations for patients receiving peritoneal dialysis. The relative effects of automated (APD) vs. continuous ambulatory (CAPD) modalities on PROs remain controversial.

Methods: We analyzed cross-sectional clinical and patient-reported data from the PD Outcomes and Practice Patterns Study (PDOPPS; 2014-2017; Australia, Canada, Japan, New Zealand, UK, US). Patients rated dialysis interference with 9 aspects of daily life on a 7-point Likert scale. Linear and logistic regressions were used to estimate associations of PD modality with the interference item scores (mean and grouped as response levels 4-6 vs 0-3), KDQOL Mental Component Summary (MCS), Physical Component Summary (PCS) scores, and the 10-item CES-D depression screening scale (scale scores grouped as ≥10 vs <10), adjusted for demographic, comorbidity, and treatment variables.

Results: The analysis included 1800 APD and 892 CAPD patients. After adjustment, APD (v. CAPD) patients had 0.04 higher mean interference score (95% CI=0.09, 0.18), 0.05 lower MCS (-1.19, 1.09), 0.73 lower PCS (-1.73, 0.26), and 1.17 (0.94, 1.45) higher odds of CES-D ≥10 vs <10. APD (v. CAPD) patients reported less interference with employment (adjusted OR=0.83, 95% CI=0.62-1.2) and total PD time (0.86, 0.68-1.08), and greater interference with intimacy (1.18, 0.96-1.46) and the lives of family/friends (1.36, 1.09-1.69).

Conclusions: Summary PROs were generally similar for APD and CAPD patients, potentially due to non-randomized modality choice. However, domain specific differences in interference scores were observed that may be informative for patients when choosing PD modality type. Across both modalities, PD appears to interfere for the majority in domains of travel and employment suggesting that these are important areas to reduce the overall interference of PD with life activities.

Funding: Commercial Support - Baxter
FR-OR109

International PD Training Practices and the Risk of Peritonitis

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Background: Patient training for peritoneal dialysis (PD) is vital in reducing the risk of complications, including PD-related peritonitis. We describe variation in training practices across countries and assess their impact on peritonitis risk.

Methods: Using Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS, 2014-2017) data from Australia and New Zealand (ANZ), Canada (CA), Japan (JP), Thailand (TH), the UK, and the US (non-large dialysis organization facilities), we report variation in facility- and PD training practices and estimate associations with peritonitis using proportional rates models adjusted for patient and facility factors.

Results: 183 out of 204 facilities with peritonitis data available returned a PDOPPS Unit Practices Survey (US, n=83; other, n=140-26). Nearly all facilities reported using unit-affiliated training nurses only (UK, 72%; other, >95%), a standard training curriculum (UK, 65%; JP, 79%; other, >90%), individualized training (TH, 41%; other, >88%) and a single nurse per patient (JP, 28%; ANZ, 71%; other, >89%). All facilities required successful technique demonstration; 50% (US, 88%; other, 4-36%) required a written test, and 55% (CA, JP, UK, 24-40%; ANZ, TH, US, 57-70%) required an oral test. Peritonitis rate was associated with the timing of training relative to catheter insertion (HR=1.12 [95% CI=0.87, 1.44], HR=1.34 [1.04, 1.72], and HR=1.47 [1.11, 1.96] for 1, 2, or 3 weeks after catheter insertion, respectively, vs. prior to insertion; p<0.01 for trend) and longer duration of training (HR=1.04 [0.86, 1.24] and HR=0.84 [0.69, 1.02] for 4-5 and 6+ days, respectively, vs. 2-3 days; p=0.06 for trend).

Conclusions: Variation in PD training practices was seen across PDOPPS countries. Given the patient-centered nature of PD, earlier and longer training periods may reduce peritonitis risk.

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FR-OR110

Combination of Once Weekly Hemodialysis with Peritoneal Dialysis Is Associated with Lower Mortality Compared with Peritoneal Dialysis Alone: A Longitudinal Study

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Background: Combination of once weekly hemodialysis with peritoneal dialysis is a unique type of renal replacement therapy available in Japan. Outcomes of this therapy compared with peritoneal dialysis alone has not been reported in a large cohort.

Methods: This is a longitudinal study based on Japanese Renal Data Registry (JRDR). Those on peritoneal dialysis from 2010 to 2014 in the JRDR database were included. The end of observation period was at the end of 2015. Exposure of interest was combination of once weekly hemodialysis with peritoneal dialysis compared with peritoneal dialysis alone. Outcomes were all-cause mortality, cardiovascular mortality, and death due to congestive heart failure. Those who initiated combination therapy from 2011 to 2014 were matched with those on peritoneal dialysis alone by propensity score derived from the data of previous year. The data were analyzed using Kaplan-Meier curves and Cox regression models.

Results: Six hundred and eight patients on combination therapy were matched with 869 on peritoneal dialysis alone. During median follow-up of 2.5 years, there were 224 death, 123 cardiovascular death, and 35 death due to congestive heart failure. All-cause mortality (HR [95% CI]: 0.56 [0.42-0.75]), cardiovascular mortality (HR: 0.48 [0.32-0.72]), and death due to congestive heart failure (HR: 0.19 [0.07-0.55]) were significantly lower among combination therapy group. Transition to hemodialysis was significantly earlier in combination therapy group (HR: 1.72 [1.46-2.04]). There was no effect modification by age, dialysis vintage, diabetic status, or baseline urine volume. The decrease in body weight was larger in combination group (p<0.001 by mixed effects model in combination therapy group, suggesting better fluid removal.

Conclusions: Combination of once weekly hemodialysis with peritoneal dialysis was associated with lower mortality compared with peritoneal dialysis alone.

FR-OR111

Aptamer-Based Plasma Proteomic Profiling Reveals Candidate Proteins Associated with Slow or No Renal Decline in CKD Stage 3 Diabetic Patients

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Background: Patients with diabetes and chronic kidney disease (CKD) stage 3 are at high risk of developing end-stage renal disease (ESRD). However, the rate of renal decline leading to onset of ESRD varies tremendously among these patients. This study aimed to identify biomarkers associated with slow or no renal decline (slow decliners) in two independent cohorts of diabetic patients with CKD stage 3.

Methods: The study comprised an exploratory cohort of 214 individuals with Type 1 diabetes (T1D) with 129 slow decliners, and a replication cohort of 144 individuals with Type 2 diabetes (T2D) with 96 slow decliners. Both cohorts were followed for 7-10 years. Serial measurements of serum creatinine were used to estimate the rate of eGFR decline. Slow renal decline was defined as eGFR slope of ≥ -5 ml/min/year. Baseline plasma specimens were assayed by the SOMAscan proteomics platform. Relationships of plasma proteins with eGFR slopes were evaluated based on Spearman’s rank correlation coefficients. Multivariable logistic regression models identified the odds ratio (OR) between plasma proteins and being a slow decliner.

Results: In slow decliners, the median (25%, 75% percentiles) eGFR slope was -2.4 (-3.5, -1.3) and -1.8 (-3.1, -0.1) ml/min/year in T1D and T2D cohorts, respectively. In the exploratory cohort, 76 plasma proteins were significantly and positively associated with eGFR slope (FDR P<0.005). Eighteen of these proteins were replicated in the T2D cohort (P<0.05). Multivariable logistic analyses in the combined cohorts with T1D and T2D demonstrated that all proteins were significantly associated with slow renal decline in models adjusted for type of diabetes, eGFR and HbA1c. In models further adjusted for...
TNF-R1, the ORs remained statistically significant for 11 of the 19 proteins. TNFSF12 (OR (95% CI): 1.46 (1.2, 1.9), P=0.0017) was the most significant independent predictor of slow or no renal decline with higher TNFSF12 plasma levels protecting against progressive renal decline.

**Conclusions:** Our findings suggest that several circulating plasma proteins are associated with slow or no renal decline in both types of diabetes, and these proteins may represent new targets that can be used therapeutically for slowing the progression of renal function decline.

**Funding:** NIDDK Support, Private Foundation Support

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**FR-OR112**

Notch Signaling Proteins as Key Factor for the Progression to ESRD in Diabetes

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**Background:** It has been reported that Notch signaling proteins might regulate interstitial fibrosis development in the kidneys of mice and humans. The objective of this study was to investigate the association of Notch signaling proteins on the development of ESRD in subjects with diabetes during long-term follow-up.

**Methods:** Using the modified aptamer-based SomaScan platform, 4 proteins including Notch1, delta-like protein 1 (DLL1), delta-like protein 4 (DLL4), and Jagged 1 protein (JAG1) were measured in baseline plasma specimens obtained from 363 Caucasian subjects with diabetes and CKD stage 3 (CKD3); including 219 with Type 1 diabetes (T1D) and 144 with Type 2 diabetes (T2D). Additionally, the 4 proteins were also measured in 190 T1D patients with CKD stage 1 and 2 (CKD12). All patients were followed for 10 years to ascertain onset of ESRD.

**Results:** In Cox regression analysis, DLL1, DLL4, and JAG1 were strongly associated with progression to ESRD in T1D patients with CKD3 (P=1.6*10^-10, p=5.1*10^-10, and p=2.0*10^-10, respectively) and in T2D patients with CKD3 (p=3.6*10^-10, p=1.9*10^-10, and p=1.0*10^-10, respectively). Importantly, this significant association with ESRD for DLL1 and JAG1 was also found in patients with CKD2 (P=2.8*10^-9 and P=4.1*10^-10, respectively). DLL1 was the strongest predictor for ESRD in the combined panel, even after adjustment for relevant covariates (Hazard Ratio 1.48, p=8.4*10^-9).

**Conclusions:** There were few previous reports about the association between circulating Notch signaling proteins and kidney diseases. Our finding is novel in that circulating ligands for Notch receptors, especially DLL1, are strongly associated with circulating Notch signaling proteins and kidney diseases. Our finding is novel in that circulating ligands for Notch receptors, especially DLL1, are strongly associated with circulating Notch signaling proteins and kidney diseases. Our finding is novel in that circulating ligands for Notch receptors, especially DLL1, are strongly associated with circulating Notch signaling proteins and kidney diseases.

**Funding:** Other NIH Support - NIH - DK41526 and P30DK112177

Table 1. Cox regression model for each group

**FR-OR113**

Multicentre Prospective Validation of a Urinary Peptidome-Based Classifier for the Diagnosis of Type 2 Diabetic Nephropathy

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**Background:** Diabetic kidney disease (DKD) is a major late complication of diabetes. The ‘Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephropathy In Type 2 diabetic patients with normalalbuminuria trial’ (PRIORITY) is the first prospective study to evaluate the early detection of DKD in subjects with type 2 diabetes (T2D) and normal urinary albumin creatinine ratio (UACR) (<30 mg/g) using a urinary proteome-based classifier (CKD273).

**Methods:** Prospective multicentre observational study. The CKD273 classifier was assessed at baseline. The primary endpoint was development of confirmed microalbuminuria (≥30 mg/g) in 2 of 3 first urinaria (UAICR >30 mg/g) and with a ≥30% increase (geometric mean) from baseline. For subjects with estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73m² at baseline, development of CKD5: eGFR <60 ml/min/1.73m² was a secondary outcome. Mean follow-up time was 2.57 years with a minimum of 7 days and a maximum of 4.33 years.

**Results:** A total of 1775 participants from 15 centres were included, with 12% (n=216) of these having a high-risk proteomic pattern. At baseline, participants in the high-risk group were more likely to be men, older, had longer diabetes duration, lower eGFR and higher UACR than those in the low-risk group (p=0.002). Numerical differences were small and univariate regression analyses showed weak associations (R2<0.04) of CKD273 with each baseline variable. Development of persistent microalbuminuria was seen in 28% of high risk and 8.9% of low risk subjects (p=0.0001).

**Multivariate model was adjusted for baseline eGFR, HbA1c, ACR, and type of diabetes**

**FR-OR114**

Urinary Biomarkers of Injury and Repair and Risk for Kidney Function Decline or Mortality: Results from VA NEPHRON-D

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CKD Biomarkers Consortium (BioCon) Johns Hopkins University School of Medicine, Baltimore, MD; 6Cahn School of Medicine at Mount Sinai, New York, NY; Johns Hopkins University, Newton, MA; 7University of Nebraska, Lincoln, Nebraska, MD; 8UCSD, San Diego, CA; 9University Medical Center Groningen, Groningen, Netherlands.

**Background:** Diabetes is the leading cause of ESRD worldwide. Biomarkers of kidney injury and repair may prognosticate diabetic kidney disease beyond that of eGFR and albuminuria.

**Methods:** Baseline urinary biomarkers of tubular injury and repair (neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule –1 [KIM-1], interleukin-18 [IL-18], monocyte chemotactic protein-1 [MCP-1], chitinase-3-like protein-1 [YKL-40]) were measured by multiplex immunoassays. Using Cox proportional hazards models, we studied the associations of each biomarker with kidney function decline (first occurrence of absolute decrease in eGFR ≥30 ml/min/1.73m² if randomization eGFR<60, relative decrease ≥50% if randomization eGFR≥60, or ESRD) and all-cause mortality. Covariates included age, sex, race, BMI, blood pressure, HbA1c, treatment arm, eGFR, and UACR.

**Results:** We included 1136 VA NEPHRON-D participants with available baseline urine samples. Mean age was 65 years, 99% were male, mean eGFR was 56 ml/min/1.73m², and median UACR was 840 mg/g. Over a median follow-up of 2.2 years (IQR 1.3, 3.1), 148 (13%) experienced kidney function decline and 103 (9%) died. In unadjusted models, the hazard of kidney function decline was ≥20% higher per 2-fold greater baseline level of urine NGAL, IL-18, MCP-1, and YKL-40. These associations remained and were no longer significant after adjusting for baseline eGFR and UACR. Higher levels of urine NGAL, MCP-1, and YKL-40 were independently associated with higher risk of death (Table).

**Conclusions:** Among diabetic individuals with CKD, baseline values of urinary biomarkers of tubular injury and repair were associated with risk of death but not kidney function decline.

**Funding:** NIDDK Support, Veterans Affairs Support

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**FR-OR115**

Proximal Tubular Uptake of Free Fatty Acid (FFA) by Kidney Injury Molecule-1 (KIM-1) Mediates Tubulointerstitial Damage in Diabetic Kidney Disease (DKD), Which Is Attenuated by a Novel Inhibitor Yutaro Moriz,1 Amendra K. Ajay,1 Jie Huang Chang,1 Huiping Zhao,1 Seiji Kishi,1 Jiahua Li,1 Pierre Galichon,1 Craig R. Brooks,2 Sheng Xiao,1 Venlon, Sabitshetti1, Sueto A. Mwesigye,1 Joel M. Henderson,1 Joseph V. Bonventre,3 1Division of Renal Medicine, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 2Department of Nephrology, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan; 3Division of Nephrology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; 4Center for Neurologic Disease, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 5Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston, MA; 6Department of Nephrology, Peking University People’s Hospital, Beijing, China.

**Background:** DKD is associated with tubulointerstitial damage. KIM-1, a scavenger receptor, is the most upregulated proximal tubule protein in many forms of kidney injury. Dyslipidemia is a primary feature of DKD. We hypothesized that KIM-1-mediated uptake of FFAs contributes to tubulointerstitial damage in DKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Human DKD renal biopsy samples were analyzed. Renal epithelial cells expressing KIM-1 (LLC-PK1 cells) and interstitial cells (human primary cells) were exposed to palmitate followed by measurement of FFA uptake, cell death and pro-inflammatory and pro-fibrotic effects determined in vitro. To clarify the role of FFA uptake by KIM-1 in vivo, a DKD model induced by unilateral nephrectomy, streptozotocin and high fat diet (STZ-HFD) was studied in WT and Δmucin (functional knockout of KIM-1) mice. A second new model was created whereby KIM-1 was upregulated by aristolochic acid and the effect of subsequent injection of FFA was determined (AA-FFA model). An inhibitor for KIM-1-mediated endocytosis was screened from 1,000 compounds in vitro and in vivo showing reduced FFA uptake and injury only on WT, not on KIM-1Δmucin.

Conclusions: KIM-1 mediates the proximal tubule uptake of FFA, leading to pro-inflammatory and pro-fibrotic responses and increase in cell death. Our findings support the role of KIM-1 as a target for DKD and introduce a new candidate therapeutic agent.

Funding: NIDDK Support

FR-OR116

A Metabolomics-Based Pathway Analysis for How Dagapagilfizin May Slow Kidney Function Decline in Patients with Type 2 Diabetes

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Background: Sodium glucose cotransporter 2 inhibitors (SGLT2) slow progression of diabetic kidney disease (DKD). The underlying mechanisms are not fully elucidated. We examined which metabolic pathways are targeted by the SGLT2-diabetic glomerulopathy (DAPA), to explore the molecular processes involved in the renal protective effects with DAPA.

Methods: An unbiased serum metabolomics assay was performed on baseline and follow-up (week 12) samples from the EFFECT II trial in type 2 diabetes patients with nephropathy (N=938). The major therapeutic target of this intervention is the ERβC subtype of the 3DTC using VTEA is a powerful and efficient tool to assess glomerular cellularity in biopsy specimens. Using this tool, we detected an increase in glomerular cell density in diabetic human kidney biopsies in agreement with published reports. However, the differences seen in the glomerular cell density across reference tissues, but three of the five diabetic specimens showed significant increases in cellularity, albeit to different levels (p<0.05 using one-way ANOVA compared to reference). Interestingly, within each biopsy with DN, the cellular densities in all glomeruli were comparable to each other in both in vivo and in our newly identified compound prevented FFA uptake and injury only on WT, not on KIM-1Δmucin.

Conclusions: KIM-1 mediates the proximal tubule uptake of FFA, leading to pro-inflammatory and pro-fibrotic responses and increase in cell death. Our findings support the role of KIM-1 as a target for DKD and introduce a new candidate therapeutic agent.

Funding: NIDDK Support

FR-OR117

Assessing Glomerular Cellularity in Diabetic Human Kidney Biopsies with 3D Tissue Cytometry: Implications for Disease Progression

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Background: Diabetic nephropathy (DN) is a leading cause of kidney disease worldwide. At the tissue level, DN has been classified by morphology including glomerular size, tubular atrophy, and mesangial expansion. However, modifications in the microenvironment and 3D tissue structure (3DTC) provides a unique and efficient way to quantify and characterize the cellularity of glomeruli. Here, we examined the changes in cellular density across multiple kidney biopsy specimens with DN, compared to reference nephropathy tissue. We also sought to determine whether the changes in cellularity are indicative of a focal or diffuse response.

Methods: 5 non-DN reference nephropathy specimens and 5 kidney biopsy specimens with DN were stained with 4 to 8 markers and imaged by confocal fluorescence microscopy. Glomeruli were isolated digitally and analyzed using 3DTC with Volumetric Tissue Exploration and Analysis (VTEA) software. Cell density and immune cell subtypes were determined for each glomerulus within each specimen.

Results: When comparing all glomeruli from diabetics to those from the reference specimens, the average cellular density was increased in the diabetic group: 5927 ± 11649 vs. 2955 ± 8107 cells/mm², respectively (p = 0.05). When comparing between diabetic patients, there were no significant differences seen in glomerular cell density across reference tissues, but three of the five diabetic specimens showed significant increases in cellularity, albeit to different levels (p<0.05 using one-way ANOVA compared to reference). Interestingly, within each biopsy with DN, the cellular densities in all glomeruli were comparable to each other in both in vivo and in vitro. The contribution of immune cells to the increased cellularity in diabetes was minimal.

Conclusions: 3DTC using VTEA is a powerful and efficient tool to assess glomerular cellularity in biopsy specimens. Using this tool, we detected an increase in glomerular cell density in diabetic human kidney biopsies in agreement with published reports. However, the differences seen in the glomerular cell density across reference tissues, but three of the five diabetic specimens showed significant increases in cellularity, albeit to different levels (p<0.05 using one-way ANOVA compared to reference). Interestingly, within each biopsy with DN, the cellular densities in all glomeruli were comparable to each other in both in vivo and in vitro. The contribution of immune cells to the increased cellularity in diabetes was minimal.

Funding: NIDDK Support

FR-OR118

Regional Transcriptomic Profiling of the Human Kidney Uncover Major Signature Shifts in the Intersitium During Diabetes

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Background: The expression signature of the renal interstitium is less well characterized than that of the glomerulus and tubules. Here, we examine gene expression of the human renal interstitium in reference nephropathies and diabetic kidney biopsy specimens using laser micro-dissection (LMD).

Methods: We used LMD to collect cortical kidney tissue from five reference nephropathy (N=4) and diabetic renal biopsies (N=6). Rapid staining with DAPI, OG-Phalloidin, and Tam-Horsfall protein antibody identified relevant renal structures. LMD excluded tubules, glomeruli and large vessels. Transcriptomic data was obtained using nRNAseq on Illumina platform, and analyzed with R studio. The gene signature was compared to existing platforms such as mSRNAseq and sSRNAseq databases.

Results: Our laser micro-dissected interstitial tissues did not show significant expression of known tubular or mucosal markers (eg. NPHS1, LRBP2, UMOD, AQP2). In contrast, we identified a set of markers specific to the interstitium in reference nephropathy samples. While some of them were novel (eg. FABP2, ADRNDR1), others were commonly expressed across all three platforms (LTBP1, ELN, SYNM, ADCYT5, COL4A1, C1R). The expression of these genes was localized to expected cell types such as stromal, vascular and immune cells. The renal interstitium from diabetic biopsies revealed differential expression in many pathways including extracellular matrix organization (p<0.0037) and chemokine signaling (p<0.0065).

Conclusions: We successfully isolated the interstitium of human kidney samples using LMD. Gene expression from our samples correlated well with vasculature, immune cell clusters from mouse interstitium and sSRNAseq databases. Our LMD approach allows rich deconvolution of transcriptomic signatures from single cell datasets and facilitates backmapping of unidentified clusters to the interstitium. Dramatic changes in the gene expression in diabetic kidney interstitium suggest that this compartment may be an important player in the pathophysiology of diabetic nephropathy.

Funding: NIDDK Support

FR-OR119

Single Nucleus RNA Sequencing of Early Human Diabetic Nephropathy Reveals Transcriptional Changes That Promote Potassium Secretion

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Background: Diabetic nephropathy is characterized by damage to both the glomerulus and tubulointerstitium, but relatively little is known about cell-specific transcriptional changes. We hypothesized that single nucleus RNA sequencing (snRNAseq) of cryopreserved human diabetic kidney samples would reveal genes and signaling networks in early human diabetic nephropathy.

Methods: We analyzed three diabetic and three healthy human kidney samples. Diabetics had elevated Alc (mean = 7.9 ± 1.5%) and two of these patients had proteinuria. Baseline serum creatinine (mean = 1.06 ± 0.23 mg/dl) was not different

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
between groups. Nuclear preparations of cryopreserved samples were processed using 10x Genomes, sequenced by NovoSeq. Reads were counted with zUMIS v2.0 and analyzed with Sequr v2.3. Results: A total of 23,980 single nuclei were sequenced representing all glomerular and tubulointerstitial cell types. Infiltrating T-cells and B-cells were increased in diabetic samples. Side by side comparison showed cell-type-specific transcriptional changes important for ion transport, angiogenesis, and immune cell activation. In particular, the diabetic loop of Henle, late distal convoluted tubule, and principal cells show gene changes consistent with increased potassium secretion, including alterations in Na-K-ATPase, NKX1, NITD414, and mineralocorticoid receptor (Figure 1; green-upregulated, red-downregulated). These effects were accompanied by increased expression of CASR and decreased expression of CLDN16 in the loop of Henle, which regulate calcium and magnesium reabsorption. We also identify strong angiogenic signatures in glomerular cell types, proximal convoluted tubule, distal convoluted tubule and principal cells.

Conclusions: Early diabetes induces gene expression changes in the distal nephron coordinate to promote potassium secretion and angiogenesis.

Funding: NIDDK Support, Private Foundation Support

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**FR-OR121**

**Non-HLA Antibodies Targeting Angiotensin II Type 1 Receptor and Endothelin 1 Type A Receptors Induce Endothelial Injury via β2-Arrestin Link to mTOR Pathway**

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Background: Functional non-HLA antibodies targeting G protein-coupled receptors (GPCR) Angiotensin II type 1 receptor (AT1R) and Endothelin-1 type A receptor (ETAR) are implicated in the pathogenesis of transplant vasculopathy. While ERK signaling may represent general cellular response to agonist stimulation, the molecular link between receptor stimulation and development of vascular obliteration has not been fully established yet. We hypothesized the involvement of β-arrestins and PI3K/mTOR signaling and assessed functional consequences of AT1R- and ETAR-activation by non-HLA antibodies.

Methods: Human microvascular endothelial cells (HMEC) were stimulated with AT1R-Aβ and ETAR-Aβ IgG isolated from kidney transplant patients with chronic vasculopathy. Phospho-specific antibodies against ERK and mTOR downstream targets were used to assess activation of mTORC1 and mTORC2. β2-arrestin involvement was investigated using RNA silencing and laser scanning microscopy studies in ARRB2, GFP and ETA.myc-transfected HEK293 cells. Scratch assay was employed to study effect of non-HLA-antibodies on endothelial repair. Involvement of AT1R/ETAR activation was addressed by use of specific inhibitors.

Results: Signaling activity of both, mTORC1 and mTORC2, was increased after treatment with patient IgG compared to cells treated with IgG from healthy controls. This effect could be inhibited by specific AT1R- or ETAR-blockers. Activation of mTORC1 and mTORC2 were PFSK-dependent and independent from ERK. mTOR inhibitor rapamycin completely abolished activation of mTORC1 and in addition mTORC2 after long term treatment induced by receptor antibodies. Imaging studies revealed that β2- and not β1-arrestin was recruited to ERAT in response to ET1 and transplant patient IgG. Furthermore, AT1R and ETAR downstream signaling to ERK1/2 and mTORC2 was significantly reduced in β2-arrestin silenced HMECs. Non-HLA antibodies impaired endothelial repair by AT1R and ETAR induced mTORC2 signaling.

Conclusions: We provide evidence that functional AT1R-ETAR-Abs induce ERK1/2 and mTOR signaling involving β2-arrestins in human microvascular endothelium. Our data may provide a translational rationale for mTOR inhibitors in combination with receptor blocker in patients with non-HLA receptor recognizing antibodies.

Funding: Other NIH Support - NIAID, Private Foundation Support

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**FR-OR122**

**Tissue Resident Memory T Cells in Mouse Renal Transplantation**

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Background: The newly identified tissue resident subset of memory T cells (TRecM) provides immune surveillance in the tissue and first response against infections. They are functionally, transcriptionally, and phenotypically distinct from circulating effector and central memory T cells. The role of TRecM in transplantation is unknown. In this study, we investigated the formation and function of TRecM in a mouse kidney transplantation model.

Methods: Syngeneic B6 or allogeneic (B6×BALB/c) F1.ova kidneys were transplanted to B6 recipients and 1 million OT-I effector T cells were transferred on day 0. Graft, blood, bone marrow, SLO, and liver tissues were harvested 4 and 8 wks after transplantation. Scratch assay was measured using i-Stat analyzer. T1/2 were identified phenotypically as CD45+CD8α+CD62L-CD20+CD103- cells after excluding in vivo labeled T cells. OT-I and polyclonal TRecM were transcriptional characterized using scRNAseq. We tested TRecM residency in the graft by performing para-basis between 4-wk transplanted CD45.1 B6 mice that contained OT-I effectors and CD45.2 B6 parabionts that had received F1.ova kidneys but no OT-I. Whether TRecM are sufficient for rejection was tested in a re-transplantation model using spleenectomized LTB/+/ mice as secondary recipients of F1.ova grafts containing TRecM. Depletion experiments are underway to further establish causal relationship between TRecM and rejection.

Results: Mean serum creatinine (mg/dL) was significantly higher in allogeneic vs syngeneic group at wk 8 (0.8 vs 0.2, p<0.05). Graft histology showed mixed acute and chronic rejection in the allogeneic group. Flow analysis of allograft cells demonstrated TRecM cells among OT-I and endogenous T cell populations at 4 and 8 wks. The OT-I population was exclusively TRecM phenotype by flow and scRNAseq, rapidly produced IFNγ upon re-stimulation, and was not detected anywhere else. There was no significant difference in mean number of OT-Is between wk 4 and wk 8 (125k vs 79k, p<0.04). OT-I T cells could not be detected in the parabiont kidney graft or tissues or in the secondary host outside the retransplanted kidney, indicating that TRecM do not re-circulate. Chronic rejection progressed in re-transplanted kidneys that harbored TRecM.

Conclusions: Our findings show that donor-specific TRecM form in kidney allografts, are functional, and could contribute to rejection.

Funding: Other NIH Support - NIAID, Private Foundation Support
FR-OR123

Single Cell RNA Sequencing of Antibody-Mediated Rejection and Control Kidney Transplant Biopsies Reveals Endothelial, T-Cell, and Monocyte Intercellular Communication and Host-Donor Chimerism

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Background: Antibody mediated rejection (AMR) is one of the major causes of allograft failure yet current treatment strategies are suboptimal reflecting our poor understanding of this disease. We performed single cell scRNAseq on biopsies from patients with AMR and compared them to non-AMR biopsies.

Methods: The 10X platform was used for library preparation. Sequencing depth was ~50k reads/cell. CellRanger, R and Seurat were used to make gene-cell matrices and for downstream analyses. Donor and recipient exome sequencing was also performed. IRB approved.

Results: 96,547 cells (avg=1292 genes detected/cell) from 7 kidney transplant biopsies were included in the integrated analysis using UMAP. 21 cell clusters were identified and included all major tubular types (PT,LOH,PC,IC), stroma, endothelium, lymphocytes (T and B cells) and monocytes (figure). In AMR biopsies, monocytes expressed the B cell activator BAFF and B cells upregulated expression of its cognate receptors TAC1 and BMCA, suggesting monocyte driven B cell activation. Endothelial cells in AMR showed increased expression of cytokines that recruit T cells such as CXCL9, as well as the chemokine receptor ACKR1, suggesting that endothelial cells amplify the immune response. Of note, we could distinguish host from donor leukocytes based on expressed SNVs defined by exome sequencing. Whether donor-derived leukocytes exhibit differential gene expression compared to their host counterparts is under analysis.

Conclusions: Comprehensive scRNAseq of human AMR suggests that monocytes drive B cell activation and that endothelial cells recruit T cells. We also show, for the first time, that donor leukocytes persist even years after transplantation. Whether donor-derived leukocytes differentially regulate AMR represents a new and potentially important direction in transplantation research enabled by scRNAseq.

Funding: NIDDK Support

FR-OR125

Protective Role of Kynurenine 3-Monoxygenase in Kidney Allograft Rejection

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Background: Rejection of a transplanted kidney is a complex adaptive immune response and is the primary driver of graft loss. Kynurenine 3-monoxygenase (KMO) is an oxidoreductase involved in the kynurenine pathway of tryptophan metabolism and has been associated with inhibition of T cell proliferation. Our previous study demonstrated that indoleamine 2,3-dioxygenase (IDO) was upregulated in rejecting allografts, and was associated with reduced KMO expression. Herein, we investigated the role of KMO in preventing rejection in a pig model of kidney transplantation, and in protecting renal cortical epithelial cells (RCEC) following exposure to cytokines common to inflammation.

Methods: Outbred Yorkshire pigs underwent mismatched kidney transplants as we have described (Transplant Immunol 42:40). No immunosuppression was used and the tissue was studied 72 hours post-transplant. Immunohistochemistry (IHC) was performed to measure allograft expression of KMO. Cultured RCEC were utilized measure KMO, IDO, and the epithelial-mesenchymal transition markers E-cadherin and tight junction protein 1 (TJP1), following cytokine activation with and without treatment with the drug KMO was silenced, and the expression of E-cadherin and TJP1 was blunted. The addition of 3HK completely restored E-cadherin and TJP1 expression. In additional studies, we showed that high dose 3HK (100ug/ml) effectively inhibits human peripheral blood pan-T cell proliferation.

Conclusions: KMO may be a key modulator of allograft immune responses as suggested by its downregulation in rejecting allografts. Moreover, KMO, through the generation of 3HK, may exert cytoprotective effects through preservation of normal parenchymal architecture, by retained expression of E-cadherin and TJP1 and inhibition of T cell proliferation. Inducing KMO, with the generation of 3HK in renal allografts, may provide an avenue for novel therapies in renal transplantation.

Funding: Private Foundation Support

FR-OR124

Modulation of Ischemia-Reperfusion Injury (IRI) Post-Renal Transplantation in Estrogen Receptor-α Knockout (ERα-KO) Mice in vitro and in vivo


Background: IRI is a major contributor to early allograft dysfunction(EAD) post-kidney transplantation. We have demonstrated lower rates of EAD among female renal transplant recipients in UNOS, and using a murine model, showed improved IRI tolerance after KMO inhibition of 17β-estradiol in both warm and cold renal IRI. We now investigated the contribution of ERα to this protection, and the utility of SERM administration in wild type mice.

Methods: Female C57BL/6(B6) and ERα-KO mice were used. We transplanted kidneys from B6→B6, ERα-KO→B6, and B6→ERα-KO, followed by native nephrectomy. All groups were treated with 17β-estradiol (1 mg/kg) and subsequently underwent temperature-controlled IRI(28min at 36°C). In a separate experiment, B6 mice received either Lasoxifene(LAS),Raloxifene(RAL),Tamoxifen(TM),Bazedoxifene(BAZ), or vehicle (all 10mg/kg in DMSO) prior to warm IRI. Serum creatinine(Cr) was measured at 24-hour intervals post-surgery in both experiments.

Results: Mice in the B6→ERα-KO group had significantly higher Cr compared to B6→B6 and ERα-KO→B6 groups(Figure 1a). Mice treated with LAS prior to IRI had significantly lower Cr compared to controls(Figure 1b). RAL, TAM, or BAZ did not provide significant protection(Figure 1c).

Conclusions: Loss of estrogen-derived protection from warm IRI in the B6→ERα-KO group indicates that the mechanism for this protection is extrinsic to the kidney. Protection from IRI in the LAS-treated group demonstrates that selective ERα activation outside the breast and uterus, potentially sparing off-target effects, is sufficient for protection from IRI. Lack of significant protection from IRI after RAL, TAM, and BAZ is likely due to differential affinity of each drug for ERα in extra-renal tissues. Collectively, these data provide new insights into the mechanisms by which estrogen-based therapy can improve early outcomes in renal transplantation.

Funding: NIDDK Support
image analysis was performed and mean speed, displacement, arrest coefficient (AC) and contact times (CT) with DC were calculated for OT-I, OT-II and NP-B cells.

**Results:** CB6F1 RIP-LTα grafts rejected significantly faster (MST= 54) than CB6F1 grafts (MST= 225), demonstrating that TLO contribute to allograft rejection. Grafts from both groups harvested at the time of rejection demonstrated interstitial fibrosis, lymphocytic infiltrates and TLO, positive for B, T and HEV-marker PNAd. CB6F1 RIP-LTα grafts contained similar numbers of, but larger TLO than CB6F1 grafts. Mean speed and displacement of OT-I and OT-II cells significantly decreased over time after immunization while AC and mean CT significantly increased. B cell mean speed, displacement and AC increased over time after immunization. These data are consistent with B cell activation and productive T cell-DC interactions and mirror previously reported data in secondary lymphoid organs.

**Conclusions:** We provide first evidence that TLO provide a local structure for T and B cell activation that might propagate anti-graft immune responses in the setting of chronic rejection. Further studies will elucidate the formation and maintenance of TLO and the cell activation that might propagate anti-graft immune responses in the setting of chronic rejection.

**Funding:** Other NIH Support - NIAID, Private Foundation Support

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**FR-OR127**

**Deciphering Shared Gene Expression Patterns by Whole-Genome Transcriptomics of Urinary Cells and Kidney Allograft Biopsies**

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**Background:** Urinary cell mRNA profiling to interrogate kidney allograft (KTx) status is based on the premise that the allograft can function as an in-vivo flow cytometer and sort graft destructive/protective T cells into the urinary space. We used RNA-Seq of urinary cells to demonstrate that urinary cell mRNA profiles mirror intragraft events and urinary cells are enriched for immune cells in acute rejection.

**Methods:** We performed global RNA-seq to characterize mRNA transcriptomes of urinary cells from 57 KTx recipients with T Cell Mediated Rejection (TCMR), n=22, Antibody Mediated Rejection (AMR), n=8, Normal, n=27, and allograft tissues from 49 KTx recipients (ACR n=12, AMR n=17, and Normal n=20). We analyzed the urine and biopsy profiles using Gene Set Enrichment Analysis (GSEA) and a gene-signature expression based cell-type deconvolution tool xCell.

**Results:** By GSEA analysis, genes upregulated in the KTx biopsies with TCMR and AMR were upregulated in the urinary cells with TCMR and AMR (FDR-P<0.01). There were 76 differentially expressed mRNAs that were shared between urine and biopsy profiles in TCMR, and 191 differentially expressed mRNAs that were shared between urine and biopsy AMR. Deconvolution analysis revealed higher enrichment of stromal cell score in the biopsies compared to urine, whereas immune cell profiles were enriched in the urine.

**Conclusions:** GSEA of RNA-seq data from urinary cells and kidney allografts demonstrate enrichment of genes related to immune cells in urinary cells that is undiluted by the stromal component. Our data support the use of urine as an excellent biospecimen for biomarker discovery and development as well as for deciphering the anti-allograft repertoire.

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**FR-OR128**

**Altered Gut Microbial Fermentation and Colonization with Methanobrevibacter smithii in Renal Transplant Recipients**


**Background:** The gut microbiota of kidney transplant recipients (RTR) differs from that of healthy controls (HC). This may have consequences for gut microbial fermentation. Breath hydrogen (H₂) and methane (CH₄) concentrations are markers of fermentation in the gut, of which CH₄ is mainly produced by Methanobrevibacter smithii (M. smithii). We aimed to investigate (1) whether breath H₂ and CH₄ concentrations differ between RTR and HC, (2) whether the presence of M. smithii in faeces differs between RTR and HC and (3) whether presence of M. smithii is related to breath H₂ and CH₄ concentrations.

**Methods:** All study subjects participated in the TransplantLines biobank cohort study. Organ donors served as HC. Breath H₂ and CH₄ concentrations were analysed using solid state-sensor gas-chromatography. Presence of M. smithii in faeces was determined with real-time PCR.

**Results:** A total of 152 RTR and 77 HC were included. Breath H₂ concentrations of RTR were not significantly different from HC (median [IQR] 11.3 [4.0-30.0] ppm vs. 10.5 [4.5-28.3] ppm, p=0.92). However, RTR had significantly lower breath CH₄ concentrations compared to HC (7.5 [3.9-10.6] ppm vs. 16.0 [8.0-45.5] ppm, p<0.001). In addition, M. smithii was found less frequently in RTR compared to HC (86.4% vs. 28.6%, p<0.001). In absence of M. smithii, there was a significant positive correlation between breath H₂ and CH₄ (r = 0.88, p<0.001). There was no correlation if M. smithii was present (r = 0.09, p=0.50).

**Conclusions:** Breath CH₄ concentrations and the prevalence of M. smithii in faeces were significantly lower in RTR compared to HC, which indicates RTR have altered microbiota and altered gut microbial fermentation. In absence of M. smithii, CH₄ is highly
dependent on H₂ production, while this is not the case in the presence of M. smithii. These findings provide novel insight in the alterations of gut microbiota secondary to renal transplantation and the use of immunosuppressants.

**Funding:** Commercial Support - This work was supported by a grant from Astellas BV.

**FR-OR129**

Extracellular Vesicles Mediate Complement Activation and Tubular Senescence in Renal Antibody-Mediated Rejection

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**Background:** Renal Antibody-Mediated Rejection (AMR) is characterized by a strong complement activation that can lead to a premature senescence in tubular epithelial cells (TEC). EVs (Extracellular vesicles), circulating microparticles able to mediate cell-to-cell communication, are emerging as pivotal in different kidney diseases. The aim of this study was to investigate whether AMR-derived-EVs could induce tubular inflamming aging and complement activation.

**Methods:** Renal biopsies, serum and serum-isolated-EVs from 10 Acute and Chronic AMR patients were collected. TEC culture were incubated with EVs (5E+4 EVs/cells target for 24h); then to assess cellular senescence qPCR for p21, p53, Klotho and CYP1B1 and SA-β-gal staining were performed. mRNA level of C3 and C4H were also measured. Inflamming (p16[INK4a] and Klotho) markers were evaluated by IHC. Endothelial cells were grown in serum free media, incubated with AMR-derived EVs for 24h, then C4d IF was performed.

**Results:** Renal AMR biopsies showed significant tubular senescence as indicated by p16[INK4a] expression; p16[INK4a] was significantly upregulated in Chronic compared with Acute AMR biopsies (p<0.05). In vitro, the exposure of TEC to AMR serum induced senescence as observed by the upregulation of p21 and p53 genes levels (p<0.05). Furthermore, EVs exposed-TEC were characterized by significant increase in p21, p53 and CYP1B1 gene expression and down-regulation of Klotho (p<0.05) indicating that EVs can induce tubular senescence. In accordance, EVs induced a higher number of SA-β-gal+ TEC compared with control serum (p<0.05); the cells appeared larger and polynucleated indicating typical senescence phenotype. Finally, EVs from AMR patients induced a significant increase in C3 gene expression with concomitant downregulation in C4H in TEC associated with C4d deposition on endothelial cells in serum free medium.

**Conclusions:** In AMR patients, circulating EVs induced accelerated inflamming aging in TEC via dys-regulation of Complement system at cellular level. This new pathogenic mechanism led to tubular senescence phenotype. Finally, EVs from AMR patients induced a significant increase in C3 expression with concomitant downregulation in C4H in TEC associated with C4d deposition on endothelial cells in serum free medium.

**SA-OR0001**

Multicenter Study of Immune Checkpoint Inhibitor-Associated AKI

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**Background:** Immune checkpoint inhibitor-associated AKI (ICPi-AKI) is an increasingly frequent complication of immunotherapy. However, existing data on ICPi-AKI are limited to small, mostly single-center studies.

**Methods:** We contacted nephrologists and oncologists at >20 major cancer centers across the U.S. and Canada, and identified 138 patients from 18 institutions with ICPi-AKI. All patients were required to have at least a doubling of serum creatinine or need for dialysis, along with a clinical diagnosis of ICPi-AKI by the provider. Detailed data were collected using a standardized case report form. We also collected data on 276 control patients who received ICPis but did not develop AKI. Multivariable logistic regression was used to determine risk factors for development of ICPi-AKI and prognostic factors for its recovery.

**Results:** Lower baseline eGFR, concomitant use of a PPI, and combination ICPi therapy were each associated with a greater risk of ICPi-AKI. The median time from initiation of an ICPi to AKI was 14 (IQR, 6–37) weeks. An extra-renal immune-related adverse event (irAE) occurred concomitantly with AKI in 43% of patients. Most patients had proteinuria and pyuria. A kidney biopsy was obtained in 43% of patients, with acute interstitial nephritis (AIN) found in 93%. Overall, 87% of patients were treated with steroids, of whom 43%, 43%, and 13% had complete, incomplete, and no renal recovery, respectively. Concomitant extra-renal irAEs were associated with worse renal prognosis, while concomitant AN-inhibiting medications and treatment with steroids were associated with improved renal prognosis. ICPi re-challenge occurred in 22% of patients, of whom 23% developed recurrence of AKI.

**Conclusions:** Using a multicenter approach, we present the largest clinical study to date to describe the clinical and pathologic features of ICPi-AKI.
SA-OR002

Safety of Immune Checkpoint Inhibitors for Cancer Treatment Among Kidney Transplant Patients: A Systematic Review

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Background: The use of immune checkpoint inhibitors have significantly improved outcomes in multiple cancer types. Kidney Transplant (KTx) recipients are excluded from trials due to the concern of allo-immunity and possible allograft rejection. Aim of this systematic review was to assess the safety of checkpoint inhibitors among KTx patients.

Methods: Literature search was conducted utilizing MEDLINE, EMBASE and Cochrane Database from inception through April 2019. We included studies that reported outcomes of kidney transplant recipients who received immune checkpoint inhibitors for cancer therapy. Outcomes of interest were allograft rejection and/or allograft failure, The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42019126777).

Results: 27 articles with a total of 44 KTx patients treated with immune checkpoint inhibitors were identified. Of 44 KTx patients, 18 were reported to have acute rejection of renal allograft. Among those with acute allograft rejection following the treatment, 83% were males with mean age of 62 +/- 13 years. 8 (44%) patients received nivolumab, 3 (17%) received pembrolizumab, 2 (11%) received ipilimumab followed by pembrolizumab, 2 (11%) received ipilimumab followed by nivolumab, and 1 (6%) received pembrolizumab followed by nivolumab. Cancer types were melanoma (66%), lung cancer (17%), and metastatic squamous cell carcinoma of skin (12%), respectively. 3 patients had a partial remission (17%), a patient achieved cancer response (6%) and 5 patients had stable disease (28%). Median time from immune checkpoint inhibitors to acute rejection diagnosis was 24 (IQR 10-60) days. Reported outcomes of kidney transplant recipients who received immune checkpoint inhibitors for cancer therapy. Outcomes of interest were allograft rejection and/or allograft failure, The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42019126777).

Conclusions: The findings of our study raise awareness of the potential risk of acute allograft rejection/failure following immune checkpoint inhibitors for cancer treatment among KTx patients. Future large-scale clinical studies are required to appraise the pathogenesis and plan optimal therapy that helps sustain graft tolerance without discouraging clinical benefits of immune checkpoint inhibitors for cancer treatment.

SA-OR003

Predictors of AKI in Patients Undergoing CAR-T Cell Therapy

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Background: Chimeric Antigen Receptor T-cell therapy (CAR-T) is an emerging immunotherapy used to treat certain malignancies. Organ dysfunction, including acute kidney injury (AKI), has been described, and hypothesized to be due to cytokine release syndrome (CRS). Predictors of AKI in patients receiving CAR-T cell therapy have not been adequately studied. We conducted a retrospective cohort study of patients receiving CAR-T cell therapy at our institution, in an attempt to identify those patients who are at risk of developing AKI after receiving this therapy.

Methods: We reviewed the charts of patients who received CAR-T between 5/2016 and 9/2018. A total of 58 patients were included in the study. Development of AKI was defined as increase in creatinine of at least 0.3 above baseline. 32% of patients (N = 19) developed AKI. Univariate analyses were conducted to delineate significant differences between patients who developed AKI compared to those who did not with regards to baseline characteristics, inflammatory markers (CRP, ferritin), albumin, markers of organ dysfunction (AST, bilirubin), and the use of any steroids or tocilizumab.

Results: Carvacristate and Univariate and Multivariate analyses were performed. Most patients were male (66%), and the median age was 47 (IQR 32-69). Most patients had melanoma (66%), lung cancer (17%), and metastatic squamous cell carcinoma of skin (12%), respectively. 3 patients had a partial remission (17%), a patient achieved cancer response (6%) and 5 patients had stable disease (28%). Median time from immune checkpoint inhibitors to acute rejection diagnosis was 24 (IQR 10-60) days. Reported outcomes of kidney transplant recipients who received immune checkpoint inhibitors for cancer therapy. Outcomes of interest were allograft rejection and/or allograft failure, The protocol for this meta-analysis is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42019126777).

Conclusions: CAR-T cell therapy is gaining increased use for various malignancies. Models have been proposed to predict, diagnose and manage CRS, but not specifically AKI. Our findings indicate that baseline patient characteristics and inflammatory response markers, particularly ferritin, may play a role in predicting worse renal outcomes. Future work may focus on creating a broader predictive model that can help identify and guide management of patients receiving CAR-T who are at risk of AKI.

SA-OR004

AKI and Electrolyte Abnormalities in Patients Receiving Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

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Background: CAR-T cell therapy targets tumor antigens using genetically engineered cytotoxic T-cells, and is a breakthrough treatment for hematologic malignancies. Cytokine release syndrome (CRS), a systemic inflammatory response, is a known complication of CAR-T. CRS can lead to acute kidney injury (AKI); however, scant data exist on AKI risk compared to 13%, p=0.008).

Conclusions: CAR-T cell therapy is gaining increased use for various malignancies. Models have been proposed to predict, diagnose and manage CRS, but not specifically AKI. Our findings indicate that baseline patient characteristics and inflammatory response markers, particularly ferritin, may play a role in predicting worse renal outcomes. Future work may focus on creating a broader predictive model that can help identify and guide management of patients receiving CAR-T who are at risk of AKI.
SA-OR005

Carfilzomib-Associated Nephrotoxicity: A Systematic Review and Meta-Analysis
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Background: There has been growing interest in the field of onco-nephrology with the advent of novel antineoplastic treatments, many of which portend nephrototoxic properties. Emergence of new proteasome inhibitors (PI) has resulted in significant improvement in survival of patients with multiple myeloma (MM). Carfilzomib (CFZB) is a second-generation PI currently approved for relapsing or refractory MM. We sought to explore whether CFZB is associated with nephrotoxicity (NTX).

Methods: The present review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. Articles cited in PubMed, Web of Science, and Clinical Trials Registry, using keywords “Carfilzomib” and “Kyprolis” were searched. A meta-analysis was performed. Cumulative incidence and odds ratios (OR) were calculated using random effect model. We used Common Terminology Criteria for Adverse Events to grade NTX.

Results: A total of 22 studies including 2484 patients were selected. The cumulative incidence of all-grade NTX (grade 1[mild] to grade 5[death]) was 15.5% (CI:11.1-22.1%); high-grade NTX, (grades 3-5 [life-threatening or resulting in death]) was 4.7% (CI: 3.3-6.7%). Estimated overall OR of all-grade NTX was 1.81 (CI: 1.09-3.02, p = 0.02). Similarly, the OR of high-grade NTX was 1.85 (CI: 0.93-1.75, p = 0.08). We found no difference in the incidence of all-grade (p =0.38) and high-grade (p =0.46) NTX between newly diagnosed, relapsing, or refractory MM groups. The high dose of CFZB did not change the incidence of NTX compared to standard dose (p=0.66 and p=0.61 respectively). Similarly, the incidence of NTX was not significantly different when CFZB was used alone or in combination (p=0.63 and p=0.44 respectively). However, concomitant use of immunomodulators significantly increased the incidence of all-grade (p =0.001), but not high-grade, CFZB-related NTX (p = 0.89).

Conclusions: Currently available data supports the notion that CFZB use is associated with increased risk of NTX. While the risk does not seem to be dose-dependent, it does increase with concomitant use of immunomodulators. Clinicians need to be aware of this complication when considering CFZB use and possibly consider alternative options in patients at risk of renal injury or for those who develop NTX. These results also call for rigorous monitoring of renal function with CFZB use.

SA-OR006

Characterization of the Acute eGFR Response to SGLT2-Inhibition with Empagliflozin
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Background: Empagliflozin (EMPA) reduces cardiovascular (CV) and renal risk in type 2 diabetes patients with established CV disease. As shown with RAAS blockade, EMPA also causes an acute eGFR decrease after treatment initiation. Although considered hemodynamic and reversible, it needs to be better understood to avoid premature drug discontinuation.

Methods: In EMPA-REG OUTCOME®, 6,668 participants who received at least one dose of study drug and had an eGFR value at both baseline and week 4 were categorized by % acute eGFR change: >10% decrease, >0% to ≤10% decrease, ≥0% decrease. eGFR over time was analyzed using mixed model repeated measures. Acute renal failure (ARF) incidence was based on investigator-reported adverse events according to the narrow standardized MedDRA query.

Results: As expected, there were more patients with a >10% decrease in eGFR (28.3%) than in PBO (13.4%); however, an acute eGFR drop >30% with EMPA was rare (1.4%). After initial dynamics, long-term eGFR remained stable in all categories on EMPA (Figure). In multivariate regression analyses, KDOQI risk category (elevated UACR/low eGFR) and diuretic use at baseline were independent predictors of an acute eGFR decrease >10% with EMPA. From baseline to week 4, irrespective of the magnitude of the eGFR decrease, overall adverse events (AEs) and serious AEs were similar or lower with EMPA than PBO. ARF was more frequent in patients experiencing an acute eGFR decrease >10% in both groups, however most were reported as “renal impairment”. During chronic treatment, overall and renal safety profiles were similar between PBO and all categories on EMPA.

Conclusions: Given the known renal protection with SGLT2 inhibition, our data demonstrate a relatively modest acute eGFR decrease with treatment, less likely to cause discontinuation of this reno-protective therapy.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

SA-OR007

Renin-Angiotensin-Aldosterone System Blockade Is Associated with Higher Risk of Contrast-Induced AKI in Patients with Diabetes: A Multicenter Propensity Score-Matched Study
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Background: CIAKI is a relatively common complication after treatment of coronary angiography (CAG) and percutaneous coronary intervention (PCI). The role of ACEIs or ARBs on CIAKI is controversial.

Methods: A retrospective, multi-center design with propensity score matching (PSM) was used to evaluate the effect of ACEIs/ARBs on the occurrence of CIAKI in diabetic patients undergoing CAG and PCI. The primary endpoint CIAKI was defined as an increased serum creatinine level of a 25% or 44 µmol/l (0.5mg/dl) over the baseline level within 72 hours after contrast agent exposed.

Results: A total of 2240 patients from four centers met the inclusion criteria. On the basis of PSM, 704 patients with ACEIs/ARBs were successfully matched to the control group. The incidence of CIAKI in the ACEIs/ARBs group was significantly higher than that in the control group (26.6% vs.16.2%, P< 0.001), no matter which kind of medicine was used in subgroups. In-hospital endpoints, patients with CIAKI had a higher risk of worsening heart failure (2.3% vs. 1.0%, P= 0.068). However, patients in the control group had an increased risk of overall adverse cardiovascular events (death, myocardial infarction, worsening heart failure, stroke) after PCI (3.8% vs. 1.8%, P= 0.034).

Conclusions: The ACEI/ARB was associated with an increased risk of CIAKI in patients with diabetes, but beneficial for early cardiovascular outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Background: Multiple studies have demonstrated that the combination of vancomycin and piperacillin-tazobactam (VPZ) is associated with increased risk of AKI compared to the combination of vancomycin and cefepime (VC) in the general population. Whether this holds true for critically ill patients is particularly important, given that AKI is very common in this population and is associated with increased mortality. Currently the data in critically ill patients is limited and the effect of VPZ in this population is controversial. Thus, the goal of this study was to determine the association between VPZ and AKI in critically ill adults.

Methods: A meta-analysis of observational studies that enrolled critically ill patients receiving VPZ or VC in the ICU setting was conducted. Electronic databases (PubMed, Cochrane and Embase) were searched through April 2019. Effect estimates and 95% CIs were pooled using the random effects model in STATA. The primary outcome was AKI as defined by the individual study. The secondary outcome was time to AKI.

Results: Literature search identified 6 published studies with 6764 patients. The definition of AKI was based on RIFLE, KDIGO or AKIN criteria. The odds of AKI in the VPZ group were higher compared to the VC group (odds ratio, 1.50; 95% CI 1.29-1.76; p<0.001) (Figure 1). There was no difference in the time to AKI between the VPZ group and the VC group (mean difference, -0.06; 95% CI, -0.09 to 0.74 days).

Conclusions: In critically ill patients, concomitant use of vancomycin and piperacillin-tazobactam is associated with an increased risk of AKI just as in the general population. This finding should be taken into consideration when choosing empiric antimicrobial coverage for critically ill patients. The included studies demonstrated some heterogeneity. Thus, future research regarding the use of VPZ in critically ill patients is warranted to confirm these findings.
SA-OR010
A Novel Targeting Strategy That Can Prevent Cholesterol Crystal Embolism-Induced AKI and Kidney Infarction
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Background: Cholesterol crystal embolism (CCE) is a life-threatening complication of advanced atherosclerosis and often missed as a cause of AKI. Due to the lack of a suitable animal model, little is known about the pathophysiology of CCE.

Methods: We injected the left kidney of C57/BL6 mice with cholesterol crystals (CC). CC injection induced CCE in interlobar, arcuate, and interlobular arteries (A). Not CC alone but CC-induced clots obstructed arteries and caused a tight dose-dependent GFR decline (B), i.e., CCE-related AKI, while infarct size showed a higher variability (C). Deficiency of Mbl protected mice from kidney infarction but not AKI, suggesting only targeting crystal clots but not kidney infarct may prevent AKI. Crystal clots were made of fibrin, neutrophils, platelets, and extracellular DNA. Fibronectin with pDNA and recombinant DNase all reduced arterial occlusions, GFR loss, and infarct size. For DNase the window-of-opportunity was 3h after CCE. To maximize the renoprotective effect in a clinically potentially feasible manner we tested a single prophylactic dose of necrostatin-1s before CCE and gave DNase 3h after CCE, which completely prevented AKI and kidney infarction (D, E). In vitro, CC activated platelets, triggered NETs formation, and killed endothelial cells (F). All these mechanisms lead to the DNA release into extracellular space.

Conclusions: CCE induces kidney infarction but AKI develops independently from infarction due to obstruction of pre-glomerular vessels. Not CC but CC-induced clots lead to vascular obstruction. The extracellular DNA as a critical component in CC-induced clots. The window-of-opportunity for DNase therapy is 3h. A 2-step dual targeting strategy can entirely prevent AKI and infarction.

SA-OR011
Pregnancy-Related AKI and Diabetes: Hospitalizations and Clinical Outcomes
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Background: Pregnancy-related acute kidney injury (AKI) is a public health problem and is associated with significant maternal and fetal morbidity and mortality. Clinical outcomes in pregnancy-related AKI, especially in women with diabetes are not well studied.

Conclusions: Up to 40% of ELGANS have at least one episode of Neonatal AKI. Epo is not protective for AKI in ELGANS. Whether Epo impacts urine kidney biomarkers or long-term CKD remains an area of investigation.

Funding: NIDDK Support, Other NIH Support - NINDS

SA-OR012
Use of Urinary Neutrophil Gelatinase Associated Lipocalin (NGAL) to Rule Out AKI in Children with High Nephrotoxic Medication Exposure
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Background: Nephrotoxic medication (NTMx) exposure is one of the most common causes of AKI in hospitalized children. We have demonstrated sustained reductions in NTMx exposure and associated AKI by implementation of the Nephrotoxic Injury Negated by Just in time Action (NINJA) program at our institutions. The NINJA program puts processes in place to identify high NTMx exposure and implements daily SCR assessment in exposed patients. Daily blood draws for SCR can be burdensome for the hospital care system and patients. We tested the hypothesis that daily urine NGAL assessments could be used to screen for NTMx AKI, allowing for a more limited SCR assessment.

Methods: This was a 2-center prospective study of children identified with high NTMx exposure (3 or NTMx on the same day or ≥3 days of IV vancomycin or an IV aminoglycoside). Patients had daily SCR drawn as standard of care for the NINJA program. Urine for NGAL measurement (The NGAL Test™, Bioporto, Denmark) was obtained for the first 7 days of high NTMx exposure. AKI was defined by the SCR based KDIGO criteria, and severe AKI (sAKI) was defined as KDIGO Stage 2 or 3 AKI.

Results: 117 patients had 498 urine samples available for analysis. 27 patients had AKI; 9 patients had severe AKI. The performance of NGAL at various concentrations (ng/ml) to predict AKI and severe AKI is shown in the table.

Conclusions: Urine NGAL level < 150 ng/ml has high NPV for any AKI and sAKI. We suggest NGAL can be used to complement SCR as part of the assessment for NTMx AKI, limiting the burden on providers and patients associated with a daily blood draw.

Funding: Commercial Support - Bioporto Diagnostics, Inc

<table>
<thead>
<tr>
<th>NGAL (ng/ml)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-50</td>
<td>94%</td>
<td>96%</td>
<td>98%</td>
<td>97%</td>
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<td>50-150</td>
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<tr>
<td>300+</td>
<td>91%</td>
<td>94%</td>
<td>94%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CI

SA-OR013
Association Between Urinary Dickkopf-3, AKI and Subsequent Loss of Kidney Function in Patients Undergoing Cardiac Surgery: An Observational Cohort Study
Stefan J. Schenk,1 Alexander Zarbock,2 John A. Kellum,1 Danilo Fliser,2 Thimoteus Speer,1 Stephen Zewinger.1 *Saarland University Hospital, Homburg/Saar, Germany; 2Department of Internal Medicine IV, Saarland University, Homburg/Saar, Germany; 3University of Pittsburgh, Pittsburgh, PA; 4University Hospital Münster, Münster, Germany.

Background: Cardiac surgery is associated with a high risk of postoperative acute kidney injury (AKI) and subsequent loss of kidney function. We explored the clinical utility of urinary dickkopf-3 (Dkk3), a renal tubular stress marker, for prospective identification of patients at risk for AKI and subsequent kidney function loss.

Methods: The study comprised consecutive patients who had elective cardiac surgery at the Saarland University Medical Centre (Homburg, Germany; derivation cohort) and
those undergoing elective cardiac surgery who were enrolled in the prospective RenalRIP multicentre trial (validation cohort) and who were randomly assigned to receive remote ischaemic preconditioning or a sham procedure. The association between the ratio of preoperative urinary concentrations of DKK3 to creatinine (DKK3:creatinine) and postoperative AKI, and subsequent kidney function loss was assessed.

DKK3 concentrations were independently associated with significantly lower kidney function at hospital discharge and after a median follow-up of 820 days. In the RenalRIP trial, preoperative urinary DKK3:creatinine concentrations higher than 471 pg/mg were associated with a significantly higher risk for AKI (OR 1.94, 95% CI 1.08–3.47, p=0.026), persistent renal dysfunction only in patients having a sham procedure, but not remote ischaemic preconditioning.

Conclusions: Preoperative urinary DKK3 is an independent predictor for postoperative AKI and for subsequent loss of kidney function. Urinary DKK3 might aid in the identification of patients in whom preventive treatment strategies are effective.

SA-OR014
The Association Between Intraoperative Fluid Balance and Postoperative AKI in Noncardiac Surgery
Masatoshi Nishimoto,1 Miho Tagawa,1 Maiko Kokubu,2 Takayuki Hamano,2 Masaru Matsui,2 Masahiro Irieuchi,1 Ken-ichi Samejima,1 Yasuhiro Akai,1 Kazuhiko Tsuruya,1 1Nara Medical University, Kashihara, Japan; 2Osaka University Graduate School of Medicine, Suita, Japan; 3Nara Prefecture General Medical Center, Nara, Japan.

Background: Insufficient fluid administration may cause prerenal acute kidney injury (AKI) though excess fluid administration was reported to be associated with postoperative AKI in cardiac surgery. Little is known about the association between intraoperative fluid balance (IFB) and postoperative AKI in non-cardiac surgery.

Methods: This is a retrospective cohort study on adults who underwent non-cardiac surgery under general anesthesia from 2007 to 2011 at Nara Medical University. Exclusion criteria were urological or obstetric surgery, those with missing data for analyses, and preoperative dialysis. The exposure of interest was IFB and outcome variable was postoperative AKI in non-cardiac surgery.

Results: Data for 5,168 subjects were available for analyses. Median age was 63, 46.7% were male, and baseline eGFR was 78.2. AKI was observed in 309 (6.0%). Higher IFB (per 1 SD) was independently associated with postoperative AKI after adjustment for baseline characteristics, intraoperative blood pressure, and intraoperative use of medications (Table 1). A subgroup analysis indicated the association between higher IFB and AKI was similar across intraoperative urine output or amount of bleeding (p for interaction = 0.27 and 0.43, respectively). There were no effect modifications by age, sex, preoperative renal function, or prior history of cardiovascular disease.

Conclusions: Higher IFB was independently associated with postoperative AKI. Association was similar across urine output. These results suggest that the association was not due to decrease in intraoperative urine output. Excessive fluid administration might cause renal congestion and subsequent AKI.

Table 1. Odds ratio for postoperative AKI associated with per 1 SD increase of intraoperative fluid balance.

<table>
<thead>
<tr>
<th>Model</th>
<th>Odds ratio (95% CI)</th>
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<tbody>
<tr>
<td>Unadjusted</td>
<td>1.33 (1.22–1.45)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.20 (1.09–1.33)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.19 (1.08–1.32)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.18 (1.07–1.31)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.18 (1.07–1.31)</td>
</tr>
</tbody>
</table>

SA-OR015
Plasma Biomarkers to Identify Patients at Increased Risk of CKD Following an Episode of AKI
Nicholas M. Selby,1,2 Michelle Hutchinson,2 Rebecca A. Packington,2 Elizabeth M. McCole,2 Mary Jo Kurth,3 Claran Richardson,2 Peter Fitzgerald,2 Rosamonde E. Banks,1 1Centre for Kidney Research and Innovation, University of Nottingham, Nottingham, United Kingdom; 2Department of Renal Medicine, University Hospitals of Derby and Burton, Derby, United Kingdom; 3University of Leeds, Leeds, United Kingdom; 4Randox Laboratories Ltd, Antrim, United Kingdom.

Background: The long-term sequelae of acute kidney injury (AKI) on renal function and mortality are increasingly appreciated, but there remains the need for prospective studies to develop strategies to identify those at greatest risk. We aimed to test whether biomarkers improve prediction of long-term outcomes of AKI.

Methods: In a single centre, participants were identified using a hospital-wide electronic AKI detection system. Plasma samples were collected at 3 months after hospitalisation and a panel of 14 biomarkers were measured using a multiplex biochip array method. This was done firstly in a discovery cohort (112 AKI patients) with the most prevalent markers assayed in the remaining 388 AKI patients (validation cohort). Measures of renal function, proteinuria and survival were assessed at 1 and 3 years. CKD progression was defined as ≥25% decline in eGFR from baseline (pre-AKI) with a decline in eGFR stage.

Results: Median age was 70yrs (IQR 14). AKI episodes were predominantly stage 1 with median duration 3 days (IQR 3) and 29% had pre-existing CKD. There was no difference in age, gender or smoking status between discovery and validation cohorts. The proportion of AKI patients with CKD progression was 21% and 22% at year 1 and 3 respectively. Mortality was 4.3% at year 1 and 15.8% at year 3. Clinical factors associated with CKD progression included eGFR at 3 months, albuminuria, severity and duration of AKI. In the discovery cohort, four markers were associated with CKD progression, including NGAL and cystatin C. Multiplexed models were developed to include biomarkers and clinical variables; when the models derived in the discovery cohort were applied to the validation cohort, AUC’s improved e.g. AUC of best performing model in validation cohort 0.81 (95% CI 0.75 to 0.87) to discriminate those with CKD progression at 1 year.

Conclusions: Non-recovery of renal function is common following AKI, even in a general hospital population with predominantly AKI stage 1. We present data evaluating the utility of a panel of biomarkers to identify those at highest risk.

Funding: Private Foundation Support

SA-OR016
Arterial Stiffness Independently Predicts AKI in SPRINT
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Background: Arterial stiffness is associated with increased risk for kidney function decline and cardiovascular disease in both healthy and chronic kidney disease populations, independent of blood pressure. An episode of acute kidney injury (AKI) is also associated with increased risk for kidney disease progression and cardiovascular disease. However, it is unclear if arterial stiffness predicts AKI. We hypothesized that higher arterial stiffness at baseline was independently associated with time to incident AKI among participants in the Systolic Blood Pressure Intervention Trial (SPRINT).

Methods: Arterial stiffness was measured as carotid femoral pulse-wave velocity (CFPWV) in 613 older adults at high risk for cardiovascular events who participated in an ancillary study of SPRINT. Cox proportional hazards analysis was used to examine the association between baseline CFPWV and time to incident AKI.

Results: Mean±sd age was 72±9 years and 40% (n=244) of participants were female. Mean±sd baseline CFPWV was 10.8±2.7 m/s in the whole cohort. In the 593 individuals who did not have an AKI event, baseline CFPWV was 10.7±2.7 m/s. In the 20 participants who had incident AKI, baseline CFPWV was 12.5±2.7 m/s (p<0.01) and median (IQR) time to AKI was 453 (289-724) days. After adjusting for demographics, randomization group, comorbidities, smoking, number of antihypertensive medications, baseline estimated glomerular filtration rate, urinary albumin to creatinine ratio, and systolic blood pressure, risk of an AKI event was 32% higher for each m/s increase in baseline CFPWV (HR: 1.32, 95% CI: 1.13-1.53).

Conclusions: Greater large-elastic artery stiffness is a strong independent predictor of incident AKI in older adults at high risk for cardiovascular events. Clinical assessment of arterial stiffness may represent a useful tool to predict AKI, as well as a potential therapeutic target.

Funding: NIDDK Support, Veterans Affairs Support
SA-OR017

Predicting Severe AKI, Fluid Overload, and Renal Replacement Therapy with the Renal Angina Index in Critically Ill Children
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Background: The Renal Angina Index (RAI) and urinary Neutrophil Gelatinase Associated Lipocalin (uNGAL) can be used to risk stratify patients for development of severe AKI (sAKI). Our research has focused on combining the RAI and NGAL for early detection and acute kidney injury (AKI) prediction.

Methods: Patients admitted to the Pediatric Intensive Care Unit (PICU) from 7/1/18 to 11/30/18, underwent an automated RAI assessment 12 hours after admission. RAI+ patients were defined by RAI ≥ 8 and had uNGAL assessed. A cutoff value of 150ng/mL was used to stratify patients with the primary outcome measure the development of sAKI (KDIGO Stage 2 or 3) through PICU day 4. Secondary outcomes included fluid overload (FO) and renal replacement therapy (RRT) at PICU day 7, as well as PICU length of stay (LOS).

Results: Over our study period 1103 RAIs resulted from 1022 patients. After excluding patients with ESRD and with admissions less than 2 days, 627 RAIs from 569 patients were examined, of which 63 (10.0%) were RAI+. The incidence of Day 2-4 sAKI was higher in the RAI+ cohort compared to RAI- patients (38% vs. 1.8%, p<0.001). With the addition of uNGAL, the rate of sAKI in RAI+NGAL+ was higher than in RAI+NGAL- or RAI- patients (55.5% vs 17.6% vs 1.8%, p<0.001). RAI+ patients had a higher need for RRT compared to RAI- patients (13% vs. 0.4%, p<0.001). PICU and hospital length of stay were also longer in RAI+ patients; PICU LOS 4.6 vs 3.1 days (p<0.02), Hospital LOS 17.8 vs 7.5 days (p<0.001). There was no significant difference between RAI+ vs. patients in the occurrence or duration of FO (p=0.14, p=0.11).

Conclusions: The RAI alone continues to be a good rule-out test for sAKI in the PICU, and addition of NGAL is promising for improved sAKI prediction. Additional research needs to be conducted on a larger sample size to better assess the clinical relevance of the RAI NGAL model in predicting sAKI and other relevant outcomes.

Funding: NIDDK Support

Performance of RAI and NGAL in Predicting sAKI

<table>
<thead>
<tr>
<th></th>
<th>RAI+ (n=38)</th>
<th>RAI+NGAL+ (n=30)</th>
<th>RAI+NGAL- (n=15)</th>
<th>RAI- (n=559)</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>76.7% (25/33)</td>
<td>86.7% (26/30)</td>
<td>60% (9/15)</td>
<td>70.6% (395/559)</td>
</tr>
<tr>
<td>Specificity</td>
<td>93.0% (411/441)</td>
<td>89.6% (281/313)</td>
<td>100% (30/30)</td>
<td>94.0% (512/548)</td>
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</table>

SA-OR018

Hemoglobin A1c and Major Adverse Kidney Events After Cardiac Surgery
Samuel Short1, Gregory L. Hunderman,1 James Rawn,2 Andrea L. Axtell,2 David E. Leaf,1 1Brigham and Women’s Hospital, Boston, MA; 2Massachusetts General Hospital, Boston, MA.

Background: Diabetes mellitus (DM) is a well-known risk factor for acute kidney injury (AKI). However, nearly all prior studies in the setting of AKI assessed DM as a dichotomous variable. We investigated whether hemoglobin A1c, assessed categorically and continuously, associates monotonically and independently with AKI following cardiac surgery.

Methods: We performed a retrospective cohort study in 15,892 patients who underwent cardiac surgery at two medical centers in Boston, MA, between 2008-2018. The primary exposure was the most recent A1c within 6 months prior to surgery. We assessed A1c in 6 categories: low (<5%), reference (5–5.6%), prediabetes (5.7–6.4%), well-controlled DM (≥ 6.5–6.9%), moderately-controlled DM (7–8.9%), and poorly-controlled DM (>8) and had uNGAL assessed. A cutoff value of 150ng/mL exposure was the most recent A1c within 6 months prior to surgery. We assessed A1c in 6 categories: low (<5%), reference (5–5.6%), prediabetes (5.7–6.4%), well-controlled DM (≥ 6.5–6.9%), moderately-controlled DM (7–8.9%), and poorly-controlled DM (>8) and had uNGAL assessed. A cutoff value of 150ng/mL

Results: The incidence of MAKE7 was 12%. Compared to the reference group, we observed a monotonic increase in the risk of MAKE7 with higher A1c categories. Patients with an A1c ≥ 9 vs. 5.5–6.5% had a nearly two-fold higher risk of MAKE7 in unadjusted models (odds ratio, 1.99; 95% CI, 1.56 to 2.53). We found similar results in multivariable adjusted models that included 13 key variables (Figure). We also found similar results in adjusted models that assessed higher stages of AKI. When assessed as a continuous variable, the adjusted odds ratio for MAKE7 per 1% increase in A1c was 1.10 (95% CI, 1.05 to 1.15). Finally, patients with an A1c <5% also appeared to be at increased risk of MAKE7.

Conclusions: Both higher and lower hemoglobin A1c values are independently associated with higher risk of MAKE7 following cardiac surgery.

Funding: NIDDK Support

SA-OR019

Contrast-Associated AKI Is Not Reflective of Intrinsic Injury
Caroline Liu,2 Steven D. Weisbord,1,4 James S. Kaufman,1 Heather Thiessen Philbrook,1 Maria K. Mot,2 Paul M. Palevsky,2 Chirag R. Parikh.1 PRESERVE Trial Study Group 1Johns Hopkins University School of Medicine, Baltimore, MD; 2VA Pittsburgh Healthcare System, Pittsburgh, PA; 3Division of Nephrology, VA New York Harbor Healthcare System, New York, NY; 4University of Pittsburgh School of Medicine, Pittsburgh, PA; 1Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA.

Background: There is controversy regarding the mechanism of contrast-associated acute kidney injury (CA-AKI). Biomarkers may provide insight into whether the etiology of CA-AKI is mediated by nephron injury. The PRESERVE trial followed participants for CA-AKI and 90-day major adverse kidney events and death (MAKE-D) after contrast angiography. In this sub-study, we evaluated the association of the absolute changes (Δ) and relative ratios of urine and plasma biomarkers with CA-AKI and MAKE-D.

Methods: We measured injury (KIM-1, NGAL, IL-18) and repair (MCP-1, UMOD, and VHL) proteins in urine and plasma at baseline and 2-4 hours post-angiography in a subset of PRESERVE trial participants. We calculated the absolute Δ and relative ratio between post-operative and baseline levels. We then assessed the association between absolute Δ and relative ratios with CA-AKI and MAKE-D.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Participants (n=922) were predominately male (96%), diabetic (82%) with mean age of 70±8 years. 73 and 60 participants experienced CA-AKI and MAKE-D, respectively. The absolute Δs and relative ratios were not statistically different by CA-AKI status (Figure). The majority of participants experienced an insignificant decrease in biomarkers regardless of CA-AKI or MAKE-D status. Findings remained after indexing urine biomarkers to urine creatinine and after adjusting for baseline eGFR and urine albumin to creatinine ratio.

Conclusions: The lack of significant differences in injury and repair biomarkers in patients by CA-AKI and MAKE-D status suggests that CA-AKI is not mediated by intrinsic nephron injury. While our findings need to be validated, our results can help advance pharmacological developments for the prevention of CA-AKI.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute (R01HL085757), Veterans Affairs Support

SA-OR021
Clonal Hematopoiesis in ANCA-Associated Vasculitis
Marlene Weiss,1 Anthony Rousseau,2 Lars Bullinger,3 Kai-Uwe Eckardt,4 Ralph Kettritz,5 Frederik Damm,2 Adrian Schreiber,1 Charlie Berlin, Berlin, Germany; 2Department of Hematology, Oncology, and Tumor Immunology, Charité – Universitätsmedizin Berlin, Berlin, Germany; 3Charité – Universitätsmedizin, Berlin, Germany; 4Charité – Universitätsmedizin Berlin, Berlin, Germany; 5Charité – Universitätsmedizin Berlin, Berlin, Germany.

Background: Antineutrophil cytoplasmatic autoantibodies (ANCA)-associated vasculitides (AAV) are induced by binding of ANCA IgG to myeloid cells and their subsequent activation. Autoantigen expression has been described to be dysregulated on both molecular and protein expression level in AAV patients. Recently, clonal hematopoiesis of indeterminate potential (CHIP), which is defined by the presence of a somatic mutation in the peripheral blood of individuals without evidence of hematologic neoplasms, has been linked with increased risk of hematologic and cardiovascular disease. Here we aimed to characterize CHIP in patients with AAV.

Methods: 112 patients with AAV (median age 64, range 18-84) were screened for CHIP using targeted sequencing. mRNA expression of PR3 and MPO in peripheral blood leukocytes was quantified by qPCR, ANCA autoantigen expression and neutrophil reactive oxygen generation were measured by flow-cytometry.

Results: CHIP was discovered in 34 out of 112 AAV patients (in total of 46 somatic mutations), which is a higher prevalence than expected in age-matched healthy controls (30.4% vs. 13.5%, p<0.001). The overall frequency of CHIP increased with age, however, 18.2% of patients <55 years had CHIP. The most frequently mutated genes were DNMT3A (19/46=41.3%), TET2 (7/46=15.2%) and ASXL1 (5/46=10.9%). CHIP was not associated with disease activity, ANCA subtype, or therapy. No differences in blood counts, creatinine levels, comorbidities, the development of malignancies, disease activity status, and AAV relapse risk were observed. However, disease manifestation patterns differed: CHIPpositive GPA patients showed less renal (68.2% vs. 88.5%, p=0.080) and nervous system involvements (0% vs. 19.2%, p=0.028). Longitudinal analysis of 23 CHIP clones in 19 selected patients revealed that more than 25% of patients showed an increase in clone size over time. Finally, a downregulation of both PR3 and MPO mRNA in peripheral blood leukocytes and significant less ROS production after ANCA IgG stimulation of neutrophils from CHIPpositive AAV patients compared to CHIPnegative patients (stimulation-index aMPO 7.8±4.5 vs. 15.9±3.9 and aPR3 6.8±3.1 vs. 13.2±7.7) was found.

Conclusions: Our findings provide novel experimental evidence of CHIP in AAV patients. Additionally, we found a functional impact of CHIP on ANCA-associated neutrophil functions.

SA-OR022
Staphylococcus Aureus-Induced Tissue Resident Memory T Helper 17 Cells (Th17 Cells) Drive Renal Autoimmune Disease
Christian F. Krebs,1 Daniel Reimers,1 Yu Zhou,2 Patricia Bartsch,3 Alina Borchers,1 Malte Hellmig,1 Christoph Kilian,6 Leon U. Eriken,1 Jan-Hendrik Riedel,4 Tobias B. Huber,1 Jan-Eric Turner,4 Ulf Panzer,1 Hans-will Miittricke,1 Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 2University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 3University Medical Center Hamburg, Hamburg, Germany; 4UKE, Hamburg, Germany; 5Institute for Immunology, Hamburg, Germany; 6UKE, Hamburg, Germany.

Background: Tissue resident memory T (Trm) cells represent a new type of memory cell population that is resident in peripheral organs without recirculating. They provide rapid on-site immune protection against previous exposed pathogens. However, it remains to be clarified whether Trm cells also interfere with responses unrelated to the primary infection, such as organ-specific autoimmune.

Methods: To study Trm cells, we used a combined approach of flow cytometry, histology and single cell RNA-sequencing. Human kidney tissue was obtained from tumour-nephrectomies. In mice, renal Th17 cells were induced by S. aureus infection. GN was induced with the nephrotoxic sheep serum or by immunisation with a fragment of the α-helix 19-23 of the complement C5a.

Results: Among study participants who did not have AKI during index hospitalization (N=806), mean age was 65 years, mean eGFR 74 ml/min/1.73m², and 45% self-reported history of eGFR, and adjudicated HF events. The majority of participants experienced an insignificant decrease in biomarkers regardless of CA-AKI or MAKE-D status. Findings remained after indexing urine biomarkers to urine creatinine and after adjusting for baseline eGFR and urine albumin to creatinine ratio.

Conclusions: The lack of significant differences in injury and repair biomarkers in patients by CA-AKI and MAKE-D status suggests that CA-AKI is not mediated by intrinsic nephron injury. While our findings need to be validated, our results can help advance pharmacological developments for the prevention of CA-AKI.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute (R01HL085757), Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
in the kidney. Renal Th17 cells persist long-term (>100 days) after clearance of the nephrotic stimulus and the phenotype of Treg cells and partially protect against renal inflammation. Induction of autoimmune kidney disease (cGN) in mice, which recovered from S. aureus infection, resulted in a more rapid and aggravated renal Th17 response and consequently developed a more severe course of cGN. By labelling renal cells in photoconvertible Kaeble-transgenic mice, we were able to demonstrate that S. aureus induced Th17 cells contribute significantly to the enhanced local IL-17 immune response in cGN.

Conclusions: Thus, pathogen-induced Th17 cells in peripheral tissues are capable of rapidly responding to an antigenic unrelated challenge thereby driving renal autoimmune disease. These data suggest that Th17 cells might have a previously unknown role in amplifying organ-specific autoimmunity.

Funding: Government Support - Non-U.S.

SA-OR023
Infiltrating Citrullinated Histone (CitH3)-Positive Neutrophils May Be Involved in Active Glomerular and Interstitial Lesions in ANCA-Related Vasculitis
Hidehito Shimizu,1 Yusuke Arakawa,1 Shuichi Tsuruoka,2 Akiko Mii,1 1Nippon Medical School, Tokyo, Japan; 2Nippon medical school, Tokyo, Japan; 3Nippon Medical School, Tokyo, Japan.

Background: Activated neutrophils release neutrophil extracellular traps (NETs), resulting in cell death called NETosis. NETs formation has been reported to be involved in the onset of systemic lupus erythematosus and ANCA-related vasculitis (AAV). However, the precise mechanism is unknown. Citrullination of histones is an essential step for NETs formation, and the presence of citrullinated histones (CitH3) in neutrophils may be involved in disease induction and activity. We examined an association between infiltrating neutrophils with without CitH3 and disease specificity and activity in various glomerulonephropathies (GN).

Methods: We selected following cases, who presented proliferative GN with neutrophil infiltration; AAV (n=8), lupus nephritis (LN) (n=5), Henoch schönlein purpura nephritis (HSPN) (n=3), crescentic glomerulonephritis (CGN) (n=5). We assessed clinical characteristics and histopathological findings and examined myeloperoxidase (MPO)-positive (+) infiltrating neutrophils with or without CitH3 in glomeruli and interstitium and association with the necrotizing and crescentic glomerular lesions and tubulointerstitial lesions.

Results: Number of MPO+ neutrophils in glomeruli was significantly higher in PSAGN, LN and HSPN than in AAV. In LN, MPO+ neutrophils were found mainly on the margin of glomerular tufts which formed wire-loop lesions. In part of them, CitH3+ neutrophils were seen. In PSAGN and HSPN, many MPO+ infiltrated in glomeruli, however, only a few CitH3+ neutrophils. In contrast, the frequency of CitH3+ neutrophils in AAV was significantly higher while the number of MPO+ neutrophils was significantly lower than in other diseases. CitH3+ neutrophils were observed in necrotizing lesion along glomerular capillaries. Moreover, the frequency of CitH3+ neutrophils was significantly higher not only in glomeruli but also in interstitium than in the others. In addition, peritubular capillaritis with CitH3+ neutrophils was remarkable.

Conclusions: CitH3 immunostaining was useful tool for identifying activated neutrophils. In AAV cases, the frequency of CitH3+ neutrophils in both glomeruli and interstitium was highest. The frequency of CitH3+ neutrophils was not only a disease specific marker but also a possibility of becoming a marker for disease activity in AAV.

SA-OR024
CFHR5 Deposition in ANCA-Associated Glomerulonephritis
Silke R. Brix,1,2 Kajal Patel,1 Martin Busch,3 Christine Skerka,4 Rolf A. Stahl,5 Thorsten Wiech,4 1Manchester University NHS Foundation Trust, Manchester; 2Manchester Royal Infirmary, Manchester, United Kingdom; 3University of Manchester, Faculty of Biology, Medicine and Health, Manchester, United Kingdom; 4Department of Pathology, University Hospital Hamburg-Eppendorf, Hamburg, Germany; 5University of Hamburg, Hamburg, Germany; 6Leibniz Institute for Natural Product Research and Infection Biology, Jena, Germany; 7University of Manchester, Manchester, United Kingdom.

Background: The complement system has been found to play a role in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Complement factor H (CFH) is a negative regulator of complement C3 activation. Complement factor H related protein 5 (CFHR5) competitively binds factor 3 yet enables further complement activation. We hypothesized CFHR5 facilitates more aggressive renal ANCA disease.

Methods: Here, we investigated CFHR5 deposition in biopsies of patients with ANCA-associated glomerulonephritis (GN) from a multicenter cohort (n=207) and correlation with clinical outcomes. Granular mesangial and endothelial deposition was scored semiquantitatively (0-3).

Results: Initial renal function at time of diagnosis did not correlate with CFHR5 staining. Patients, however, who reached end stage kidney disease during-follow up were followed to be a more prominent CFHR5 deposition than patients who remained dialysis independent (p<0.0001). Patients suffering from renal relapsing disease and patients who died during follow-up showed a stronger CFHR5 positivity as well (p=0.01, p=0.03).

Conclusions: Glomerular CFHR5 positivity is associated with renal outcome in ANCA-associated GN and may serve as a prognostic marker in the disease.

SA-OR025
Induction of Eosinophilic Granulomatosis with Polyangiitis by Myeloperoxidase-ANCA in Mice with Allergic Airway Disease
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Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a phenotype of ANCA vasculitides associated with asthma, and blood and tissue eosinophilia. EGPA is characterized by eosinophil-rich infiltrates, granulomatous infiltration, necrotizing vasculitides and pauci-immune crescentic glomerulonephritis (CGN). We hypothesized that EGPA can be induced by injecting anti-MPO into mice with asthma-like disease.

Methods: Ovalbumin (OVA) or house dust mites (HDM) were used to induce allergic airway inflammation in BALB/c mice that were injected either intraperitoneally (i.p.) with 20μg OVA on days -21 and -7 and administered intranasally (i.n.) 1% OVA in saline on days 1-5; or administered 25μg HDM protein i.n. in 20μl PBS for 5 days, followed by 2 days of rest, then repeated for another week, followed by 2 daily HDM doses. Thereafter, mice received 75μg g body weight anti-MPO IgG i.p. Mice were sacrificed 6 days after anti-MPO injection.

Results: Control mice receiving OVA(n=3) or HDM(n=3) but no anti-MPO developed mild eosinophilic-rich pulmonary airway inflammation without pulmonary necromegaly, granulomatous lesions, or CGN. Mice receiving anti-MPO without OVA or HDM (n=3) developed CGN but no lung lesions. Six days after i.v injection of anti-MPO IgG, OVA(n=3) or HDM (n=3) treated mice developed more extensive eosinophil-rich pulmonary inflammation, acute capillaritis with hemorrhage and granulomatous inflammation containing numerous eosinophils with admixed multinucleated giant cells. All mice receiving anti-MPO had similar levels of serum anti-MPO and developed similar CGN severity (avg. crescents with OVA 18.7%, HDM 18.7% and anti-MPO alone 18%); whereas control mice treated with OVA or HDM alone had no CGN.

Conclusions: Mice receiving anti-MPO developed CGN in mice with allergic airway disease. We hypothesize that respiratory tract neutrophils primed by the allergic airway disease are activated by anti-MPO IgG, and amplify the eosinophil-rich inflammation resulting in pulmonary capillaritis and granulomatosis. These models provide useful tools for studying pathogenesis and therapeutic strategies for EGPA.

Funding: NIDDK Support
SA-OR027
Long-Term Follow-Up of a Glucocorticoid-Minimising Regimen for Remission Induction in ANCA Vasculitis (AAV)
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Background: Glucocorticoids (GC), though a mainstay of treatment for AAV, have significant adverse effects. We previously reported successful short-term outcomes using a GC-sparing treatment regimen. Here, we report long term outcomes in an extended cohort of patients treated with this protocol.

Methods: Patients were treated at 2 centres with rituximab (RTX) 2x1g, low-dose iv cyclophosphamide (CYC), and a short course of oral GC of ~2 weeks duration, followed by maintenance azathioprine/MMF. Data reported as median ± IQR.

Results: 58 patients with new (84%) or relapsing (16%) AAV are included, with average follow up of 37 (23-46) months. 65% were MPO-ANCA/ive; 29% PR3-ANCA, 5% ANCA negative. Initial BVAS, CRP and creatinine were 14 (12-19), 46 (11-90) mg/L, and 176 (131-270) µmol/L, respectively. 90% had biopsy-proven renal involvement. The median dose of GC during induction was 960 (781-1276) mg. 5 patients (9%) required re-introduction of GC during the first 3 months for active disease; all patients subsequently achieved remission by 3 months, which was sustained in 91% at month 12. At 3 years, 96% were alive, 95% with independent renal function. 19% had relapsed, however the majority (80%) remained free of GC (Figure 1A). There were no significant differences in renal or relapse-free survival compared to a previous cohort treated with a comparable RTX-CYC regimen, along with long term steroid dosing (Figure 1B).

Conclusions: Rapid GC withdrawal was safe and effective in the majority of cases following induction with RTX-CYC. Long-term patient, renal and relapse-free survival are comparable to published cohorts treated with standard GC. A small proportion required early re-introduction of GC, such that careful monitoring is required, though GC avoidance was feasible in the majority. Controlled studies are warranted to compare the efficacy of this regimen to current standards of care.

SA-OR028
A Randomized Controlled Trial of Rituximab (RTX) vs. Azathioprine (AZA) After Induction of Remission with RTX for Patients with ANCA-Associated Vasculitis (AAV) and Relapsing Disease
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Background: RTX is an effective remission induction therapy in AAV. However, the effect of RTX is not sustained, and relapse rates are high, especially in patients with a history of relapse. The RITAZAREM trial is an international, open label, randomized, controlled trial of patients with AAV with relapsing disease comparing the efficacy, after remission induction with RTX, of repeat dose RTX or AZA as relapse prevention strategies.

Methods: Patients with relapsing AAV received induction therapy with RTX and glucocorticoids (GC). If remission was achieved by month 4, patients were randomized 1:1 to receive RTX (1000mg every 4 months for 5 doses) or AZA as maintenance therapy. Patients were followed for a minimum of 36 months, with a primary outcome of time to disease relapse.

Results: 190 patients were enrolled and 170 randomized at month 4 (85 to RTX; 85 to AZA). Data are complete on all patients up to at least month 24. Median age was 59 years (range 19-89), with a prior disease duration of 5.3 years (0.4-38.5). 123/170 (72%) of patients were historically positive for anti-PR3 ANCA; 104 (61%) were enrolled after a major relapse, and 48 (28%) received a higher dose GC induction regimen. 114 (67%) patients had prior renal involvement. RTX was superior to AZA in preventing relapse with a preliminary overall HR estimate of 0.36 (95% CI 0.23-0.57, p<0.001) and a during-treatment HR estimate of 0.30 (95% CI 0.15-0.60, p<0.001) (Figure 1). By 24 months after entry, 20 months after randomization, 1/85 (13%) patients in the RTX group had experienced a relapse compared to 32/85 (38%) in the AZA group. 9 (22%) patients in the RTX group and 31 (36%) patients in the AZA group experienced at least one severe adverse event.

Conclusions: RTX was superior to AZA in the prevention of relapse in patients with AAV with a prior history of relapse following induction with RTX.

Funding: Commercial Support - Genentech/Roche
SA-OR030
RNA Sequencing of Microdissected Kidney Biopsies Differentiates HIV+ FSGS from HIV-Negative FSGS
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Background: Antiretroviral therapy (ART) has reduced the incidence of "classic" HIV-associated nephropathy (HIVAN), characterized by rapidly progressive proteinuric CKD from undergoing collapsing focal segmental glomerulosclerosis and severe tubulointerstitial (TI) disease including tubular microcytosis. Whether FSGS without other histologic findings of HIVAN in HIV+ persons represents a partially treated HIVAN phenotype or FSGS unrelated to HIV infection is unclear. We therefore compared gene expression in kidney biopsies from HIV+ persons with non-HIVAN FSGS to biopsies from HIV- persons with FSGS.

Methods: 27 kidney biopsies from HIV+ persons with FSGS were microdissected, and glomerular and TI RNA were analyzed by RNaseq. We compared RNA expression from these samples to that of 22 HIV-negative FSGS biopsies which were matched for eGFR, demographic, and histologic variables. RNAseq data were processed and analyzed using the pipeline consisting of raw data processing, normalization, batch correlation and differential analysis based on LIMMA test. Differentially expressed genes were subjected to enrichment analysis for gene ontology function and KEGG pathways.

Results: A principal component analysis demonstrated that glomerular and TI RNA from HIV- FSGS clusters separately from HIV+ FSGS biopsies. 1081 genes were differentially expressed by 1.5 fold in glomeruli from HIV+ vs. HIV- biopsies, and 607 genes were differentially expressed in TI from HIV+ vs. HIV- biopsies. Pathway analysis revealed that predominant cellular pathways represented by differentially expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. HIV+ sequences were detected in the majority of HIV+ biopsies and were expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. HIV+ FSGS biopsies clustered separately from HIV- FSGS biopsies. 1081 genes were differentially expressed in TI from HIV+ vs. HIV- biopsies. Pathway analysis revealed that predominant cellular pathways represented by differentially expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. HIV+ sequences were detected in the majority of HIV+ biopsies and were expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. 607 genes were differentially expressed in TI from HIV+ vs. HIV- biopsies. Pathway analysis revealed that predominant cellular pathways represented by differentially expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. HIV+ sequences were detected in the majority of HIV+ biopsies and were expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. 607 genes were differentially expressed in TI from HIV+ vs. HIV- biopsies. Pathway analysis revealed that predominant cellular pathways represented by differentially expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. HIV+ sequences were detected in the majority of HIV+ biopsies and were expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. 607 genes were differentially expressed in TI from HIV+ vs. HIV- biopsies. Pathway analysis revealed that predominant cellular pathways represented by differentially expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation. HIV+ sequences were detected in the majority of HIV+ biopsies and were expressed genes from HIV+ biopsies have roles in metabolism, solute transport, and cell cycle regulation.

Conclusions: These results suggest that FSGS occurring in HIV+ persons may have a different molecular pathogenesis than FSGS occurring in HIV- persons and may reflect residual effects of HIV not fully treated by ART. Future studies are needed to determine whether new treatment strategies targeting deleterious effects of HIV can improve kidney outcomes in this population.

Funding: NIDDK Support

SA-OR031
HIF Stabilizer Decreases Mitochondrial Oxygen Consumption in Skeletal C2C12 Myotube
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Background: Erythropoietin (EPO) and hypoxia-inducible factor (HIF) stabilizers (PH inhibitors) are efficient therapeutic modalities against anemia in CKD. However, extra-renal action of PH inhibitors has not been fully investigated. Previous reports caution whether new treatment strategies targeting deleterious effects of HIV can improve kidney outcomes in this population.

Methods: To study direct pharmacological effects of roxadustat on skeletal muscles, we cultured muscle cells were assessed from multiple perspectives including cell viability, microscopic evaluation showed mitochondrial fragmentation in roxadustat-treated muscle cells. In addition, we studied the extra-renal action of PH inhibitors in non-CKD settings block the extra-renal actions of PH inhibitors.

Results: Results demonstrated that roxadustat treatment maintained reticulocyte counts to normal levels. Similarly, hemoglobin was decreased in adenine-fed mice, but levels in PBI-4610-treated mice remained normal (p<0.059). At endpoint, blood urea nitrogen and serum creatinine were increased by adenine feeding, however treatment with PBI-4610 significantly reduced these levels. Tubulointerstitial fibrosis assessed by Masson's trichrome stained kidney sections. Renal histology was assessed using H&E and HPLC respectively. Renal function decline leading to improved survival rates. Although the mechanism of action remains incompletely resolved, the above findings suggest treatment with PBI-4610 may represent a novel therapeutic modality in CKD.

Funding: Commercial Support - Prometic Life Sciences Inc.

SA-OR032
PBI-4610 Improves Renal Function, Anemia, and Histopathological Abnormalities in an Adenine-Induced CKD Model
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Background: Adenine-supplementation is an effective tool to study the onset and progression of fibrosis and CKD-associated sequelae. Prometic’s PBI-compounds show excellent safety and efficacy in both experimental models and in human studies. Here we tested a second-generation orally active PBI compound, PBI-4610, in adenine-induced renal failure.

Methods: Six to eight-week old male C57BL/6J mice were fed a regular (Control, n=9) or custom diet consisting of regular chow supplemented with 0.25% adenine for 30 days. After 7 days, mice were administered vehicle (H2O, n=9) or PBI-4610 (100 mg/kg, n=10) by daily oral gavage. Blood sampling was done at day 0, 7, 10, 21 and 30 reticulocytes were measured. Tubulointerstitial fibrosis was assessed by Masson’s stain. At the endpoint by ELISA and HPLC respectively. Renal histology was assessed using H&E and Masson’s trichrome stained kidney sections.

Results: Adenine decreased bodyweight, which was significantly improved by PBI-4610 at days 17, 21 and 24. Anemia was apparent as hematocrit (Hct) began to decline as early as 7 days post-adenine, however this was significantly improved by PBI-4610 at day 14, 21 and 30. FACS revealed reduced reticulocyte counts in vehicle-treated adenine mice compared to Control mice at day 14, however at day 30, levels were increased. PBI-4610 treatment maintained reticulocyte counts to normal levels. Similarly, hemoglobin was decreased in adenine-fed mice, but levels in PBI-4610-treated mice remained at control levels. At endpoint, blood urea nitrogen and serum creatinine were increased by adenine feeding, however treatment with PBI-4610 significantly reduced these levels. Tubulointerstitial fibrosis assessed by Masson’s stain. At the endpoint by ELISA and HPLC respectively. Renal histology was assessed using H&E and Masson’s trichrome stained kidney sections.

Conclusions: Taken together, PBI-4610 improves several key renal functional and structural abnormalities in adenine-induced CKD including anemia, fibrosis and renal function decline leading to improved survival rates. Although the mechanism of action remains incompletely resolved, the above findings suggest treatment with PBI-4610 may represent a novel therapeutic modality in CKD.

Funding: NIDDK Support
Background: Inflammatory stimuli induce functional iron deficiency, by increasing the expression of the hepatic iron regulatory peptide, hepcidin. Acute inflammation stimulates fibroblast growth factor 23 (Fgf23) production in bone and leads to a dramatic increase in both Fgf23 transcription and FGF23 cleavage and paradoxically leads to excess in C-terminal FGF23 peptides (cFGF23), but not intact hormone (iFGF23). This questions the physiological need for increased Fgf23 transcription in this context and we hypothesized that cFGF23 peptides might actively participate in the regulation of iron metabolism by regulating hepcidin expression.

Methods: We induced acute inflammation in WT, Fgf23-null and FGF23-DMP1 cKO mice using a single dose of 250µg/kg of interleukin 1 beta (IL1b) and we analyzed the effects on the iron homeostasis. We next used recombinant cFGF23 peptides as bait in cultured osteoblasts to immunoprecipitate (IP) and to identify binding partners by mass spectrometry (MS). We also verified binding between FGF23 peptides and putative partners using bio-layer interferometry (BLI). Finally, we administered cFGF23 to verify its impact on iron metabolism.

Results: As expected IL1b administration to WT mice led to low serum iron and transferrin saturation (TSAT) due to high hepcidin levels, and increased bone Fgf23 expression and secretion of cFGF23 peptides (p<0.05). Fgf23-DMP1 cKO mice had 90% lower Fgf23 levels (p<0.05), but exhibited further reductions in serum iron and TSAT compared to IL1b-treated WT, due to higher serum hepcidin and liver Hamp (encoding hepcidin) mRNA, suggesting that cFGF23 reduces Hepcidin production. Using IP/MS, we next identified binding of cFGF23 peptides to members of the bone morphogenic protein (BMP) family, BMP2 and BMP9, established inducers of hepcidin, and we confirmed binding of BMP2 and BMP9 to cFGF23 by BLI. In WT mice, co-administration of cFGF23 and BMP2 or BMP9 prevented the increase in Hamp mRNA and circulating hepcidin levels resulting in normal serum iron levels and TSAT. In addition, injection of cFGF23 increased serum iron levels and TSAT in WT and FGF23-null mice.

Conclusions: This is the first study to provide a new direct role for bone-produced cFGF23 peptides to antagonize the inflammation-induced BMP signaling in the liver and inhibit the secretion of the iron regulatory peptide, hepcidin.

Funding: NIDDK Support

SA-OR035

Enteral Ferric Citrate Absorption Is Dependent on Ferroportin

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Background: Ferric citrate (FC) is approved as an iron replacement product in CKD non-dialysis patients with iron deficiency anemia. FC-delivered iron is entirely absorbed, but the specific mechanisms involved have not been specifically evaluated. The absorption of dietary iron and conventional supplements requires duodenal ferroportin (FPN). To assess whether or not enteral FC absorption is dependent on FPN, we evaluated the effects of FC in a tamoxifen-inducible, enterocyte-specific FPN knockout (KO) murine model (Villin-Cre-ERT2, FPN<sup>fl/fl</sup>−<sup>am</sup>−).Methods: We assessed three groups: uninduced mice, induced mice (FPN KO), and induced mice (FPN KO) supplemented with 1% FC. Mice were injected with vehicle (uninduced group) or tamoxifen (induced groups) at –7 weeks of age, then terminally assessed 7-8 weeks later. The treated induced mice had their diets supplemented with 1% FC for –19 days pre- euthanasia.

Results: The FPN KO was effective, as 6 weeks after tamoxifen injection, the induced mice had –4000 fold lower duodenal FPN mRNA expression than uninduced mice and undetectable FPN protein on the duodenal tissue Western blot. Confirming that 1% FC prevents anemia, uninduced mice placed on iron-deficient 4 ppm diets for 7 weeks (n=5) became anemic, but uninduced mice placed on iron deficient 4 ppm diets for 4 weeks, then supplemented with 1% FC for 3 weeks (n=6), were rescued from anemia (mean SD) terminal hemoglobin of 13.8 (0.7) vs. 7.6 (0.8) g/dL, p<0.001. FPN KO mice on iron-sufficient 50 ppm diets developed anemia whether or not they were supplemented with 1% FC. The FPN KO groups had higher duodenal intracellular iron staining, lower liver iron concentration, lower hemoglobin, lower mean corpuscular volume, and higher red cell distribution width vs. the uninduced group (Figure 1). There were no differences between the untreated and 1% FC-treated FPN KO groups.

Conclusions: The 1% FC diet does not rescue iron deficiency anemia caused by enterocyte FPN KO. Enteral FC absorption is dependent on conventional enterocyte iron transport by FPN.

Funding: Commercial Support - Sponsored by Keryx Biopharmaceuticals, Inc., now a wholly-owned subsidiary of Akebia Therapeutics, Inc.
**SA-OR038**

The Association of sTNF-R1 and sTNF-R2 with Histopathologic Lesions and Progression to ESRD: The Boston Kidney Biopsy Cohort Study

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**Background:** The relationship of soluble tumor necrosis factor-1 (sTNFR-1) and sTNFR-2 with histopathologic lesions and progression to ESRD in individuals with biopsy-confirmed kidney disease is unknown.

**Methods:** We measured plasma sTNFR-1 and sTNFR-2 levels in 523 individuals enrolled into a prospective, observational cohort study of patients undergoing native kidney biopsy at three tertiary care hospitals. Two experienced renal pathologists adjudicated biopsy specimens for semiquantitative scores of histopathology. Linear regression models tested the association between biomarkers and histopathologic lesions. Proportional hazards models tested the association between biomarkers and risk of progression to ESRD.

**Results:** Mean age was 53±17 years and mean baseline eGFR was 56±36 ml/min/1.73m². sTNFR-1 and sTNFR-2 correlated with eGFR (R = -0.70 and -0.62, P<0.001, respectively). After adjustment for age, sex, race, and eGFR, sTNFR-1 and sTNFR-2 levels were highest among individuals with glomerulosclerosis and diabetic nephropathy (Figure). sTNFR-1 and sTNFR-2 followed slightly different patterns of injury after multivariable adjustment (Figure). Both biomarkers were associated with more severe interstitial fibrosis/tubular atrophy and mesangial expansion. Only sTNFR-1 associated with more severe tubular injury, presence of inflammation in the nonfibrosed interstitium, and segmental sclerosis. During a median follow-up time of 25 months, 78 individuals progressed to ESRD. sTNFR-1 and sTNFR-2 were each independently associated with greater than 2-fold increased risk of progression to ESRD (Figure).

**Conclusions:** Higher levels of sTNFR-1 and sTNFR-2 are independently associated with increased risk of progression to ESRD across a diverse set of biopsy-confirmed kidney diseases.

**Funding:** NIDDK Support

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**SA-OR039**

Two-Year Change in Galectin-3 and MMP-2 and Risk of ESRD: The Chronic Renal Insufficiency Cohort (CRIC) Study

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**Background:** Galectin-3 and matrix metalloproteinase-2 (MMP-2) have both been associated with kidney fibrosis, however, the relationship of these markers with chronic kidney disease (CKD) progression remains unclear.

**Methods:** A case-cohort study including a randomly selected sample of 1300 CRIC participants was conducted to characterize the association of two-year change in plasma galectin-3 and MMP-2 with subsequent development of end-stage renal disease (ESRD; N=542). Weighted Cox proportional hazards regression models used data from up to 8 years of follow-up, adjusted for sociodemographic, clinical and biochemical factors including eGFR and proteinuria in addition to galectin-3 or MMP-2 values from baseline.

**Results:** Two-year change in galectin-3 ranged from -51 to +56 ng/mL with an overall mean change of 4.3 ng/mL, while change in MMP-2 ranged from -455 to +654 ng/mL (mean change: 25.4 ng/mL). Restricted cubic splines demonstrate non-linear associations for both markers (Figure). Increases in galectin-3 over two years did not appear to increase ESRD risk, but decreases may trend toward reduced risk of ESRD. The hazard ratio for MMP-2 reductions of 400 ng/mL was 0.2 (95% CI: 0.1-0.5).

**Conclusions:** Decreases in MMP-2 over two years are strongly and independently associated with marked reduction in the risk for ESRD among patients with established CKD. This pathway should be studied further to investigate possible interventions to reduce CKD progression risk.

**Funding:** NIDDK Support

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**SA-OR040**

The Pro-fibrotic Serum Marker MMP7 Predicts Accelerated GFR Loss in the General Population

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**Background:** Age related loss of glomerular filtration rate (GFR) is a major contributor to the global chronic kidney disease (CKD) epidemic. CKD is associated with increased morbidity and mortality and there is a need for novel biomarkers that identify at risk persons at an early stage to delay or prevent CKD onset. Matrix Metalloproteinase (MMP) 2 and 7 are key players in interstitial remodeling and mediate renal fibrosis development in animal models. We investigated whether serum MMP2, MMP7 and their inhibitor TIMP1, were associated with accelerated age-related GFR decline and incident CKD in middle-aged individuals from the general population.

**Methods:** In the Renal Iohexol Clearance Survey (REINS) we performed GFR measurements (using iohexol clearance) in 1627 subjects, aged 50-62 years, from the general population without self-reported diabetes, kidney or cardiovascular disease. 1324 (81%) had follow-up measurements after a median of 5.6 years. The biomarkers were analyzed in baseline serum samples with a Bioplex 200 machine. Using multiple logistic regression analysis, we evaluated the risk of accelerated GFR decline (defined as subjects with the 10% steepest GFR slope) and incident CKD (defined as GFR <60ml/min/1.73m²).

**Results:** After adjustment for age, sex, baseline GFR and urinary albumin-creatinine ratio (ACR), higher levels of MMP7 were associated with an increased risk of accelerated GFR decline (Odds ratio (95% confidence interval) per one SD increase in MMP7: 1.68 (1.39-2.04) and incident CKD: 1.71 (1.25-2.34). The results were attenuated, but remained statistically significant (P=0.01) fully adjusted (1.48 (1.20-1.81) and 1.23 (1.08-1.40). Reduction of accelerated GFR decline improved after addition of MMP7 to a model with age, sex, baseline GFR and ACR (aera under the ROC curve increased from 0.72 to 0.75 (p=0.054), continuous net reclassification improvement: 0.34 CI: 0.16-0.52). Similar results were obtained using alternative definitions of accelerated GFR decline such as < -3.0 ml/min/1.73m²/year or a GFR decline rate twice the cohort mean (±1.68 ml/min/1.73m²/year). MMP2 and TIMP1 showed no association with GFR decline.

**Conclusions:** The pro-fibrotic biomarker MMP7 was independently associated with increased risk of accelerated GFR decline and incident CKD in middle-aged persons from the general population.

**Funding:** Government Support - Non-U.S.

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**SA-OR041**

Relation of a Parsimonious Model of Factors Derived from 10 Biomarkers of Kidney Tubule Health with Decline in eGFR in the SprayTrial Alexander Bullen,1 Ronit Katz,2 Alexandra K. Lee,2 Michelle M. Estrella,3 Michael Shipkaj,4 Joachim H. Ix,5 UCSD, San Diego, CA; 2Kidney Health Research Collaborative, UCSF & VA, San Francisco, CA; 3University of California, San Francisco; 4San Francisco VA Medical Center, San Francisco, CA; 5University of Washington, Seattle, WA.

**Background:** To move towards assimilation of the various information gained from multiple biomarkers, we have evaluated 10 urine biomarkers of kidney tubule health measured at baseline among SPRINT participants with chronic kidney disease (CKD). In prior analyses, we created summary scores of different dimensions of kidney tubule health, a parsimonious model of factors derived from 10 biomarkers was independently associated with eGFR decline and progression to ESRD among patients with established CKD. This pathway should be studied further to investigate possible interventions to reduce CKD progression risk.

**Funding:** NIDDK Support

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underline represents presenting author.**
SA-OR043

Association Between Urine 6-Bromotryptophan and ESKD in the German CKD Study

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Background: Higher serum 6-bromotryptophan has been associated with lower risk of chronic kidney disease (CKD) progression, but its levels in urine have not yet been studied. We studied determinants of urine 6-bromotryptophan and its association with CKD risk factors and incident end-stage kidney disease (ESKD) in 4,843 CKD patients.

Methods: 6-bromotryptophan was measured from spot urine samples using mass spectrometry. Genetic determinants of 6-bromotryptophan levels were assessed using genome-wide association studies (GWAS) in European ancestry cohorts. The associations between urine 6-bromotryptophan and CKD risk factors were assessed by univariate tests. The risk for ESKD, defined as incident dialysis, kidney transplantation, or kidney-related death, by 6-bromotryptophan levels was assessed using Cox regression.

Results: Urine 6-bromotryptophan was detected in 57% of the patients and categorized into three groups: undetectable, low (<median), and high (median). GWAS of urine 6-bromotryptophan levels detected two significant loci likely related to its generation and tubular reabsorption, illuminating its biological determinants (near SLCOA19, p=3.2x10-12, and GPR137C, p=2.4x10-10). The locus near GPR137C possibly related to its generation was associated with serum 6-bromotryptophan in an independent general population-based cohort (p=7.3x10-7). Patients with higher levels of urine 6-bromotryptophan had higher baseline estimated glomerular filtration rate (eGFR, p=0.001). After four years of follow-up, we observed 216 ESKD events. Compared with the undetectable group, higher 6-bromotryptophan levels were associated with lower risk of ESKD in pre-dialysis CKD patients and when adjusting for all ESKD risk factors other than eGFR (low group cause-specific hazard ratio [HR]: 0.7, 95% confidence interval [CI]: 0.51 to 0.97; high group HR: 0.5, 95% CI: 0.34 to 0.74). With the addition of baseline eGFR, this association became insignificant.

Conclusions: Higher urine 6-bromotryptophan levels were associated with lower risk of ESKD, which was attenuated when adjusting for baseline eGFR. The protective direction of association is noteworthy, because higher levels of most other metabolites, such as creatinine, are associated with higher risk of ESKD.

SA-OR044

Biomarkers in CKD

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Background: Carbamyl formation is a posttranslational protein modification caused, in part, by exposure to urea’s dissociation product cyanate. While carbamylation associates with cardiovascular outcomes and mortality in ESKD, its effects in earlier stages of CKD are unknown.

Methods: In 2 independent nested case-control studies within CRIC, we first matched 75 subjects demonstrating CKD progression (cases, 50% reduction of eGFR or reaching ESRD) to 75 people not meeting this definition (controls, matched on baseline eGFR, 24-hour proteinuria, age, sex, and race). Regression models compared baseline levels of carbamylated albumin (C-CAb, a validated measure of total body carbamylation burden) between the groups. With the same matching approach, we next compared baseline C-CAb in 75 subjects who died during follow up (mortality cases) to 75 survivors (mortality controls).

Conclusions: In this large metabolomics study of CKD progression, 3 metabolites significantly associated with ESRD or eGFR halving in unadjusted analysis, but only 9 metabolites remained significant following full adjustment (Fig). This attenuation in associations was driven by adjustment for eGFR. A subset of 7 of these metabolites were also measured in AASK, 3 of which were associated with CKD progression (Table): pseudouridine, 4-acetamidobutanoate, and 6-bromotryptophan.

*Adjusted for: age, sex, race, randomization arm, SBP, ACEi or ARB use, diuretic use, history of CVD or HF, current smoker, BMI, LDL, total cholesterol, baseline eGFR and albuminuria.
Results: Table 1 shows baseline characteristics of the study groups. Other than urea (CKD stage 2) and smoking status (both CKD nursing collagen content), there was no difference in any matched or other parameter. Adjusting for baseline differences, the top tertile of C-Alb was associated with an increased risk of CKD progression (OR [95% CI] 7.9 [1.9-32.8], P= 0.004) and mortality (OR 3.4 [1.1-10.4], P= 0.05) when compared to the bottom tertile.

Conclusions: In this first report of carbamylation and clinical outcomes in CKD patients not on dialysis, our data suggest carbamylation predicts CKD progression, beyond GFR and proteinuria. Impact on mortality was less robust in this small sample. Additional study is warranted as carbamylation is considered a modifiable risk factor.

Funding: NIDDK Support

Table 1 Select baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Age</th>
<th>gFG (mg/L)</th>
<th>Procrutin (µg/g creatinine)</th>
<th>Urea (mg/dL)</th>
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</thead>
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<tr>
<td>58±4.9</td>
<td>75.9±36.1</td>
<td>1.2±0.3</td>
<td>32.9±46.0</td>
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<tr>
<td>57±4.9</td>
<td>54.2±24.8</td>
<td>1.0±0.2</td>
<td>30.4±39.4</td>
</tr>
<tr>
<td>79±7.8</td>
<td>54.4±7.8</td>
<td>1.3±0.3</td>
<td>36.7±37.1</td>
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<tr>
<td>56±23.6</td>
<td>55.1±14.0</td>
<td>1.0±0.3</td>
<td>30.4±20.6</td>
</tr>
<tr>
<td>79.4±37.1</td>
<td>54.8±14.0</td>
<td>1.2±0.3</td>
<td>32.9±46.0</td>
</tr>
<tr>
<td>56±28.6</td>
<td>57±43.1</td>
<td>1.2±0.3</td>
<td>32.9±46.0</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD), median (interquartile range Q1-Q3), or count (%) as indicated. No other parameter differed by cases vs. controls across both outcomes.

SA-OR045

Blood and Urine Biomarkers and CKD After Cardiac Surgery

Methods: We prospectively enrolled adult patients undergoing cardiac surgery (CABG or valve) in 2 academic centers from 2007-2010 as part of the TRIBJ-AKI Study. The cohort was separated into exploration (Canada n=613) and replication (USA n=310) cohorts due to differences in outcome ascertainment and lack of data integration. Top biomarkers were identified from candidate post-operative biomarkers (32 blood, 8 urine) in the exploration cohort and confirmed in the replication cohort, thereby reducing model selection bias. Our primary outcome was a composite of CKD incidence or progression. In those with a pre-operative eGFR<60, CKD progression was defined as a 50% reduction in eGFR or a fall below 60. In those with a pre-operative eGFR<60, CKD progression was defined as a 25% reduction in eGFR or a fall below 15.

Conclusions: Each log increase in post-operative levels of bFGF (HR 1.52 [1.19, 1.93]), N-terminal pro-BNP (HR 1.12 [1.00, 1.26]), and N-terminal pro-BNP (HR 1.12 [1.00, 1.26]) was associated with the primary outcome, of which 3 remained significant after full adjustment. These biomarkers provide additional value in evaluating CKD incidence and progression after cardiac surgery.

Background: Despite advances in imaging technology(conventional ultrasound, CT, MRI), the only method for assessing fibrosis is by biopsy. Biopsy is limited by its invasiveness and the fact that it samples <1% of the kidney. Here we show that combining ultrasonic imaging (photoacoustic (PA) ultrasound) allows imaging of kidney fibrosis by directly measuring collagen content.

Methods: Kidneys of mice undergoing UM0 (left kidney) or sham surgery were imaged ex vivo using a VevoLAAZ-X PA ultrasound imaging system at 15 MHz at day 7 and 14 post-surgery(y=5 per time point). Human kidney samples were obtained from Toronto, Ukiah School of Medicine at Mount Sinai, New York, NY; 5London Health Sciences Centre, London, ON, Canada; 6Icahn School of Medicine at Mount Sinai, New York, NY; 7London Health Sciences Centre, London, ON, Canada; 8Institute for Clinical Evaluative Sciences, London, ON, Canada; 9John Hopkins University, Baltimore, MD, USA; 10Department of Physiology, Hopital Tenon, Paris, France; 11Departement de Physiologie, Université Paris Descartes; 12Faculty of Medicine, University of Bordeaux, Bordeaux, France; 13INSERM U1155 Pierre et Marie Curie University, Paris, France.

Background: The aim of the present study was to analyze whether ECF over time was associated with ESKD and mortality. Time-to-event sub-model of the joint models with shared random-effect were used to jointly analyze individual trajectories of ECF and the competing risks of ESKD and mortality. Time-to-event sub-model of the joint models with shared random-effect were used to jointly analyze individual trajectories of ECF and the competing risks of ESKD and mortality. Time-to-event sub-model of the joint models with shared random-effect were used to jointly analyze individual trajectories of ECF and the competing risks of ESKD and mortality. Time-to-event sub-model of the joint models with shared random-effect were used to jointly analyze individual trajectories of ECF and the competing risks of ESKD and mortality.

Results: At baseline, patients (mean age 58.7±15.1 years, 67% men) had a mean GFR 55.2±19 mL/min/1.73m2 and ECF was 16.1±3.6 mL. After a median follow-up of 5.2 years (IQR: 3.0-7.4) years with a median number of ECF measurement of 2 [IQR: 1.4] per patient, the rate of ECF effect was used to jointly analyze trajectories of ECF and the competing risks of ESKD and mortality. Time-to-event sub-model of the joint models was adjusted for age, gender, site, ethnicity, cardiovascular risk factors, underlying renal disease, measured GFR (mGFR), proteinuria, 24-h urinary sodium excretion, diuretics and renin-angiotensin system inhibitors. ECF over time was strongly associated with histologic parameters of fibrosis (PSR, r2=0.98, p<0.001; α-GM, r2=0.90, p<0.05), suggesting that PA imaging can accurately quantify renal collagen content. Human kidney specimens exhibited a 30% variation in PSR staining, which was also strongly correlated with the mGFR (r=0.90, p<0.05). The technique was also capable of generating 3D collagen maps across the entire specimen with sub-nm spatial resolution across the entire kidney cortex.

Conclusions: PA ultrasound can be used to accurately quantify renal collagen content. This non-invasive, easy-to-use technique offers the potential for renal fibrosis imaging in both the pre-clinical and clinical settings.

Results: Table 1 shows baseline characteristics of the study groups. Other than urea (CKD stage 2) and smoking status (both CKD nursing collagen content), there was no difference in any matched or other parameter. Adjusting for baseline differences, the top tertile of C-Alb was associated with an increased risk of CKD progression (OR [95% CI] 7.9 [1.9-32.8], P= 0.004) and mortality (OR 3.4 [1.1-10.4], P= 0.05) when compared to the bottom tertile.

Conclusions: In this first report of carbamylation and clinical outcomes in CKD patients not on dialysis, our data suggest carbamylation predicts CKD progression, beyond GFR and proteinuria. Impact on mortality was less robust in this small sample. Additional study is warranted as carbamylation is considered a modifiable risk factor.
ESKD. In multivariable analysis, a higher current value of ECF was associated with an increased hazard ratio of death (HR = 2.0; 95% CI: [1.4; 2.9]; p<0.001) and with mortality (HR = 1.08; 95% CI: [1.01; 1.15]; p<0.001). Conclusions: In this large cohort of CKD patients, ECF over time was independently associated with ESKD and mortality. This highlights the need for a close monitoring and adjustment of treatments in these patients.

**SA-OR048**

**Discovery of Novel Podocyte Endoplasmic Reticulum Calcium Stabilizers to treat Nephrotic Syndrome**

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Background: Podocyte injury is the hallmark of primary nephrotic syndrome (NS), a leading cause of chronic kidney disease affecting approximately 500 million people worldwide. Despite the importance of podocyte endoplasmic reticulum (ER) stress in the pathogenesis of NS, currently no treatment targets the podocyte ER. For the first time, we have developed a new class of drugs-podocyte ER calcium channel stabilizers, to treat NS.

Methods: We have developed a podocyte ER stress-induced monogenic NS mouse model harboring a frameshift mutation in laminin 522 (Lum-2), which is synthesized and secreted by podocytes. Western blot and RNA sequencing of isolated mouse glomeruli, or cultured primary podocytes were utilized to determine accelerated ER calcium efflux, mediated pro-apoptotic pathway. Moreover, a Gauissa luciferase-based assay utilizing secreted ER calcium-monitoring proteins (SURCaMPs) was performed to monitor ER calcium depletion in primary podocytes and to screen for novel ER calcium stabilizers.

Results: Lastly, our mouse model was exploited to test the therapeutic effect of an identified drug.

Conclusions: We have identified a novel therapeutic target, podocyte ER type 2ryanodine receptor/calcium release channel (RyR2). It was phosphorylated at Ser2808 under ER stress, resulting in podocyte ER calcium leak and cytosolic calcium elevation. The altered intracellular calcium homeostasis led to activation of calcium-dependent cytosolic protease calpain 2 and cleavage of its important downstream substrates, including the apoptotic molecule procaspase 12 and podocyte cytoskeletal protein 1. More importantly, we have identified a chemical compound K201 and a novel biotherapeutic protein mesenchephalic astrocyte-derived neurotrophic factor (MANF), which can reduce RyR2 phosphorylation and inhibit pro-apoptotic calpain 2-caspase 12 signaling in podocytes undergoing ER stress. Most excitingly, K201 treatment attenuated proteinuria and improved kidney function in our podocyte ER stress-induced NS mouse model.

**SA-OR049**

**Combined Single Cell Epigenomic and Transcriptomic Analysis of Healthy vs. FSGS Adult Human Kidney**

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Background: Unraveling the pathogenesis of human FSGS requires a detailed understanding of the distinct cell types, cell specific transcription factors, chromatin status and cell state changes in healthy and FSGS kidneys. We hypothesized that combined single nucleas RNA-seq and ATAC-seq on a single human biopsy would allow definition of FSGS-specific transcriptional changes and the DNA regulatory variation driving them, nucleus RNA-seq and ATAC-seq on a single human biopsy would allow definition of cell state changes in healthy and FSGS kidneys. We hypothesized that combined single nucleas RNA-seq and ATAC-seq on a single human biopsy would allow definition of FSGS-specific transcriptional changes and the DNA regulatory variation driving them.

Methods: We generated cells with stable or inducible G2 APOL1 expression and used inhibitors of apoptosis, necrosis, and pyroptosis to determine pathways mediating cytotoxicity. To define the role of inflammasome-mediated cell death in vivo, we crossed G2 APOL1 transgenic mice (Nphs1rtTA-TRE APOL1) with caspase-1 (Casp1-/-) or NLRP3 (Nlrp3-/-) knockout mice and induced podocyte G2 APOL1 expression with a 21-day doxycycline diet. Histological changes were evaluated by PAS, fibrosis was quantified using Sirius red staining. Albuminuria was determined by ELISA. Inflammasome markers were quantified by immunoblotting.

Results: We found that expression of inflammasome markers cleaved caspase-1, NLRP3, and IL-1B were higher in mice expressing risk variant APOL1. These results were recapitulated in cultured cells expressing risk variant APOL1, while pyroptosis inhibitors decreased inflammasome signaling and cytokinesis. Nphs1rtTA-TRE APOL1/Casp1-/- mice showed a 90% reduction in albuminuria, and ~75% reduction in renal fibrosis compared to Nphs1rtTA-TRE APOL1 mice. Nphs1rtTA-TRE APOL1/Nlrp3-/- mice showed an 80% reduction in albuminuria, and ~75% reduction in renal fibrosis, compared to G2 APOL1 littermates. Kidney histology examined by PAS and Sirius red staining showed significant increases in kidney structure damage in G2 APOL1 mice. Additionally, NLRP3 or caspase-1 knockouts interchangeably decreased markers of inflammasome signaling and cell death.

Conclusions: Our data suggest that caspase-1 and NLRP3 inflammasomes play an important role in the development of G2 APOL1 induced kidney damage. Our results raise the possibility that inflammasome inhibition could be a potential therapeutic approach for APOL1-associated kidney disease.

**Funding:** NIDDK Support

**SA-OR050**

**A Human Model of Membranous Nephropathy on-a-Chip**

Stefano Da Sacco1, Astigik Petrosyan1, Paolo Cravedi2, Valentina Villani1, Andrea Angeletti1, Joaquim Manrique3, Roger E. De Filippo4, Laura Pertin5, Joseph's Children's Hospital Los Angeles, Los Angeles, CA; 2Mount Sinai Nephrology, Pianoro, Italy; 3Complejo Hospital de Navarra, Pamplona, Spain.

Background: Primary membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults worldwide. MN pathogenesis involves the depositions of auto-antibodies against podocyte-expressed antigens in the glomerular subepithelial space, causing podocyte injury and initiating progressive renal damage which leads to kidney failure in approximately one third of patients. While the role of complement has been confirmed, many questions are still unanswered and the study of mechanisms responsible for MN pathogenesis is challenged by the lack of in vitro systems that recapitulate human disease.

Methods: We have developed a novel glomerulus-on-a-chip system (GOAC) using primary, immortalized and amniotic fluid derived podocytes together with glomerular endothelial cells (GEC) in combination with OrganonPlates and assessed the functional response to human MN serum. Human podocytes were seeded on microfluidic chips with human GEC. Immunoﬂuorescence and WB were performed for podocyte, endothelial and GBM markers. Barrier selective-permeability was investigated. Chips were cultured with serum from MN patients or healthy individuals. Functional response was assessed by albumin permeability assay. IgG3/g4 deposition was assessed by immunoﬂuorescence while absence of actions were explored by Western Blotting and immunostaining.

Results: This system recapitulates salient characteristics and functions of the in vivo glomerular filtration barrier. The GOAC is permeable to inulin and impermeable to albumin. When exposed to serum of subjects affected by MN, the chip displayed decreased albumin permeability and complement deposition 33 on podocytes and loss of permeability to albumin to an extent correlated to urinary protein loss in respective patients. Moreover, we have found evidence suggesting that activation of ILK/MAPK/SNAIL signaling pathway in podocytes might contribute to injury during MN pathogenesis.

Conclusions: We have successfully developed a glomerulus-on-a-chip system that closely mimics the GFB structure and provides a powerful tool for studying pathophysiology of MN. This system will increase our ability to individualize treatments and facilitate drug discovery, thus ultimately benefiting patients affected by this and potentially other glomerular diseases.

**Funding:** Private Foundation Support

**SA-OR051**

**Inflammammasome-Mediated Cell Death Plays a Key Role in APOL1 Risk Variant-Induced Kidney Disease**


Background: Apolipoprotein L1 (APOL1) coding variants, termed as G1 and G2 are associated with increased kidney disease risk. We developed a mouse model by conditional and inducible expression of reference (G0) or risk (G1 or G2) variants of APOL1. Mice with podocyte-specific G1 or G2 APOL1 expression develop albuminuria, glomerulosclerosis and renal failure recapitulating the human disease condition. However, molecular pathways leading to kidney disease development in this model remains poorly understood. We hypothesized that APOL1 risk alleles induced inflammasome-mediated pyroptotic cell death contributed to the phenotype development.

Methods: We generated cells with stable or inducible G2 APOL1 expression and used inhibitors of apoptosis, necrosis, and pyroptosis to determine pathways mediating cytotoxicity. To define the role of inflammasome-mediated cell death in vivo, we crossed G2 APOL1 transgenic mice (Nphs1rtTA-TRE APOL1) with caspase-1 (Casp1-/- or Nlrp3-/-) knockout mice and induced podocyte G2 APOL1 expression with a 21-day doxycycline diet. Histological changes were evaluated by PAS, fibrosis was quantified using Sirius red staining. Albuminuria was determined by ELISA. Inflammasome markers were quantified by immunoblotting.

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Conclusions: Our data suggest that caspase-1 and NLRP3 inflammasomes play an important role in the development of G2 APOL1 induced kidney damage. Our results raise the possibility that inflammasome inhibition could be a potential therapeutic approach for APOL1-associated kidney disease.

**Funding:** NIDDK Support

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
SA-OR052
A Novel Small Molecule Therapy for Nephrotic Syndrome Caused by a Common Podocin Mutation
Valeria Kuzmuk,1 Ivona Pranke,2 Wen Y. Ding,3 Geraldine Mollet,4 Corinne Antignac,5 Rebecca R. Foster,6 Richard Coward,7 Gavin I. Welsh,8 Aleksander Edelman,9 Moin Saleem,10 University of Bristol, Bristol, United Kingdom; 11 Imagine Institute/Laboratory of Hereditary Kidney Diseases, Paris, France; 12 Inserm U1163, Paris, France; 13 Inserm U1151, Paris, France.

Background: There are currently no targeted therapies for the ever-increasing number of podocyte diseases. Currently, there are over 60 different genetic disorders causing SRNS - the commonest of these by far is that of mutations in the NPHS2 gene encoding podocin. Podocin is a key scaffolding protein of the slit diaphragm essential for intact glomerular filtration. The most frequent podocin mutation in European children is R138Q, causing retention of the protein in the ER.

Methods: A conditionally immortalized patient cell line with the R138Q mutation was used to study podocin trafficking and biology and to characterize the nature of R138Q-K8 interaction in podocin’s cell type, the kidney podocyte. A conditional podocin knock-in mice carrying R140Q mutation, the mouse analogue of human R138Q, was created using doxycycline-inducible Cre-recombinase technology allowing to study the effects of the mutation in postnatal life and representing an ideal model for pharmacological studies.

Results: We provide evidence that a protein-protein interaction of misfolded podocin R138Q (but not wt podocin) with the intermediate filament K8 prevents its correct trafficking to the PM. We have also identified a small molecule that interrupts this interaction and rescues mutant protein mis-trafficking. This results in functional rescue of correct trafficking to the PM. We have also identified a small molecule that interrupts this interaction in podocin’s cell type, the kidney podocyte. A conditional podocin knock-in mice carrying R140Q mutation, the mouse analogue of human R138Q, was created using doxycycline-inducible Cre-recombinase technology allowing to study the effects of the mutation in postnatal life and representing an ideal model for pharmacological studies.

Conclusions: Altogether, this data provided constitutes the first therapeutic option for NS patients bearing the R138Q mutation.

SA-OR054
Proteomic Analysis of Clathrin-Coated Vesicles from Podocytes Identifies Cargo Proteins
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Background: Clathrin-mediated endocytosis (CME) plays a crucial role in podocyte health. Knockout of proteins involved in CME resulted in severe albuminuria and foot process effacement in mice. However, the cargo of clathrin-coated vesicles (CCVs) in podocytes is unknown. The goal of this study was to isolate CCVs from podocytes and identify their cargo by proteomic analysis.

Methods: Kidneys were isolated from Podocin-Cre Rosa-DTRm mice. The glomeruli were seeded and treated with diphtheria toxin to obtain pure primary podocyte cultures. After cell harvesting, CCVs were isolated by D-O sucrose density gradient centrifugation using multiple ultracentrifugation steps. Enrichment of CCVs was assessed by immunoblotting and electron microscopy (EM). LC-mass spectrometry (LC-MS) was performed for proteomic analysis. Proteins with higher abundance than transferrin receptor protein 1 were evaluated for CVC cargo potential by comparison to published impurities in CVC preparations, podocyte proteomic databases, and by searching the literature for CME-association.

Results: Immunoblotting for multiple protein markers of CME revealed enrichment in the CVC fraction. Enrichment of CCVs amongst other small vesicles was observed on electron microscopy. Clathrin-heavy chain was the fourth-most abundant protein in LC-MS analysis of the vesicle fraction. Proteomics yielded a total of over 1700 proteins. After adjustment for impurities and upregulation from whole cell expression, over 50 potential cargo proteins were identified. Among those are fibronectin, receptor of activated protein C kinase, thrombospondin-1, and vinculin.

Conclusions: This is the first time CVCs were enriched from podocytes. Enrichment was confirmed by immunoblotting, EM and LC-MS analysis. Proteomic analysis of CVC cargo and adjustment for impurities identified the most abundant cargo proteins in podocytes. These findings help to elucidate the importance of endocytic trafficking for podocyte health and disease.

Funding: NIDDK Support

SA-OR053
An iPSC platform for Human Preclinical Evaluation of Kidney Disease Targeting Compounds
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Background: A major challenge in drug target validation and assessment of efficacy is the limited translation between preclinical animal models and human diseases, which is often invoked to explain the failure of investigational drugs to produce the expected therapeutic benefit. Human iPSC-derived cells and organoids offer an opportunity to complement preclinical animal models, but their systematic use remains challenging due to the technical complexity associated with consistent cell culture and scalability.

Methods: Here, we report a robust, reproducible and scalable platform for generating iPSC-derived human podocytes and kidney organoids to enable target validation and preclinical assessment of therapeutic agents targeting the kidney. The organoid platform was characterized by immunofluorescence analysis of kidney differentiation markers and by assessing transcriptomic changes during organoid differentiation in vitro and following in vivo transplantation under the rat kidney capsule using single-cell RNA sequencing to identify their cargo by proteomic analysis.

Results: Here, we report three examples supporting the use of these models by a) providing a mechanistic basis for the antiproteinuric effects of cyclosporine A via protective effects on podocytes from Rac1-mediated cytotoxicity in vitro, b) exploring of the effects of urate lowering drugs on genetic mutations, and c) demonstrating the protective effect of a novel TRPC5 channel blocker, GFB-887. In vivo transplantation resulted in vasculatization of human iPSC derived kidney organoids, with functional perfusion confirmed by pharmacokinetic measurement of GFB-887 in the organoid after dosing by oral gavage.

Conclusions: Our kidney disease-targeted human iPSC platform provides a valuable complement to pre-clinical models for target validation and assessment of drug efficacy.
Conclusions: We have generated a new mouse model that mimicks the course of disease in patients with hereditary late-onset SRNS and FSGS. This new mouse model allows the investigation of early disease stages prior to the onset of podocyte depletion, glomerular scarring and massive proteinuria. Based on our data of foot process morphology and slit diaphragm integrity, glomerular filtration rate and albuminuria, we developed a model where the occurrence of albuminuria to a decreased compression of the GBM. In addition, the proposed mechanism of albuminuria can be adapted to other albuminuric pathologies.

SA-OR056

APOL1 Risk Variants Affect Podocyte Lipid Homeostasis and Energy Production in FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) is the most common primary glomerular disorder causing chronic kidney disease. Susceptibility to FSGS in African Americans is associated with the presence of genetic variants of the Apolipoprotein L1 gene (APOL1) names G1 and G2. We recently published that mice with a podocyte-specific doxycyline(Dox)-inducible expression of constitutively active Nfatc1uc (NFAT; Podocin-rTA, DT) represent a valuable new model for FSGS.

Methods: Human urinary podocyte-like epithelial cells (HUPECS) carrying different APOL1 genetic variants were established from patients with FSGS and used for in vitro studies and human BAC transgenic mice expressing the APOL1 genetic variants (G0, G1 or G2) under the endogenous promoter for in vitro studies. DT mice were expanded for consecutive breeding to G0, G1 or G2 mice to generate triple transgenic mice (TT) Nfatc1uc transgene expression was induced by feeding of Dox (chow 200 ppm) for 4 months.

Results: HUPECS carrying G1/G2 alleles are characterized by lipid droplet remodeling in association with decreased oxygen consumption, ATP generation and reduced mitochondrial membrane potential, while an increased abundance of super complexes was observed. In vivo, we tested the relative contribution of APOL1 risk variant expression to podocyte injury in APOL1 transgenic mice at baseline as well as in TT mice. Glomerular expression of APOL1 mRNA was similar among transgenic mice carrying APOL1 G0 and G1, but significantly lower in G2 carrying mice and these mice did not develop proteinuria at least up to 7 months of age (G2 mice were then excluded due to the low APOL1 mRNA levels). Meanwhile, TT mice carrying the G1 allele showed increased proteinuria, less body weight gain, higher serum BUN levels, more severe glomerulosclerosis and kidney cortex mass compared to mice with G0 or G1. G1 TT and G2 TT mice demonstrate a strong correlation between serum BUN and kidney cortex cholesterol esters was observed.

Conclusions: Our data reveal that APOL1 risk variant expression may play a role in modulating lipid homeostasis and energy production in podocytes. APOLG1 risk variant expression in mice does not impair kidney function at baseline whereas APOL1 G1 expression may contribute to APOL1 mediated susceptibility in Nfatc1uc-mediated FSGS.

Funding: NIDDK Support, Private Foundation Support

SA-OR057

Adeno-Associated Virus Gene Therapy Prevents Progression of Kidney Disease in Genetic Human and Mouse Models of Nephrotic Syndrome

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Background: Gene therapy targeting the kidney has proven challenging thus far. Adeno-Associated Virus (AAV) has been used successfully for gene therapy targeting other organs, with particular success demonstrated in targeting monogenic diseases. Here we aimed to advance gene therapy in the kidney by targeting a monogenic disease of the kidney. The association between podocyte injury in children with a mutation in NPHS2 encoding podocin. Here, AAV-mediated gene therapy was tested on a conditional podocin knock-out mouse model (IpD NPHS2/2), and on human podocytes with the commonest podocin mutation, R138Q.

Methods: AAV 2/9 expressing mouse podocin with a podocyte-specific promoter (either a mouse or human nephron promoter) was delivered via tail vein injection to IPD NPHS2/2. AAV serotypes LK03 and 2/9 were used to transduce immortalised human kidney cell lines to test for transduction efficiency. AAV LK03 expressing human podocin with a terminal nephron promoter was used to transduce immortalised R138Q podocin mutant human podocytes. AAV 2/9 expressing podocin demonstrated successful transduction of podocytes in ipD NPHS2/2. Treated mice showed a significant improvement in urinary albumin excretion ratio (AER) group, p<0.001 at day 42 and prolonged survival (n=3-4 group, p=0.049). In vitro, AAV LK03 transduced the human podocyte with a transduction efficiency of close to 100%. Transduction of the R138Q podocin mutant human podocyte with AAV LK03 expressing podocin demonstrated functional rescue in vitro.

Conclusions: This is the first study demonstrating successful gene transfer using AAV 2/9 in a monogenic kidney disease in a mouse model. AAV LK03 demonstrated highly efficient transduction of the human podocyte, making it a promising potential serotype for translation of gene therapy targeting the kidney.

Funding: Private Foundation Support

SA-OR058

Consolidation in the Dialysis Industry in the Era of Health Reform, 2006-2013

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Background: In the last 15 years, the dialysis industry has become dominated by two for-profit large dialysis organizations (LDO) that control 85% of the market. For-profit LDOs have been shown to have higher costs, greater use of expensive medications, lower transplant rates and higher mortality rates. We describe trends in dialysis industry consolidation in the current era of health reform, 2006-2013, and identify factors that put dialysis chains and independently-owned facilities at risk of closure or acquisition by LDOs.

Methods: We conducted a retrospective cohort study of non-federal US outpatient dialysis facilities that were independently-owned or affiliated with small chains (<20 facilities) for ≥1 year in 2006-2013. These facilities were deemed to be eligible for acquisition by large dialysis organizations. We used data from Center for Medicare and Medicaid Services, US Renal Data System and Area Health Resource File to evaluate facility and market characteristics throughout the study period. The outcome of interest was acquisition in dialysis facility ownership (i.e. acquisition) or facility closure. We used a generalized estimating equation with a logit link, clustered at the regional level, to examine the association between facility characteristics and closure or acquisition.

Results: Overall, 1686 dialysis facilities (27% of all US facilities) were eligible for acquisition for at least one year of the study period, 61% were independently-owned and 39% were affiliated with small chains. The number of independently-owned and small-chain-affiliated facilities declined by 192 from 2006 to 2013 (135 to 1164), while LDO-affiliated facilities increased by 1473 (3214 to 4687). Facilities at highest risk of acquisition and closure were not-for-profit (p=0.001), smaller in size (p=0.02), and in regions with lower hospital density (p=0.001) and more monopolistic markets (p=0.006).

Conclusions: Small dialysis chains and independent facilities retain a declining share of the dialysis market. Policy makers should work to maintain (or even increase) the current diversity of dialysis organizations and help maintain competition in markets at risk of antitrust violation. Efforts should be directed toward facilities that are particularly vulnerable to acquisition and closure.

Funding: NIDDK Support, Veterans Affairs Support

SA-OR059

Patient Experience with Care as a Critical Component of the Medicare ESRD Quality Incentive Program (QIP)

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Background: Medicare has long required dialysis facilities to assess patient experience as a condition for Medicare participation. More recently, the ESRD QIP introduced the In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH-CAPS) pay-for-performance measure in payment year (PY) 2014, which is pay-for performance starting in PY18. The ICH-CAPS performance measure is based on patient-reported data from 3 global ratings and 3 composite ratings from 35 survey questions.

Methods: We used facility ICH-CAPS survey results reported in the ESRD QIP Performance Score Summary Reports and CROWN db data during 2012-2018 to examine facility eligibility and ICH-CAPS performance from PY14-19. We evaluated ICH-CAPS performance by facility case-mix and by receipt of payment reduction using linear regression.

Results: In PY18 and 19, <50% of QIP-eligible facilities were scored on ICH-CAPS. Over 2,200 facilities were not scored due to obtaining <30 complete surveys. Among scored facilities, scores increased slightly from PY18 to PY19; the share of facilities receiving a score of 0 decreased from 8.5% to 4.2%. Performance was highest of the composite “providing information to patients” and lowest on the global rating of nephrologists. Important determinants of low ICH-CAPS scores included facility Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
case-mix (e.g., patient race and Medicaid eligibility) and ownership by the two large dialysis organizations. On average, facilities in PY18 posted reductions scored 2.5 points lower on ICH-CAPHS scores in PY19. Similarly, facilities penalized in PY18 had lower ICH-CAPHS scores in PY19.

**Conclusions:** Patient experience with care is an important component of the CMS Meaningful Measures framework, and by extension, the ESRD QIP. The use of ICH-CAPHS results in the Medicare ESRD QIP was limited to about half of facilities in PY18 and 19; improving survey response rates in moderately sized facilities may include more facilities. Survey results varied by facility case-mix and ownership. QIP-penalized facilities achieved lower ICH-CAPHS scores in the performance year and the subsequent year.

**Funding:** Other U.S. Government Support

**SA-OR060**

**Urban Segregation and Hospitalization Outcomes in Patients on Hemodialysis**

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**Background:** Patients receiving hemodialysis treatments in communities with a high percentage of Black residents have worse morbidity and mortality outcomes. To better understand drivers of this increased risk, we analyzed data from the United States cohort of Black patients receiving dialysis in facility zip codes located in communities with a higher (tertile 3: 40% to 60%) Black population. We analyzed hospitalization rates, while adjusting for multiple confounders.

**Methods:** This analysis included 4567 patients on hemodialysis from 154 facilities in 127 zip codes from the US-DOQPS phases 4–5 (2010-2015) linked to American Community Survey (ACS) data. Negative binomial regression was used to test the association of community-level tertile of Black residents in dialysis facility zip code with hospitalization rates, while adjusting for multiple confounders.

**Results:** The hospitalization incidence rate was 1.18 per year. Patients receiving dialysis in facility zip codes located in communities with a higher tertile 3: 40–60% Black, live in urban areas, of lower socio-economic class, more likely to have a catheter as a vascular access, and had fewer comorbidities. These tertile 3 facilities were more likely for-profit and had higher patient counts, but did not differ with respect to clinical quality benchmarks or dialysis adherence. Compared to tertile 1, the covariate-adjusted IRR (95% CI) for hospitalization was 1.32 (1.13–1.55) for tertile 2 and 1.32 (1.14–1.54) for tertile 3 of percent Black residents. This association remained significant in multiple strata examined.

**Conclusions:** Patients receiving dialysis in communities with a high percentage of Black residents have higher adjusted hospitalization rates, despite having equivalent dialysis care benchmarks. Prospective studies to assess the role of social support, access to pre-ESRD and specialty service care, and patient engagement strategies from healthcare systems and nephrologists caring for these vulnerable populations are warranted.

**Funding:** Other NIH Support - Clinical and Translational Science Award: 1UL1TR002556-01

**Table 2: Incidence Rate Ratios (IRR) of Hospitalization Count with Tertile of Percent Black Residents in the Community**

<table>
<thead>
<tr>
<th>Tertile of Black residents (with dialysis facility zip code)</th>
<th>IRR (95% CI)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1 (0–30%)</td>
<td>1.00 (0.87–1.15)</td>
<td>0.81</td>
</tr>
<tr>
<td>Tertile 2 (30–40%)</td>
<td>1.10 (0.96–1.26)</td>
<td>0.00</td>
</tr>
<tr>
<td>Tertile 3 (40%–60%)</td>
<td>1.18 (1.04–1.34)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

CI: confidence interval

**SA-OR061**

**Sodium Zirconium Cyclosalicate (SZC) Improves Potassium Balance in Hypokalemic Hemodialysis Patients: Results from the Phase 3b, Randomized, Placebo-Controlled DIALIZE Study**

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**Background:** Patients with end-stage renal disease frequently have persistent predialysis hyperkalemia (HK) despite hemodialysis (HD). The phase 3b, randomized, double-blind, placebo (PBO)-controlled DIALIZE trial (NCT03305521) investigated the effect of SZC on predialysis serum potassium (sK+) after the long interdialytic interval in HD pts with HK. To further examine the effect of SZC, several post hoc analyses were conducted.

**Methods:** In DIALIZE, 196 pts of mean age 58.1 [SD 13.7] years were randomized 1:1 to receive PBO (n=99) or SZC (n=97) 5 g once daily starting dose on non-dialysis days for 8 weeks, comprising a 4-week SZC dose titration phase (max 15 g) to achieve target predialysis sK+ 4.0–5.0 mmol/L, and 4-week stable-dose evaluation phase (SZC 0, 5, 10 or 15 g). Post hoc analyses included assessment of the number of visits at which pts had sK+ 4.0–5.5 mmol/L and the maximum sK+ during the evaluation phase. Change in K+ gradient (difference between the predialysis sK+ and diastolic K+ [dK+]) from baseline to end of evaluation phase was also assessed by cross tabulation of categorized dK+ (dK+ 2–3, 3–4, 4–5 and ≥5.5 mmol/L).

**Results:** A high sK+ to dK+ gradient at the start of HD permits rapid lowering of sK+, but can also be associated with a greater risk of adverse events, such as cardiac arrhythmias and hospitalizations. SZC was associated with more pts achieving sK+ 4.0–5.0 mmol/L and being maintained at sK+ 3.5–5.5 mmol/L vs PBO for 1, 2, 3 and 4 visits. 56 pts had severe predialysis HK (sK+ ≥6 mmol/L) in the PBO group during the evaluation period, compared with only 14 in the SZC group. A shift in K+ gradient towards values below the reported higher risk threshold of 3 mmol/L was observed in the SZC group, with 30.6% of pts (n=11/36) moving from gradient 4–5 to 2–3 mmol/L and 55.6% (n=25/45) from 3–4 to 2–3 mmol/L.

**Conclusions:** These findings suggest that treatment with SZC improves management and reduces the frequency of severe HK in HD pts, which could potentially modify the risks associated with these factors.

**Funding:** Commercial Support - AstraZeneca

**SA-OR062**

**Hospitalization Risk Among Younger Adult Hemodialysis Patients: Psychosocial Predictors in the ACTIVE-ADPOSE Study**

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**Background:** Association of younger age with hospitalization burden and 30-day readmission risk among adult hemodialysis (HD) patients is an unexpected observation in recent national studies, and predictors may be psychosocial in nature (Li et al. 2018; Chan et al. 2017). Smoking reflects individuals’ priority on health maintenance, and hospitalization risk is known to be elevated among HD patients who smoke, especially younger persons (Li et al. 2018). A dataset that captures granular patient-level data including smoking status and HD treatment adherence facilitates examination of age-stratified risk predictors.

**Methods:** The ACTIVE-ADPOSE Study (AAS) is a USRDS special study of a multi-center cohort of prevalent HD patients aged 20-92 conducted 2009-2013 at 14 outpatient dialysis clinics in the Atlanta GA and San Francisco areas. Institutional review boards (Emory University, University of California San Francisco) approved the study and all participants provided written informed consent. Study coordinators conducted patient interviews and abstracted patient medical records. In a multivariable regression analysis adjusted for AAS participants’ sociodemographic characteristics and comorbidity, we estimated the association of age, smoking, and HD treatment adherence with all-cause hospitalization burden.

**Results:** Among 759 AAS participants with data for all variables, younger age was associated with increased odds of hospitalization (p = 0.002). Smoking was associated with 30% increased odds (p = 0.03), and higher frequency of HD sessions skipped was associated with 20% increased odds (p = 0.001), for hospitalization. Compared with non-smokers (n=621), AAS participants who were current smokers (n=138) were younger.
Timing of Intradialytic Exercise and Its Impact on Intradialytic Hypotension: A Randomized Crossover Study

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Background: Intradialytic cycling improves physical function and quality of life in hemodialysis and appears safe. Due to concerns regarding increased intradialytic hypotension (IDIH), experts recommend that intradialytic cycling be completed during the last half of treatment. However, this recommendation limits the use of intradialytic cycling as a therapeutic tool to improve intradialytic symptoms, which are more common in the latter half of treatment. We compared the rate of IDIH while cycling during the first half of hemodialysis (early) versus the second half (late).

Methods: We performed a multi-centre randomized crossover study in adults (>18 years old) on chronic (>3 months), in-centre hemodialysis who were participating in a clinical intradialytic cycling program at three Canadian academic centres between July 1, 2018 and Mar 31, 2019. Group A cycled in the first half of hemodialysis for 2 weeks and then in the second half for the subsequent 2 weeks. In Group B, the exercise schedule was reversed. Blood pressure was measured every 15 minutes throughout hemodialysis. We compared rate of IDIH (episodes IDIH/100 hemodialysis hours) with early and late intradialytic exercise. IDIH was defined as a >20 mmHg drop from baseline BP OR a drop in systolic BP to <90 mmHg during hemodialysis. Data was analyzed using a general linear mixed model with random intercept and negative binomial regression.

Results: Eighty-four participants were included in the analysis. Group A (n=43, 32.6% female, 64.5±11.9 years) had a mean time on hemodialysis of 3.93 (0.26) hours and exercised for an average of 50.2 minutes. Group B (n=41, 52.6±13.5 years) had a mean time on hemodialysis of 3.90 (0.23) hours and exercised for an average of 50.2 minutes. The rate of IDIH per 100 hemodialysis hours was 35.7 and 37.6 when cycling during the first half and second half of hemodialysis, respectively; p=0.11.

Conclusions: There was no association between IDIH and the timing of intradialytic cycling. Exercise late in hemodialysis will facilitate expansion of intradialytic cycling programs by optimizing resource use and will enable the use of cycling as a potential non-pharmacological means of improving hemodialysis-related symptoms.

SA-OR064

The Effects of a 6-Month Structured Programme of Intradialytic Cycling on Cardiovascular Remodelling, Myocardial Fibrosis, and Aortic Stiffness: Results from the CYCLE-HD Study

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Background: Cardiovascular disease (CVD) is the leading cause of death in patients on haemodialysis (HD). Traditional and non-traditional risk factors drive pathological changes that relate to cardiovascular outcomes, including left ventricular mass (LVM), reverse LV remodelling (LVM/LVEDV), myocardial fibrosis (MF) and aortic stiffness. Exercise improves many of the risk factors that drive these processes. In this study we assessed the effects of a 6-month programme of intra-dialytic cycling (IDC) compared to usual care on prognostically significant measures of CVD in HD patients using cardiac MRI (CMR).

Methods: In an open-label, blinded end-point, cluster randomised controlled trial, adults undergoing maintenance HD were assigned to either a 6-month structured programme of IDC or usual care. Subsequent CMR scanning with assessment of LVM, LVM/LVEDV, native T1 mapping and aortic pulse wave velocity (aPWV) at baseline and study completion. Outcomes were analysed as intention-to-treat, using linear mixed-effects models, adjusted for baseline value.

Results: 130 subjects completed baseline assessments (65 per group) with 10% completing the study protocol (control group n=50, IDC group n=51). Patient demographics were well matched between groups. There was a significant between group reduction in LVM of -11.1g (95% CI -15.8,-6.4; p<0.001) with reverse LV remodelling (LVM/LVEDV) -0.07/ml (95% CI -0.12,-0.07; p<0.01) favouring the IDC group. There was a significant reduction in native T1 between groups over the study period of -32.2ms (95% CI -46.1,-18.3; p<0.001), with significant reductions in septal native T1 (-23.7ms, 95% CI -37.2,-10.3) and non-septal native T1 (-37.5ms [95% CI -54.3,-20.7]) favouring the IDC group (both p<0.001). There was a significant improvement in aPWV between groups over the study period of -0.70ms (95% CI -3.16,-0.09, 0.01) favouring the IDC group.

Conclusions: A 6-month programme of IDC associated with significant reductions in LVM and reverse LV remodelling, as well as reductions in native T1 and aPWV. These data suggest IDC is associated with beneficial LV remodelling, improvements in extent of MF and severity of aortic stiffness compared to usual care.

Funding: Other NIH Support - NIH-Geisinger Health System

SA-OR065

Effect of a Pedometer-Based Intervention on Body Composition in ESRD

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Background: A randomized trial of a pedometer-based intervention with weekly activity goals led to a modest increase in step count among dialysis patients. However, the effect of this intervention on body composition parameters has not been determined.

Methods: 60 dialysis patients were randomized to standard care or a 3-month intervention program with pedometers and weekly step count targets. We obtained bioelectrical impedance spectroscopy (BIS) data on 54 of these patients (28 control, 26 intervention). At baseline, at 3 months, and 6 months and used linear mixed modeling (adjusted for sex and dialysis modality) to estimate differences in change in total-body muscle mass (TBMM) adjusted for height2, fat mass (kg), and body mass index (BMI) (kg/m2) between control and intervention groups.

Results: At baseline, there was no significant difference between groups in age, BMI, race, or body composition. There was no statistically significant difference in change between groups in muscle mass, fat mass, or BMI at 3 months. However, at 6 months, participants in the intervention had a significantly greater increase in TBMM of 0.4 kg/m2 (95% CI 0.2, 0.7) but there was no dose-response relationship with TBMM2 or BMI.

Conclusions: Patients assigned to a pedometer-based intervention lost weight compared with controls who did not have intervention. Weight loss was driven primarily by changes in fat mass with relative preservation of muscle mass. The between-group differences appear to reflect a combination of negative changes in the control group as well as decrease of fat mass and increase of muscle mass in the intervention group. Achieved changes in step counts were correlated with changes in fat mass. These data support the use of our intervention in improving body composition measures in this population.

Funding: NIDDK Support, Private Foundation Support

SA-OR066

Development of an Automatic Risk-Prediction System for Hemodialysis Patients Using Artificial Intelligence: A Nationwide Dialysis Cohort Study in Japan

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Background: Dialysis patients are at high risks of death and cardiovascular disease. An accurate prediction of these risks at an individual level is required to improve the prognosis of dialysis patients. In this study, we developed a new system for predicting individual risk of death using machine learning and big data from a nationwide prospective cohort study of the Japanese Society for Dialysis Therapy Renal Data Registry.

Methods: We categorized hemodialysis patients in Japan into new clusters generated by k-means clustering method. The associations between clusters and an outcome (death) in five years were evaluated using multivariate Cox proportional hazards model. Then, the accuracy of the prediction of five-year mortality was compared among the machine learning models.
SA-OR067

Hyperkalemia Excursions and Mortality in Hemodialysis Patients: Results from the DOPPS

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Background: Hyperkalemia (HK) has been associated with adverse clinical events in hemodialysis (HD) patients when analyzing a single potassium (K) measurement or time-averaged K values, but the mean value of serial pre-dialysis K measurements does not reflect variability or excursions out of K target range.

Methods: We used data from 21 countries in phases 4-6 (2009-2018) of the Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective cohort study. We assessed the number of HK excursions over 4-month periods using 3 definitions – severe K >5.0, >5.5, and >6.0 mEq/L – and investigated the association with all-cause mortality over the subsequent 4 months using Cox regression and adjusted for potential confounders, including hypokalemia (K <4.0) excursions and other markers of malnutrition.

Results: We studied 245,866 4-month periods across 61,897 HD patients; the prevalence of at least 1 HK excursion over a 4-month period was 58%, 30%, and 12%, respectively, for serum K >5.0, >5.5, and >6.0 mEq/L; HK excursions >5.5 were most common in Russia (68%) and least common in the US (25%). Patients with HK excursions tended to be younger, with longer HD vintage and higher serum levels of albumin and phosphorus. Compared to 4-month periods with no HK excursions, adjusted models showed that the mortality rate over the subsequent 4 months was 10-20% higher with exactly 1 HK excursion (even at only >5.0 mEq/L), and 20-30% higher with 2+ HK excursions (Figure).

Conclusions: A clear association between one or more HK excursions and all-cause mortality was observed regardless of the hyperkalemic threshold. This method to assess target K achievement may be more sensitive at identifying patients with greater mortality risk over short-term intervals at lower thresholds (5.1-5.5 mEq/L) than previously reported, prompting reassessment of existing HK severity ranges and exploration of strategies to avoid HK excursions.

Funding: NIDDK Support, Commercial Support - This analysis was supported by AstraZeneca. The DOPPS Program is supported by Amgen (since 1996, founding sponsor), Kyowa Hakko Kirin (since 1999 for Japan DOPPS), and Baxter Healthcare Corp. Additional support for specific projects and countries is provided by Akebia Therapeutics, AstraZeneca, European Renal Association-European Dialysis & Transplant Association (ERA-EDTA), Fibrogen, Fresenius Medical Care Asia-Pacific Ltd, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGfN), Italian Society of Nephrology (SIN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Otsuka America, Pocemon Therapeutics, the Association of German Nephrology Centres, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Belgian Federal Public Service of Public Health in Belgium, Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN) in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRIN), and Kidney Research UK (KRUK) in the United Kingdom, and the Agency for Healthcare Research and Quality (AHRQ) and National Institutes of Health (NIH) in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health and not to Mr. Karayiannis directly.

SA-OR068

Identification of Dicarbonyl and L-Xylulose Reductase (DCXR) as a Therapeutic Target in Human CKD

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Background: Deregulation of renoprotective factors contributes to development and progression of chronic kidney disease (CKD).

Methods: Renal gene expression profiles of 197 renoprotective factors were analyzed in a cohort of 63 CKD patients. Median follow-up time was 6.9 years and association with disease outcome was assessed in Kaplan-Meier analysis and log-rank statistics. The multicenter NEPTUNE study served as validation cohort [n=225]. Associations with histological and clinical parameters were evaluated for the most significant renoprotective factor DCXR. The impact of SGLT2 inhibition on DCXR levels was furthermore assessed in human renal proximal tubular cells.

Results: DCXR was significantly associated with outcome in the discovery cohort (p-val < 0.0001) and the NEPTUNE validation cohort (p-val = 0.0001). Reduced expression of DCXR was significantly associated with the degree of histological damage as well as with lower estimated glomerular filtration rate and increased urinary protein levels. DCXR expression was positively correlated to enzymes involved in dicarbonyl stress detoxification. The SGLT2 inhibitors canagliflozin and empagliflozin showing a beneficial effect on renal proximal tubular cells under diabetic stimuli enhanced DCXR gene expression up to 2.35 and 2.22 fold.

Conclusions: Lower expression of the renoprotective factor DCXR is associated with more severe disease and worse outcome in human chronic kidney disease.

Funding: Government Support - Non-U.S.
SA-OR069

NLRP3 Inflammasome Inhibition Attenuates Cisplatin-Induced Renal Fibrosis by Decreasing Oxidative Stress and Inflammation

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Background: The mechanisms of cisplatin-induced chronic kidney disease are ill-defined.

Methods: Renal fibrosis was induced via a series of three injections of cisplatin to male C57BL/6 mice (7.5mg/kg body weight), and mice were euthanized at 6 weeks after the first cisplatin treatment. To validate the protective effect of NLRP3 inflammasome inhibition, MCC950 or gene deletion was used.

Results: Male C57BL/6 mice were administered three doses of cisplatin. BUN and serum creatinine increased time-dependently, accompanied tubular interstitial fibrosis. The protein level of NLRP3, ASC, and caspase-1 maturation was upregulated, and expression of IL-1β was markedly increased in renal tubular epithelium. MCC950, the specific inhibitor of NLRP3 inflammasome, was daily injected into multiple-cisplatin-treated mice intraperitoneally (20mg/kg body weight) for 14 days, starting from 4 weeks after the third dose of cisplatin. MCC950 reduced renal dysfunction, tubular damage, interstitial collagen deposit, and the expression of profibrotic parameters. MCC950 treatment also alleviated oxidative stress and inflammation. Furthermore, NLRP3 gene knockout halted the progression of cisplatin-induced renal fibrosis.

Conclusions: The activation of NLRP3 inflammasome promoted renal dysfunction and interstitial fibrosis induced by multiple injections of low-dose cisplatin. Blockade of NLRP3 inflammasome, by a selective inhibitor of NLRP3 inflammasome, MCC950, or by genetic NLRP3 deficiency, attenuated cisplatin-induced oxidative stress, inflammation, renal injury and fibrosis.

Funding: Government Support - Non-U.S.

SA-OR070

Macrophage Mitophagy Deficiency Promotes Experimental and Human Kidney Fibrosis

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Background: Mitochondrial quality control by mitophagy is critical for normal kidney function. We examined the role of PINK1, Mitofusin 2 (MFN2) and Parkin-mediated mitophagy in macrophage-induced kidney fibrosis, using experimental models of adenine diet (AD) or unilateral ureteral obstruction (UUO) and in human kidney fibrosis.

Methods: Kidney fibrosis in Pkn1-/- or Pkn2-/- mice was induced by AD or UUO. Role of MFN2 was studied using LysMC-Cre-Ã¢â‡â€Mfn2+/- mice. Kidney tissues and primary macrophages were analyzed by flow cytometry, confocal and electron microscopy, qPCR, western blot, ELISA, and Mitostress test. PBMCs, plasma and kidney biopsies from patients with severe-CKD (GFR<30 ml/min/1.73m2,â€”15) or biopsy-proven interstitial fibrosis & tubular atrophy (IFTA,â€”6) were compared to patients with mild/moderate-CKD (GFR>30â€”8) or controls (no CKD,â€”9).

Results: Expression of PKN1, MFN2, and Parkin was decreased in kidneys and renal macrophages after AD or UUO, as well as in TGF-ß1-treated bone-marrow-derived macrophages (BMDMs), human renal macrophages, and THP-1 cells. Kidney fibrosis from Pkn1-/- and Pkn2-/- mice showed higher fibronectin, collagen-I, TGF-ß1, galectin-3, and arginase-1 after AD or UUO vs corresponding wild-type mice. Renal macrophages from AD-fed Pkn1-/- mice had a higher number of abnormal mitochondria. LysMC-Câ‡“CD11b+ cells and CCL2 levels were increased in blood and kidneys from Pkn1-/- and Pkn2-/- mice after AD or UUO. Mitochondria from TGF-ß1-treated Pkn1-/- BMDMs showed lower respiration, higher mitochondrial ROS (mROS), and reduced colocalization with LC3. Mitophagy inhibition by Pkn1-/-RNA or Mdivi-1 resulted in decreased phosphorylation of downstream MFN2 and increased fibrotic response by human macrophages. LysMC-Câ‡“Mfn2+/- macrophage mitochondria displayed lower recruitment of Parkin and mitophagy. Plasma, PBMCs, and kidney biopsies from patients with severe-CKD and IFTA showed higher CCL2 and mROS, and lower PKN1, MFN2 and PRKN expression.

Conclusions: Our study is the first to demonstrate that deficiency of PINK1/MFN2/Parkin-mediated mitophagy promotes macrophage-induced oxidative stress and fibrotic response, and is associated with human kidney fibrosis. Therapeutically targeting macrophage mitophagy pathway may protect against kidney fibrosis.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-OR071

The PAR-1 Antagonist Vorapaxar Ameliorates Kidney Injury and Tubulointerstitial Fibrosis in Experimental Obstructive Nephropathy

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Background: In addition to its role in tumor invasiveness and metastasis, protease-activated receptor-1 (PAR-1) has emerged as an inducer of kidney fibrosis. Whether it can be exploited as a therapeutic target remains unknown.

Methods: We assessed the effect of direct inhibition of PAR-1 on renal fibrosis by vorapaxar (a PAR-1 antagonist), a drug currently undergoing clinical trials for cardiovascular disease, in murine unilateral ureteral obstruction (UUO) model, and in cultured rat renal proximal tubular epithelial cells (NRK-52E). PAR-1 signaling was studied by real-time quantitative PCR, Western blotting and immunohistochemical staining.

Results: In UUO kidneys, PAR-1 and its activator, thrombin, were highly expressed in tubular cells. Mice treated with vorapaxar showed diminished renal fibrotic changes with attenuated fibroconnectin, a-smooth muscle actin and collagen expression versus control. Macrophage infiltration and EKR1/2 activation were also reduced in vorapaxar treated UUO kidneys. In NRK-52E cells, vorapaxar inhibited PAR-1 signaling, ameliorated thrombin-induced EKR1/2 activation and suppressed the downstream TGF-B signaling via both Smad-dependent and non-Smad-dependent MAPK signaling pathways.

Conclusions: Vorapaxar protects against kidney fibrosis in UUO model, partly via inhibition of thrombin/TGF-ß3/MAPK signaling. This PAR-1 targeted therapeutic strategy may provide a novel treatment approach for chronic renal fibrotic diseases.

Funding: Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 05153596), Research Grants Council of Hong Kong (Collaborative Research Fund, grant no. C7018-16G), and Hong Kong Society of Nephrology/HK Kidney Foundation Research Grant 2018.

Funding: Government Support - Non-U.S.
SA-OR072
A New Therapeutic Target for CKD: Activins Facilitate TGF-β1 Profibrotic Signaling in Kidney Mesangial Cells
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Background: Chronic kidney disease (CKD) is a rising health issue for approximately 11% of American population and is characterized by progressive renal fibrosis and loss of kidney function leading to end-stage renal disease requiring dialysis or transplantation. The profibrotic cytokine TGFβ1 is a central mediator of kidney fibrosis in CKD; blocking it is not feasible due to adverse effects thereby requiring alternate therapeutic approaches. We have shown that TGFβ1 requires activins, a TGFβ superfamily member, for its profibrotic effects. However, since they both signal via the same canonical Smad pathway, how activins enable TGFβ1-induced fibrosis is not known and was investigated here.

Methods: Primary mouse mesangial cells were used. Activin A (AA) and B (AB) were inhibited with a neutralizing antibody, follistatin or siRNA to their receptor, ALK4. Smad3 transcriptional activity was assessed using a CAGA12 luciferase reporter.

Results: TGFβ1 induced strong early activation (60min) of Smad3, while AA/AB caused later activation (48h). TGFβ1 also induced the secretion of AA, with minimal β1-induced activation and upregulation. Finally, we confirmed that TGFβ1-induced expression of the extracellular matrix proteins fibronectin and collagen IV were prevented by activin inhibition in mesangial cells. Future experiments will investigate the relevance of Activin-induced β1 fibrotic signaling in a mouse model of CKD.

Conclusions: AA facilitates TGFβ1 profibrotic effects through regulation of both canonical and non-canonical signaling. Thus, targeting AA represents a novel antifibrotic strategy.

Funding: Other NIH Support - Canadian Institutes of Health Research (CIHR)

SA-OR073
A Computational Drug Screening Approach to Identify Compounds Increases Vascular Injury
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Background: Aging is a key driver for chronic kidney disease (CKD) and counterbalancing of renal aging processes depicts a way of preventing development and progression of CKD.

Methods: We generated a set of renal age-associated genes (RAAGs) making use of two transcriptomics datasets complemented by information extracted from scientific literature and dedicated aging databases. We evaluated the association of RAAG expression with CKD progression in an independent transcriptomics dataset of 63 CKD patients with a median follow-up time of 6.9 years. Genes showing concordant expression in aging and CKD were computationally screened for compounds reversing expression patterns using the L1000 Characteristic Direction Signature Search Engine. The impact on gene expression of key RAAGs in a human renal proximal tubular cell culture model of renal aging was validated for selected compounds.

Results: 31 of the 634 identified RAAGs were significantly associated with CKD progression. 23 RAAGs (74%) showed concordant regulation with CKD progression, i.e. being upregulated in progressive CKD patients as well as with increasing age or vice versa. Among the top-ranked compounds reversing expression of these RAAGs were drugs being in use in the clinical setting in the context of diabetes and kidney disease, namely rosiglitazone, valsartan, captopril, and atorvastatin. All four compounds significantly affected gene expression in a beneficial way in the cell culture model of renal aging. Rosiglitazone had the strongest impact on RAAG expression in HK2 cells significantly downregulating levels of TNFRSF11B (p-value < 0.001), MMP7 (p-value = 0.007), CTB (p-value < 0.001), LTβ (p-value = 0.029), and C3 (p-value = 0.002) as compared with untreated controls.

Conclusions: We have (i) generated a list of RAAGs, (ii) identified a subset being also associated with CKD progression, and (iii) identified compounds that have a positive impact on expression levels of the RAAGs signature in renal proximal tubular cells.

Funding: Government Support - Non-U.S.

SA-OR074
Single Cell Landscapes of Human Kidney in Health and Disease
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Background: Chronic kidney disease is a global health concern and yet therapies to prevent or halt its progression remain scarce. The emergence of single-cell genomics has provided the opportunity to simultaneously characterize the transcriptomic profile of thousands of individual cells and their respective states, revealing differences previously hidden by bulk analyses. As part of an effort to expand knowledge of regional cell identity, function and diversity within the kidney as a basis to understand and treat disease, we set out to catalog the cell types in different regions of the kidney and the perturbations seen with disease. The detailed identification of cellular landscapes across a variety of kidney diseases using single-cell and single-nucleus RNA sequencing (RNA-seq) aims to illuminate therapeutic targets for the development of precision therapies.

Methods: Macroscopically normal, fresh kidney tissue from patients undergoing tumor nephrectomies and frozen tissue sampled from diagnostic renal biopsies, were used to generate single cell and nuclei suspensions respectively. Droplet-based single-cell or single-nucleus RNA-seq libraries were prepared, amplified by PCR and sequenced. Established computational analytical techniques and a panel of canonical marker genes curated in our laboratory, were used to cluster the different cell types present.

Results: We identified heterogeneous cell populations characteristic of expected kidney cell types and detected regional differences predicted from known anatomy. The changing landscape in the setting of disease was revealed by changes such as the presence of additional immune cell populations.

Conclusions: Having established single-cell dissociation and single-nuclei isolation protocols for fresh and frozen human kidney specimens, this study represents an unprecedented cell mapping effort to identify disease-specific pathophysiological mechanisms and reveal novel therapeutic opportunities. The ability to prevent the potentially inexorable decline to kidney failure would represent a major advance and revolutionize the outlook for renal patients worldwide.

Funding: Private Foundation Support

SA-OR075
Capillaries Are Primary Targets in CKD and Loss of Tie2 Signaling Increases Vascular Injury
Maria Jeansson,1 Christer Betsholtz,1 Karolinska Institutet, Huddinge, Sweden; 2Uppsala University, Uppsala, Sweden.

Background: Progressive renal diseases are associated with capillary rarefaction of proximal capillaries, but the functional alterations and mechanisms are not well described. In both mouse models and patients a decline in endothelial tyrosine kinase receptor (Tie2) signaling can be seen in CKD. Here, we investigate the role of Tie2 signaling on capillary function and fibrosis in models of CKD.

Methods: Tie2 floxed mice were crossed with tamoxifen inducible endothelial specific Cadh5-Cre and a reporter line expressing TdTomato upon Cre-activation (Tie2 ECKO). This line enables both an endothelial specific KO of Tie2 and an endothelial lineage tracer. Mice were induced at 4 weeks of age to avoid developmental effects from the knockout. To study the role of Tie2 signaling in progressive renal disease we utilized the unilateral ureter obstruction (UUO) model. Additional lines (Pdgfra-H2b-GFP, Pdgfrb-GFP) were crossed into the line, resulting in reporters of myofibroblasts.

Results: Endothelial injury started already 1 day after UUO and was significantly worse in Tie2 ECKO mice compared to WT mice, including reduced capillary density, capillary fenestrations and vessel perfusion, increase tubular vacuolization and hypoxia. Blood pressure was not different between WT and Tie2 ECKO mice. Later than the endothelial injury was tubulointerstitial fibrosis starting 3 days after UUO. Fibrosis could be seen 3 and 10 days after UUO with significantly more fibrosis in Tie2 ECKO mice at each time point. Although capillary markers decreased and capillary morphology changed, the number of endothelial nuclei, as measured by the lineage tracer TdTomato, did not change. To investigate if the endothelial lineage had undergone endothelial-mesenchymal transition we utilized a myofibroblast reporter, Pdgfra-GFP, to investigate if GFP and Tgfα were co-localized after UUO. Investigation 3 and 10 days after UUO show no co-localization with TdTomato lineage although the up to 3-fold increase in total number of Pdgfra-GFP cells reflects the onset of fibrosis. Ongoing studies are analyzing single cell transcriptomics from the endothelial lineage in the above experiments.

Conclusions: Our results demonstrate that blood vessel function is central in progressive renal disease and that Tie2 signaling affects blood vessel function and that pro-Tie2 signaling could be an interesting therapy.

Funding: Private Foundation Support, Government Support - Non-U.S.
Heat Shock Proteins Prevent Mitochondrial Dysfunction In Uremic Cardiomyopathy: Results from the CAIN Study

Michelle D. Song, Arvin Halim, Li-jun Ho, Thomas F. Hiemstra, Kenneth Lim, Tzongshii Lu.

Brigham and Women’s Hospital, Harvard Medical School, Natick, MA; Brigham and Women’s Hospital, Arlington, MA; University College London, London, United Kingdom; Massachusetts General Hospital, Harvard Medical School, Boston, MA; Massachusetts Institute of Technology, Quincy, MA.

Background: Uremic cardiomyopathy is a life-limiting condition that occurs in chronic kidney disease (CKD). Emerging evidence has shown that mitochondrial dysfunction is critical in the pathogenesis of the failing heart. We previously showed that impairment of mitochondrial bioenergetics, fusion and division activities is a cardinal event in heart failure in CKD. Heat Shock Proteins (HSP) 70 is an inducible HSP that has been shown to exert self-cytoprotective effects. We previously report that HSP70 prevents vascular calcification in uremic conditions and mitochondrial dysfunction in various stress models. In this study, we hypothesized that induction of HSP70 can prevent mitochondrial dysfunction in the failure heart in CKD.

Methods: Human left ventricular tissues collected from advanced CKD on dialysis (n=15) and healthy donors (n=15) were subjected to RNA sequencing, ex vivo. We developed a digital cell sorting study model using deconvolution method to enhance interpretation of heterogeneous transcriptomic profiles inherent of mixed-cell type tissue. Primary human cardiac myofibroblast were treated with uremic serum and calcification medium (CM, 5 mM calcium chloride and 5 mM β-glycerolphosphate disodium), in vitro.

Results: Our data shows that HSP70, as well as HSP27 and HSP90 were significantly down-regulated in CKD hearts compared to control group (p=0.001). Additionally, cytoprotective mHSP70 (HSPA9) and the HSP70 co-chaperone, Bcl2 associated Athanogene 1 (BAG1) were highly expressed in human left ventricular heart cells compared to CKD. However, mitochondrial fusion regulation genes MFN1 and OPA1 were down-regulated in CKD hearts (p=0.01). Analysis of primary human cardiac myofibroblast treated with CM and uremic serum revealed the same pattern of changes, in vitro. Induction of HSP70 by HST in cardiac myofibroblasts significantly prevented mitochondrial dysfunction, in vitro (p=0.001).

Conclusions: Our data shows that mitochondrial dysfunction and downregulation of HSPs are involved in the development of uremic cardiomyopathy. Induction of HSP70 prevents mitochondrial dysfunction in cardiac cells under uremic stress. Further studies are warranted to investigate therapeutic strategies targeting HSP70 in uremic cardiomyopathy.

Funding: Private Foundation Support

Oral Abstract - Saturday: 100

Renal, Cardiovascular, and Safety Outcomes of Canagliflozin (CANA) According to Baseline Kidney Function: A CREDECE Secondary Analysis

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Background: CANA is approved in people with type 2 diabetes and eGFR 45mL/min/1.73m2. We assessed its efficacy and safety according to eGFR strata including the 30–<45mL/min/1.73m2 stratum.

Methods: The CREDECE study enrolled 4401 participants with eGFR 30–<90mL/min/1.73m2 and urinary albumin:creatinine ratio >300-5000mg/g, randomizing them within eGFR-based strata to CANA 100mg daily or matching placebo. Primary and prespecified secondary composites and safety outcomes were analyzed using Cox proportional hazards regression within each screening eGFR stratum 30–45, 45–60 and 60–90mL/min/1.73m2.

Results: At screening, 1313 (29.8%), 1279 (29.1%), and 1809 (41.1%) participants had an eGFR 30–<45, 45–60 and 60–90mL/min/1.73m2. Overall, CANA reduced the primary outcome, the renal composite of ESKD, sustained doubling serum creatinine (SCr) or renal death, a range of CV outcomes and serious adverse events with no impact on fractures or amputations. There was no evidence the impact of CANA differed between eGFR subgroups (all P-interaction >0.11, Figure). The benefits of CANA were individually significant in people with a screening eGFR 30–45mL/min/1.73m2 for the primary composite, renal composite and composite of CV death or hospitalization for heart failure (95%CI upper limit <1.00).

Conclusions: CANA safely reduces the risk of renal and CV events in people with type 2 diabetes and substantial albuminuria, and these benefits are preserved across a spectrum of eGFR 30–<90mL/min/1.73m2, including eGFR 30–<45mL/min/1.73m2.

Funding: Commercial Support - Janssen Research & Development, LLC
Cost Effectiveness Analysis of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors Treatment in Patients with Diabetic Kidney Disease for Cardiovascular and Renal Protection in Singapore

SA-OR080

Canagliflozin and Renal-Related Adverse Events in Type 2 Diabetes and CKD: Results from CREDENCE

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Background: Canagliflozin (CANA), a sodium glucose co-transporter 2 inhibitor, has been shown to reduce the risk of major renal outcomes in patients with type 2 diabetes and chronic kidney disease (CKD) in the CREDENCE trial. The aim of this analysis was to examine the incidence of renal-related adverse events (AEs) during treatment with CANA.

Methods: The CREDENCE trial randomly assigned 4401 participants with type 2 diabetes and CKD stages 1 to 3B to CANA 100 mg/day or placebo (PBO). Rates of renal-related AEs were analyzed using an on-treatment approach overall and by screening eGFR strata (30–45, 45–<60, and 60–90 ml/min/1.73m²).

Results: The incidence rate of renal-related AEs was lower in the CANA versus the PBO group (Table), with consistent results for the majority of specific AEs, including acute kidney injury, azotemia, blood creatinine increased, glomerular filtration rate decreased, nephropathy toxic, renal failure, and renal impairment. The incidence rate of serious renal-related AEs was also lower in the CANA compared to the PBO group (Table). The incidence rates of renal-related AEs were lower with CANA relative to PBO across three eGFR strata (HRs of 0.73, 0.60, and 0.81 for eGFR 30–<45, 45–<60, and 60–<90, respectively; P-interaction=0.31). Renal-related serious AEs were also lower with CANA relative to PBO across the three eGFR strata (Table).

Conclusions: CANA decreased the incidence of serious and non-serious renal-related AEs in patients with type 2 diabetes and CKD. These data highlight the renal safety of CANA in this population.

Funding: Commercial Support - Janssen Research & Development, LLC

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<th>Table: renal-related AEs using an on-treatment approach</th>
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<td>Total renal-related AEs, IR per 1000 PY</td>
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<td>Total renal-related AEs, n (%)</td>
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<td>Nephropathy toxic, n (%)</td>
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<td>Renal failure</td>
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<td>Total renal-related AEs by screening eGFR, n (%)</td>
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<td>Serious renal-related AEs, IR per 1000 PY</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
SA-OR081
Clinical Events in Type 2 Diabetes and Moderate-to-Severe CKD by Albuminuria Status: Dulaglutide vs. Insulin Glargine
Katherine R. Tuttle,1 Brian Rayner,2 Mark Lakshmanan,3 Brad Woodward,4 Anita Kwan,5 Maniçe Konig,6 Fady T. Brotot,7* University of Washington School of Medicine, Spokane, WA; 1Department of Nephrology and Hypertension, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa; 2Eli Lilly and Company, Indianapolis, IN.

Background: In participants with type 2 diabetes and moderate-to-severe chronic kidney disease (CKD), in the AWARD-7 trial, treatment with dulaglutide (DU) compared to insulin glargine (IG) led to slower estimated glomerular filtration rate (eGFR) decline at similar levels of glycemic control and blood pressure. Methods: To determine risk of a composite endpoint of ≥40% eGFR decline or end-stage kidney disease (ESKD) by albuminuria status (eGFR decline thresholds of 30%, 40%, and 50% predict end-stage kidney disease), this post hoc analysis used Cox proportional hazards modeling for time to first event. Participants were randomized (1:1:1) to DU 0.75 mg or 1.5 mg weekly versus IG daily for one year. eGFR was calculated using the CKD-epidemiology (eGFR) creatinine and cystatin C equations.

Results: At baseline, treatment groups had similar eGFR within albuminuria subgroups (Table). Through the 1-year treatment period, the majority of events occurred in patients with macroalbuminuria; the incidence rate of the composite endpoint was significantly lower for DU 1.5 mg compared to IG, which was mainly driven by effects in participants with macroalbuminuria.

Funding: Commercial Support - Eli Lilly and Company

SA-OR082
Renoprotection with Semaglutide and Liraglutide: Direct or Indirect Effects?
Johannes F. Mann,1 John Buse,2 Thomas Idlom,3 Lawrence A. Leiter,4 Richard E. Prattley,5 Soren Rasmussen,6 Tina Vilsholt,7 Benjamin Wolthers,7 Vlad Perkovic,8* Friedrich Alexander University of Erlangen, Erlangen, Germany; 2University of North Carolina School of Medicine, Chapel Hill, NC; 3Novo Nordisk A/S, Søborg, Denmark; 4St. Michael’s Hospital, University of Toronto, Toronto, ON, Canada; 5AdventHealth Translational Research Institute for Metabolism and Diabetes, Orlando, FL; 6Novo Nordisk A/S, Søborg, Denmark; 7Steno Diabetes Center Copenhagen, Gentofte; University of Copenhagen, Hellerup, Hellerup, Denmark; 8Novo Nordisk A/S, Søborg, Denmark; 9The George Institute, UNSW, Sydney, NSW, Australia.

Background: The SUSTAIN 6 and LEADER cardiovascular (CV) outcome trials indicated that the glaglucagon-like peptide-1 analogues semaglutide and liraglutide may provide renal as well as CV benefits. This post hoc analysis used Cox proportional hazards modeling for time to first event. Participants were randomized (1:1:1) to DU 0.75 mg or 1.5 mg weekly versus IG daily for one year. eGFR was calculated using the CKD-epidemiology (eGFR) creatinine and cystatin C equations.

Conclusions: The risk of the composite endpoint of ≥40% eGFR decline or ESKD was lower by approximately half for DU 1.5 mg compared to IG, which was mainly driven by effects in participants with macroalbuminuria.

Funding: Commercial Support - Eli Lilly and Company

SA-OR083
Combination Therapy of Empagliflozin and Linagliptin vs. Metformin and Insulin Glargine on Intra- and Renal Hemodynamics in Type 2 Diabetes
Carsten Ort, Dennis Kannekerl, Susanne Jung, Roland E. Schmieder, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany.

Background: To determine risk of a composite endpoint of 40% eGFR decline or ESKD was lower by approximately half for DU 1.5 mg compared to IG, which was mainly driven by effects in participants with macroalbuminuria.

Results: In the SUSTAIN 6 and LEADER, the rate of a renal event was reduced by 36% (95% CI 12%–54%; P=0.005) and 22% (95% CI 83±33%; P=0.003) in the semaglutide and liraglutide groups, respectively, versus placebo. A1C was estimated to mediate 26% and 24% of the benefit in SUSTAIN 6 (95% CI 7.1–7.63) of the benefit of semaglutide and liraglutide, respectively, whereas the contributions of SBP (22% and 9% [95% CI 2.8;22.7]) and BW (8% and 9% [95% CI 7.9;35.5]) were smaller. In adjusted analyses, the contribution of A1C increased to 36% (SBP as confounder) and 30% (95% CI 4.5;81.1; SBP and BW as confounders) in the semaglutide and liraglutide groups, respectively.

Conclusions: The renal benefits of semaglutide and liraglutide appear mediated to a modest extent by changes in A1C, SBP and BW, and are therefore likely to be also driven by other, potentially direct, mechanisms.

Funding: Commercial Support - Novo Nordisk

SA-OR084
Risks of eGFR Decline Thresholds by CKD, Diabetes, and Albuminuria Status
Kamila Daratha,1 Cami R. Jones,1 Katherine R. Tuttle,2 Providence Health Care, Colbert, WA; 2University of Washington School of Medicine, Spokane, WA; 3Providence St. Joseph Health, Spokane, WA.

Background: Thresholds for estimated glomerular filtration rate (eGFR) decline are increasingly used as chronic kidney disease (CKD) outcomes and clinical trial endpoints. eGFR decline thresholds of 30%, 40%, and 50% predict end-stage kidney disease. However, data from large clinical populations to determine risks of reaching these thresholds among patients with and at-risk of CKD (diabetes mellitus (DM), pre-DM, and diabetes with hypertension (HTN)) and by DM or albuminuria status among patients with CKD are lacking.

Methods: CURE-CKD is a meticulously curated registry of clinical and administrative data extracted from health records of two major healthcare systems in the western United States. eGFR (CKD-EPI) was calculated as the mean value during a 90-day baseline and for each subsequent year (2006-2017). Adults with baseline eGFR ≥15 ml/min/1.73m² and at least two follow-up years were included. Albuminuria was defined as urine albumin-to-creatinine ratio ≥30 mg/g. Time-to-event models examined eGFR decline thresholds, controlling for age, gender, race/ethnicity, baseline eGFR, and medication use. An alpha of p<0.001 was chosen a-priori.

Results: A total of 1,005,986 patients with mean follow-up of 5.4 years were included (table 1). For patients with established CKD compared to those at-risk of CKD, adjusted hazard ratios (aHRs) for eGFR decline thresholds (30%, 40%, and 50%) were increased (1.93, 2.05, 2.16). For patients with CKD, those with DM compared to without DM had increased aHR (1.57, 1.71, 1.75). For patients with CKD and DM, aHR were increased for those with albuminuria compared to without albuminuria (1.38, 1.41, 1.44). Among patients with DM, compared to without albuminuria, increased aHR were increased for those with albuminuria compared to without albuminuria (1.81, 1.93, 1.97).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: Patients with CKD had increased risk of reaching clinically relevant eGFR decline thresholds compared to patients at-risk with DM, pre-DM, or HTN. Among patients with CKD, DM or, albuminuria independently predicted thresholds of eGFR decline. Study findings inform the design of observational studies and clinical trials in patients with and at-risk of CKD.

Funding: Private Foundation Support

SA-OR085

CKD Progression for Patients with Diabetes and Reduced eGFR Treated with Metformin or Sulfonylurea

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Background: Safety concerns limit metformin use in kidney disease. We compared the incidence of renal events between metformin and sulfonylureas users with reduced estimated glomerular filtration rate (eGFR).

Methods: A retrospective cohort combined Veterans Administration, Medicare, and National Death Index data. Metformin or sulfonylurea users were followed from renal function threshold (eGFR <60 ml/min/1.73m2) until a renal event, treatment change, loss to follow up, death or study end. Renal event was defined as persistent decline in eGFR from baseline of 40% or more (eGFR event) or a diagnosis of end-stage renal disease (ESRD). The analysis compared renal event hazard for metformin vs. sulfonylureas users and estimate cumulative risk in a propensity score matched weighted cohort accounting for the competing risks of non-persistence or death.

Results: There were 74,101 and 28,976 persistent metformin and sulfonylurea users with diabetes and CKD, DM or, albuminuria. The incidence of renal events between metformin and sulfonylureas users with reduced eGFR was associated with a lower risk of kidney function decline or ESRD.

Conclusions: Compared to sulfonylureas, metformin use in patients with reduced eGFR was associated with a lower risk of kidney function decline or ESRD.

Funding: Veterans Affairs Support

SA-OR086

Verinurad Plus Febuxostat Rapidly Reduces Albuminuria in Type 2 Diabetes Independent of Preexisting Kidney Disease

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Background: Elevated serum uric acid predicts new-onset albuminuria, the earliest clinical indicator of kidney disease. We evaluated the effects of intensive uric acid lowering on albuminuria by combining verinurad with febuxostat in patients with type 2 diabetes mellitus (T2DM) and albuminuria.

Methods: In a phase 2, parallel group, multicenter, randomized, double-blind, placebo-controlled trial (NCT03118739), adults with T2DM, albuminuria, and hyperuricemia were randomized to verinurad 9 mg plus febuxostat 80 mg once daily, or placebo, and followed for 24 wks. The primary outcome was reduction in urinary albumin to creatinine ratio (UACR) at 12 wks compared with baseline. Changes in UACR were evaluated according to baseline characteristics including UACR and estimated glomerular filtration rate (eGFR).

Results: Baseline UACR was 439 (±825) mg/g in the verinurad plus febuxostat group (n=32) and 412 (±584) mg/g in the placebo group (n=28). Improvement in UACR with verinurad plus febuxostat was rapid, sustained over time, and met prespecified criteria for significance, with 39%, 39%, and 49% reductions vs placebo at wks 1, 12, and 24, respectively (wk 12: 90% CI: -62%, -4%; P=0.0047). Reduction was consistent across subgroups including those based on UACR and eGFR (Figure). Verinurad plus febuxostat was well tolerated.

Conclusions: Intensive urate lowering with verinurad plus febuxostat significantly reduced UACR in patients with T2DM, albuminuria, and hyperuricemia. Reduction was rapid, sustained, and similar regardless of baseline eGFR and degree of albuminuria. A larger study is underway to determine which patient groups might benefit most from verinurad combination therapy.

Funding: Commercial Support - AstraZeneca

SA-OR087

Correction of Anemia by Dapagliflozin in Patients with T2D

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Background: Type 2 diabetes (T2D) is one of the most common causes of chronic kidney disease (CKD) and the most frequent cause of renal anaemia. Most patients (pts) with T2D show no overt symptoms of renal impairment, consequently, unrecognized anaemia is common. Increased hemoglobin (Hb) levels have been observed with dapagliflozin (DAPA) treatment. This study investigated the efficacy and safety of DAPA 10mg in pts with and without anaemia at baseline.

Methods: This post-hoc analysis evaluated the effect of the sodium-glucose cotransporter 2 inhibitor, DAPA, 10mg, on Hb over 24 weeks (w) across 14 placebo (PBO)-controlled studies in T2D pts with or without anaemia (women Hb<12.0 g/dL; men Hb<13.0 g/dL).

Results: A total of 5324 pts were included, 700 (13%) pts had anaemia at baseline. There were 1168 (22%) pts with CKD (eGFR 60–<90 ml/min/1.73m2), 324 (28%) had anaemia at baseline. As expected, pts with anaemia vs those without anaemia were older (mean age:63 vs 59y), had a longer duration of T2D (14 vs 9y) and more advanced CKD (mean eGFR: 66.3 vs 78.6 ml/min/1.73m2 and mean UACR: 274 vs 89 mg/g). Longitudinal repeated measures analysis showed an Hb increase at w 24 in the DAPA 10mg anaemia and no-anaemia subgroups (Fig 1A). Anemia: (Mean g/dL(SEM)[95% CI], DAPA 0.81(0.066) [0.68,0.93], PBO 0.28(0.067) [0.15,0.41]; difference vs PBO 0.53(0.076) [0.38,0.68]). No-anaemia: (DAPA 0.56(0.017) [0.53,0.60] and PBO -0.20(0.018) [-0.23,0.16]; Difference
The effect of DAPA 10mg on Hb in pts with and without anemia over 24 weeks

SA-OR088

Polycystin 1 Regulates Actomyosin Contraction and the Cellular Response to Extracellular Stiffness

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Background: The polycystins are transmembrane multidomain proteins that function as mechanosensors. PC1, the α-subunit of the polycystin complex, is composed of a N-terminal ciliary domain, a cytosolic domain containing a high stretch exponent extensible domain, and a C-terminal extracellular domain. We have shown that PC1 is a mechanosensitive ion channel that is activated upon stimulation of the extracellular (EC) domain; this activation is necessary for the Wnt9b-induced ciliobentraction that results in intracellular calcium influx. In this study, we investigated the role of PC1 in the cellular response to extracellular stiffness.

Methods: To study the role of PC1 in the cellular response to extracellular stiffness, we generated a stable PC1−/− mouse embryonic fibroblast (MEF) cell line. We subjected these cells to different stiffness conditions ranging from 0.4 to 40 kPa, and we measured their response in terms of actomyosin contraction, ciliobentraction, and calcium influx.

Results: We observed that PC1−/− MEFs showed reduced actomyosin contraction and ciliobentraction in response to EC stiffness. Furthermore, we found that the calcium influx induced by EC stiffness was significantly reduced in PC1−/− MEFs compared to wild-type MEFs.

Conclusions: These findings suggest that PC1 plays a crucial role in the cellular response to extracellular stiffness, and that its absence leads to impaired mechanotransduction.

SA-OR089

Polycystin 1 Acts as an Atypical Adhesion G-Protein-Coupled Receptor (GPCR) That Responds to Non-Canonical WNT Signals and Inhibits GSK3β

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Background: Polycystin 1 (PC1) is a member of the polycystin family of proteins that function as mechanosensors. PC1 is known to be activated by extracellular stiffness, which results in intracellular calcium influx and ciliobentraction. Recent studies have suggested that PC1 may also act as an atypical GPCR that responds to non-canonical WNT signals and inhibits GSK3β.

Methods: We generated a stable PC1−/− mouse embryonic fibroblast (MEF) cell line and subjected these cells to different WNT signal conditions. We measured the response of PC1−/− MEFs in terms of actomyosin contraction, ciliobentraction, and calcium influx.

Results: We observed that PC1−/− MEFs showed reduced actomyosin contraction and ciliobentraction in response to WNT signal stimulation. Furthermore, we found that the calcium influx induced by WNT signal stimulation was significantly reduced in PC1−/− MEFs compared to wild-type MEFs.

Conclusions: These findings suggest that PC1 plays a crucial role in the cellular response to non-canonical WNT signals, and that its absence leads to impaired mechanotransduction.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Pathogenesis of Cystic Kidney Diseases

SA-OR092
CD4 T Cells Promote Renal Cystic Disease
Kurt Zimmerman, Michal Mrug, Bradley K. Yoder. University of Alabama at Birmingham, Birmingham, AL.

Background: The majority of renal cystic diseases are caused by mutations in proteins associated with primary cilia formation or function. Previous data indicate that mice with dysfunctional primary cilia have an enhanced innate immune response following injury and that these cells are required for accelerated cyst formation. Despite this knowledge, little work has studied the complementary adaptive immune system during injury induced cyst formation.

Methods: Herein, we set out to identify and determine the importance of adaptive immune cells, particularly CD4 T cells, during injury induced rapid cyst formation in conditional Il688 mice (here after referred to as cilia mutant mice) and in the Il688 and adult induced conditional Il688 slowly progressive models of cystic disease.

Results: Our data show that the number of T cells, including CD4, CD8 and double negative (DN) T cells, are increased in injured cilia mutant mice compared to controls. In addition, we showed that the number of CD4, CD8, and DN T cells are also increased in the Il688 and adult induced, non-injured conditional Il688 mouse models of slow cystogenesis. Further subtyping of CD4 T cells in these models shows that the number and percentage of Foxp3+ Tregs is increased in all 3 models of cystic disease compared to their respective controls. To test our hypothesis that adaptive immune cells are promoting cystic disease, we crossed our cystic mouse models to RAG1-/- mouse that lack all adaptive immune cells. Our data indicate that loss of adaptive immune cells reduces cyst formation in the rapid injury-induced model of cystogenesis but not in the slowly progressive models.

Conclusions: We tested that the number of Tregs is increased in autosomal dominant polycystic kidney disease patients compared to controls. Our data show that the number of T cells, including CD4, CD8 and double negative (DN) T cells, are increased in injured cilia mutant mice compared to controls. In addition, we showed that the number of CD4, CD8, and DN T cells are also increased in the Il688 and adult induced, non-injured conditional Il688 mouse models of slow cystogenesis. Further subtyping of CD4 T cells in these models shows that the number and percentage of Foxp3+ Tregs is increased in all 3 models of cystic disease compared to their respective controls. To test our hypothesis that adaptive immune cells are promoting cystic disease, we crossed our cystic mouse models to RAG1-/- mouse that lack all adaptive immune cells. Our data indicate that loss of adaptive immune cells reduces cyst formation in the rapid injury-induced model of cystogenesis but not in the slowly progressive models.

Funding: NIDDK Support, Private Foundation Support

SA-OR093
The Ciliary Phosphoinositide Pathway Controls the Dosage of Polycystins in Cilia
Chuan Chen. Department of Biochemistry and Molecular Biology, Mayo Clinic, Rochester, MN.

Background: ADPKD is a progressive genetic disorder characterized by the development of fluid-filled renal cysts. It is mainly caused by mutations in PKD1 and PKD2 genes encoding respectively PC1 and PC2. PC1 and PC2 function as a complex and localize predominantly in primary cilium. However, the molecular mechanism underlying the trafficking and maintenance of PC1/PC2 in cilium is unclear. PIs are a group of signaling phospholipids that regulate membrane trafficking and organelle identity. Alarming phosphoinositide metabolism correlates with variant human diseases. Recent studies showed that PI(4,5)P2 and PI(4,5)P3 exhibit unique compartmentalization in the ciliary membrane and regulate the ciliary trafficking and signaling, suggesting this PI pathway may function in the trafficking of polycystins to cilia.

Methods: We manipulate the PI contents and determine the ciliary level of PC1 and PC2 using IF. The global protein levels are determined by immunoblotting. We use the 3D spherical model and the embryonic kidney culture to determine the effect of the ciliary PI pathway on renal cystogenesis. Moreover, in vitro cellular assays are used to monitor cell survival and proliferation.

Results: We found increased PI(4,5)P2 level in ciliary membrane increases the ciliary level of PC1 in normal cells. Moreover, in renal epithelial cells carrying ADPKD mutations, the ciliary level of PC1 and PC2 can also be restored by increasing PI(4,5)P2 in cilia. These data indicate the 3D structure and ciliary kidney culture assays to detect the renal cystogenesis, and discovered that our specific inhibitor reduced the cyst formation both in vitro and ex vivo. In addition, the inhibitor showed no obvious effect on phosphatidyl inositol kinase or AKT expression, as well as cell proliferation in MTT assays, suggesting that the impaired cystogenesis were very likely resulted from recovered ciliary polycystins.

Conclusions: The effective treatment of ADPKD is extremely limited and Tolovaptan as the only FDA approved drug shows limited benefits with substantial side effects. The functional dosage of polycystins directly influences the disease severity in ADPKD patients. We found that manipulating the ciliary PI pathway as well as their products increases the ciliary polycystins, and exhibits suppression effects on cystogenesis. These results suggest that the ciliary PI pathway could be a novel therapeutic target for ADPKD.

Funding: NIDDK Support, Private Foundation Support

SA-OR094
Aurora A Kinase Is Required for Development of Renal Cysts in a Ciliopathy Model

Background: Aurora A Kinase (AURKA) is classically regarded as a mitotic cell kinase necessary for progression through the cell cycle. It is also associated with dysregulation of the primary cilium. We have previously shown that in vitro inhibition of AURKA is sufficient to reverse many of the cilia associated phenotypes in cultured cells lacking the Joubert Syndrome gene, INPP5E. This raises the possibility that therapies aimed at limiting AURKA actions may represent an approach to preventing cyst development in this and other ciliopathies.

Methods: To investigate a causative role for AURKA in renal cyst initiation and progression we have independently inhibited its kinase activity (using Alisertib) and deleted the Aurora gene in a mouse model of PKD development in Joubert Syndrome. We have then studied the impact of these alterations on cystogenesis and cell signaling.

Results: We find that treatment with Alisertib results in the generation of more, rather than less, renal cysts and provide evidence that the drug actually increases the amount of AURKA protein in kidney cells. Conversely, we find the whole AURKA deletion does not affect the development or homeostasis of the ciliopathy, its co-deletion with Innp5e is able to almost completely prevent PKD - over the long term. Analysis of these models indicates that AURKA over-expression in PKD is associated with increased AKT signalling and that genetic deletion of AURKA normalises this pathway and cyst development in PKD mouse.

Conclusions: These studies demonstrate that while AURKA is dispensable for renal development and tubule homeostasis, it acts as a key driver of cyst formation. The failure of Alisertib to ameliorate cyst formation contrasts with the profound prevention of disease mediated by AURKA gene deletion. Taken together, these findings suggest that kinase independent functions of AURKA are central to cystogenesis. The correction of AKT signalling and the close association between AURKA/AKT highlights dysregulation of this pathway as being critically important for cyst initiation, suggesting a potential avenue for therapeutic development.

Funding: Government Support - Non-U.S.

SA-OR095
Carbonic Anhydrase II (CAII) and Intercalated Cells (ICs) Drive Kidney Cystogenesis in Tuberous Sclerosis Complex (TSC)
Sharon L. Barone,1,2 Kamary A. Zahedi,1,2 Marybeth Brooks,1,2 Alicia A. McDonough,1 Stefan Somlo,1 Elizabeth P. Henske,1,3 Jane J. Yu,1,3 Manoocher Soleimani,1,31University of Cincinnati, Cincinnati, OH; 2Research Services, Veterans Affairs Medical Center, Cincinnati, OH; 3Koch School of Medicine of USC, Los Angeles, CA; 4Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 5Yale University, New Haven, CT.

Background: TSC is caused by mutations in either TSC1 or TSC2 genes and affects multiple organs, including kidney, lung and brain. In the kidney, TSC presents with benign tumors (angiomyolipomas) and cysts, which eventually lead to kidney failure. Little is known about the factors that promote cyst generation and enlargement in tubulointerstitial disease.

Methods: Principal cell (PC) specific inactivation of Tsc-1 or Tsc-2 was accomplished by crossing mice with either a Tsc-1 or Tsc-2 flanked construct with mice expressing cre recombinase under the control of Aag-2 promoter. In Tsc-1 KO as well Tsc-2 KO (Physiol. Report 2019) develop numerous ICS H+-ATPase, Cl-/HCO3- dependent angiohyelolipomas and cysts, which eventually lead to kidney failure. Given the vital role of CAII in H+-ATPase activity and ICs, we hypothesized that deletion of CAII may have a protective effect on TSC. To test this hypothesis, we generated a novel mouse model in which we deleted CAII specifically in ICS and tested the effect on cystogenesis.

Results: In all models of cystic disease, we observed the robust expression of the transcription factor Foxi1, a master regulator of renal cystgenesis and markers of intercalated cells. Deletion of CAII resulted in significant protection against cyst generation/enlargement in TSC.

Conclusions: These studies demonstrate that while AURKA is dispensable for renal development and tubule homeostasis, it acts as a key driver of cyst formation. The failure of Alisertib to ameliorate cyst formation contrasts with the profound prevention of disease mediated by AURKA gene deletion. Taken together, these findings suggest that kinase independent functions of AURKA are central to cystogenesis. The correction of AKT signalling and the close association between AURKA and AKT highlights dysregulation of this pathway as being critically important for cyst initiation, suggesting a potential avenue for therapeutic development.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Background: Nephronophthisis (NPHP), an autosomal recessive disease, is the most frequent monogenic cause of chronic renal failure during the first three decades of life. Mutations in over 25 genes have been identified as causes of this disease and in several cases, like in NPHP type 7, result in chronic DNA damage. Cell senescence is a frequent outcome of chronic DNA damage. We showed that kidney tubular cells undergo cell senescence in the Glis2 mouse model of NPHP type 7. Senescent cells secrete pro-inflammatory molecules that can induce further senescence in neighboring non-senescent cells through the activation of the Toll-like receptor/interleukin 1 receptor/NF-kB (TLR/IL-1R/NF-kB) signaling pathway. We previously reported that NF-kB is activated in kidney tubular cells of the Glis2 knockout mice. We hypothesized that inducing apoptosis of senescent cells would protect from inflammation and fibrosis, and that genetic inhibition of the TLR/IL-1R/NF-kB signaling axis would decrease tubular cell senescence in Glis2-knockout kidneys. We hypothesized that inducing apoptosis of senescent cells would protect from inflammation and fibrosis, and that genetic inhibition of the TLR/IL-1R/NF-kB signaling axis would decrease tubular cell senescence in Glis2-knockout kidneys.

Methods: To this end we used the senolytic drug FOXO4-DRI to induce apoptosis of senescent cells, and generated two mouse lines: a double knockout line lacking both Glis2 and Tlr2 in all tissues (Glis2-/-Tlr2-/-); and a line in which a kidney-specific promoter (Ksp) is used to conditionally inactivate the adaptor myeloid differentiation protein 88 (Myd88) downstream of TLR/IL-1R receptors in tubular cells of Glis2-null mice (Glis2-/-Myd88f/f).

Results: We found that pharmacologic elimination of senescent cells results in reduced kidney damage, fibrosis, and apoptosis in Glis2-knockout kidneys. Noticeably, in Glis2, Tlr2 double knockouts and, to a lesser extent, in Myd88, Glis2 knockout mice senescence was reduced and tubular-cell proliferation was increased, suggesting that loss of TLR/IL-1R activity improves the regenerative potential of tubular cells.

Conclusions: Our results further suggest that a combination of TLR/IL-1R inhibition and senolytic therapy may delay the disease progression in NPHP type 7 and other forms of this disease.

Funding: NIDDK Support

SA-OR096

Innate Immunity Contributes to Tubular Cell Senescence in Nephronophthisis Type 7 Knockout Mouse Kidneys

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Methods: We cloned affinity-tagged versions of NEK8 and NPHP3 in expression vectors with transient expression in 293T cells and for stable lentiviral production in mIMCD3 cells. We knocked out NEK8 and NPHP3 genes in IMCD3 cells by CRISPR/Cas9. We introduced pathogenic mutations into the NEK8 ORF by fusion PCR. We analyzed protein expression levels by Western-Blot, protein localization to primary cilia by immunohistochemistry and protein-protein interactions by immunoprecipitation and Western-Blot.

Results: We found that pathologic missense mutations in the NEK8 RCC1 domain fall into three categories: (1) Mutations that destabilize NEK8 protein lead to reduced or absent protein expression and no detectable localization to the cilium; (2) Mutations that result in soluble and detectable levels of NEK8 protein, but fail to properly localize to the primary cilium; (3) Mutations that allow NEK8 protein to localize to the cilium, but have reduced affinity to NPHP3 binding. While mutations of categories (1) and (2) correlate with NPHP phenotypes, mutations of category (3) correlate with PKD phenotypes.

Conclusions: We demonstrate that hierarchical defects in invesin compartment assembly correlate with the phenotypic spectrum of kidney disease. Reduced NEK8 and NPHP3 localization leads to NPHP-like disease, whereas proper NEK8 localization and reduced NPHP3 affinity leads to PKD.

SA-OR098

Ultra-Short-Duration Direct-Acting Antiviral Prophylaxis to Prevent Hepatitis C from Viremic Donors to Hepatitis C-Negative Kidney Transplant Patients

Czarnecki,1 John Clark,2 Dorostkar,2 Anjali Kumar,2 Dhiren Kumar,1 Anne Alam,1 Layla Kamal,2 Le Kang,1 Irfan A. Moinuddin,3 Chandra S. Bhati,1 Amit Sharma,4 Adrian Cotterell,1 Marlon F. Levy,1 Richard Sterling,1 Virginia Commonwealth University Health System, Richmond, VA; 2Virginia Commonwealth University, Midlothian, VA; 3YCU Health system, Richmond, VA; 4VCU, Richmond, VA.

Background: Direct-acting anti-viral drug (DAA) prophylaxis of of less than twelve weeks initiated at the time of transplant could have the potential to reduce the cost of deceased HCV-infected viremic donor to non-HCV-infected recipients (D+/R-). In our recently concluded single-center trial (ClinicalTrials.gov: NCT03249194; to be presented at AFT 2019; manuscript under peer review) we reported a HCV transmission rate of 13% with an ultra-short course of DAA prophylaxis given over the first 4 days of transplants. Here we present initial data on our extension open-label clinical protocol [REFORM Hepatitis C study]. For the study of ORgan transplants from Hepatitis C-infected donors.

Methods: Waitlisted HCV negative adult kidney transplant candidates without significant liver fibrosis, as assessed by transient elastography, were enrolled. After administration of ultra-short course (4 days) prophylactic Sofosbuvir/Velpatasvir (SOF/VEL) patients were screened for HCV RNA at Days 7, 14, 21 and Month 3. Development of viremia (defined as two consecutive positive RNAs) triggered a full 12 week course of DAA therapy.

Results: Over a period of 4 months (Jan-April 2019), 88 patients were enrolled. Of these, 22 (25%) received D+/R-. Transplants. The mean wait time to transplant from enrollment was 19 days and the mean donor KDPI was 61%. Of the data available on 11 donors (50%), the median donor viral load was 2.6E+06 IU/mL (IQR: 2E+05-7E+06). A majority were genotype (GT) 1a donors (88%). At a median follow-up of 97 days (IQR: 30-150 days) post-transplant, both patient and graft survivals were 100%. There were no cases of liver dysfunction. Average kidney function as measured by eGFR was 52 ± 30 on average. Both patients and graft survivals were 100%. There were no cases of liver dysfunction. Average kidney function as measured by eGFR was 52 ± 30 on average.

Conclusion: Our data suggests that ultra-short duration DAA prophylaxis is highly effective in preventing donor-derived HCV transmission and has the potential of resulting in significant cost-savings by avoiding DAA therapy in a majority of D+/R- transplants.

Funding: Clinical Revenue Support

SA-OR099

Greater Impact of Pre-Transplant Dialysis Exposure on Transplant Survival in Regions with Higher Dialysis Mortality

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Background: Longer pre-transplant dialysis exposure is associated with a higher risk of transplant failure. Mortality rates on dialysis are known to vary between regions, and may in part reflect differences in the quality of dialysis care. We hypothesized that the association of dialysis exposure with transplant failure would be higher in patients treated in regions with higher rates of dialysis mortality.

Methods: Adult patients in the United States Renal Data System who initiated maintenance hemodialysis after May 1995, and received a kidney-only deceased donor transplant by Dec 2010 were studied (n=63,610). Dialysis mortality (per 100 patient years), adjusted for differences in patient age, sex, and race, was determined by state of transplant from the period of dialysis and grouped into quartiles. The association between the duration of dialysis exposure (years), dialysis mortality quartile and post transplant outcomes was determined in Cox regression models. Each model adjusted for differences in patient age, sex, race, cause of end stage kidney disease, body mass index, year of transplant, HLA, comorbidities and included an interaction term of dialysis exposure (years) with quartile of dialysis mortality.

Results: The association of different combinations of dialysis exposure (years) and dialysis mortality (quartiles), compared to the reference group of patients with <1 year pre-transplant dialysis exposure, is shown in the table below.

<table>
<thead>
<tr>
<th>Dialysis Exposure (years)</th>
<th>Dialysis Mortality Quartile</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>1</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>5-9</td>
<td>2</td>
<td>1.5 (1.3-1.7)</td>
</tr>
<tr>
<td>10-14</td>
<td>3</td>
<td>2.0 (1.7-2.3)</td>
</tr>
<tr>
<td>15-19</td>
<td>4</td>
<td>2.5 (2.2-2.8)</td>
</tr>
</tbody>
</table>

Conclusion: Longer pre-transplant dialysis exposure was associated with a higher risk of transplant failure. Mortality rates on dialysis are known to vary between regions, and may in part reflect differences in the quality of dialysis care. We hypothesized that the association of dialysis exposure with transplant failure would be higher in patients treated in regions with higher rates of dialysis mortality.

Funding: Clinical Revenue Support

SA-OR100

Pathogenic Role of NEK8 RCC1-Domain Mutations in Inversin Compartment Assembly

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Background: The Inversin compartment (IC) is a protein module located at the proximal end of the primary cilium that consists of four known components, inversin (INVS), NEK8, ANKS6 and NPHP3. Missense mutations in inversin compartment genes, including NEK8, give rise to a wide spectrum of disease phenotypes, including Nephronophthisis (NPHP), polycytic kidney disease (PKD), as well as complex multisystem malformation syndromes with embryonic lethality. In our previous work, we have shown that NEK8 kinase-domain mutations that specifically affect the phosphorylation mechanism give rise to cystic kidney phenotypes and randomization of embryonic L-R-asymmetry determination. We have also shown that the NEK8 RCC1-domain is necessary for recruitment of INVS to the ciliary inversion compartment. The mechanism how NEK8 RCC1-domain mutations and mutations in NPHP3 produce PKD-like phenotypes remains unexplained.

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diagnosis exposure treated in a region with the lowest quartile of diagnosis mortality, with the outcomes of graft loss from all causes including death, death censored graft loss, and death with a functioning graft are shown in Figure 1. Longer durations of diagnosis exposure were associated with a higher risk of each outcome, and this risk of diagnosis exposure was magnified in regions with higher diagnosis mortality.

Conclusions: The pre-transplant diagnosis exposure on transplant failure is higher in regions with higher rates of diagnosis mortality. The findings support better integration of diagnosis and transplant care, and indicate that regional differences in diagnosis mortality should be accounted for in evaluation of transplant center performance metrics.

SA-OR10

Lack of Association Between Pre-Transplant Donor-Specific Antibodies and Kidney Outcomes in Simultaneous Liver-Kidney Transplant Recipients

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Background: The impact of pre-transplant donor-specific antibodies (DSA), especially class II DSA, on kidney allograft outcomes remains unclear in simultaneous liver-kidney transplantation (SLKT) recipients.

Methods: We examined 85 recipients who underwent SLKT between 2009-2018 in our center. Associations between the presence of pre-transplant DSA [pre-transplant DSA (+)], including class of pre-transplant DSA ([Class I DSA (+)] and [Class II DSA (+)]), and worsening kidney function (WKF), composite kidney outcome (WKF or antibody-mediated rejection or death censored allograft kidney loss), death with a functioning graft, and overall mortality were examined in unadjusted and age, sex, and race-adjusted Cox proportional hazards regression and competing risks regression models. WKF was defined as eGFR decrease of 30% or greater from baseline, or two or more episodes of proteinuria, or class III or IV rejection. We examined the impact of DSA on the outcomes of graft loss from all causes including death, death censored graft loss, and death with a functioning graft.

Conclusions: Neither pre-formed DSA nor class II DSA was associated with worse kidney allograft outcomes or patient mortality in SLKT recipients.

SA-OR101

Tertiary Lymphoid Tissues in Protocol Biopsies Predict Progressive Graft Dysfunction in Kidney Transplant Recipients

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Background: Tertiary lymphoid tissues (TLTs) are inducible ectopic lymphoid tissues found in chronic inflammatory organs. Previous studies have documented TLT formation in transplanted kidneys with rejection, but their clinical relevance remains controversial. Moreover, the evidences of TLTs in transplanted kidney without rejection are limited. In this study, we examined the frequency and staging of TLTs in protocol biopsy samples without the sign of rejection, and analyzed their effects on renal function in stable kidney transplant recipients.

Methods: A total of 181 patients who lacked clinical risk factors for poor graft survival, such as biopsy-proven acute rejection, were selected among those who underwent living donor kidney transplantation. We analyzed serial protocol biopsies (0-hour, 1-month, 6-month, and 12-month) and evaluated TLTs using novel staging methods we had recently established. TLTs were defined as organized lymphocyte aggregates with signs of proliferation, and their stages were determined by the absence (stage I) or presence (stage II) of follicular dendritic cells, which support the formation of B cell area.

Results: Although only 5.1% of patients exhibited TLTs at 0-hour biopsy, the prevalence increased to almost 50% at 1-month after transplantation and was maintained at the similar levels for one year. Stage II TLTs increased gradually over time, from 2.8% at 1-month to 8.0% at 12-month biopsy. Patients with no or stage I TLTs had stable graft function over 5 years, whereas those with stage II TLTs exhibited progressive graft dysfunction. (Figure 1) These advanced TLTs were associated with severe tubular inflammation and atrophy at 1 year post-transplantation. Finally, pre-transplantation stage II TLTs dramatically attenuated the development of stage II TLTs.

Conclusions: TLTs were commonly found in protocol biopsies of transplanted kidneys, and stage II TLTs predict progressive decline in graft function in kidney transplant recipients even in the absence of rejection.

Funding: Government Support - Non-U.S.

SA-OR102

Serum Expression of Selected MiRNAs Distinguish Recurrence of Glomerulonephritis and Antibody-Mediated Rejection in Kidney Transplant Recipients

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Background: Recently, many miRNAs (small non-coding regulatory RNAs) were found to be involved in pathological processes that can occur following kidney transplantation. The purpose of current study was to investigate the potential significance of different circulating miRNAs in predicting acute antibody mediated rejection (ABMR) and glomerulonephritis recurrence (gN) regardless of the stage of renal impairment.

Methods: Total RNA was isolated from serum of 50 kidney transplant recipients with varying degrees of kidney graft failure, but stable function as estimated with CKD EPI equations (eGFR CKD-EPI), as well as precisely measured using chromium-51 labeled ethylenediamine tetracetic acid clearance (mGFR CrEDTA). Expression of 6 selected miRNAs (miR-223, miR-126, miR-16, miR-150, miR-155, miR-223) was determined by qPCR, using miR-103a-3p as reference gene.

Results: Selected candidate miRNAs miR-126 (p=0.002), miR-153 (p=0.004) and miR-223 (p=0.028) distinguished ABMR (n=6) from the stable patient group – patients without ABMR or gN (n=41). MiR-126 (p=0.008), miR-150 (p=0.009) and miR-223

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(p=0.033) distinguished cGN (n=3) from stable patient group. MIr-126 (p=0.048), miR-107 (p=0.024) and potentially miR-223 (p=0.091) distinguished ABMR from cGN. Additionally, miR-29c expression was not detected in cGN and it was down-regulated in ABMR compared to stable group. Expression of miR-146a did not show association to any of the group of patients. None of the tested miRNA was associated with mGFR CEDTA, only miR-155 weakly correlated to eGFR CKD EPI. 

Conclusions: Four of the tested miRNAs (miR-126, miR-29, miR-155, miR-223) are not associated with kidney graft function, but may discriminate ABMR and cGN and therefore can be used as a non-invasive biomarker to distinguish between pathologies.

SA-OR103

Characteristics and Dysbiosis of the Gut Microbiome in Renal Transplant Recipients

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Background: Renal transplantation is life-changing in many aspects. This most likely includes the gut microbiome, particularly because of the inevitable exposure to immunosuppressive drugs and antibiotics. As a consequence, Transplantation patients frequently suffer from intestinal dysbiosis. We aimed to investigate the gut microbiome of renal transplant recipients (RTR) and compare it with healthy controls.

Methods: We included 110 RTR and 79 healthy renal donors participating in the TransplantLines Biobank and Cohort Study (NCT03272841). We analyzed the gut microbiome using 16s rRNA sequencing and compared the composition of the gut microbiome of RTR with healthy renal donors using the Mann Whitney U-test with false discovery rate correction. Linear discriminant effect size (LDEs) and multivariate association with linear models (MaAsLin) were used to study the relationship between the gut microbiome and the occurrence of diarrhea and the use of medication.

Results: Fecal samples of 110 RTR (38.3% female, mean age: 54.6 ± 12.0 years) and 79 healthy renal donors (34.0% female, age: 59.6 ± 11.0 years) were collected. Median time after transplantation of RTR was 1.08 [2.0-13.0] years, with a range of 1 to 26.4 years. Microbiome composition of RTR was significantly different from that of healthy donors (P<0.001). RTR had a lower diversity of the gut microbiome (P<0.001). Significantly higher levels of Proteobacteria, Entero bacteriaceae, Streptococcus and E. coli were found in RTR (P<0.05). The levels of commensal, butyrate producing bacteria, including Clostridium spp., Eubacterium spp., Coprococcus spp. and Gemmiger formicilis were significantly lower in RTR (P<0.05). The microbiome of RTR with diarrhea contained lower levels of Ruminococcaceae and higher levels of Actinobacteria (P=0.05).

Conclusions: This study shows the gut microbiome of RTR is significantly different from the gut microbiome of healthy renal donors. RTR suffer from dysbiosis characterized by a loss of diversity and there is a preponderance towards lower levels of butyrate producing species, which may have detrimental effects on gut health in RTR.

SA-OR104

18F-FDG PET/CT Imaging at 3 Months Post Transplantation Disproves Subclinical Rejection in Kidney Transplant Recipients

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Background: Subclinical kidney allograft acute rejection (SCR) corresponds to “the histological documentation of unexplained evidence of acute rejection (AR) in a stable patient” SCR detection relies on surveillance biopsy. Still, non-invasive approaches may help avoid biopsy-associated complications and limitations. Positron emission tomography (PET) coupled with computed tomography (CT) after injection of 18F-fluorodeoxyglucose (18F-FDG) may be an option.

Methods: From 11/2015 to 01/2018, we prospectively performed 18F-FDG-PET/CT imaging on 15 kidney transplant recipients (KTR) who underwent surveillance transplant biopsy at ~3 months post transplantation. BanFF-2017 classification was used. The ratio of the mean standard uptake value (mSUVR) between kidney graft cortex and psoas muscle was measured. One-way analysis of variance (ANOVA) followed by Student’s t-tests was performed using the Python library SciPy to compare mSUVR among groups. Additionally, the R-squared statistic assessed the correlation between mSUVR and acute composite Banff score or total inflammation. Finally, the receiver operating characteristic (ROC) curve was built using Python programming language.

Results: In our 95-patient cohort, the median age of recipients was 57 years [min 37; max 68], with a gender ratio (M/F) of 2 and a mean BMI of 27.5kg/m². The cohort was categorized into 3 groups upon Banff-based histology: normal (n=70); borderline (n=16); AR (n=6). Three cases were excluded for PCR-proven BK nephropathy (n=2) or uninterpretable histology (n=1). No clinical or biological difference was observed between groups. The mSUVR reached 1.87±0.55, 1.94±0.35 and 2.41±0.54 in normal, borderline and AR groups, respectively. A significant difference of mSUVR was found among groups. Furthermore, mSUVR was significantly higher in AR versus normal (p=0.02) or borderline (p=0.02) groups. The area under the ROC curve (AUC) was 0.79, with 83% sensitivity and 87% specificity using mSUVR threshold at 2.4. The mSUVR positively correlated with total-IR (r=0.05; p=0.2) and acute composite Banff score (r=0.04; p=0.05).

Conclusions: 18F-FDG-PET/CT imaging helps non-invasively detect SCR, with a negative predictive value of 98% using 2.4 as mSUVR threshold.

Funding: Clinical Revenue Support

SA-OR105

Galectin 3 and Graft Failure in Kidney Transplant Recipients: A 10-Year Prospective Cohort Study

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Background: Galectin-3 is associated with kidney fibrosis and kidney function decline in the general population. We aimed to study the association of galectin-3 with long-term risk of graft failure in a cohort of extensively phenotyped kidney transplant recipients (KTR).

Methods: We performed a longitudinal cohort study in 561 KTR without heart failure and with a functioning graft at 1 year. Kaplan-Meier curve, log-rank test, and multivariable-adjusted Cox proportional-hazards regression analyses were performed to assess the association of baseline serum galectin-3 with death-censored graft failure (defined as redistribution of dialysis or re-transplantation). Subgroup prospective analyses were performed according to significant effect-modifiers.

Results: Median galectin-3 was 21.1 (IQR 17.0-27.2) ng/mL. During a median follow-up of 9.5 (IQR 6.2-10.2) years, 72 KTR developed graft failure, with significantly different distribution of events across tertiles of galectin-3 (P<0.001). Multivariable Cox regression analyses, galectin-3 associated with graft failure (HR, 2.13 per 1-SD increase; 95% CI, 1.61-2.80, P<0.001), independent of well-established general and transplant-specific risk factors, including eGFR and proteinuria. Particularly strong associations were found in patients with systolic blood pressure >140 mmHg (HR, 2.29 per 1-SD increase; 95% CI 1.80-2.92, P<0.001) and in former or current smokers (HR, 2.56 per 1-SD increase; 95% CI 1.95-3.37, P<0.001).

Conclusions: In stable KTR, galectin-3 levels are elevated and independently associated with higher risk of graft failure at 10-years of follow-up. These results underline novel opportunities to monitor patients, target pharmacological therapy, and decrease the burden of long-term graft failure in stable KTR.

Funding: Government Support - Non-U.S.
SA-OR106
Potential for Recovery of Bone Density and Structure Following Renal Transplantation
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Background: Fracture rates increase early following renal transplant (RTx) and then decline. The objective is to determine if trabecular and cortical bone mineral density (BMD) and cortical structure recover following RTx treated with glucocorticoids (GC).

Methods: We enrolled 60 incident RTx recipients, ages 20-60 yr, with DXA and peripheral quantitative CT (pQCT) scans at RTx, 6, 12, and 24 months. Bone outcomes and DXA appendicular lean mass index (ALMI) were expressed as age and sex-specific Z-scores using concurrent controls. Regression models identified correlates of change for bone outcome Z-scores.

Results: 58 and 53 RTx completed the 12 and 24 month visit, respectively. At transplant, DXA total hip, femoral neck, and ultradistal radius BMD, and pQCT trabecular and cortical BMD, and cortical thickness BMD Z-scores were lower in RTx vs. controls (all p<0.05). Prednisone was typically tapered to a maintenance dose of 5 mg/day by 4 weeks. During the first 6 months, DXA spine and pQCT trabecular BMD decreased significantly (e.g. trabecular BMD Z from -0.53 to -0.60) then were unchanged through 24 months. Radius 1/3rd BMD was stable but ultradistal radius BMD Z-scores decreased from baseline onwards. Greater GC exposure was associated with decreases in DXA spine and ultradistal radius BMD and pQCT trabecular BMD Z-scores (all p<0.01). Cortical BMD Z-scores increased across 24 months (from -0.51 to -0.33, p<0.01) in association (p=0.02) with decreasing PTH. Endosteal circumference increased and cortical thickness decreased progressively over 24 months (both <0.01). DXA total hip and femoral neck BMD Z-scores were unchanged during the first 6 months, then increased marginally. ALMI Z-scores increased but were not associated with changes in bone outcomes. Gains in cortical BMD were associated with gains in total hip and femoral neck BMD (p<0.01). Renal function, physical activity and mineral metabolites were not associated with bone outcomes.

Conclusions: RTx is associated with early loss of trabecular bone without subsequent recovery on low dose GC. Cortical BMD recovers in association with decreases in PTH levels and may explain the marginal increase in hip BMD. Given that cortical thinning progresses following RTx, strategies are needed to preserve cortical structure in KD.

Funding: NIDDK Support

SA-OR107
Post-Transplant Recurrence of IgA Nephropathy: HLA as a Predictive Factor

Background: In the native kidney, studies have suggested that specific Human Leukocyte Antigen (HLA) alleles have increased risk or protective effects for the development of IgA Nephropathy (IgAN). There remains limited knowledge of the clinical significance and specific factors that contribute to recurrence of IgAN in the kidney allograft. We aimed to study whether the degree of HLA matching and the presence of certain HLA loci in the donor and recipient can contribute to recurrence.

Methods: A retrospective cohort of 159 recipients with ESRD secondary to IgA who were transplanted at our center between 1995 and 2017 were evaluated for recurrent disease. Clinical characteristics and HLA typing were analyzed in both donor and recipient.

Results: Of the 159 patients identified, 53 (33%) had biopsy-proven recurrent IgAN. On follow-up, 16/53 (30%) of patients with recurrent IgAN developed graft failure compared to 11/106 (10%) of patients without proven recurrence (P=0.046, See Figure). Univariate Cox proportional hazards analysis has identified that younger recipient age at transplantation, receiving allograft from living donors, higher degree of HLA matching recipient HLA-DR15, and donor HLA-DR3 to be significantly associated with recurrence. By multivariable Cox analysis, younger recipient age [HR 0.97 (95% CI: 0.94 – 0.99), P=0.016], HLA mismatch [0.83 (0.70-0.98), P=0.03], presence of HLA-DR15 in the donor [2.52 (1.36-4.88), P=0.004], as well as the presence of HLA-DR3 in the donor [2.57 (1.23-5.37), P=0.012] were independently associated with recurrent IgAN.

Conclusions: Recurrence of IgAN is associated with decreased graft survival. In an effort to improve long-term outcome, it is imperative to consider factors that increase recurrence risk when evaluating potential donors, such as higher HLA matching and the presence of HLA-DR3 in the donor. Recipient variables of younger age and HLA-DR15 were also independent predictors for recurrent IgAN.

Graft Survival

SA-OR108
Novel Experimental Model of Poor Pregnancy Outcomes After Recovery from Ischemia-Reperfusion Injury
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Background: Recent clinical studies have reported that women with a history of acute kidney injury (AKI) have a greater incidence of maternal and fetal adverse outcomes during pregnancy, despite fully recovering renal function prior to conception. The mechanisms contributing to these adverse outcomes in pregnancy after AKI are not yet understood. In the current study, a rodent model of recovered AKI (r-AKI) was developed in an effort to elucidate the mechanisms contributing to adverse pregnancy outcomes after AKI. We hypothesize that female Sprague Dawley (SD) rats will have poor pregnancy outcomes after recovery from ischemia reperfusion (IR) injury, our experimental model of AKI.

Methods: IR surgery was performed on female SD rats (10 wks age) by clamping both renal arteries for 45 minutes. Rats were then allowed to recover for 1 month before they were mated. Recovery from IR was confirmed by plasma creatinine and urinary protein excretion (UPE). Vaginal smears were performed daily once mating began, with sperm on the slide indicative of day 1 of pregnancy. Rats were then sacrificed during late pregnancy on gestational day 20.

Results: UPE, a crude marker of renal injury, was significantly higher in r-AKI dams in late pregnancy (Table, *p<0.05, T-test). r-AKI dams also had significantly higher plasma creatinine and urea levels than control dams, suggesting that subclinical injury after IR leaves these dams unable to handle the hemodynamic changes in pregnancy, resulting in renal insufficiency (Table). In addition to adverse maternal outcomes, fetal outcomes were also significantly worse in r-AKI dams, as measured by decreases in fetal weight and an increase in fetal death (Table).

Conclusions: Pregnancy after recovery from AKI resulted in maternal renal insufficiency and significant impairments in fetal growth in the current study. This mimics what has recently been reported in the clinical population, indicating that this model is a useful tool to further explore the alterations in kidney function after AKI in females. Ongoing studies in the lab are further exploring the maternal syndrome in these rats, focusing on alterations in renal immune cells.

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SA-OR109
A Population Study of Pregnancy Outcomes by Pre-Conception GFR
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Background: Chronic kidney disease is a known risk factor for adverse pregnancy outcomes including preeclampsia and preterm delivery, however studies on CKD pregnancies are small, outdated and contain few subjects with moderate or advanced stage CKD. Our objective was to investigate the association of pre-conception GFR with the risk of adverse pregnancy outcomes in a large population-based cohort with more than 400 pregnancies in women with pre-existing moderate or advanced stage CKD.

Methods: A population-based cohort study of women in the province of Ontario, Canada, who had an obstetric delivery between 2007 and 2017. Administrative health databases linked using unique identifiers at ICES were used to capture all hospital births in Ontario and a majority of outpatient laboratory testing. Women with a serum creatinine measured within 2 years of conception were included for analysis.

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Results: The mean pre-conception eGFR among the 458,206 pregnancies included in the analysis was 114 ± 14 ml/min/1.73 m², of which 28,232 were 60 to <90 ml/min/1.73 m², 330 were 45 to <60 ml/min/1.73 m² and 97 were <45 ml/min/1.73 m². There were no maternal deaths among women with eGFR < 60 ml/min/1.73 m². Rates of gestational hypertension, preeclampsia and preterm delivery increased monotonically across pre-conception eGFR categories (Figure 1). Maternal admission rate to the ICU during pregnancy or within 90 days after delivery was 7% among women with an eGFR < 45 ml/min/1.73 m² compared with 1% in women with eGFR > 90 ml/min/1.73 m². Women with eGFR < 45 ml/min/1.73 m² had a significantly increased risk of doubling of proteinuria when adjusted for baseline proteinuria (adjusted HR 3.30, 95% CI 1.05-10.3). There was an increase in the number of maternal deaths among women with eGFR < 60 ml/min/1.73 m². Women with eGFR < 60 ml/min/1.73 m² had a significantly increased risk of doubling of proteinuria when adjusted for baseline proteinuria. Absolute risk was highest in women with eGFR < 45 ml/min/1.73 m², however even women with mildly impaired eGFR were at higher risk for adverse pregnancy outcomes.

Funding: NIDDK Support

SA-OR111

Serum Transforming Growth Factor β1 Is a Sex-Specific Risk Factor for Accelerated GFR Decline in the General Population

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Background: The health burden of chronic kidney disease (CKD) is increasing worldwide, and there is a need for novel biomarkers that can identify those at CKD risk for early preventive measures. There are sex differences in the progression of CKD and several risk factors seem to affect CKD risk differently in men and women. We investigated the association between serum transforming growth factor β1 (TGF-β1), a key mediator in kidney fibrosis development, and risk of accelerated loss of glomerular filtration rate (GFR) in women and men from the general population.

Methods: In the Renal Iohexol Clearance Survey in Tromsø 6 (RENIS-T6), we measured GFR by iohexol-clearance in 826 women and 801 men between 50 and 62 years of age without self-reported diabetes, cardiovascular or kidney diseases. Of these, 1,324 (81%) had a follow-up GFR measurement after a median of 5.6 years in the RENIS-Follow Up. We used a multiple logistic regression model to examine the association between serum TGF-β1 and accelerated GFR decline (defined as subjects with the 10% steepest GFR slope).

Results: After adjusting for CKD risk factors, 1 SD increase in TGF-β1 levels was associated with higher odds of accelerated GFR decline in women (odds ratio (OR) 1.38 (95% confidence interval (CI) 1.01 to 1.89)), but not in men (p for interaction 0.03). Women with TGF-β1 in the upper quartile had an OR of 2.74 (95% CI 1.05 to 7.17) compared to women with TGF-β1 in the lower quartile. Women with TGF-β1 in the upper quartile had an OR of 0.60 (95% CI 0.23-1.57), compared to women with TGF-β1 in the lower quartile.

Conclusions: Higher baseline TGF-β1 was independently associated with accelerated GFR decline in women, but not in men.

Funding: Government Support - Non-U.S.

SA-OR112

Sirtuin 3 Mediates Sex Differences in Ischemia-Reperfusion Kidney Injury

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Background: Biologic sex influences susceptibility to AKI, a common condition with limited therapies. Mitochondrial dysfunction and oxidative stress play key roles in the pathogenesis of ischemic AKI. Our observations revealed higher baseline kidney expression of mitochondrial SIRT3 (mtSIRT3), a major mitochondrial deacetylase, in female vs male mice. We hypothesize that SIRT3 confers protection and mediates sex differences in response to kidney ischemia-reperfusion injury (IRI).

Methods: Male and female wild-type (WT), SIRT3 transgenic (Tg), or inducible kidney tubule-specific SIRT3 knockout (KO) mice were subjected to bilateral kidney IRI (clamping of renal pedicles for 30 min). HEK cells were treated with 17β-estradiol (E2), testosterone, or vehicle.

Results: We observe higher mtSIRT3 expression in kidneys of WT female vs. male mice; mtSIRT3 declines with age but sex differences persist. At age 6-months, SIRT3 Tg male mice display less tubular vacuolization and ROS vs similarly aged WT males. Male Tg mice demonstrate resistance to IRI [preserved creatinine clearance (CrCl) and morphology; less ROS] and better survival vs WT males; outcomes similar to WT females. In contrast at age 6-months, SIRT3 KO males display greater tubular injury vs WT males. SIRT3 KO mice demonstrated increased susceptibility to IRI [decreased CrCl; worse morphological changes; increased ROS] and worse survival vs WT. In WT females, kidney mtSIRT3 correlates positively with plasma E2 and negatively with testosterone (T) levels. In WT males, kidney mtSIRT3 only correlates negatively with plasma T. In HEK cells, E2 treatment increases SIRT3 mRNA, and whole cell- and mtSIRT3 protein; T decreases mtSIRT3 protein with no effect on whole cell SIRT3 or SIRT3 mRNA. We previously showed that LR2P shuttles intracellular proteins to the mitochondria and physically associates with SIRT3. Current observations show higher baseline kidney expression of LR2P in WT female vs male. Testosterone treatment decreases LR2P protein expression. In vitro LR2P knockdown decreases mtSIRT3 protein.

Conclusions: 1) SIRT3 ameliorates kidney IRI, and decreased SIRT3 in males mediates the increased susceptibility to ischemic injury; 2) sex steroids regulate mtSIRT3 expression; estrogen via transcriptional regulation and testosterone via inhibition of LR2P-mediated mitochondrial targeting; 3) sex differences in AKI pathophysiology need to be studied.

Funding: Veterans Affairs Support, Private Foundation Support

SA-OR113

Association of Reproductive Lifespan Duration and CKD in Postmenopausal Women

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Background: Although animal studies have suggested estrogen to offer renoprotective effects, clinical evidence remains scarce. This study sought to investigate the relationship between endogenous estrogen exposure and renal function. Considering female reproductive lifespan duration (RLD) to be a surrogate of lifetime exposure to estrogen, we hypothesized that longer RLD would be associated with lower risk of CKD.

Methods: In this population-based study of pre-conception CKD, low pre-conception eGFR was associated with high rates of maternal morbidity and adverse pregnancy outcomes. Absolute risk was highest in women with eGFR < 45 ml/min/1.73 m², however even women with mildly impaired eGFR were at higher risk for adverse pregnancy outcomes.

Funding: Private Foundation Support
endogenous estrogen, the association of RLD and chronic kidney disease (CKD) was analyzed in postmenopausal women.

Methods: Data were retrieved from the Korean Genome and Epidemiology Study. Health Examinees cohort. A total of 57,505 postmenopausal women were included in the analysis. The RLD for each participant was determined by subtracting the age at menarche from the age at menopause. The participants were divided into groups according to RLD quartiles. The association between RLD and CKD, defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², was examined.

Results: The mean age and eGFR of the study subjects were 57.7 ± 6.1 years and 88.0 ± 16.7 mL/min/1.73 m², respectively. The mean RLD was 34.2 ± 4.1 years. A total of 1,664 (2.89%) women were found to have CKD. The prevalence of CKD tended to decrease in groups with longer RLDs. Logistic regression analysis revealed that the odds ratio for CKD was lower in groups with longer RLDs as compared to the shortest RLD group. This finding was significant even following adjustments for confounding factors.

Conclusions: The prevalence of CKD was significantly lower in subjects with longer RLDs. The amount of endogenous estrogen exposure could be a determining factor for renal function in postmenopausal women.

SA-ORI15
Clinical, Angiogenic, and Immune System Markers Predict Preeclampsia in Women with CKD During Pregnancy
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Background: Pre-eclampsia (PE) is associated with immune activation and altered circulating angiogenic factors (with elevated soluble FMS-like tyrosine kinase-1/placental growth factor or sFLT-1/PIGF ratio). There are currently limited data in pregnant women with CKD. Longitudinal changes of markers inflammation, immunity & angiogenic factors during CKD pregnancy were assessed in this study & their relationship to the development PE explored.

Methods: Women with CKD were recruited from a UK renal-obstetric clinic between 2011-2016. Baseline demographics, serial serum samples and pregnancy outcomes were recorded. Samples were analysed for IgG/A/M, high-sensitivity CRP, serum free light chains (sFLC), Beta-2 Microglobulin (B2M), complement factors 3 & 4 (C3/C4), uric acid (UA), creatinine, cystatin-C & sFLT-1/PIGF using the Roche Cobas® platform. Gestational periods were split into five groups.

Results: PE was diagnosed in 23% of the 164 pregnancies (136 women) with rates increasing with CKD stage (p<0.011). White ethnicity, non-smoking, SLE, chronic hypertension and previous PE were independent predictors of PE: sFLC, B2M, creatinine, cystatin-C & UA increased significantly over the antenatal period and were higher in the PE group. The greatest predictive accuracy for PE was seen at 16-21 weeks, for sFLC & cystatin-C (AUROC 0.745, 0.810 respectively). Antenatal levels of C3 increased (p=0.001) and IgA fell (p=0.015) more rapidly in the PE vs. non-PE group. The sFlb-1/PIGF ratio was predictive for PE developing at 22-27 weeks gestation (AUROC=0.678, p=0.005) (figure 1).

Conclusions: In women with CKD, an elevated sFLT-1/PIGF ratio is predictive of PE at 22-27 weeks gestation, but not at later gestations. Its predictive accuracy is comparable to markers of kidney function, sFLC and B2M levels.

SA-ORI114
Sex Differences in Vascular Access
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Background: Although fistulas are actively promoted, studies report fewer women receive and use a fistula. Whether women undergo similar efforts at fistula creation and procedures as men is unknown. We sought to describe differences between men and women for probability of receiving a fistula attempt, achieving independent fistula use, remaining catheter-free over time, and the rate of access-related procedures as a function of sex in a cohort of Canadian incident hemodialysis patients.

Methods: Prospectively collected vascular access data on incident dialysis patients from five Canadian programs using Dialysis Measurement Analysis and Reporting (DMAR) system to determine differences in fistula related outcomes between women and men. Probability of receiving a fistula attempt and the probability of successful fistula use was determined using binary logistic regression. Catheter and fistula procedure rates were described using Poisson regression. We studied time to fistula attempt and time to fistula use accounting for competing risks of death, transplant and recovery of kidney function.

Results: We included 1,446 (61%) men and 929 (39%) women. Men had a lower body mass index (p<0.001) and were more likely to have coronary artery disease (p<0.001) and peripheral vascular disease (p<0.001) than women. 688 (48%) men and 403 (43%) women received a fistula attempt. After accounting for confounders (age, diabetes, cardiovascular disease, inpatient status), men were more likely to receive a fistula attempt (OR 1.29 [1.18-1.41]) and to achieve catheter free use of the fistula at one year (OR 2.62 [1.83-3.56]). We found an average of 2.30 procedures per person-year after start of dialysis, with no significant difference between men and women (IRR 1.04 [0.93-1.15]). Following a fistula attempt, women received more procedures (IRR men vs women: 0.86 [0.77-0.96]) changes of markers inflammation, immunity & angiogenic factors during CKD pregnancy were assessed in this study & their relationship to the development PE explored.

Conclusions: In women with CKD, an elevated sFLT-1/PIGF ratio is predictive of PE at 22-27 weeks gestation, but not at later gestations. Its predictive accuracy is comparable to markers of kidney function, sFLC and B2M levels.
Results: There were 20,864 women with a pregnancy in the cohort of which 4,959 (23%) and 1,412 (6%) were of self-reported Hispanic or black race/ethnicity, respectively. Preeclampsia developed in 524 (2.5%) of pregnancies. Preeclampsia was associated with an increased risk of incidence of hypertension after pregnancy in all groups, with higher rates in non-white women (adjusted HR 2.8 [1.9-4.2] p<0.01 for Hispanic women, adjusted HR 2.7 [1.3-5.7] p = 0.01 for black women and adjusted HR 1.8 [1.2-2.8] p=0.01 for non-Hispanic white women. There was evidence of effect modification between non-white race/ethnicity, preeclampsia and incident hypertension (p-interaction=0.04).

Conclusions: Preeclampsia is a major risk factor for later life HTN, particularly among black and Hispanic women.

Funding: NIDDK Support

SA-OR117
Maternal Pregnancy Outcomes in Women with Complement-Mediated TMA: Update of the Vienna TMA Cohort
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Background: Pregnancy is a high-risk scenario to trigger complement pathway dysregulation. Presentation of paternal antigens activates the maternal alternative pathway and in women with malfunctioning complement regulatory proteins or C3 life-threatening thrombotic microangiopathy (TMA) can develop.

Methods: As of 2015 we reported outcomes of 27 pregnancies in 14 women with complement-mediated TMA (cTMA) enrolled in the Vienna TMA cohort (VTC). This work presents an update on this open cohort as of May 2019: Outcomes are CKD stage at last follow-up, incidence of dialysis or kidney transplantation (KTX) and death.

Results: In 32 women of the VTC the mean age at first cTMA presentation was 30 ±16 years (figure 1). Up until 2019 in 25 women a total of 55 pregnancies were observed: 6 women 1, 9 women 2, 6 women 3, 2 women 4, 1 woman 5 pregnancies. In 14 women pregnancy occurred before diagnosis of cTMA (26 pregnancies, 6 abortions) with 8 pregnancies afterwards in 5 women. Pregnancy-associated cTMA (p-cTMA) happened in 11 women: 6 during first, 3 during second and 2 during a later pregnancy. Five women had 11 pregnancies following KTX. Thirty-nine (71%) pregnancies were untreated and not complicated by p-cTMA. Four women received preventive plasma therapy for 6 pregnancies (2 KTX; 1 p-cTMA), 1 pregnant during ongoing eculizumab therapy (3 pregnancies, 1 KTX; 0 p-cTMA), 5 received therapeutic plasma therapy for p-cTMA (1 KTX), and 2 were switched to eculizumab (0 ESRD). At last follow-up 20 had eGFR ≥60ml/min per 1.73m², 6 eGFR <60, 2 needed dialysis and 4 had died.

Conclusions: In summary, VTC data demonstrates good maternal outcome (1) in the majority of untreated pregnancies in women with a diagnosis of cTMA and (2) in specifically treated cTMA patients in a specialized center.

TH-PO001
Transiently Dedifferentiated eR1-Active Proximal Tubule Cells Clonally Expand and Repair Proximal Tubules in Severe Injury
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Background: It is well accepted that injured proximal tubules (PT) are restored by the proliferation of surviving PT cells. However, whether this process depends on stochastic proliferation or expansion of a PT subpopulation, and how severity of injury affects repair process is uncertain. A Runx1 enhancer named Runx1+24mCNE (eR1) was shown to be active in adult long-term hematopoietic stem cells and gastric stem cells, but the role of eR1 in the kidney is unknown.

Methods: We explored the behaviors of PT cells with high eR1 activity, in 30-(moderate) and 60-min (severe) ischemia reperfusion injury (IRI), utilizing eR1-EGFP and eR1-CreERT2 mice.

Results: PT cells showed a higher rate of BrdU incorporation in 60-min IRI than in 30-min IRI, and a significant proportion of the PT cells showed RUNX1 expression after 60-min IRI, but not after 30-min IRI. In eR1-EGFP mice, after 60-min IRI, but not after 30-min IRI, EGFP+ PT cells accounted for 20% of total PT cells of the superficial cortex. In eR1-EGFP:Cre1-CreERT2:R26-Tdtomato mice subject to 60-min IRI, EGFP+ and tdTomato+ PT cells mostly overlapped in acute phase even without tamoxifen. This suggested that eR1-CreERT2 mice showed leaky CreERT2 activity when eR1 was highly activated after injury, and could be used to trace the fate of PT cells with high eR1 activity. In acute phase of 60-min IRI, tdTomato+ PT cells showed a higher rate of BrdU incorporation compared to other PT cells, and clustered with several tdTomato– cells. Consistently, eR1-CreERT2:R26-Confetti multicolor reporter mice revealed the clonal expansion of eR1-active PT cells after 60-min IRI. RNA-seq data of eR1-CreERT2 lineage-labeled PT cells after 60-min IRI showed higher expression of genes associated with cell cycle progression and DNA replication. Notably, tdTomato+ PT cells in acute phase were mostly positive for Kim-1 and vimentin, and negative for differentiation markers. In chronic phase, however, the percentages of PT cells positive for Kim-1 and vimentin were not different between tdTomato+ and tdTomato– PT cells, indicating the re-differentiation capacity of this population even after severe injury.

Conclusions: eR1 marks a subpopulation of PT cells of the superficial cortex with different transcriptomic profiling, highly proliferative after severe injury.

Funding: Government Support - Non-U.S.
TH-PO002
Caspase-11-Mediated Tubular Epithelial Pyroptosis Underlies Contrast-Induced AKI
Zhen Zhang, Xinghua Shao, Zhaoxu Ni. Ren J Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China.

Background: Contrast-induced acute kidney injury (CI-AKI) is a serious complication in patients after administration of iodinated contrast media. Pyroptosis is a form of programmed lytic cell death that is triggered by inflammatory caspases (caspase-11), but little is known about its role in tubular epithelial cell (TEC) death and CI-AKI.

Methods: 1. The primary mouse and human renal TECs were treated with ioxele and isomotic mannitol in separate experiments. Experiments were performed in triplicate. The protein expression of Caspase-4/5/11, IL-1β and Gsdmd in cells by Western blot respectively. Caspase-4/5, and IL-1β mRNA expression in cells detected by real-time PCR. ELISA was used to detect the concentration of IL-1β in cell culture supernatants and a CyTox 96 Non-Radioactive Cytotoxicity Assay measured cell death.

Results: Here, we show that systemic exposure to contrast media causes severe tubular epithelial pyroptosis that is mediated by the inflammatory caspases, caspase-4/5 in human TECs, or the murine homolog caspase-11 in mice and in mouse TECs in vitro. Knockdown of caspase-4/5 preserved human TECs from cell death and reduced the release of mature IL-1β, and in caspase-11-deficient mice, contrast-induced acute kidney injury was abrogated, indicating a central role for caspase-11 in acute kidney injury. Additionally, deletion of caspase-11 in TECs reduced Gsdmd cleavage, which is the key process for execution of pyroptosis.

Conclusions: These results establish the requisite role of caspase-11-mediated epithelial pyroptosis in CI-AKI, and suggest that epithelial inflammatory caspases are an important therapeutic target for AKI.

Funding: Other NIH Support - the National Science and Technology Major Project (No. 81570604)

TH-PO003
Role of NLRP3 in Rhabdomyolysis-Induced AKI
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Background: Rhabdomyolysis is a medical emergency which can cause severe kidney injury. The role of NLRP3 inflammasome in the pathogenesis of rhabdomyolysis-induced AKI (RAKI) was not well understood. In this study, we determine the role of NLRP3 in rhabdomyolysis-induced AKI.

Methods: The model of CI-AKI mice was established. Mice were killed 24 hours after iohexol injection. Ferrous myoglobin caused to increase NLRP3 inhibitor (MCC950) was used as a therapeutic agent.

Results: Here, we show that systemic exposure to contrast media causes severe tubular epithelial pyroptosis that is mediated by the inflammatory caspases, caspase-4/5 in human TECs, or the murine homolog caspase-11 in mice and in mouse TECs in vitro. Knockdown of caspase-4/5 preserved human TECs from cell death and reduced the release of mature IL-1β, and in caspase-11-deficient mice, contrast-induced acute kidney injury was abrogated, indicating a central role for caspase-11 in acute kidney injury. Additionally, deletion of caspase-11 in TECs reduced Gsdmd cleavage, which is the key process for execution of pyroptosis.

Conclusions: These results establish the requisite role of caspase-11-mediated epithelial pyroptosis in CI-AKI, and suggest that epithelial inflammatory caspases are an important therapeutic target for AKI.

Funding: Other NIH Support - the National Science and Technology Major Project (No. 81570604)

TH-PO004
Kynureninase Is Essential for Protection from AKI by Caloric Restriction
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Background: Experimental work shows that preconditioning by caloric restriction (CR) or hypoxia (HP) prevents acute kidney injury (AKI) reliably. Recently, we have identified Kynu as one of the top gene candidates conveying organ protection in a transcriptome analysis of renal tissue after preconditioning. Here, we further characterize the impact of Kynu in a mouse model of renal ischemia-reperfusion injury (IR).

Methods: We generated a conventional Knockout (KO) of Kynu using CRISPR/Cas9 genome editing in non-homologous end joining (NHEJ) in C57Bl/6 mice. Following a functional and histological phenotyping, wildtype and KO mice were preconditioned by CR and subsequently were subject to IR.

Results: Kynu encodes kynureninase, which represents a key player in tryptophan metabolism. We confirmed the knockout of our newly generated mouse line by immunoblot, immunohistochemistry and mass spectrometry. The basal phenotyping of the KO mice did not differ from that of wildtype mice (appearance, weight, kidney function, histology). Renal function as well as histological features of AKI 24h after IR were similar in KO mice without protection, but wildtype mice were effectively protected from AKI after CR, this effect was significantly diminished in the Kynu KO animals after CR.

Conclusions: The induction of Kynu is associated with HP and CR. Our results confirm the pivotal role of Kynu as a key player of preconditioning-mediated renal protection. Further investigations to determine the mechanistic features of Kynu are required now.

TH-PO005
Kidney-Centered Radiotherapy Attenuates Renal Ischemia-Reperfusion Injury in Mice
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Background: Whole-body irradiation has been associated with renal ischemic preconditioning in mice. Here, we investigate the functional and fundamental impact of radiotherapy centered on the kidneys before renal ischemia/reperfusion (IR) in mice.

Methods: 1. Animals (n=6) were anesthetized and placed in the irradiator. Two beams of X-rays (225Kv, 13 mA) specifically targeted both kidneys to deliver a dose of 8.5 Gy. Irradiation was performed 1 month after a functional and histological phenotyping. The left renal ischemia was induced for 30min. After 48 hours of reperfusion, the left kidney was collected, as well as blood. Control group (n=6) underwent a similar renal IR procedure, with no prior irradiation.

Results: Two irradiation of the left kidney (8.5 Gy) was performed in one month. One month later, the left (irradiated) kidney was collected. Additionally, the left kidneys were collected from non-irradiated mice (n=5). Total RNAs were extracted from irradiated and control kidneys to perform comparative high-throughput RNA-Seq. BaseSpace Sequence Hub Illumina was used. Functional enrichment analysis was performed using DAVID program. Both experimental protocols have been approved by the IACUC of Liège, Belgium.

Conclusions: Kidney irradiation induces ischemic preconditioning in mice, with improved renal function and decreased inflammation following renal IR. The aforementioned signaling pathways may play a role in irradiation-associated kidney resistance to IR.

Funding: Government Support - Non-U.S.

TH-PO006
Renal Protective Effect by Vagus Nerve Stimulation After Kidney Injury
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Background: We previously reported that the macropages with vagus nerve stimulation (VNS) before bilateral ischemia-reperfusion injury (IRI) protect the kidney from injury by activating the cholinergic anti-inflammatory pathway (CAP) in mice. Clinically, more beneficial if VNS after injury could protect the kidney. We evaluated the effect of VNS after the injury both in vitro and in vivo model.

Methods: 1. Both murine macrophage cell line RAW 264.7 and primary peritoneal macrophages were administered LPS (100 ng/ml). Human monocyte cell line U937 also received LPS (1 ng/ml) to cause a7 nicotinic receptor agonist of neural crest cell in the CAP, all of the cells were treated with a7nicotinic receptor agonist GTS-21 (50 mM for each) and 6 hours after LPS administration, followed by assessment of the inflammatory status (TNF-α, IL-1β). In vivo, C57Bl/6 mice were injected with LPS (5 mg/kg) and LPS (1 ng/ml) intraperitoneally, and GTS-21 (10 μg/kg) was administered in the C57Bl/6 mice, C57Bl/6 mice underwent unilateral IRI (uniIRI). Following, VNS or sham stimulation was performed 3 times a week for 2 weeks, then the extent of kidney fibrosis (a-SMA, Masson's trichrome staining) was evaluated 2 weeks after the injury.

Results: GTS-21 decreased TNF-α expression level induced by LPS in macrophages / monocyte we use. In vivo, GTS-21 significantly suppressed LPS-induced kidney injury scores as increased Kim-1 expression, as well as inflammation such as increased plasma TNF-α and splenic IL-1β. The progression of kidney fibrosis was also suppressed in VNS-treated uniIRI mice, compared to the sham stimulation-treated group.

Conclusions: CAP activation after injury could also exert organ protective effect.

Funding: Commercial Support - Kyowa-Hakko-Kirin, Government Support - Non-U.S.
TH-PO007

Human Recombinant α-1-Microglobulin Protects Against AKI in Rat Models of Ischemia-Reperfusion Injury (IRI)

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Background: Acute kidney injury (AKI) is a global health concern associated with high morbidity, mortality, and progressive chronic kidney disease (CKD). RMC-035, a recombinant human α1-microglobulin (A1M), has demonstrated protective antioxidant effects in several injury models. The principal mechanisms of RMC-035 are heme binding, reductase activity, radical scavenging and protection of mitochondria. RMC-035 is being developed for the prevention of cardiac surgery associated-AKI, and are currently evaluated in a Phase 1 study. We present preclinical data for RMC-035, supporting its protective effect in ischemic AKI and AKI on a CKD background.

Methods: RMC-035 (0.5-5 mg/kg, i.v.) was administered at various time-points and doses prior and/or post renal ischemia in rats exposed to unilateral nephrectomy followed by a 30 minute pedicle clamp ischemia. AKI was evaluated at 1-5 days post injury by serum creatinine (sCr), BUN and 24 hr urinary creatinine clearances (CrCl). Furthermore, RMC-035 (2 mg/kg, i.v.) was administered prior and/or post renal clamp ischemia in rats previously subjected to unilateral and renal ischemia (“AKI on CKD model”). Texas Red-x labeled RMC-035 (TR-RMC-035) trafficking and handling by proximal tubule cells (PTC) was studied via intravital imaging.

Results: RMC-035 caused a dose-dependent decrease in AKI measured as reduced proteinuria, sCr and BUN levels, and improved 24 hr CrCl. In a single AKI model, RMC-035 given prior and/or post renal IRI was more effective for protection vs a single dose given either before or after IRI. In a CKD model with two successive episodes of AKI over 28 days, RMC-035 given at the second IRI episode significantly reduced renal injury by sCr and CrCl. TR-RMC-035 was rapidly filtered and bound to the apical brush border in PTC. Accumulation of RMC-035, tubular-vesicular extensions and vesicular trafficking was seen from 30 minutes through 24 hr post infusion.

Cytosolic release was seen as early as 70 minutes.

Conclusions: RMC-035 demonstrates dose-dependent protective effects against AKI in multiple IRI models including AKI on CKD, had a prolonged PTC half-life including release into the cytosol, thus being a novel and promising therapeutic candidate for the treatment of cardiac surgery associated-AKI.

Funding: NIDDK Support, Other NIH Support - O'Brien Center for Renal Imaging, Commercial Support - A1M Pharma

TH-PO008

A Novel Angiotensin-Converting Enzyme 2 Truncate Markedly Improves Ischemic AKI

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Background: RAS is overactive in AKI and therefore RAS blockers could be beneficial. Their use, however, is usually avoided because of their hypotensive and hemodynamic effects. An alternative approach to blocking the formation or action of angiotensin II (Ang II) is to foster its degradation. ACE2 is a tissue enzyme that degrades Ang II to Ang 1-7. Despite its large size, native ACE2 is not filterable. We therefore used a novel ACE2 truncate (1-619) to test the therapeutic potential in a unilateral model of ischemia-reperfusion injury (IRI).

Methods: IRI was induced in C57 mice by clamping the left renal pedicle for 30 min. ACE2 1-619 or vehicle (PBS) was administered 20 min prior to, and 5-6 h and 30 h after IRI. Renal function and tubular injury were assessed 24h and 48h post IRI. Filtration and renal uptake of 1-619 was assessed by SPECT/CT imaging.

Results: In 1-619-treated mice, GFR was higher at 24h (103±16 vs. 63±11 µl/min, p<0.001) and 48h (127±22 vs 38±31 µl/min, P<0.01) post IRI as compared to vehicle mice. Consistent with a better preserved GFR, BUN and Cr were lower in the 1-619-treated group as compared to their vehicle counterparts at 24h and 48h post IRI. ACE2 1-619 attenuated injury to the renal tubules as reflected by an improved tubular injury score and reduced kidney NGAL at 48h post IRI compared to vehicle mice. SPECT/CT showed comparable parenchymal activity of infused 1-619 in a mouse subjected to IRI 24h prior to imaging and an Nx control mouse. ACE2 activity was increased in kidneys of 1-619-injected mice as compared to vehicle mice at 48h post IRI (64±8 vs. 46±3 RFU/ig protein/h, P<0.01).

Conclusions: We conclude that the use of our novel ACE2 truncate downregulates the kidney RAS and provides a preventive/therapeutic approach to attenuate AKI.

Funding: NIDDK Support

TH-PO009

Knockout of Leucine Rich α-2 Glycoprotein Protects Against Renal Ischemia-Reperfusion Injury Through Reduction of Fibrosis and Apoptosis

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Background: Leucine-rich α2-glycoprotein (LRG) is one of serum glycosylated proteins with 347 amino acids, and serum LRG is reported as a novel disease activity biomarker for inflammatory bowel disease. However, little is known about the role of LRG in acute kidney injury (AKI) pathogenesis. We examined renal LRG expression and urinary LRG level using mice AKI model and clinical samples.

Methods: We evaluated LRG function in the bilateral renal ischemia-reperfusion injury (IRI) AKI model by using LRG knockout (KO) and wild-type (WT) mice. We at first evaluate the localization of LRG in AKI of WT mice. The effects of LRG on phosphorylation of Smads were examined in primary cultured renal tubular cells. In clinical study, we measured urine LRG in AKI patients, and immunohistological examination of LRG in AKI and minimal change renal biopsy sample.

Results: In WT mice with IRI-induced AKI, renal mRNA and protein expression of LRG were reduced from 6 h and 12 h and peaked at 24 h and 48 h after IRI, respectively. In control mice kidney, only a very few expression of LRG was observed. Urine and serum LRG are increased after IRI in WT mice. Immunohistochemical examination showed that LRG expression was observed mainly in renal distal tubular cells in AKI mice. LRG KO mice had significantly lower PcR (0.61±0.13 versus 1.67±0.38 mg/dl), BUN (102.3±21.8 versus 234.5±48.5 mg/dl) at 48h after IRI compared to WT mice. Immunohistological examination showed mild tubular injury, fibrotic change, collagen IV deposition, and fewer KiM-1 positive and apoptotic cells in LRG KO mice. In primary cultured renal tubular cells, TNF-a and LPS stimulated LRG expression. LRG KO reduced TGF-b stimulated-phosphorylation of Smad2. Notably, in contrast media-induced AKI patients, urinary LRG levels were increased from 6 h LRG staining were enhanced in AKI renal-biopsy samples.

Conclusions: Our results demonstrate that LRG is up-regulated in renal tissues in both mice and human AKI, and that urine and serum LRG are increased in early phase of AKI. Inflammatory cytokines such as TNF-a stimulates expression of LRG in renal tubular cells. Thus, LRG could serve as a potential early biomarker in AKI, and LRG knockdown could serve as a potential therapeutic target in AKI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Mineralocorticoid Receptor Antagonist Counteracts the Acute and Chronic Effects of Renal Ischemic Injury in Rodents and the Large White Pig

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Background: Mineralocorticoid receptor antagonists (MRA) prevent ischemic acute kidney injury (AKI) and its transition to chronic kidney disease (CKD) through macroporation polarization modulation. The specific contribution of interleukin-4 (IL-4) signaling to this effect is unknown. Whether the MRA protective effect reported in rodents can be transmitted to the human remains to be elucidated. Here, we explore the role of IL-4 signaling in the protective effect of Finerenone and we evaluate the effect of MRA against the acute and chronic effects of ischemic AKI in the Large White pig.

Methods: Male C57Bl/6 mice (24) were divided in: sham, renal ischemia for 22.5 min (IR), IR plus the non-steroidal MRA finerenone (10 mg/kg) at +48, -24 and -1 h before IR and IR-finenone plus Tolvaptan (15mg/kg), a JAK3 inhibitor. The mice were followed-up for 4 weeks to evaluate the AKI to CKD transition. Large White male pigs (18) were divided in: sham, bilateral renal ischemia for 60 min + vehicle or IR + Soludactol (potassium canrenoate-7mg/kg, i.v.) at 48 h, 24 h and 30 min before the induction of the ischemia and 24 h and 48 h after reperfusion.

Results: In mice, the AKI to CKD transition was evidenced by a 40% increase in plasma creatinine, interstitial fibrosis and increased mRNA levels of α-SMA, fibronectin and collagen I. Finerenone protected against these alterations while the JAK3 inhibitor partially reversed this protective effect. In the Large White pig, tubular injury protection by Finerenone was evidenced by significant reduction in urinary protein. Vehicle: 1.08 ± 0.02 mg/ml vs canrenoate: 0.94 ± 0.02 mg/ml, L-FAHBP (Vehicle: 39.2 ± 2 ng/ml vs canrenate: 19.1 ± 1.5 ng/ml), NAG excretion (Vehicle: 109.2 ± 1.1 U/L vs canrenoate: 59.2 ± 1 U/L) and by the recovery of the urinary concentration capacity after 24 h of renal ischemia. After 3 months, the untreated pigs presented proteinuria (0.03±0.1 g/ml) which was absent in the canrenoate-treated pigs (0.01±0.01 g/ml).

Conclusions: MR antagonists prevent the acute and chronic IR-kidney effects in the mice and in the Large White pig. The IL-4 receptor-JAK3 signaling pathway is involved in the benefit of the MRA finerenone. These findings support clinical trials testing the potential benefits of MRAs in the kidney transplantation setting.

Funding: Commercial Support - BAYER, Government Support - Non-U.S.

The V1a Receptor Activator Terlipressin (TLP) Attenuates Hemorrhagic Shock (HS)-Induced AKI

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Background: Although HS is still the leading cause of mortality, early vasopressor use can restore hemodynamic parameters and organ perfusion, reducing the need for aggressive fluid therapy and avoiding fluid overload. In shock, TLP improves hemodynamics, decreasing pulmonary capillary leak and avoiding fluid overload. The AVP/V1a receptor system also stimulates RAS activity and inhibits apoptosis. This study aimed to compare levels of lactated Ringer’s (LR) fluid therapy: aggressive (LR 3 mL/kg/h); and conservative (2LR), aimed to compare levels of lactated Ringer’s (LR) fluid therapy: aggressive (LR 3 mL/kg/h); and conservative (2LR). At 15 min after LR/TLP administration, we used the drawn blood to evaluate 4 groups of rats—control (no intervention); 3LR; 1LR+TLP (10 mL/kg/h); and 2LR. At 48 h, 24 h and 30 min before the induction of the ischemia and 24 h and 48 h after reperfusion.

Results: In mice, the AKI to CKD transition was evidenced by a 40% increase in plasma creatinine, interstitial fibrosis and increased mRNA levels of α-SMA, fibronectin and collagen I. Finerenone protected against these alterations while the JAK3 inhibitor partially reversed this protective effect. In the Large White pig, tubular injury protection by Finerenone was evidenced by significant reduction in urinary protein. Vehicle: 1.08 ± 0.02 mg/ml vs canrenoate: 0.94 ± 0.02 mg/ml, L-FAHBP (Vehicle: 39.2 ± 2 ng/ml vs canrenate: 19.1 ± 1.5 ng/ml), NAG excretion (Vehicle: 109.2 ± 1.1 U/L vs canrenoate: 59.2 ± 1 U/L) and by the recovery of the urinary concentration capacity after 24 h of renal ischemia. After 3 months, the untreated pigs presented proteinuria (0.03±0.1 g/ml) which was absent in the canrenoate-treated pigs (0.01±0.01 g/ml).

Conclusions: MR antagonists prevent the acute and chronic IR-kidney effects in the mice and in the Large White pig. The IL-4 receptor-JAK3 signaling pathway is involved in the benefit of the MRA finerenone. These findings support clinical trials testing the potential benefits of MRAs in the kidney transplantation setting.

Funding: Commercial Support - BAYER, Government Support - Non-U.S.

Aryl Hydrocarbon Receptor Agonist FICZ Alleviated Rhabdomyolysis-Induced Acute Kidney Injury (AKI) and Its Transition to Chronic Kidney Disease (CKD) in Mice

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Background: Aryl hydrocarbon receptors (AhR) are ubiquitous in the cytoplasm of various cells in various organs. They can bind to multiple ligands and affect different downstream pathways. Previous studies have found that activating AhR could alleviate inflammation and apoptosis through the NFκB pathway in ulcerative colitis, psoriasis and metabolic diseases induced by high-fat diet. However, whether AhR agonist FICZ can alleviate acute kidney injury (AKI) remains unclear. Thus, we explored the role of FICZ in AKI and its related mechanisms through rhabdomyolysis-induced AKI model.

Methods: C57BL/6 mice were randomly divided into three groups: control, glycoler and glycerol+FICZ. The glycerol group were injected with glycerol at bilateral back legs. The glycerol+FICZ group was administered intraperitoneally for 3 days before the glycerol injection. The mice were sacrificed at 24h after the glycerol injection, blood and organs were collected. Renal histological injury was measured by PAS staining. Renal tissues of mice were analyzed by immunohistochemical, immunofluorescence, western blot and qPCR assay.

Results: Immunofluorescence staining and western blot showed that AhR was mainly expressed in proximal renal tubular epithelial cells, and the expression of AhR was decreased in rhabdomyolysis-induced AKI. Activation of AhR by FICZ pretreatment significantly attenuated rhabdomyolysis-induced AKI in mice. Moreover, the expressions of p65, iκBα and p-IκBα were significantly decreased, as well as attenuated renal tubular damage in glycerol-injured kidneys. AhR activation also resulted in reduced TUNEL-positive tubular cells, suppressed cleaved caspase-3, BAX levels, and preserved Bcl-2, Bcl-2 XL expression, indicating that FICZ regulated tubular cell apoptosis. Moreover, the expressions of MCP1 and IFNγ were reduced, as well as the expressions of IL-6, -18 and TNFα in the glycerol+FICZ group were significantly reduced, compared with the glycerol group. The transcription levels of those inflammatory factors, MCP1 and IFNγ genes were detected by qPCR. These data suggested that FICZ showed renoprotective effects also by regulating inflammation via the NFκB pathway.

Conclusions: In summary, our findings demonstrated that AhR agonist FICZ protects against rhabdomyolysis-induced AKI via the regulation of inflammation and apoptosis in tubular epithelial cells.
**Methodology:**

**Objective:** The test was conducted to evaluate the effect of 

**Result:** The test showed that the measured value of the objective was significantly different from the control group.

**Conclusion:** The study concluded that the test substance had a significant impact on the measured variable.

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at 24 hours and began to decrease at 48 hours compared to the saline group. In align with these observations Cat B and Z protein levels were elevated at both time points. Legumain mRNA expression gradually increased after LPS administration and was markedly elevated at 6 hours in EP and 24 and 48 hours in LPS. A significant increase in legumain protein levels was detected by MS at 48 hours and validated by WB. Legumain activity showed a marked increase at 48 h in comparison to the saline group.

Conclusions: The current results suggest that cysteine cathepsins and legumain may play a role only in the late phase of LPS-induced preconditioning.

Funding: Government Support - Non-U.S.

TH-PO019

Modeling of Tacrolimus Nephrotoxicity Using Kidney Organoids Derived from Human iPS Cells
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Background: Tacrolimus, a calcineurin inhibitor, was clinically used as an immunosuppressive agent in organ transplantation or glomerulonephritis. Despite the therapeutic benefits, tacrolimus’s use is limited due to its nephrotoxicity. To reduce tacrolimus nephrotoxicity, the effective experimental models are essential. Recently, we and others have established protocols for the generation of kidney organoids from human pluripotent stem cells, containing nephron-like structures with podocytes, proximal tubules, and distal tubules. Here, we recapitulated tacrolimus nephrotoxicity using kidney organoids and investigated its pathogenic mechanism.

Methods: Kidney organoid differentiated from the CMC11 iPS cell line (human male donor). Kidney organoids were re-seeded in 96-well plates and tacrolimus was treated at doses of 0 µM, 30 µM, 60 µM, or 120 µM for 24 h.

Results: The size of kidney organoids decreased at dose-dependent manner. Cell viability assessed by CCK-8 assay and live/dead cell staining decreased at dose-dependent manner. Proximal tubule cells, as well as distal tubule cells were decreased according to the concentration of tacrolimus. Podocyte loss and injured podocytes with unpolaredized and diffuse pattern of ZO-1 tracks were observed after treatment of tacrolimus. Ultrastructural analyses showed the vacuoles throughout the cytoplasm of tule-like structures, which were enhanced to those of human tacrolimus nephrotoxicity. Autophagic activity was enhanced after treatment with tacrolimus in kidney organoids, which were similar patterns in mouse model of tacrolimus nephrotoxicity. Rapamycin, as an autophagy inhibitor, attenuated cell death in kidney organoids model of tacrolimus nephrotoxicity, whereas 3-methyladenine, as an autophagy inhibitor, accelerated cellular toxicity.

Conclusions: Our data suggest that human iPS-derived kidney organoids can recapitulate tacrolimus nephrotoxicity and serve the effective in vitro model to investigate its pathogenic pathway.

TH-PO020

Spatiotemporal ATP Dynamics In Podocytes During Ischemic Reperfusion Injury Predicts Later Foot Process Effacement
Masahiro Takahashi, Shiigenori Yamamoto, Masamichi Yamamoto, Motoko Yanagita. Department of Nephrology, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Background: Mitochondrial dysfunction, genetic or postnatal, is closely related to podocyte injury, suggesting the possibility that hypoxia or oxidative stress during ischemic AKI causes podocyte injury. Indeed, some studies report proteinuria after kidney transplantation, however, little is investigated regarding pathophysiologic changes of podocytes during AKI. Here we investigated the dynamics of adenine 5′ triphosphate (ATP) in podocytes during ischemic AKI, because ATP is essential for stabilization of foot process.

Methods: To enable spatiotemporal ATP imaging, we utilized ATeam mice, which expressed the FRET-based ATP biosensor systemically, and monitored ATP changes of podocytes during IRI by multi-photon microscopy. Furthermore, we performed microstructural analysis of podocytes two weeks after IRI, and assessed the correlation between the ATP recovery in acute phase and morphological change in chronic phase.

Results: While the ATP levels of podocytes gradually decreased to the plateau level in twenty minutes after ischemia induction, they recovered rapidly in less than five minutes after reperfusion. The % ATP recoveries after 15, 30, 37, 45 and 60 minute-ischemia were 95%, 93%, 87%, 84% and 80% respectively, and were dependent on the length of ischemia. Electron microscopy two weeks after IRI revealed significant foot process effacement and mitochondrial fragmentation in mice subjected to severe IRI. Foot process widths were 367, 361, 381, 450 and 480 nm, and mitochondrial circularities, an indicator of mitochondrial fragmentation, were 0.80, 0.80, 0.83, 0.86 and 0.88 after 15, 30, 37, 45 and 60 minute-ischemia, respectively. Mitochondrial circularities were strongly correlated with foot process widths, supporting the importance of energy metabolism in the maintenance of foot processes. Notably, the % ATP recoveries in acute phase were well correlated with the foot process widths and mitochondrial circularities in chronic phase.

Conclusions: We, for the first time, succeeded in visualizing ATP dynamics of podocytes during IRI. Our results show the close link between podocyte energy metabolism and ultrastructural changes after AKI, and provide the basis for understanding the mechanism of proteinuria after AKI or kidney transplantation.

TH-PO021

A Novel Kidney Slice Culture System Visualizing Intrarenal ATP and Segment-Dependent Energy Metabolism
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Background: The kidney constantly utilizes adenine 5′ triphosphate (ATP), and ATP depletion plays a crucial role in the progression of kidney diseases. Recently, we generated a mouse line, which expresses the FRET-based biosensor systemically, and reported spatiotemporal ATP dynamics in the kidney during AKI model using two-photon microscope. In our previous observation from the kidney surface, however, deeper nephron segments such as S3 segment of proximal tubules (PTs), glomeruli, and thick ascending limbs of Henle (TALs) cannot be observed. Additionally, we cannot analyze ATP dynamics in the presence of the reagents with systemic effects in vivo.

Methods: We established ATP imaging system using the kidney slice culture of ATP visualizing mice and evaluated ATP dynamics in the presence of pharmacological inhibitors of oxidative phosphorylation (OXPHOS) and glycolysis. We also evaluated ATP dynamics after cisplatin administration in this system.

Results: While the ATP levels of PTs, TALs and DTs rapidly and significantly decreased by the administration of 4mM NaN3, an OXPHOS inhibitor, those of podocytes were well maintained as long as 60 min after the administration. On the other hand, the administration of 0.2mM phloretin, a glucose transporters inhibitor, decreased ATP levels in podocytes, but not apparently in PTs, TALs, and DTs. When the kidney slice was incubated in the buffer containing 1mM cisplatin, the ATP levels of PTs and DTs decreased after 60 min, while those of podocytes and principle cells showed no apparent changes even after 120 min. Interestingly, mitochondrial cristae deformation were observed by electron microscopy in the slice incubated with cisplatin for 120min.

Conclusions: Utilizing this novel slice culture system, we, for the first time, directly demonstrated the segment-specific ATP depletion in ATP metabolism. While PTs, TALs and DTs are more or less dependent on OXPHOS for ATP production, suggesting their possible vulnerability to ischemia, podocytes rely more on glycolysis for ATP production than on OXPHOS. In addition, we succeeded in demonstrating the different sensitivity to cisplatin among nephron segments. This method could be useful for the elucidation of the metabolic changes in the pathophysiological conditions and for screening of renal toxic drugs.

TH-PO022

Pannexin 1 Channels Regulate Mitochondrial Function, Autophagy, and Cell Survival During Kidney Ischemia-Reperfusion Injury in Mice
Nabin Poudel,1 Jakub Jankowski,2 Shi Morikoa,2 Colleen Schinderle,1 Shuqiu Zheng,1 Diane L. Rosina,1 Mark D. Okusa.1 1Division of Nephrology and Center for Immunity, Inflammation, and Regenerative Medicine, University of Virginia, Charlottesville, VA; 2Department of Microbiology, Immunology, and Cancer Biology, University of Virginia, Charlottesville, VA.

Background: Pannexin 1 (Panx1) channels are membrane associated non-selective channels that are activated by mechanical/physiological stimuli during injury and serve as a conduit for release of small molecules, including ATP. We have previously shown that pharmacological inhibition or genetic deletion of Panx1 in mice is protective against renal ischemia reperfusion injury (IRI), and Panx1 deficiency in murine proximal tubule-derived (TKPTS) cells results in reduced extracellular ATP and concomitant increase in intracellular ATP (PMID: 29866797). While the effects of extracellular ATP released from cells during IRI during injury have been extensively studied, the physiological role of Panx1 in cellular homeostasis is unknown.

Methods: Mice were subjected to IRI (26 mins of ischemia and 24 hrs of reperfusion) to assess plasma creatinine and kidney ATP levels. Control and Panx1 deficient TKPTS cells were subjected to hypoxia reperfusion (HR). Mitochondrial biogenesis and autophagy were assessed using real-time PCR and western blotting. Mitochondrial membrane potential was assessed by flow cytometry. Mitochondrial respiration was assessed using an Agilent Seahorse® assay. Cyclic AMP levels were measured using cAMP biosensor. For ATP depletion studies, cells were pretreated with 100 nM oligomycin prior to HR.

Results: Panx1 mice have higher kidney ATP levels 24 hours after IRI than control mice. Panx1 mice have higher levels of p62 in kidneys. In vitro findings show that Panx1 deficient cells retain more intracellular ATP after HR and have better survivability. Panx1 deficient cells have reduced mRNA expression of Pgc1a and Tim, increased intensity of Mitotracker Red CMXROS® staining, and reduced CAMP-dependent signaling.

Conclusions: Our findings demonstrate that Panx1 deficiency leads to increased intracellular ATP, reduced CAMP signaling, reduced autophagy, increased mitochondrial function, and better cell survival during hypoxia. We conclude that deficiency of Panx1 leads to improved mitochondrial health and increased tubule cell survival during hypoxia resulting in protection during IRI. The development of selective pharmacological inhibitors of Panx1 could provide a novel approach to the treatment of acute kidney injury by targeting mitochondrial health during stress and injury.

Funding: NIDDK Support
**TH-PO023**

**Effects of Tubular Mitochondrial Pyruvate Carrier 1 Deletion on Redox Metabolism**


**Background:** Kidney injury results in mitochondrial dysfunction, oxidative stress, change to tubular glycolytic metabolism, and disruption of lactate and pyruvate metabolism. Pyruvate treatment is protective in different kidney injury models. The Tubular Mitochondrial Pyruvate Carrier 1 (MPC1) transports pyruvate from the cytosol into the mitochondrial matrix and mediates the metabolic decision committing glycolytic carbon to mitochondrial oxidative phosphorylation. Understanding the implication of impaired tubular mitochondrial pyruvate transport may provide critical knowledge on the effect of mitochondrial metabolic adaptations in redox balance and injury response.

**Methods:** Pax8lox/lox mice line to generate Pax8lox/lox;Mpc1f/f (Tu-MPC1-KO) and Pax8lox/lox;Mpc1f/f;Tu-Mpc1-KO (Tu-MPC1-WT) littermates to disrupt Mpc1 in tubular epithelial cells. Mice 8-13 weeks of age were assessed for renal function and biomarkers of kidney injury. C13-lactate/C13-pyruvate tracing was employed to determine the metabolic consequences of MPC1-KO. Finally, upon sacrifice markers of oxidative stress were studied and kidney tissue was examined histologically. A second cohort of Tu-MPC1-KO and -WT mice underwent cisplatin-induced kidney injury to evaluate survival.

**Results:** Tu-MPC1-KO resulted in accumulation of C13 labeled lactate/pyruvate and the concomitant decrease of C13 labeled TCA cycle intermediate metabolites. Significant reduction of C13 incorporation into glutamine suggests that mitochondrial oxidative metabolism was severely impaired via glutaminolysis. Tu-MPC1-KO mice show no difference in renal histology or renal function compared to Tu-MPC1-WT. Tu-MPC1-KO kidney tissue had a significant increase in oxidative stress markers including 3-nitrotyrosine, % total glutathione as glutathione disulfide, and MnSOD activity. Finally, while Tu-MPC1-KO mice exhibited increased markers of oxidative stress prior to cisplatin treatment compared to WT, no significant difference in survival was observed.

**Conclusions:** In vivo inhibition of tubular mitochondrial pyruvate transport leads to disruption of renal redox metabolism and increased oxidative stress markers in renal tubule cells, which does not affect survival after cisplatin-induced CKD.

**Funding:** Other NIH Support - NICHD K12 HD027748, DK104998, Private Foundation Support

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**TH-PO025**

**Mitochondrial Transplantation by Intra-Arterial Injection Prevents Renal Ischemia-Reperfusion Injury**

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**Background:** Mitochondrial transplantation (MT) is a novel clinically validated strategy for the amelioration of organs subjected to ischemia-reperfusion injury (IRI). In this study we investigated the safety of autologous MT and the therapeutic use for renal protection in a swine model of bilateral IRI.

**Methods:** Yorkshire pigs (n=24; female; 40-50 kg) underwent selective catheterization of the renal arteries under Fluoroscopy (Fig. 1 A). Mitochondria (1 x 10^11 in 10 ml buffer) were delivered as a single bolus (n=6) or serially (3 injections over 60 minutes, n=6) in each of the renal arteries of healthy animals. Another group of animals underwent bilateral temporary occlusion with balloon-catheters (60 minutes of ischemia) followed by 24 hours of reperfusion. Mitochondria (n=6) or Vehicle (n=6) were delivered as a single bolus in each of the renal arteries at the time of reperfusion. Uptake was confirmed by PET-CT images after intra-arterial injection of 18F-Rhodamine-labeled mitochondria (Fig. 1 B).

**Results:** MT temporally increased renal function in the healthy kidney. Intra-arterial injection of mitochondria had no side effects on hemodynamics, systemic inflammatory response and organ function. After 24 hours of reperfusion, MT significantly improved renal function in terms of renal output (p=0.02), serum creatinine (p=0.01), estimated glomerular filtration rate (p=0.03) and blood urea nitrogen (p=0.01) compared to vehicle treated animals (Fig. 1 C-D).

**Conclusions:** Mitochondrial transplantation by intra-arterial injection is safe and prevents renal IRI.

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**TH-PO024**

**Treatment with Isolated Mitochondria 5 Days After Kidney Ischemia-Reperfusion Injury Reduces Progression to Interstitial Fibrosis and Tubular Atrophy**

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**Background:** Ischemia induces altered bioenergetics with increased mitochondrial swelling, reactive oxygen species and ultimately degradation of cellular function. Therapeutic interventions that target to improve mitochondrial health to repair, regrow or replace mitochondria to restore respiratory functions are beneficial for treatment of disease.

**Methods:** Renal injury was assessed by plasma creatinine (PCr; mg/dl). 8-wk old C57BL/6 mice were i.v. injected with healthy isolated mitochondria (2.5 mg/g) 1 day prior to analysis that included measurement of ATP levels, mitochondrial functions (Seahorse), cytokines (RT-PCR), and IF microscopy.

**Results:** In vivo studies demonstrated treatment of mice with 2.5 mg/g of mitochondria at 1, 3 or 5 days after IRI significantly protected the IRI kidney compared to vehicle treated mice [PCr (0.60±0.04 (+1d) vs 0.54±0.18 (+3d) vs 0.46±0.18 (+5d) vs 1.24±0.2, p<0.05]. The mice treated with mitochondria 1d, 3d or 5d after IRI had significantly less MT labeling compared to vehicle treated mice. The injected mitochondria is found in kidney in proximal tubule cells (anti-CD13 labeled) and co-localizes with endogenous mitochondria. The mitochondria treated mice had significantly lower levels of fibrosis genes (Acta and Col3a1) and significantly higher Pgc1α compared to vehicle treated mice. The mitochondria treated mice had significantly higher populations of Ki67 positive cells in both IRI and contralateral control kidneys compared to vehicle. Treatment of TKPTS cells with mitochondria have significantly higher levels of ATP, higher basal oxygen consumption rate and spare respiratory capacity. Similar to IRI studies, addition of mitochondria on TKPTS significant increases PGC1α gene expression, mtDNA/nDNA ratio, and induces proliferation.

**Conclusions:** Transfer of healthy mitochondria help maintain bioenergetics through upregulation of PGC1α and induced regeneration of PT cells to lessen progression to fibrosis after IRI. Treatment with healthy mitochondria could be used as a therapeutic modality to lessen progression to IFTA.

**Funding:** NIDDK Support, Private Foundation Support

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**TH-PO026**

**Mitochondrial Damage Causes Inflammation via cGAS-STING Signaling in AKI**

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**Background:** Acute kidney injury (AKI) is characterized by mitochondrial dysfunction and activation of the immune response. The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway detects cytosolic DNA and induces innate immunity. We investigated the role of mitochondrial damage and subsequent activation of the cGAS-STING pathway in cisplatin (cis)-induced AKI.

**Methods:** The human proximal tubular cell line, HK-2, treated with 20 μM of cis and the renal cortex of WT (C57BL/6) or STING KO mice injected with 25 mg/kg of cis for 48 or 72 hr were analyzed. The changes in cGAS-STING activation, mitochondrial damage, mitochondrial DNA (mtDNA) leakage or neutrophil infiltration were evaluated by flux analyzer, mitochondrial membrane potential analysis, real-time PCR, western blotting, or immunostaining. The culture supernatants of cis and/or STING siRNA-treated HK-2 were used for cytokine arrays and migration assays. Ethidium bromide (EtBr) and extracted mtDNA from HK-2 were used for mtDNA depletion and mtDNA transfection (to increase cytosolic mtDNA), respectively.

**Results:** In cis-treated HK-2 or kidney cortex of cis-induced AKI mice, cGAS and STING were upregulated and STING translocated from the ER to the Golgi apparatus,

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
indicating STING activation. Subsequently, the cGAS-STING axis was activated via cROS production and phosphorylation of TBK-1 and PKCδ, leading to induction of inflammatory cytokines (IL-6, IL-8, ICAM-1, CXCL10, and GM-CSF) and neutrophil chemotaxis. The inflammatory response by cis was ameliorated in STING-knockdown HK-2 or STING KO mice. Cis impaired tubular mitochondrial function: reduction of mitochondrial respiration and mitochondrial fatty acid β-oxidation with subsequent decrease in ATP production. Moreover, cis permeabilized mitochondrial membrane. Following the mitochondrial dysfunction, cis-mediated mtDNA leakage to the cytosol was induced in tubular cells both in vivo and in vitro. mtDNA depletion inhibited the inflammation by cis. Subsequently, the cGAS-STING axis was activated, indicating that cytokotic mtDNA acts as a ligand for the cGAS-STING pathway in cis-induced tubular inflammation.

Conclusions: Mitochondrial damage leads to mtDNA leakage, activating cGAS-STING signaling and subsequent inflammation in cis-induced AKI.

TH-PO027 Mitochondrial Dysfunction in an In Vitro and In Vivo Model of Aristolochic Acid Nephropathy Pauline Messoray,1 Inès Jafot,1 Louise Pierre,1 Florian Juszcak,2 Olivia Botton,1 Joelle L. Nortier,1 Thierry Arnould,1 Anne-Emilie Declères,2 Nathalie Caron.1 1University of Namur, NAMUR, Belgium; 2UMONS, Mons, Belgium; 1Hospital Erasme, Brussels, Belgium.

Background: Mitochondrial (mt) dynamics is a key player during AKI and CKD. Indeed, mt provide energy to cells thereby supporting many cellular processes. They are of high importance in kidneys, more specifically regarding proximal tubular epithelial cells (PTEC). Aristolochic Acid Nephropathy (AAN) is a rapidly progressing tubulointerstitial nephropathy induced by aristolochic acid (AA). In these cells, cis-mediated mtDNA leakage to the cytosol was induced in tubular cells both in vivo and in vitro. mtDNA depletion inhibited the inflammation by cis. In the present study, we investigated whether cis-induced mtDNA leakage activates the cGAS-STING pathway in cis-induced tubular inflammation.

Methods: C57Bl/6 male mice were divided into CTX or AA groups. AA groups received 4 intraperitoneal injections of AA (3.5 mg/kg) from D1 to D4 and were sacrificed at D5, D6 and D10. The mtraulysate’s were prepared by TEM while kidney function and structure were assessed by BUN, plasma and urinary creatinine, GFR and histological analysis. For the in vitro part, confluent HK-2 cells (human PTEC) were exposed to AA at 0, 1, 10, or 25 µM during 24, 48 or 72h. Fluorescence and confocal analysis were performed to analyze the mt abundance and network as well as the cellular granularity. Moreover, cellular ATP contents were quantified.

Results: During progression of AAN in mice, structural damages in mt, consisting in the loss of mt cristae and/or contents, were observed, attesting the loss of their integrity and function. These observations were consistent with AAN progression and development of AAN, as shown by a significant increase in BUN and plasma creatinine as well as a significant decrease of GFR. Moreover, at day 10, mt were either absent or only observable as mt debris in necrotic cells where the population of mt exhibiting autofluorescence was increased in remaining cells. During AA-intoxication in HK-2 cells, the fragmentation of mt network and an increase of cellular granularity were observed throughout the protocol while an increase of mt abundance was reported at three days of AA-intoxication, concomitant with a decrease of ATP contents.

Conclusions: We demonstrated the impairment of mt morphology and network during AA-intoxication in both models. Regarding the data, proteins involved in fusion and fission process must be investigated in order to identify molecular actors that may lead to mt dysfunction.

TH-PO028 TREM1/3 Deficiency Impairs Tissue Repair After AKI and Mitochondrial Metabolic Flexibility in Tubular Epithelial Cells Alessandra Tammaro,1 Amsterdam UMC, Amsterdam, Netherlands.

Background: Long-term sequelae of acute kidney injury (AKI) are associated with incomplete recovery of renal function and the development of chronic kidney disease (CKD), which can be due to a maladaptive repair characterized by aberrant innate immune activation, mitochondrial pathology and accumulation of senescent tubular epithelial cells (TECs). TREM-1 is an innate immune receptor expressed by inflammatory and epithelial cells, both players in renal repair after ischemia/reperfusion (IR)-induced AKI. Despite this, our understanding of how TREM-1 deficiency drives senescent AKI reparative failure has never been investigated.

Methods: WT and TREM1/3 KO mice were subjected to different models of renal IR (severe and mild). Animals were sacrificed 1, 5 and 10 day after surgery. Blood was collected to determine renal function parameters. Kidneys were harvested for histological examination and protein determinations. In vivo, kidneys were subjected to unilateral nephrectomy and cell proliferation in TREM1/3 KO TECs. This was associated with G2/M arrest and increased ROS accumulation. Further exposure of cells to ROS-generating triggers drove the cells into a stress-induced senescent state, which was partly reverted by treatment with a mitochondria anti-oxidant.

Results: TREM1/3 KO mice displayed no major differences during the acute phase of injury, but increased mortality was observed in the recovery phase. This detrimental effect was associated with maladaptive repair, characterized by persistent tubular damage, inflammation, fibrosis, TEC senescence and metabolic reprogramming. In vitro, we observed no altered renal homeostasis and cellular proliferation in TREM1/3 KO TECs. This was associated with G2/M arrest and increased ROS accumulation. Further exposure of cells to ROS-generating triggers drove the cells into a stress-induced senescent state, which was partly reverted by treatment with a mitochondria anti-oxidant.

Conclusions: In summary, we have unraveled a novel (metabolic) mechanism by which TREM-1/3 deficiency drives senescent in TECs. This involves redox imbalance, mitochondrial dysfunction and a decline in cellular metabolic activities. These findings suggest a novel role for TREM-1 in maintaining tubular homeostasis through regulation of mitochondrial metabolic flexibility. Finally, this study demonstrates a novel link between immunometabolism and tubular epithelial senescence.

TH-PO029 Sulfotransferase IC2 or Its Mitochondria Membrane Product Cholesterol Sulfate, Increases Maximum Rates of Mitochondria Redox Reactions and Utilization of Tricarboxylic Acid Intermediates Robert L. Bacalla,2 Glenn T. Nagami,3 David P. Basile.1 1Indiana University School of Medicine, Indianapolis, IN; 2Medicine, Richard Roudebush VAMC, Indianapolis, IN; 3VA Greater Los Angeles Healthcare System, Los Angeles, CA.

Background: In prior communications we have demonstrated that the SULT1C2 gene can induce a state of ischemia preconditioning in the kidney by increasing state II/III mitochondria respiration and membrane potential. In other studies, we have found sulfotransferase IC2 increases state II/III mitochondria respiration when added to purified mitochondria. Thin layer chromatography studies demonstrated that sulfotransferase IC2 converts mitochondria membrane cholesterol to cholesterol sulfate. Furthermore, adding cholesterol sulfate to purified mitochondria recapitulates the effect sulfotransferase IC2 has on mitochondria function.

Methods: To assess the substrate specificity of carbon source utilization in S3 proximal tubule cells, we measure reduction rates of tetrazolium red in response to a supply of a single source of substrates. These studies were performed in permeabilized S3 cells with baseline measurements or following treatment with sulfotransferase IC2 or cholesterol sulfate. OD560 was measured every 5 minutes for 12 hours at 37° C. The maximum rate of change in OD per minute was calculated from the colorometric assay.

Results: Both cholesterol sulfate or sulfotransferase IC2 triple maximum reduction rates were greater than tetrazolium red in response to the following substrates: cis-acetic acid, α-keto-glutarate, succinate, fumarate, α-keto-butyrate, glutamate, glutamine, and pyruvate with 100 µM malic acid (p < 0.001 for all reactions) (See accompanying graph).

Conclusions: This data demonstrates that sulfotransferase IC2 and its mitochondria product, cholesterol-SO4 increase substrate utilization rates of tricarboxylic acid intermediates in immortalized S3 proximal tubule cells. The results show that sulfotransferase IC2 has a novel role in cellular control of mitochondria physiology.

Funding: Veterans Affairs Support

TH-PO030 Cyclophilin D Interacts with PPARα to Regulate Fatty Acid Oxidation in Cisplatin AKI Hee-Seong Jang,1 Mira Noh,1 Babu J. Padanilam,1,2 1Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, NE; 2Internal Medicine, Section of Nephrology, University of Nebraska Medical Center, Omaha, NE.

Background: Regardless of the etiology, acute kidney injury (AKI) involves aspects of mitochondrial dysfunction and ATP depletion. Fatty acid oxidation (FAO) is the preferred energy source of the kidney and is inhibited during AKI. A pivotal role for the mitochondrial matrix protein, cyclophilin D (CypD), in regulating overall cell metabolism is being unraveled. We hypothesize that mitochondrial interaction of proximal tubule CypD and PPARα modulate FAO in cisplatin-induced AKI (cisplatin AKI).

Methods: Using genetic and pharmacological intervention and protein-protein interaction studies, we investigated whether proximal tubule CypD modulates FAO in cisplatin AKI through mitochondrial CypD-PPARα binding and its sequestration.

Results: Cisplatin injury resulted in histological and functional damage in the kidney with downregulation of FAO genes and increase of intrarenal lipid accumulation. However, proximal tubule (PT)-specific deletion of CypD protected cisplatin-induced renal damage by inhibiting impairment of FAO and intrarenal lipid accumulation. Immunoprecipitation and BioID methods demonstrated mitochondrial translocation of PPARα and its binding to CypD and sequestration. This led to inhibition of nuclear translocation of PPARα and downregulation of PPARα responsive genes in cisplatin AKI. Genetic or pharmacological inhibition of CypD suppressed mitochondrial CypD-PPARα binding in cisplatin AKI, preventing the impairment of FAO and intracellular lipid accumulation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Conclusions: These results uncover a novel mechanism by which mitochondrial injury leads to AKI. Cyclophilin D specifically impacts ROS and FAO in cisplatin AKI. Targeting this interaction may be a potential therapeutic strategy to prevent energy depletion and cell death in AKI.

Funding: NIDDK Support

TH-PO031

The Role of Cyclophilin D in Acute vs. Chronic Arteriosclerotic Acid Necroptosis

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Background: Cyclophilin D (CypD) facilitates mitochondrial-dependant cell death during pathological conditions. CypD-/- mice are protected from acute kidney injury (AKI) following ischemia/reperfusion injury and show reduced renal fibrosis in the unilateral ureteric obstruction model. However, the contribution of CypD in arteriosclerotic acidosis (AA) induced AKI or AA-induced chronic kidney disease (CKD) is unknown. We aim to determine the role of CypD in: 1) acute AA-induced necroptosis (NAP); and 2) chronic AA.

Methods: Groups (n=10) of CypD-/- and wild type (WT) C57BL/6J mice were used. Study 1: Mice were given an intraperitoneal (IP) injection of 5mg/kg AA and killed 3 days later. Study 2: Mice were given IP injections of 2mg/kg AA every 2nd day and killed on day 28. Controls were untreated.

Results: Study 1: Acute high dose AA caused renal failure in WT mice (39.7±1.1mmol/L vs 13.5±2.2mmol/L serum creatinine (Scr) in controls; P<0.0001) with evidence of tubular damage and cell death on PAS sections and increased cleaved caspase-3+ cells. Acute AA also caused inflammation with infiltrating neutrophils and T cells and up-regulation of IL-36α mRNA levels. CypD-/- mice were protected from AA-induced acute renal dysfunction (9.5±1.4 mmol/L SCr; P<0.0001 vs WT AAN). CypD-/- mice showed reduced tubular damage and cell death in PAS sections and reduced cleaved caspase-3+ cells (both P<0.001 vs WT AAN), as well as reduced neutrophil infiltration and IL-36α mRNA levels (both P<0.001 vs WT AAN).

Study 2: Chronic AA administration caused renal impairment in WT mice (34.3±9.9 mmol/L Scr), with evidence of chronic tubular damage (KIM-1 & α-klotho matrix accumulation, increase in tubular cell death (cleaved caspase-3+ cells), and significant renal fibrosis (increased collagen IV deposition). However, CypD-/- mice were not protected from chronic AA-induced renal dysfunction (37.0±1.4 mmol/L Scr; P=NS) and showed no reduction in tubular damage, cell death or renal fibrosis.

Conclusions: CypD contributes to tubular cell death and renal inflammation in acute AA. However, CypD does not contribute to the transition of AKI to CKD in chronic AA.

TH-PO032

Succinate Dehydrogenase Plays a Critical Role in Hypoxia/Reoxygenation-Induced Apoptosis in Renal Proximal Tubular Cells

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Background: Acute kidney injury (AKI) has become a worldwide public health problem because high risk of death and progression to chronic kidney disease. Renal ischemia-reperfusion injury (IR) is one of the major causes of AKI. Many pathological factors and mechanisms are involved in IR injury. Among them, overproduced reactive oxygen species (ROS) plays an important role in mitochondrial dysfunction and endoplasmic reticulum stress (ERS) which finally lead to the cell apoptosis. Succinate dehydrogenase (SDH) is an intermediate both of the mitochondrial citric acid cycle and electron cycle transport. Recent studies demonstrate that ischemia-related succinate accumulation followed by increased SDH activity after reperfusion as key drivers of ROS formation in heart and brain IR injury. But it is still unclear and controversial in kidney IR injury. We hypothesized that accumulated succinate during hypoxia and increase SDH activity during reoxygenation contribute to a large burst of ROS. Increased ROS levels induced mitochondrial damage and ERS which finally lead to cell apoptosis.

Methods: For hypoxia/reoxygenation, renal proximal tubular cells (RPTC) were cultured in hypoxic conditions for 4 hours followed by normoxic conditions for 2 hours. Succinate abundance, SDH activity were assessed by kits and mitochondrial ROS was assessed by confocal. Mitochondrial function and dynamics were assessed by measuring mitochondrial membrane potential (ΔΨm), ATP content, Mn2+/Drp1 expression and mitochondrial morphology. ATP was assessed by TUNEL assay and Caspase-3 activity.

Conclusions: Inhibition of SDH activity can attenuate hypoxia/reoxygenation induced ROS overproduction, mitochondrial dysfunction, ERS and apoptosis in RPTC. Our findings provide a new perspective in treating renal ischemia-reperfusion injury.

Funding: Government Support - Non-U.S.

TH-PO033

GSK3β Regulates Toxic Nucleophosmin (NPM)-T95 Phosphorylation During Ischemic AKI

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Background: GSK3β promotes regulated renal cell death partly by phosphorylating and activating Bax. Here, we document that GSK3β also phosphorylates and activates NPM, a key Bax chaperone, during ischemic renal injury in vitro and AKI in vivo. We hypothesize that: (1) antagonizing NPM phosphorylation is effective for ameliorating acute renal cell injury that contributes to organ failure during AKI and (2) phosphorylated NPM detects acute renal cell injury.

Methods: To determine the extent to which GSK3β mediates ischemia-induced NPM phosphorylation, constitutively active or inactive GSK3β mutant proteins were expressed in primary murine and human proximal tubule cells (PTEC). GSK3β was also subjected to pharmacological inhibition by TDZD-8 or CRISPRi-mediated knockdown. GSK3β activity was estimated from steady state p-NPM-T95 content and correlated with intracellular NPM localization and cell survival.

Results: Transfection of primary PTEC with constitutively active, inactive or wild type GSK3β resulted in an expected increase in total GSK3β content compared with empty vector. In contrast, CRISPRi caused an 80% reduction in GSK3β expression. TDZD-8 decreased GSK3β kinase activity without affecting its content. Only active GSK3β promoted NPM T95 phosphorylation, NPM translocation from the nucleus to the cytosol was significantly correlated with cell death during ischemia. Both TDZD-8 and CRISPRi- mediated GSK3β knockdown significantly reduced NPM T95 phosphorylation and cell death induced by constitutively active GSK3β. Furthermore, T95 NPM is detectable in both urine and cortical kidney homogenates harvested from humans and mice within hours after renal ischemia.

Conclusions: GSK3β promotes ischemia-induced renal cell death by phosphorylating an activating NPM, an essential partner for Bax during regulated cell death. Thus, manipulation of NPM phosphorylation is likely to be an effective therapeutic maneuver after inducing AKI and phosphorylated NPM is a novel marker of acute renal cell injury.

Funding: NIDDK Support

TH-PO034

SIRT5 Alleviates Ischemia-Induced Mitochondrial Dysfunction in Human Proximal Tubular Epithelial Cells

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Background: Acute kidney injury (AKI) is a major global health concern with a high mortality and poorly effective therapies. The most common cause of AKI is renal hypoperfusion, leading to ischemia/reperfusion injury (IRI). Mitochondria are highly dynamic organelles required for energy production that undergo constant fission and fusion to meet metabolic requirements. Accumulating evidence has identified excessive mitochondrial fragmentation causing mitochondrial dysfunction as a central pathologic feature of IRI. Recently, the mitochondrial NAD+-dependent lysine-desuccinyllase/demalonylase sirtuin 5 (SIRT5) has emerged as a key regulator of mitochondrial form and function, but its role in renal IRI is still unknown.

Methods: Male C57Bl/6J mice underwent renal IRI or sham-surgery. Kidneys were screened for SIRT5 by immunohistochemistry. Human proximal tubular (PT) cells (HKC-8) were exposed to oxygen/nutrient-deprivation (OND; 1%O2,4%H2S), in an in vitro model developed to mimic renal ischemia in vivo, and analysed by qPCR and Western blot (WB). A SIRT5 RNA interference (RNAi) strategy combined with OND was applied, followed by assessment of mitochondrial form and function using confocal/ transmission electron microscopy, ATP assay, Seahorse, FACs and WB.

Results: SIRT5 expression was increased in human PTs after renal IRI and in HKC-8 cells exposed to OND. Knockdown of SIRT5 in HKC-8 cells exposed to OND induced mitochondrial fragmentation (Miro1 and PGC1α) and decreasing pro-fusion proteins (Mfn1 and OPA1), and that this effect was exacerbated by OND. Finally, combining the OND model with SIRT5 RNAi showed that SIRT5 reduced mitochondrial swelling and increased respiration (OXPHOS) to improve mitochondrial function in PT cells exposed to ischemia.

Conclusions: Our findings suggest SIRT5 is a central component of the endogenous stress response that alleviates ischemia-induced mitochondrial dysfunction in PTs and, therefore, may be a promising therapeutic target in AKI.

Funding: Commercial Support - Astrazeneca, Private Foundation Support
Sirt3 Modulates Fatty Acid Oxidation and Attenuates Cisplatin-Induced AKI in Mice

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Background: Acute kidney injury (AKI) induced by cisplatin is very common in the clinic. Fatty acid oxidative damage is an important mechanism of renal fibrosis. Sirt3 has been shown to alleviate AKI by improving mitochondrial function and was found to be involved in the regulation of fatty acid oxidation (FAO) in other disease models. However, it is not clear whether Sirt3 is involved in regulating FAO to improve the prognosis of AKI.

Methods: Male SV129 and Sirt3 knockout (KO) mice were administered a single intraperitoneal (i.p.) injection of cisplatin (20 mg/kg) with or without treatment with fis1 (5 mg/kg/day). Additionally, cultured mouse renal tubule epithelial cells (mRTecs) were treated with cisplatin (5 µM). Then, FAO and renal injury were evaluated.

Results: Oil red O staining and free fatty acids (FFA) analysis of kidney tissues from WT cisplatin-treated mice showed fatty acid oxidative damage and extensive lipid deposition in the mice. Metabolomics analysis revealed decreased ATP production and the presence of disordered energy metabolism. Additionally, fatty acid accumulation induced the apoptosis of mRTecs. The expression of Sirt3 was decreased in mice with cisplatin-induced AKI compared to that in control mice. Sirt3 deletion aggravated FAO dysfunction, resulting in the increased apoptosis of kidney tissues and aggravated renal injury. The activation of Sirt3 by honokiol improved FAO and renal function and reduced fatty acid deposition. In vivo experiments confirmed that Sirt3 regulates fatty acid oxidation by deacetylating LKB1 and activating AMPK. In addition, Sirt3 increased ATP production and reduced ROS and lipid peroxidation by improving mitochondrial function.

Conclusions: These findings indicate that activated Sirt3 could protect against cisplatin-induced acute kidney injury, possibly by improving FAO and mitochondrial function, and that improving FAO in AKI may be a potential therapeutic strategy in the future.

Funding: Government Support - Non-U.S.

Sirtuin 3 Suppresses Ferroptosis in Cisplatin-Induced AKI

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Background: Sirtuin 3 (SIRT3) is a mitochondrial deacetylase that protects against acute kidney injury (AKI) by mitigating renal oxidative stress. Ferroptosis, a recently discovered form of programmed cell death that is characterized by iron-dependent accumulation of reactive oxygen species, has been shown to alleviate AKI by improving mitochondrial function and was found to be involved in the regulation of fatty acid oxidation (FAO) in other disease models. However, it is not clear whether Sirt3 is involved in regulating FAO to improve the prognosis of AKI.

Methods: Male 129 wild type (WT) and SIRT3 knockout (KO) mice received a single intraperitoneal injection of cisplatin (20 mg/kg) with or without treatment with fis1 (5 mg/kg/day). Additionally, cultured mouse renal tubule epithelial cells (mRTecs) were treated with cisplatin (5 µM). Then, FAO and renal injury were evaluated.

Results: Oil red O staining and free fatty acids (FFA) analysis of kidney tissues from WT cisplatin-treated mice showed fatty acid oxidative damage and extensive lipid deposition in the mice. Metabolomics analysis revealed decreased ATP production and the presence of disordered energy metabolism. Additionally, fatty acid accumulation induced the apoptosis of mRTecs. The expression of Sirt3 was decreased in mice with cisplatin-induced AKI compared to that in control mice. Sirt3 deletion aggravated FAO dysfunction, resulting in the increased apoptosis of kidney tissues and aggravated renal injury. The activation of Sirt3 by honokiol improved FAO and renal function and reduced fatty acid deposition. In vivo experiments confirmed that Sirt3 regulates fatty acid oxidation by deacetylating LKB1 and activating AMPK. In addition, Sirt3 increased ATP production and reduced ROS and lipid peroxidation by improving mitochondrial function.

Conclusions: These findings indicate that activated Sirt3 could protect against cisplatin-induced acute kidney injury, possibly by improving FAO and mitochondrial function, and that improving FAO in AKI may be a potential therapeutic strategy in the future.

Funding: Government Support - Non-U.S.

Myeloid Ferritin Heavy Chain Protects Against Ferroptosis in Ischemic AKI


Background: Ferritin is classically involved in iron storage and metabolism and is made up of 24 subunits of two distinct types: light chain (FL) and heavy chain (FH). The latter confers ferroxidase activity, allowing for storage of iron in a safe, bioavailable form in the ferritin core. Iron metabolism is an important part regulated by myeloid cells. Furthermore, acute kidney injury (AKI) causes perturbations in iron metabolism, both highlighting the importance of studying the importance of FH in preventing oxidative damage during AKI.

Methods: Previously characterized mice deficient in myeloid-FH (FH<sup>−/−</sup>) and their floxed controls (FH<sup>fl/fl</sup>) were subjected to bilateral renal ischemia-reperfusion injury (IR; 20 minutes). We measured renal function, inflammatory response, cell death, and cell proliferation on days 1 and 2 post-IR.

Results: Though FH<sup>−/−</sup> and FH<sup>fl/fl</sup> mice both showed a similar rise in serum creatinine (S/CoX), FH<sup>−/−</sup> mice revealed a substantial rise in myeloperoxidase (MPO) levels over FH<sup>fl/fl</sup> mice (1.6 ± 0.12 mg/dL) and structural damage on day 1 following IR, renal function and damage in myeloid-FH deficient
Funding: NIDDK Support

TH-PO040

Identification of Anti-Ferroptosis Drugs Functioning as Lipid Peroxyl Radical Scavengers and Its Protective Effect Against AKI

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Background: Ferroptosis, a lipid oxidation-dependent cell death mediated by free radical reactions, is a therapeutic target because of its role in organ damages including acute kidney injury (AKI). Ferroptosis-causing radicals that are targeted by ferroptosis suppressors have not been unequivocally identified. Because certain cytochrome P450 (CYP) substrate drugs can prevent lipid peroxidation via obscure mechanisms, we evaluated their anti-ferroptotic potential and used them to identify ferroptosis-causing radicals.

Methods: We screened of CYP substrate compounds by a cell-based assay to identify drugs with anti-ferroptotic activity, and investigated the mechanism. Radical scavenging activity was evaluated using ESP-spin trapping methods and NBD-Pen, a lipid radical probe that we established. We evaluated the therapeutic potency of the drugs in mouse cisplatin-induced AKI models.

Results: We identified clinically-available various drugs and hormones with anti-ferroptotic properties including rifampicin, promethazine, onaprazole, indole-3-carbinol, carnosine, propionate, etretinate, and thyroid hormones. The anti-ferroptotic effects of the drugs were closely associated with the scavenging activity of lipid peroxyl radicals and not much related to interactions with other radicals. The elevated lipid peroxyl radical levels were associated with ferroptosis onset, and known ferroptosis suppressors such as ferrostatin-1 were also lipid peroxyl radical scavengers. The drugs showed anti-ferroptotic effect in various types of cells including tubular cell, podocyte, and renal fibroblast. Moreover, the drugs suppressed tissue lipid peroxidation and ameliorated cisplatin-induced renal injury.

Conclusions: The elevated lipid peroxyl radical would be a trigger for onset of ferroptosis, whereas lipid peroxyl radical scavenging drugs can control ferroptosis-related disorders including AKI.

TH-PO041

Asparaginyl Endopeptidase Deficiency Protects Against AKI via Inhibition of Tubular Ferroptosis

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Background: Lysosomal endopeptidase AEP (Asparaginyl Endopeptidase) is required for the maintenance of normal kidney physiology and homeostasis; AEP knockout aggravates intestinal fibrosis in the mouse model of obstructive nephropathy. However, role and underlying mechanism of AEP in the acute kidney injury (AKI) is unclear.

Methods: AKI was induced by bilateral ischemia–reperfusion of renal arteries or folic acid treatment in AEP+/+ and AEP−/− mice. We assessed the indexes of renal tubular injury, inflammatory infiltration and programmed cell death. Tubular injury markers Kin-1 and NAGL was measured as well. In vitro, ferroptosis was evaluated via assessment of MDA, 4-HNE and degradation of GPX4. In vitro, we compared hypoxia- or erastin-induced ferroptosis in the primary tubular cells isolated from AEP+/+ and AEP−/− mice. Supplement of FAC and downregulation of GPX4 were used to evaluate the role of AEP in hypoxia- or erastin-induced ferroptosis. In addition, we analyzed the hypoxia-induced degradation of GPX4 in TCM. Coimmunoprecipitation was used to determine the interaction between AEP and GPX4.

For tentative treatment, a synthetic AEP inhibitor RR-11a was delivered by AEP-targeted nanoparticles was used in the IRI model.

Results: AEP deficiency attenuated IRI-induced tubular injury, inflammation and programmed cell death compared with control. Ferroptosis, a regulated necrosis characterized by the accumulation of iron-dependent membrane lipid peroxides. At present, ferroptosis is widely studied in rhabdomyolysis and ischemia/reperfusion-induced acute kidney injury (AKI), but the research on nephropathic AEP is not well enough. In this study, we explore whether ferroptosis occurs in cisplatin-induced AKI and the effect of paracilcalciton on ferroptosis.

Funding: Government Support - Non-U.S.

TH-PO042

Pretreatment with Roxadustat (FG-4592) Attenuates Folic Acid-Induced Kidney Injury by Decreasing Ferroptosis

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Background: Folic acid (FA)-induced kidney injury model is characterized by progressive tubular damage at early stage and interstitial fibrosis at later stage. Ferroptosis, has been thought to be one of the main causes for the acute kidney injury (AKI) by the iron-dependent accumulation of lipid peroxidation, therefore disrupting antioxidant defense system. FG-4592 is hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor (HIF-PHI) often used for improving anemia in patients with chronic kidney disease (CKD) through activating HIF-1α. What is more, precondition HIF-1α can enhance antioxidant capacity and iron mobilization through Nuclear erythroid 2 related factor 2 (Nrf2) signaling. Nrf2 is a key transcriptional factor which regulates almost all genes that are associated with ferroptosis. Given its anti-oxidant roles, FG-4592 was introduced in this study as a preconditionor to see if it had effects on FA-induced AKI and the mechanism.

Methods: Mice were divided into 4 groups, control group (n=12); FG-4592 group (n=12) pretreatment with FG-4592 for 2 days, mice were sacrificed 2 days (n=6 per group) or 4 days later (n=6 per group); FA; (folic acid-induced kidney injury) group (n=12); FA + FG-4592 group (n=12). In FA and FA+FG-4592 groups, mice were sacrificed 2 days (n=6 per group) or 4 days later (n=6 per group) after folic acid injection. Renal function, renal morphology, MDA, 4-HNE, GSH, Fe, HIF-1α, Nrf2, GPX4, HO-1, SLC7A11, ferroptosis, IL-1β,TNF-a,F4/80, F4/80,Vimentin were assessed.

Results: pretreatment with FG-4592 improved kidney injury and inflammation in FA-induced kidney at early stage by upregulating antioxidative enzymes (GPX4 and HO-1) and GSH, meanwhile downregulating lipid peroxidation (MDA and 4-HNE) and iron. Furthermore, FG-4592 activated Nrf2 and upregulated antioxidant enzyme (GPX4 and HO-1), SLC7A11 (responsible for GSH synthesis) and ferroportin (an iron export protein) resulting in a reduction of ferroptosis. Further studies showed that Nrf2 was up-regulated by increased AKT and GSK-3β phosphorylation. Finally, pretreatment with FG-4592 ameliorated kidney fibrosis at later stage after FA-induced kidney injury.

Conclusions: pretreatment with FG-4592 plays an important role in the prevention of the transition from AKI to CKD through Nrf2-mediated anti-ferroptosis, and pretreatment with FG-4592 prevents FA-induced kidney injury partially via the AKT-GSK-3β-mediated Nrf2 activation.
Insights into the Pathophysiological Role of Gaseous Molecules in Acute Kidney Injury

**TH-PO044**

**Insights into the Pathophysiological Role of Gaseous Molecules in Acute Kidney Injury**

**Objective:** To investigate the role of gaseous molecules in the pathophysiology of acute kidney injury (AKI).

**Methods:** Utilized in vivo and in vitro models of AKI to study the effects of gaseous molecules on kidney function and structure.

**Results:** Observations included alterations in gaseous molecule levels and their correlation with AKI severity.

**Conclusions:** Gaseous molecules play a crucial role in AKI pathophysiology, offering potential therapeutic targets.

**Funding:** Supported by NIH grants.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
endothelial cells have intrinsic signaling properties that impair growth and angiogenesis, thereby contributing to poor vascular repair.

Methods: Rat or mouse primary endothelial cells (rKEC) or mKEC were isolated using Dynabeads conjugated to CD45 (negative selection) and CD31 (positive selection) antibodies. Cells were grown in EM2 (Lonza) on collagen-coated plastic to evaluate growth rates (MTT) or placed on Matrigel to quantify branching capacity.

Results: Previous studies demonstrated that rKEC grew slower than rat pulmonary EC (rPEC). rKEC consistently grew slower (~5% increase in cell number between day 1-4) than EC from brain, spleen or aorta (~60-100%, p<0.01 vs rKEC). rKEC could not form branching structures on matrigel, but integrated into networks formed by rPEC when plated at a 1:100 ratio (KEC to rPEC). Increasing ratios of rKEC:rPEC lead to a decline in branch formation with no rPEC branches at a ratio of 50:50. Co-culture of rKEC also inhibited branching of rat brain and aortic EC and human cord blood derived endothelial colony forming cells (ECFC), while EC from other tissues did not convey similar inhibitory activity. Increasing rKEC proliferation with HiTERT overexpression did not attenuate rKEC’s ability to disrupt branch formation of ECFC. We hypothesized that KEC secrete an anti-angiogenic factor which may impair cell growth. Conditioned media (CM) isolated from rKEC reduced growth of the highly proliferative human ECFC, by ~50% (p<0.001). Similar CM isolated from primary mKEC decreased ECFC growth by ~50–% (p<0.001). CM isolated from mouse heart or lung EC did not contain inhibitory activity. Specifically, only the extracellular vesicle (EV) fraction isolated from mKEC inhibited growth (40% decrease, p<0.001), while the EV depleted supernatant had no effect on ECFC proliferation.

Conclusions: Kidney endothelial cells possess an anti-angiogenic activity that is not observed in EC from other tissues. EV secreted from KEC may contain anti-angiogenic cargo that slow EC growth in vitro. Such activity may underlie impaired renal vascular growth by ~50% (p<0.001).

Funding: NIDDK Support, Other NIH Support - NIH/NHLBI R01HL1 29843-01, Private Foundation Support

TH-PO049

PAC-Mediated AKI Protection Is Critically Mediated but Does Not Exclusively Depend on Cell-Derived Microvesicles

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Background: Acute Kidney Injury (AKI) significantly worsens the prognosis of hospitalized patients. In recent years, cell-based strategies have been established as reliable option for improving AKI outcomes in experimental AKI. Own studies focused on so-called Proangiogenic Cells (PACs). Mechanisms that contribute to PAC-mediated AKI protection include production / secretion of extracellular vesicles (EV). In addition, the cells most likely act by paracrine processes (secretome). The current study evaluated whether AKI may be preventable by the administration of either PAC-derived EV and / or the secretome alone.

Methods: AKI was induced in male C57/Bl6n mice (8-12 weeks) by bilateral renal ischemia (IRI - 40 minutes). Syngeneic murine PACs were stimulated with either melatonin, Angiopoietin-1 or -2, or with Bone Morphogenic Protein-5 (BMP-5) for one hour, respectively. The four mediators were chosen since previous own studies showed improved PAC-mediated AKI protection after cell preconditioning with these substances. PAC-derived EV and the vesicle-depleted supernatant were subsequently collected and i.v. injected post-ischemia. Mice were analyzed 48 hours later.

Results: IRI induced significant kidney excratory dysfunction as reflected by higher serum cystatin C levels. The only measure that improved AKI was the injection of EV, collected from native PACs. The following conditions worsened post-ischemic renal function even further: EV-Ang-1, EV-BMP-5, EV-melatonin, and EV-secretome-Ang-1.

Conclusions: Together, our data show that PAC-mediated AKI protection substantially depends on the availability of cell-derived EV. The secretome, either collected from native or preconditioned cells does not prevent mice from ischemia-induced dysfunction. However, since previous data showed improved AKI-protection by PACs after cell preconditioning with certain mediators (Ang-1 and -2, melatonin, BMP-5), other than exclusively vesicle-dependent mechanisms must be involved in PAC-mediated AKI protection. We suggest, that the mere presence of intact cells in the post-ischemic tissue is necessary for improving functional and structural outcome parameters under certain conditions.

TH-PO050

Microparticles Released in Response to Oxidative Stress from the Renal Epithelium Carry Active Neprilysin

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Background: Acute kidney injury (AKI) is associated with significant morbidity, including remote organ dysfunction. In response to stress, cells release phenotype- and quantitatively distinct microparticles (MP). MP are microvesicles (1000 nm) derived from cell organelles (ECFC), which are released in response to stress or injury. Neprilysin (CD10), is a membrane-bound zinc activated endopeptidase, richly expressed in the renal proximal tubular epithelial cell (RPTEC) brush border. Neprilysin catalyzes the degradation of endogenous vasodilator/natriuretic peptides suggesting that its physiological action mediates the renal homeostasis. Whether MP containing neprilysin released by renal epithelium can be mediators of biological activity is not known.

Methods: Human RPTEC immortalized cell line was used. Cells were exposed to 0.03 molar H2O2, for 1 hour and compared to controls in 3 or more different sets of experiments. We evaluated the levels of neprilysin using an ELISA assay and enzymatic activity with a fluorometric assay. Human samples (citrated plasma) were tested for the presence of biologically active neprilysin (Neprilysin levels and peptidase assay) derived from prospectively collected samples in AKI cases and controls.

Results: We have shown that neprilysin is present in RPTEC using immunofluorescence. We also reported that under conditions of oxidative stress the level of released MP is significantly different when compared to controls. To evaluate if the released MP are biologically active, we assessed the protease activity characteristic of neprilysin. The results showed that the maximal activity of neprilysin was in healthy cells and was 5-fold lower after treatment with oxidative stress. We then evaluated the protease activity in MP released from RPTEC under the same conditions. Our results showed that the peptidase activity was present and the activity correlated directly with the protein concentration. In a pilot of 30 cases and controls of AKI, we were able to measure the levels of plasma neprilysin using the ELISA assay as well as the confirm the peptidase activity in the MP derived from human samples.

Conclusions: The release of Neprilysin in microparticles derived from renal tubular epithelial cells are functionally active, and could serve as a biological link between epithelium and micro-vasculature.

Funding: Clinical Revenue Support

TH-PO051

Long-Term Outcome of Biopsy-Proven Cholesterol Crystal Embolism

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Background: Cholesterol crystal embolism (CCE) causes renal damage, and there is an extremely high risk of end-stage renal disease. However, the time course of CCE-related renal deterioration varies and little is known about the subsequent risk of dialysis among patients with biopsy-proven CCE.

Methods: We performed a retrospective cohort study of 38 Japanese patients in whom a histological diagnosis of CCE was made from September 1992 to July 2005. Competing risk regression analysis was used to investigate the association between declining renal function (a 1.5-fold elevation of serum creatinine within 26 weeks after CCE) or its subtypes (acute [<1 week after CCE], subacute [1 to ~6 weeks], and chronic [6 to ~26 weeks]) and the risk of dialysis, with adjustment for age, baseline serum creatinine, and the precipitating event.

Results: During a median follow-up period of 25.9 weeks, 14 patients (35.9%) started dialysis. Multivariable analysis showed that patients with declining renal function had a higher risk of commencing dialysis than those without declining function (subdistribution hazard ratio [SHR]: 9.47; 95% confidence interval [CI]: 1.34-66.8). Patients with different renal presentations had a similarly increased risk of commencing dialysis, with the risk being significantly higher for the subacute and chronic patterns of declining renal function (adjusted SHR [95% CI] for acute, subacute, and chronic declining renal function vs. no decline: 7.36 [0.85-63.0], 11.9 [1.36-101], and 10.7 [1.49-77.0], respectively).

Conclusions: Declining renal function after CCE, even later than 6 weeks, was significantly associated with the subsequent risk of dialysis.
**TH-PO052**

**Urinary Neutrophil Gelatinase Associated Lipocalin Is Elevated in Neonates Who Develop AKI After General Surgical Procedures**

*Cara L. Slagle, Kelli A. Krallman, Brennan Pointdexter, Alexandra Schmerge, Bradley S. Gerhardt, Melinda Tepe, Meera Kotagal, Alexander Bondoc, Stuart Goldstein. Cincinnati Children’s Hospital Medical Center; Cincinnati, OH.*

**Background:** Acute Kidney Injury (AKI) occurs commonly in critically ill neonates after surgery. AKI diagnosis by serum creatinine and urine output has significant limitations in this population. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) has been shown to predict AKI in many pediatric cohorts, but no study has assessed uNGAL performance to predict AKI in neonates after general surgical intervention.

**Methods:** Infants undergoing a surgical procedure were prospectively enrolled in this observational study. Urine was obtained pre-operatively and at 12, 24, 36, 48, 72 and 96 hours post-operatively. uNGAL was measured by The uNGAL Test™ (BioPorto, Denmark). AKI was defined by 2014 modified Kidney Disease Improving Outcomes Group (KDIGO) criteria. Mann-Whitney U tests were performed to compare uNGAL levels of AKI and non-AKI groups.

**Results:** A total of 61 neonates had 70 surgical procedures at an average corrected gestational age of 41 weeks (SD: ±8 weeks). AKI occurred in 18 (25%) patients. uNGAL levels above the published normative values occurred after 41 (58%) procedures - in 72 (71%) patients with AKI and in 28 (34%) patients without AKI. Post-op uNGAL values were elevated in infants with AKI with peak uNGAL values most commonly occurred approximately 48 hours after surgical intervention. (Table 1). The AUC-ROC for uNGAL to predict AKI at 48 hours was 0.74 (0.61-0.88).

**Conclusions:** Elevation of uNGAL occurs at 36-72 hours post-operatively in neonates who develop AKI after general surgical procedures. A substantial proportion of non-AKI patients had elevated uNGAL levels suggesting potential sub-clinical renal insult and this relationship should further be explored. Few patients were premature, however given that normative uNGAL values vary with gestational age, we intend to examine this relationship in the future.

**Funding:** Private Foundation Support

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**Table 1 – Median [IQR] uNGAL levels in patients with vs. without AKI after surgery**

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>AKI (n=34)</th>
<th>Non-AKI (n=27)</th>
<th>Median [IQR] uNGAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>228 [157]</td>
<td>80 [60.5]</td>
<td>228 [157]</td>
</tr>
<tr>
<td>24</td>
<td>332 [209]</td>
<td>100 [70]</td>
<td>332 [209]</td>
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<tr>
<td>36</td>
<td>244 [157]</td>
<td>100 [70]</td>
<td>244 [157]</td>
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<td>244 [157]</td>
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<td>96</td>
<td>244 [157]</td>
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<td>Max</td>
<td>343 [209]</td>
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<tr>
<td>Max (IQR)</td>
<td>343 [209]</td>
<td>100 [70]</td>
<td>343 [209]</td>
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</table>

**TH-PO053**

**Fibroblast Growth Factor 23, a Novel Biomarker for AKI in Patients with Acute Decompensated Heart Failure**

*Nattah Pramong,1 Pongsathorn Gojasaeni,2 Sarunnyo Suttipongkeat,2 Kraiwporn Kiattisunthorn,2 Anutra Chittinandana.11 Bhumibol Adulyadej hospital, Bangkok, Thailand; 2Siriraj Medical School, Mahidol University, Bangkok-noi, Thailand.*

**Background:** Acute kidney injury (AKI) in acute decompensated heart failure (ADHF) is associated with poor prognosis. Recent evidence has proved that early rising of plasma fibroblast growth factor 23 (FGF23) could predict AKI and adverse events in patients undergoing cardiac surgery and critically ill patients, but it remains unknown in ADHF patients. This study aimed to investigate the prognostic value of plasma FGF23 for predicting the occurrence of AKI.

**Methods:** A single center cohort study is performed in patients admitted for ADHF in Bhumibol Adulyadej hospital. Plasma c-terminal FGF23 (c-FGF23) was measured 2 times at baseline and 24 hours later after diagnosing ADHF. Serum creatinine was measured every other day or more frequently as appropriate according to general treating standards and AKI was assessed and defined using KDIGO criteria.

**Results:** The study enrolled 62 patients diagnosed with ADHF. The incidence of AKI is 45% and significantly increased risk of death. Patients who developed AKI had significantly higher levels of plasma c-FGF23 at baseline in comparison with AKI-free patients (median value 1,258.5 µg/L vs. 230.2 µg/L, p = 0.005). During the first 24 hours, plasma c-FGF23 levels in AKI-free group decreased more than AKI group, but the difference is not statistically significant. ROC analysis of both first time and second time of plasma c-FGF23 collecting yielded an AUC of 0.71 for prediction of AKI incident. With the cut-off point at 450 RU/mL, the sensitivity and specificity of plasma c-FGF23 at baseline for predicting AKI were 71.4% and 61.8% respectively.

**Conclusions:** Plasma c-FGF23 may serve as a novel biomarker for incident of AKI in patients with acute decompensated heart failure which should be measured immediately or within 24 hours after diagnosing ADHF.

**Funding:** Government Support - Non-U.S.

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**TH-PO054**

**Serum Cystatin C on Admission: A Potential Predictor for Hospital-Acquired AKI in Patients with an Acute Exacerbation of Chronic Obstructive Pulmonary Disease**

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**Background:** Hospital-acquired acute kidney injury (HA-AKI) was associated with poor prognosis. In this study, we performed to determine whether serum Cystatin C on admission could predict AKI in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

**Methods:** This study was conducted from January 2014 to January 2017, and data from adult inpatients with AECOPD were analyzed retrospectively. A total of 1035 patients were included, 79 patients were identified with HA-AKI. Univariate and multivariate logistic regression analyses were used for investigating the predictors for HA-AKI in patients with AECOPD.

**Results:** Prevalence of HA-AKI was 7.6%. HA-AKI was also associated with poor prognosis and was an independent risk factor for inpatient mortality for patients with AECOPD. Compared with patients without AKI, age, and the level of urea, Cystatin C, and platelet count on admission were four independent factors for HA-AKI in patients with AECOPD. Cystatin C (OR, 5.22; 95% CI, 2.49-10.95; P < 0.001) was the independent and significant predictor for AKI in patients with AECOPD. HA-AKI in patients with AECOPD could be identified with a sensitivity of 73.5% at specificity of 75.9% (AUC = 0.803, 95% CI 0.747 - 0.859) by Cystatin C (cut-off value = 1.3 mg/L). In addition, HA-AKI in patients with AECOPD could be identified with a sensitivity of 75.9% at specificity of 82.0% (AUC = 0.853, 95% CI 0.810 - 0.890) by the model.

**Conclusions:** Serum Cystatin C on admission may be adopted to predict the potential risk of HA-AKI in patients with AECOPD.

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**TH-PO055**

**Urinary Activin A: A Novel Biomarker for Monitoring the Severity of AKI in Patients with AECOPD**

*Izumi Nagayama, Akito Maeshima, DaiSuke Nagata, Jichi Medical University, Shottsukke, Japan.*

**Background:** Acute kidney injury (AKI) is a common but complex condition that is associated with increased morbidity and mortality. There is a need for biomarkers to predict AKI development and severity in critically ill patients. We previously reported that urinary activin A, which was almost undetectable in pre-renal AKI, rapidly decreased before the normalization of serum creatinine, NGAL, alpha-1 microglobulin, but not with L-FABP, urinary protein, serum creatinine, and serum albumin. There was a significant correlation of urinary activin A level with urinary NGAL, NAG, and alpha-1 microglobulin, but not with L-FABP, urinary protein, serum creatinine, and serum albumin in one patient with drug-induced AKI who recovered renal function to normal, urinary activin A rapidly decreased before the normalization of serum creatinine, NGAL and L-FABP. In another patient with AKI due to contrast nephropathy, who did not recover renal function, urinary activin A remained at high level at 1 month after the initiation of hemodialysis therapy.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusion: Urinary activin A can be detected in human with AKI and might be a useful and non-invasive biomarker for monitoring the severity of AKI.

Funding: Government Support - Non-U.S.

TH-PO056

Description of [TIMP-2] [IGFBP7] Significative Values at 72 Hours After Cardiac Surgery for Predicting AKI

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Background: AKI is common in critically ill patients and has been identified as an independent mortality predictor. Multiple biomarkers has been discovered in order to improve tools for AKI diagnosis. The aim of this study was AKI within the first 72 hours after cardiac surgery. Secondary endpoints were severity of AKI within 72 h, need for RRT, length of stay in the ICU and death during the ICU stay in relation with [TIMP-2] [IGFBP7].

Methods: Observational, prospective study. Patients 18y, with or without AKI who underwent cardiac surgery, June to December 2016. A statistical analysis was performed. Urine samples for measurement of [TIMP-2] [IGFBP7] were collected 4 h after ICU admission. High risk for AKI was defined as urinary [TIMP-2] [IGFBP7] 0.3 (ng/mL)2/1000.

Results: 383 patients, 77 (20.1%) developed AKI within 72 h. At baseline (pre-ICU) age was AKI group [67 (58 – 74) vs 74 (70 – 80); p<0.0001]. The diuretic use [122 (41.5%) vs 42 (56.8%); p=0.026]. Vancomycin during the surgery was significantly higher in the AKI group [6 (6 – 14) vs 3 (1 – 10); p<0.0001]. The prevalence at 72 h of ICU admission was 77 (20.1%) patients and the severity AKI 1 60 (15.7%) patients, AKI 2 11 (2.9%) patients and AKI 3 6 (1.6%) patients. In those patients with AKI within 72 hours and [TIMP-2][IGFBP7] >0.3 (ng/mL)2/1000 had higher significantly FB in the first 6h [2.05 ± 1.93 vs 252.97 ± 761.26; p=0.016]. Cardiac arrest [1 (0.3%) vs 6 (8.2%); p<0.0001], reintervention during the ICU stay [6 (6.2%) vs 6 (8.2%); p=0.017], LOS in ICU [7 (6 – 10) vs 9 (7 – 15.5); p<0.0001] and death [52 (17%) vs 23 (29.9%); p=0.015] were significantly higher in the AKI group.

Conclusions: In high risk patients, [TIMP-2][IGFBP7] should be considered together with other clinical parameters to predict AKI and adverse outcomes (Cardiac arrest, Length of stay and death).

TH-PO058

Time of Surgery Is Associated with Greater Increase in Urinary KIM-1 in Patients with Major Elective Abdominal Nonvascular Surgery-Associated AKI

Graziela R. de Souza. Clinical, Sao Paulo University, Sao Paulo, Brazil.

Background: Acute kidney injury (AKI) is a complex syndrome that occurs in a wide variety of surgical situations, and has been associated with the surgery time (ST). The aim of this study is to assess if the ST in patients (pts) developing AKI after major elective abdominal non-vascular surgeries (MEANSV) is associated with the intensity of urinary biomarkers (uBMs) changes after surgery.

Methods: We studied a prospective cohort of MEANSV pts, which did the postoperative (post-op) period in intensive care units (ICU) in a university hospital. AKI diagnosis was made by serum creatinine (Scr) or urinary output (UO) KDIGO criteria. Scr was analyzed in pre-operative period (post-op) and ICU admission. Time of surgery was calculated from time up until ICU discharge. UO was evaluated hourly (mL/kg/h) trough 24 h every day. The uBMs (NGAL, NAGA, KIM-1 and Nephrin - NC) were analyzed in the immediate post-op (time 0, ICU admission) and 12 h after ICU admission. Diagnosis of chronic kidney disease stages IV/V, nephrotoxic drugs use before surgery and ICU stay < 48 h were exclusion criteria.

Results: The sample was composed by 297 pts as 18 y old. The most frequent surgeries were hepatectomy and gastrectomy. Among the 297 pts, 197 (66.3%) developed AKI, mainly KDIGO stage 1 (60% of 197). Using Scr criteria 71 pts were diagnosed, while the UO criteria diagnosed 126 pts (62 pts has simultaneous Scr and UO changes). Eight pts (2.6%) needed hemodialysis. Mortality in AKI pts was 9.1% and without AKI 1.9%, p = 0.0149. Among pts developing AKI 53.3% had SA 300 min. The values of all uBMs were higher at 12 h in pts developing AKI. Among pts developing AKI 53.3% had SA 300 min. The values of all uBMs were similar at time 0, independent of not AKI. At 12 h in KIM-1 values were significantly higher em pts with SA 300 min as compared to < 300 min: 2.42 vs 1.62 mL/g, p = 0.011. The values of NGAL and NC were higher at 12h in the ST ≥ 300 group, but did not reach statistical significance: 214 vs 147 ng/mL for NGAL, p = 0.387 and 18.9 vs 14.6 mL/g, p = 0.223, for NC.

Conclusions: In conclusion, longer ST was associated with increased KIM-1 in MEANSV-Associated AKI pts, suggesting an occurrence of more severe tubular injury.

TH-PO009

Hemoglobin Is a Strong and Independent Predictor of Major Adverse Kidney Events

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Background: Anemia is an established risk factor for acute kidney injury (AKI). However, most prior studies assessed anemia as a dichotomous variable, and were further limited by modest sample sizes, incomplete adjustment for confounders, and failure to account for dialysis and death as competing risks.

Methods: We performed a retrospective cohort study of patients who underwent cardiac surgery (CS) or were admitted to an ICU at two medical centers in Boston, MA, between 2005-2018. We excluded patients with ESRD and those who already had AKI. Our final cohort included 18,784 CS and 30,633 ICU patients. The primary exposure was the most proximal Hgb before surgery or ICU admission. The primary endpoint was any Major Adverse Kidney Event within 7 days (MAKE7) after CS or ICU admission. MAKE7 was defined as an increase of serum creatinine (SCr) ≥100% , dialysis, or death. We used multivariable logistic regression to adjust for potential confounders.

Results: The incidence of MAKE7 was 6% in the CS cohort and 14% in the ICU cohort. In both cohorts, we observed a monotonic increase in risk of MAKE7 with lower
Red Blood Cell Distribution Width and Risk for Contrast-Induced AKI After Percutaneous Coronary Intervention

**Background:** Contrast-induced acute kidney injury (CI-AKI) is a major complication following percutaneous coronary intervention (PCI) and is associated with greater morbidity and mortality. Accumulating evidence suggests that inflammation and oxidative stress play an important role in the development of CI-AKI. Red blood cell distribution width (RDW) is a possible marker of oxidative stress and inflammation. In this study, we performed a systematic review and meta-analysis to investigate the association between RDW levels and CI-AKI after PCI.

**Methods:** We assessed clinical studies through PubMed, Embase, and the Cochrane Library. The reference lists of the retrieved articles were also checked to identify further studies. We included randomized controlled trials comparing RDW and CI-AKI in patients after PCI. The primary outcome was CI-AKI.

**Results:** A total of five observational studies met the inclusion criteria. The pooled population consisted of 2,432 patients. Using multivariable logistic regression analysis, the risk of CI-AKI after PCI (pooled adjusted odds ratio (OR), 1.48; 95% confidence interval (CI), 1.32 to 1.67; I² = 0%) was significantly increased. Subgroup analysis in patients with ST elevation myocardial infarction demonstrated a similar trend (OR, 1.58; 95% CI, 1.35 to 1.85; I² = 0%).

**Conclusions:** Increased RDW is associated with increased risk of CI-AKI after PCI. Further studies are needed to assess the utility of RDW as a risk-stratifier for CI-AKI.

**Funding:** NIDDK Support.
TH-PO063
Predicting AKI After Cardiac Surgery by Using Machine Learning Methods
Po-Yu Tseng,1 David Chih-Yu Yang,2 Far Eastern Memorial Hospital, New Taipei, Taiwan; 1Taipei Veterans General Hospital, Taipei, Taiwan.
Background: Acute kidney injury (AKI) is an important complication of the cardiac surgeries. Small increases in serum creatinine (SCr) after cardiac surgery have been associated with a significant increase in 30-day mortality. A model that accurately estimates a patient’s risk for AKI after cardiac surgery is important in clinical practice. Several risk models have been developed to predict postoperative AKI after cardiac surgery. However, there is less study analyzing clinical big data with the application of machine learning to predict AKI after cardiac surgery.
Methods: We retrospectively enrolled the patients undergoing cardiac surgery (coronary artery bypass graft or valve surgery) in Far East Memorial Hospital from August 2016 to August 2018. The primary outcome was the development of AKI. The following machine learning techniques were used: decision tree, random forest, gradient boosting, and support vector machine. The performance of these techniques was compared with that of logistic regression analysis regarding the area under the receiver-operating characteristic curve (AUC). We also used importance matrix plot and shape value to determine the importance of each variable.
Results: A total of 671 cases received cardiac surgery. AKI developed in 163 (24.3%) patients during the first postoperative week. The highest AUC was 0.829 by the random forest with oversampling. The important matrix plot of random forest revealed that intraoperative urine output, pRBC transfusion during the surgery and preoperative preoperative serum creatinine were the top three variables contribute to the model.
Conclusions: We successfully use the perioperative parameters to develop the predictive model for AKI after cardiac surgery by using machine learning methods.
Funding: Other NIH Support - MOST, Taiwan (108-2633-B-009-001); Taipei Veterans General Hospital (V106D25-003-MY3); National Yang-Ming University School of Medicine (107F-M01); MOE, Taiwan (Center for Intelligent Drug Systems and Smart Bio-devices)

TH-PO064
Central Venous Pressure and the Risk of Diuretic-Associated AKI in Patients After Cardiac Surgery
Ian Mccoy, Maria E. Montez-Rath, Glenn M. Chertow, Tara I. Chang. Stanford University School of Medicine, Stanford, CA.
Background: Clinicians strive to weigh the benefits of diuretic therapy for treating and preventing fluid overload against the risks, including acute kidney injury (AKI) due to excessive or overly rapid diuresis. We hypothesized a lower risk of AKI after diuretic administration in patients with higher central venous pressure (CVP) following cardiac surgery.
Methods: We used the MIMIC-III database to study adults admitted to the post-cardiac surgical intensive care unit between 2001 and 2012, excluding those on maintenance dialysis, at an urban academic medical center. Multivariable logistic regression models included adjustments for demographics, comorbidities, admission diagnosis, procedures (cardiopulmonary bypass, coronary artery bypass grafting, left heart catheterization), medications, and severity of illness (mean arterial pressure, admission creatinine, vasopressor use, mechanical ventilation, and platelet count). Inverse probability treatment weighting estimated the risk of diuretic-induced AKI across tertiles of CVP.
Results: Among 4,164 patients receiving intravenous loop diuretics, in contrast to our a priori hypothesis, the adjusted odds of subsequent AKI were 1.11 (95% confidence interval [CI] 1.08-1.13) times higher per mmHg increase in mean CVP on ICU day 1. This association was log-linear across the entire range of CVP observed. The odds ratios were higher for more severe AKI (KDIGO Stage 1: 1.09 [95% CI 1.06-1.11], KDIGO Stage 3: 1.23 [95% CI 1.15-1.31]). Among the 5,396 patients including those not on intravenous loop diuretics, the risk ratio for AKI with diuretic use was 1.59 (95% CI 1.39-1.82); results did not materially differ when examined by CVP tertile.
Conclusions: Higher rather than lower CVP is an independent marker of AKI risk. Further research should aim to identify better tools to assess volume status and to determine ICU patient groups for whom diuretics can be most safely administered.
Funding: NIDDK Support

TH-PO065
Relation Between Biomarkers of Decongestion and Kidney Function with Outcomes in Acute Decompensated Heart Failure
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Background: In-hospital acute declines in kidney function occur in approximately 20-30% of patients admitted with acute decompensated heart failure (ADHF), but it remains unknown whether these declines are associated with improved or worse outcomes, and whether incorporation of markers of congestion modifies these associations.
Methods: Using data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, multivariable Cox regression models were used to evaluate the association between in-hospital changes in eGFR and changes in brain natriuretic peptide (BNP) and other surrogate markers of congestion including N-terminal prohormone of brain natriuretic peptide, hematocrit, and weight.
Results: Among 3,988 patients over a median 8-month follow-up, in-hospital decline in eGFR was not significantly associated with outcomes (HR=1.09 [95% CI 0.96, 1.24] for death per every 30% decline in eGFR; 1.03 [95% CI 0.95, 1.12] for composite per every 30% decline in eGFR), whereas there was a 24% reduction in risk of death for every halving of BNP (HR=0.76 [95% CI 0.71, 0.83]). There was no significant interaction between decline in eGFR and change in BNP for either death (p-interaction=0.09) or the composite of death or rehospitalization (p-interaction=0.35) (Figure). Decline in eGFR was not found to be significantly associated with either improved or worse outcomes in any subgroups of either increasing or decreasing markers of congestion (p-interaction>0.12 for all subgroups).
Conclusions: Achieving decongestion is an important goal for patients with ADHF and declines in BNP are associated with better prognosis. The prognostic significance of declines in eGFR, however, remains less clear, even if occurring in the setting of achieving decongestion.
Funding: Other NIH Support - NH Training Grant T32 DK077777
TH-PO066
A Modified Renal Angina Index by Using the Kinetic Glomerular Filtration Rate for Predicting AKI
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Background: Reliable prediction of AKI has the potential to optimize its treatment. Recently Goldstein SL et al. proposed an empirical clinical model of renal angina to identify critically ill children who would be at higher risk of AKI. In children the combination of the renal angina index (RAI) and AKI biomarkers has an excellent diagnostic performance. The purpose of this study was to evaluate the performance of a modified RAI using kinetic glomerular filtration rate (keGFR) for the prediction of AKI in a cohort of critically ill adults.

Methods: We included 208 consecutive patients admitted to our medical ICU. Serum creatinine (sCr) was measured every 24 hours for 7 consecutive days following ICU admission. RAI was calculated 24 hours after ICU admission (day 1) using the following formula: Risk level (presence of sepsis, use of vaspressors and/or use of invasive mechanical ventilation, and presence of diabetes mellitus) x Injury level (changes in kidney function based on KeGFR). KeGFR was calculated from the change in consecutive values of sCr using the formula developed by Chen S. We used K/DIGO AKI sCr criteria to diagnose AKI. In patients with no baseline sCr available we back calculated baseline sCr using MDRD equation (for an eGFR = 75 ml/m/1.73m2). We analyzed if a modified RAI score ≥6 points could predict subsequent AKI (after 48 hours).

Results: From 208 patients enrolled in the study 101 patients developed AKI (48.6 %). Age, baseline sCr, and eGFR (CKD-EPI) were not different between patients with AKI and patients without AKI. At 24 hours post ICU admission patients with AKI had lower KeGFR (47.7 ml/m vs. 81.1 ml/m; p < 0.0001). A renal angina index ≥6 points was able to identify individuals who developed AKI after 48 hours of ICU admission, with a ROC-AUC of 0.697 (95% CI 0.626-0.769), p < 0.0001. A Renal Angina Index of ≥6 points had an OR of 9.9 (95% CI 2.65 – 37.11; p < 0.0001) for subsequent development of AKI after 48 hours of ICU admission for both groups. Of those who did not have AKI at admission, 17 developed eGFR (Fig 1) for both groups. keGFR was 85.5 mL/min/1.73 m2 compared to eGFR of 79.5 mL/min/1.73 m2.

Conclusions: A modified renal angina index by using the keGFR provides a clinically feasible methodology to identify critically ill adults at high risk of developing AKI before a rise in serum creatinine occurs. This tool would permit the early identification of AKI to initiate preventive and treatment strategies minimizing extension of kidney injury.

TH-PO067
Using Kinetic GFR to Predict AKI in Pediatric Intensive Care Unit
Shina Menon,1 Stuart Goldstein,2 Rajit K. Basu.1 Seattle Children’s Hospital, Seattle, WA; 2Children’s Hospital & Regional Medical Center, Seattle, WA; 3Children’s Healthcare of Atlanta, Atlanta, GA.

Background: Acute kidney injury (AKI) is common in intensive care unit (ICU). The ability to distinguish between functional and persistent AKI is important. Creatinine (Cr), commonly used for diagnosis is imperfect; combining it with urinary biomarkers may help differentiate the two. Kinetic estimated GFR (keGFR) has been used to predict AKI and likelihood of renal recovery. It uses creatinine values at two time points for a dynamic assessment of renal function. It can improve understanding of AKI trajectory and has been used to predict AKI. There are limited data on its use in pediatrics. We hypothesized keGFR would improve clinical and prognostic information beyond Cr or eGFR (modified Schwartz GFR).

Methods: We performed secondary analysis of data from Acute Kidney Injury in Children Expected by Renal angina and Urinary Biomarkers (AKI-CHURUB), a prospective, observational study of children 3months- 25 years age admitted to ICU. For this analyses, only those with complete data upto day 3 were analyzed. keGFR was calculated on Days 1-3. Functional AKI (fAKI) was defined as return to baseline Cr by Day 3 and persistent AKI (pAKI) was absence of recovery by Day 3. Primary outcome was fAKI and secondary outcomes were AKI stage 2/3 during the first 7 days and fAKI.

Results: 169 patients were analyzed (50% female). AKI at admission was seen in 40 (23.6%). Of those, 23 had fAKI and 13 had pAKI. keGFR pattern was similar to that of eGFR (Fig 1) for both groups. Of those who did not have AKI at admission, 17 developed stage 2/3 AKI during the first 7 days in PICU. Median keGFR for these patients was 85.5 mL/min/1.73 m2 compared to eGFR of 79.5 mL/min/1.73 m2.

Conclusions: AkI diagnosis is mostly dependent on a rise in Cr which is an imperfect and late marker. The key to improving outcome in AKI is early prediction of Cr trajectory and appropriate intervention. Although keGFR has been used in adults for this purpose, our analysis shows that it may not be ready for use in pediatrics. It can be used in conjunction with eGFR to identify AKI patterns but it is not superior to eGFR.
TH-PO069

Novel Algorithm for AKI Detection in Outpatient Settings

Chin-Chi Kuo, Big Data Center, China Medical University Hospital, Taichung, Taiwan.

Background: Existing acute kidney injury (AKI) diagnostic criteria is restricted to inpatients. We proposed an AKI algorithm for outpatients (AKIOPT) and evaluated how AKIOPT modifies the course of chronic kidney disease (CKD).

Methods: The occurrence of AKIOPT was analyzed retrospectively among CKD patients who were enrolled into the pre-dialysis care program in a tertiary hospital in Taiwan. AKIOPT was detected by the definition of a 50% increase in serum creatinine (S-Cre) or a fall in eGFR by 35% in the 180-day period prior to pre-dialysis care program enrollment. Outcomes were progression to end-stage renal disease (ESRD) and all-cause mortality. The association analyses were performed using multiple Cox regression and coarsened exact matching (CEM) analysis.

Results: Among the total of 6064 patients, 31.5% (1905 patients) had ever developed AKIOPT. AKIOPT was associated with 1.78 (95% CI, 1.50, 2.12) and 1.50 (1.32, 1.71), respectively, compared with those without AKIOPT. We found a complete reversal in the eGFR slope before and after the AKIOPT event, modeled using the growth piecewise linear mixed model by incorporating random effects. Blue and orange points represent eGFR measurements before and after the AKIOPT event, respectively.

Conclusions: The new AKIOPT diagnostic algorithm fits the outpatient setting and provides a prognostic significance in patients with CKD.

Funding: Government Support - Non-U.S.

TH-PO070

Development and Validation of a Risk Score for AKI After Cardiac Surgery

Subhash Chander, Shreyak Sharma, Samuel Short, James Rawn, David E. Leaf.
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Background: AKI is a frequent and important complication of cardiac surgery. However, existing prediction models for cardiac surgery-associated AKI are limited by reliance on diagnostic and billing codes, lack of external validation, and inclusion of variables that can only be determined postoperatively (e.g., cardiopulmonary bypass time).

Methods: We performed a retrospective cohort study of ICU patients with AKI in a university hospital, Thailand. Risk factors of 7-day AKI requiring ARRT (7d-ARRT) were derived from the medical records between January 2013 and June 2015 (derivation cohort; der-cohort). We generate an ARRT score by the significant risk factors from the multiple logistic analysis. To find the best model, we applied the area under the receiver operating characteristic curve (AUROC) analysis and Akaike information criterion (AIC). The ARRT score was validated by the data between June 2015 and December 2015 (validation cohort; val-cohort).

Results: The study included 292 patients in a der-cohort and 57 patients in a val-cohort. We found the best model to predict 7d-ARRT was oliguria (<0.5 ml/kg/hr after resuscitation), advanced CKD (eGFR < 45 ml/min/1.73m2) and severity of AKI at ICU admission [der-cohort: AUROC = 0.788, AIC = 201.02, val-cohort: AUROC = 0.845, AIC = 57.04]. These risk factors were used for generation of ARRT score by weighting their score from coefficients value of each risk factors (figure 1). At 4 points of the ARRT score, specificity was 84.2%, 81.6% and sensitivity was 55.8%, 73.7% for der-cohort and val-cohort respectively.

Conclusions: We strongly recommend that ARRT score a 4 points could predict 7d-ARRT. We suggest further large prospective cohort study to validate our ARRT scoring.

Funding: Government Support - Non-U.S.
The Role of Concurrent Major Complications in the Association Between AKI and Survival After Coronary Artery Bypass Grafting Surgery

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Background: Acute kidney injury (AKI) is associated with decreased survival following coronary artery bypass grafting (CABG). In this study, we evaluated the impact of AKI and concurrent major complications on short- and long-term survival after CABG.

Methods: A retrospective study of all isolated primary CABG cases in Iceland in 2001-2013. AKI was defined by the KDIGO criteria and major postoperative complications comprised myocardial infarction, reoperation, stroke, mediastinitis, sternal dehiscence, acute respiratory distress syndrome and multiple organ failure. Patients were divided into four groups: AKI with or without major complications and non-AKI with or without major complications. Survival was plotted by Kaplan-Meier method and 30-day mortality evaluated by logistic regression. Predictors of short- and long-term survival were only evaluated for patients without concurrent major complications using Cox regression.

Results: Of 1710 patients, 184 (11%) developed AKI. Major complications occurred in 21% of the AKI patients compared with 10% non-AKI patients (p=0.001). Overall survival was lower in patients with AKI compared with non-AKI patients (p=0.001). Figure 1. In adjusted analysis, AKI patients with major complications (OR=30.3 [95% CI, 9.1-105.8]) and non-AKI patients with major complications (OR=11.6 [4.2-34.9]) had higher risk of 30-day mortality than non-AKI patients without major complications, while the risk of death for AKI patients without major complications was not significantly increased (OR=3.4 [8.13.3]). AKI was not significantly associated with 5-year mortality (HR=1.4 [0.8-2.4]). However, when the entire follow-up time (median 6 years, range, 0-13.5) was included, AKI predicted higher mortality (HR=1.6 [1.1-2.2]).

Conclusions: AKI associated with decreased survival following CABG. However, this relationship can to a great extent be explained by concurrent major complications, particularly in case of early mortality.

Funding: Government Support - Non-U.S.

Figure 1. Overall unadjusted survival of AKI vs. non-AKI patients categorized based on whether they developed concurrent major complications or not.

Incidence and Risk Factors of AKI After Total Knee Arthroplasty (TKA) or Revision (TKA-R) in Kidney Transplant Recipients (KTx)

Sorkko Thirunavukarsanu, Ziad Zoghby. Mayo Clinic. Rochester, MN.

Background: Kidney transplant recipients have an increased risk of complications following knee arthroplasty and revisions compared to non-transplant patients. The incidence of AKI is reported to be as high as 15.6% and has been associated with increased mortality, morbidity, and length of hospital stays (LOS). Our AIM was to determine the incidence of AKI in KTx recipients undergoing primary knee arthroplasty (TKA) or secondary revision (TKA-R), identify risk factors associated with AKI and evaluate its effect on allograft function at one year.

Methods: Using the orthopedic and transplant databases we designed a case-control study of 82 patients undergoing a total of 101 TKA and knee revisions between 2000 and 2018 at the Mayo Clinic. Information not available through the databases was obtained through chart review. AKI was defined per current KDIGO guidelines.

Results: The average age at surgery was 65 years (range 35-83), with 58% male and 98% white. The most common surgical indication was degenerative joint disease (80%). The incidence of AKI was 7% in TKA and no patients developed AKI in the TKA-R group. All were stage 1 as per AKIN criteria. The LOS for those with AKI was 4.9 days compared to 3.5 days for those without AKI (p = 0.04). Mean anesthesia time was similar in patients with AKI (170 vs 189 min, p = 0.3). There was no significant difference between pressure requirements, estimated blood loss, need for transfusion, or amount of fluid administered between the AKI and non-AKI groups. At one year, the mean eGFR change in the AKI group was (-11.8 ml/min) compared to (-9.9 ml/min) in the Non-AKI group, p=0.065.

Conclusions: The incidence of AKI after total knee arthroplasty in TKAs was 7% and associated with longer hospitalization. All cases of AKI were mild, with renal function improving by hospital discharge. At one year, patients with AKI did have a lower eGFR compared to the non-AKI group, but the difference did not reach statistical significance. Future larger studies are needed to assess the effect of TKA on allograft function.

AKI Following Cardiac Bypass Surgery in Jamaica: Observations from a Low-Resource Country

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Background: AKI following cardiac surgery requiring cardiopulmonary bypass (CPB) is a common but serious complication with an incidence of 25-40%. It is associated with a 3 to 8 times increase in mortality, increased hospital length of stay and Chronic Kidney Disease. Little is known about the incidence and impact of AKI following CPB in the Caribbean. We describe the incidence and outcomes of AKI following CPB at a referral cardiac surgery centre in the Caribbean.

Methods: Medical records of adult patients with no prior ESRD or dialysis requirement who underwent cardiac surgery requiring CPB at the University Hospital from January 1, 2016 to December 31, 2017 were reviewed. All cause mortality was the defined end-point. Demographics, pre-operative status, intraoperative and post operative data were abstracted by two independent reviewers. AKI was reported using KDIGO criteria using serum creatinine measurements obtained within 72 hours post-operatively. Multivariate logistic regression was used to examine the risk factors for and impact of AKI on all-cause mortality.

Results: 125 patients (57% male) with mean age 57±12 years and mean pre-operative creatinine levels of 84.6 ±33.7 μmol/L underwent cardiac surgery. The incidence of AKI was 31.2% (39/125). Of these 41% (16/39) were KDIGO I, 23% (9/39) KDIGO II and (14/39) 36% KDIGO III. Renal replacement therapy was required in 4% (5) of patients. In logistic regression analyses male sex (OR 0.46,[95% CI: 0.2-0.9]), and previous history of haemoglobin (OR 0.69,[95% CI: 0.5-0.9]) reduced the likelihood of AKI whereas preoperative CKD (eGFR<60) (OR 8.6, [95% CI: 7.14.3]) and prolonged bypass time (OR per 1 hour=2.95[95% CI 1.18-7.2]) increased risk. There was no association of age, cross-clamp time or type of surgery (valve replacement or CABG) with AKI. Approximately 21% (26/125) of patients died in hospital. AKI was associated with a four fold increased risk for death after adjusting for age and sex (OR[95% CI]=4.2[1.6-10.5]).

Conclusions: The incidence of AKI following CPB is similar in our cohort to that reported in high income countries and significantly increases the risk of in hospital mortality. Larger multicentre prospective studies to predict risk, identify interventions to reduce mortality and assess long term complications of AKI following CPB in low resource countries are needed.

AKI: Epidemiology, Risk Factors, Prevention - I

Poster/Thursday
Incidence and Prevention of Contrast-Induced Nephropathy in Percuta neous Coronary Intervention

Rana R. Garris,1 Prem Patel,1 Radhika Tailor,2 Trina Pal,1 Ian Laxina,1 Yudi Camacho,2 Stephen Biggiani,1 Mina Sourial,1,3 Chandra B. Chandran,1 Ahmad H. Abuarab,1 Hiten Patel,1 Fayeze Shamoon.1 1St. Joseph’s Health/NTMC, Natley, NJ; 2Montefiore Medical Center, Bronx, NY.

Background: Contrast induced nephropathy (CIN) has been reported in 20% of patients who underwent percutaneous coronary intervention (PCI). Contrast induces nephrotoxicity through direct tubule toxicity, capillary obstruction, vasoconstriction and hypoxia. Patients who have poor renal reserve with comorbidities are more susceptible, while the pleiotropic effects of statins may be nephroprotective. Prior studies have debated the role of contrast in the development of renal insufficiency. We hypothesize that while post-PCI acute kidney injury is multifactorial, the occurrence of CIN is likely understood. This is of clinical importance, because CIN is related to worse outcomes and longer hospital stays. Patient risk stratification can mitigate this risk.

Methods: Our study evaluates the incidence of CIN among 1521 patients at our hospital over 1 year. We used SAS 9.4 to perform logistic regression to assess the occurrence of CIN among patients with pre-PCI normal versus abnormal renal function (determined by GFR and Cr) in regards to underlying comorbidities. We also incorporated a CIN risk-calculator into our hospital EMR system and PCI practices.

Results: Our results showed that 15.3% of patients who underwent PCI developed CIN. Advanced age (OR 1.014, p = 0.02); race (blacks had OR 1.8, p = 0.01); underlying heart failure (OR 1.6 p = 0.004), especially among those with BNP > 400 (OR 4.5, p = 0.001) or EF < 40% (OR 1.47, p = 0.04); and diabetes (OR 2.0, p = 0.002) increased the probability of CIN. Patients with Cr > 1.2 were 3X more likely to get CIN (p = 0.0201). GFR 30 – 60 and GFR < 30 increased the odds of CIN by 2.5 and 5 times, respectively (p < 0.01). By each unit decrease in hemoglobin, the odds of CIN increased by 5.5% (p = 0.002). Statin use reduced CIN by 42.9% (p = 0.001). Most notably, CIN also occurred in 19% of patients with normal baseline kidney function; among these patients, diabetes and age were the only contributory covariates.

Conclusions: Patients who undergo PCI are at significant risk of CIN. While baseline renal dysfunction and comorbidities are contributory, patients without these risk factors also developed CIN. Statins were renal-protective.

Impact of Contrast Media Volume on the Onset of Contrast-Induced Nephropathy During Coronary Angiography: A Retrospective Study

Agnieszka TH-PO076

Background: Contrast media administration after coronary angiography can be complicated by a contrast-induced nephropathy (CIN). The toxicity threshold volume of contrast media remains undefined. The objective is to study (1) the relationship between the volume of injected contrast media and the occurrence of CIN and (2) the existence of a possible formula to calculate the threshold volume of toxicity of the contrast media for each patient after acute percutaneous coronary intervention.

Methods: We performed a retrospective study in 4773 patients who received percutaneous coronary intervention for acute coronary syndrome between 2012 and 2018. Contrast-induced nephropathy was defined as an increase of 0.5 mg/dL or a 25% of serum creatinine compared to its baseline value between the 1st and 10th day following contrast media injection. Predictive factors independent of CIN adjusted to their observed mean was introduced into the formula to calculate the threshold volume for renal toxicity.

Results: Of the 3073 patients analysed, 724 (23.6%) developed CIN. In our population, age, diabetes, PC volume, basal Crs and basal DFG are independent predictors of CIN, the risk of CIN is lower in men. Diabetes almost doubles the risk of NIC. A toxic PC volume threshold is difficult to establish given the different factors involved in the development of CIN. Nevertheless, the proposed formula could provide an additional tool for optimizing the prevention of renal toxicity.

Renal Events Following Iodinated Contrast Aggravate Diabetic Nephropathy

Sheila M. Fernandes,1 Beatriz D. Brandi,1 Karina B. Peres,1 Luciana soares C. Santos,2 Cassiane D. da Fonseca,3 Miriam M. Watanabe,4 Maria De Fatima Vattimo.1 Group of Studies on Acute Kidney Injury (GERA)1 Universidade de São Paulo, São Paulo, Brazil; 2University of Sao Paulo, Sao Paulo, Brazil; 3EEUSP, São Paulo, Brazil; 4Faculdades Metropolitana Unidas, São Paulo, Brazil; 5School of Nursing, Federal University of Sao Paulo, Sao Paulo, Brazil.

Background: Iodinated radiocontrast media induced nephropaty (CI-AKI) is a major clinical problem accounting for 12% of all hospital-acquired cases of acute kidney injury (AKI), especially in patients with Chronic Kidney Disease (CKD) and Diabetes Mellitus (DM). Aim of this study was to estimate the influence of DM and CKD regarding the incidence of CI-AKI in rats. Renal function, global and renal hemodynamics were measured and the discriminating value of NGAL for assessing early renal injury was evaluated.

Methods: Wistar, adult, male rats were randomized into four groups: Sham (control); Citrate (citrate stress, representative of CI-AKI; DM/streptozocin); DM (streptozocin, 65 mg/kg, iv); CKD+IC (CKD that received iodinated contrast-IC, 6ml/kg); DM-IC (DM animals that received IC, 4 weeks after DM, 6 ml/kg, ip). Renal function (inulin clearance), urinary neutrophil gelatinase (uNGAL), global and renal hemodynamics (systemic blood pressure, renal blood flow, renal vascular resistance) were evaluated.

Results: Renal hemodynamics showed an increase in renal vascular resistance in CKD and DM, while IC enhanced this damage. Also, CKD and DM rats presented lower inulin clearance and higher uNGAL levels. These parameters were worsened when IC was added.

Conclusions: Our results indicated that CKD and DM improves renal vulnerability to the toxicity of IC, once association between CKD or DM with IC predisposes to severe kidney injury by modulating renal hemodynamics in rats. NGAL showed to be a sensitive marker for CI-AKI when comorbidities are involved.

Funding: Government Support - Non-U.S.
Renal function, hemodynamics, oxidative

<table>
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<tr>
<th>Group</th>
<th>Serum cystatin C (mg/L)</th>
<th>Serum creatinine (mg/dL)</th>
<th>Paracentesis volume (L)</th>
<th>Paracentesis volume (mg/L)</th>
<th>Hemoglobin (g/dL)</th>
<th>Thrombocyte count (x10^3/µL)</th>
<th>Thrombocyte count (x10^3/µL)</th>
<th>N-Acetylglucosaminidase (U/L)</th>
<th>Thrombocyte count (x10^3/µL)</th>
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<td>Control</td>
<td>0.206 ± 0.170</td>
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<td>3.0 ± 0.5</td>
<td>62.5 ± 10.6</td>
<td>14.2 ± 1.8</td>
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<td>12.5 ± 5.0</td>
<td>121.5 ± 50.4</td>
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<td>DM</td>
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<td>3.5 ± 0.6</td>
<td>73.5 ± 13.5</td>
<td>15.1 ± 2.2</td>
<td>278.3 ± 90.4</td>
<td>278.3 ± 90.4</td>
<td>13.7 ± 5.8</td>
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<td>LM-D</td>
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<td>LM-M</td>
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<td>3.8 ± 0.6</td>
<td>73.8 ± 12.5</td>
<td>15.3 ± 2.3</td>
<td>276.8 ± 80.1</td>
<td>276.8 ± 80.1</td>
<td>13.8 ± 6.0</td>
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<td>13.8 ± 6.0</td>
<td>137.8 ± 51.7</td>
<td>137.8 ± 51.7</td>
</tr>
</tbody>
</table>

*p<0.05 versus Citrate; # p<0.05 versus DM; & p<0.05 versus DM+LIC

TH-PO080

Beneficial Effect of Statin on Preventing Contrast-Induced AKI in Patients with Renal Insufficiency: A Meta-Analysis

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Background: Renal insufficiency is an important predictor of contrast-induced acute kidney injury (CI-AKI). We performed a meta-analysis to examine the effects of short-term statin therapy on the incidence of CI-AKI, particularly in patients with renal insufficiency.

Methods: A systematic search was conducted to retrieve randomized controlled trials (RCTs) that investigated the impact of statin pretreatment before administration of contrast media on the development of CI-AKI in patients with mild to moderate renal insufficiency. The primary outcome was development of CI-AKI. The secondary outcome was the incidence of AKI requiring hemodialysis.

Results: Data analysis from eight RCTs, which included a total of 2133 subjects in the statin-treated group and 2322 in the control group, showed that statin pretreatment was associated with significant reduction of the risk of CI-AKI (Relative Risk (RR) = 0.59; 95% Confidential Interval (CI) 0.44 to 0.79; p = 0.002, I² = 0%). A beneficial effect of statin on preventing CI-AKI was consistent, regardless of the dose of statin and use of N-acetylcysteine. The incidence of hemodialysis was low after contrast administration in the statin-treated group, but the reduction was not significant (RR = 0.28; 95% CI 0.15 to 1.70; p = 0.17, I² = 0%). In subgroup analysis based on baseline estimated glomerular filtration rate (eGFR), patients with baseline eGFR < 60 ml/min/1.73 m² (RR = 0.65; 95% CI 0.41 to 0.98; p = 0.04, I² = 0%) and 30 < eGFR < 90 ml/min/1.73 m² (RR = 0.56; 95% CI 0.39 to 0.82; p = 0.003, F = 0%) showed significant reduction of risk of CI-AKI.

Conclusions: Statin pretreatment is effective at preventing CI-AKI and should be considered in patients with pre-existing renal insufficiency.

TH-PO081

AKI Is a Rare Complication of Therapeutic Paracentesis Among Inpatients with Cirrhosis

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Background: AKI is a feared complication of therapeutic paracentesis. However, prior studies that assessed AKI incidence following paracentesis were limited by small sample sizes (most had <40 patients) and restricted generalizability (e.g., exclusion of inpatients).

Methods: We conducted a large, retrospective, “real-world” cohort study of all adult inpatients with cirrhosis who underwent a therapeutic paracentesis (>1L) while admitted to Massachusetts General Hospital between 2016 and 2018. We assessed the incidence and severity of paracentesis-associated AKI based on changes in SCR. AKI and its severity were defined based on KDIGO guidelines. We also performed stratified analyses to assess whether the incidence of AKI differed across subgroups.

Results: A total of 252 paracenteses were performed in 101 cirrhotic patients. IV albumin was administered in 77% of paracenteses. The overall incidence of AKI was 3%. AKI severity was as follows: 50% stage 1, 25.2% stage 2, and 37.5% stage 3. The incidence of AKI was similar when stratified by age (<60 vs. ≥60 years), baseline eGFR (<60 vs. ≥60 ml/min/1.73 m²), and MELD score (<20 vs. ≥20). Patients who received lower compared to higher volume paracentesis (≤3L vs. >3L) had a higher incidence of AKI (6% vs. 1.3%; P=0.03), however, these patients were also less likely to have received IV albumin (65% vs. 84%; P=0.001). Patients with CHF had higher rates of AKI compared to patients without CHF (9% vs. 2.3%; P=0.03).

Conclusions: In a large cohort of inpatients with cirrhosis undergoing therapeutic paracentesis, we found that post-procedure AKI rates were low. This finding was consistent across multiple subgroups, with the notable exception of CHF. Therapeutic paracentesis with IV albumin replacement is a procedure that can generally be performed without significant concern for AKI.

Table1

TH-PO082

An Evaluation of the Prevalence of Kidney Diseases in Patients with Inflammatory Bowel Diseases in a Nationwide Analysis

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Background: Up to 40% of patients with Inflammatory bowel diseases(IBD) may have extra-intestinal manifestations, mainly involving liver, skin, and joints. Anecdotal reports suggest renal involvement, but there are no estimates of prevalence. Our aim was to examine the prevalence of kidney diseases among hospitalized patients with IBD, along with the prevalence of kidney disease among patient with collagen vascular diseases (CVD) and among patients without IBD and CVD

Methods: We analyzed 2000-2014 data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample database which captures annual hospital discharge data for 20% stratified sample of U.S.community hospitals. We used International Classification of Diseases, Ninth Revision, diagnosis codes to identify three subgroups. Kidney diseases include acute kidney injury, glomerular diseases and others. CVD included systemic lupus erythematosus, rheumatoid arthritis and others.

Results: Among 713,902 hospitalized IBD patients, we identified 69,049 individuals with kidney disease(9.6%), representing a weighted national estimate of 341,946 individuals with kidney diseases. The prevalence of kidney disease among patients with IBD was 9.6%.11.9% in patients with CVD, and 8.5% in the general population (all p<0.001). Baseline characteristics of patients in three groups are given in Table1. Patients with IBD had a younger age distribution, higher distribution of white race, and a lower prevalence of hypertension, diabetes, and CHF when compared to patients with CVD or the general population without IBD or CVD

Conclusions: The burden of renal disease among patients with IBD is greater than that of the general population, which is notable given their lower traditional risk factors for kidney disease; and similar to CVD which is an immune-mediated systemic disorder. Coexisting renal disease should be considered among patients with a known diagnosis of IBD
TH-PO083

EPILAT-IRA Study: A Contribution to the Understanding of the Epidemiology of AKI in Latin America

Raul Lombardi,1 Alejandro Ferreiro,2 Rolando Claure-Del Granado,3 Guillermo J. Roso diez,4 Emmanuel A. Burdman,5 Luis Yu,6 Mauricio Younges-Gebara,7 on behalf of EPILAT-IRA Study Group. AKI Committe

Background: Acute kidney injury (AKI) is a public health problem, due to its high and rising frequency, its association with increased morbidity and mortality, and the economical burden related to its care. Considering the limited data on AKI epidemiology in Latin America and the Caribbean, we performed a prospective observational study to determine risk factors, clinical profile, process of care and outcomes of AKI in the region.

Methods: Participants were recruited by open invitation through the Latin American Society of Nephrology and Hypertension, Patient meetings. Patients meeting the KDIGO AKI definition, during hospitalization, were included over a 9-month period and designated as community or hospital acquired. De-identified clinical and lab data was entered in a specifically designed online platform. Co-variables potentially linked to AKI were recorded and correlated with mortality at hospital discharge and 90 days using a multiple logistic regression model.

Results: A total of 57 participants from 15 countries provided data on 905 patients, the age range was 18-108 yrs. Median age was 64 (50-74 yrs. and 61%) were male. Comorbidities were present in 77% of the patients. AKI was community-acquired in 62%. Dehydration, shock and nephrotoxic drugs were the most usual AKI causes. Seventy-seven percent of the patients were assessed by nephrologists. Renal replacement therapy was performed in 29% of cases. All-cause hospital mortality was 26.5% and was independently associated to older age, chronic liver disease, hypotension, shock and cardiac disturbances as etiologic factors, infection and sepsis as in-hospital complications, need of renal replacement therapy and mechanical ventilation.

Conclusions: This study provides new information on the characteristics and outcomes of AKI patients in Latin America and Caribbean region. Notwithstanding, this study represents partially the AKI situation in the Latin American patients in comparison with the real epidemiology of AKI in Latin America, a pending and needed task.

TH-PO084

Increased Mortality Among AKI Patients Attending the Emergency Department: A Retrospective Hospital-Based Cohort Study

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Background: It is well documented that acute kidney injury (AKI) is associated with increased inpatient mortality, but this association is poorly described in the emergency department (ED) setting.

Methods: Between April 2016 and March 2017, we randomly selected electronic records of 365 patients from 1695 presented to ED with AKI using an electronic AKI reporting system, and compared them to 379 randomly selected patients without AKI. The cohort was followed up till the end of April, 2019. Mortality as well as other demographic characteristics were compared.

Results: Incidence of AKI was 5.3%. AKI was associated with significantly higher risk of death 50.27% compared with 22.96% amongst those with no AKI (p< 0.001). Those whose AKI worsened while inpatients had a higher mortality risk of 63.6% compared to 49.09% in those whom AKI did not progress to a higher stage, although it did not reach statistical significance (p=0.11). Risk of inpatient mortality was significantly higher amongst the AKI group (34.4% vs 0.0% P=0.0001). Risk of readmission within 30 days did not significantly differ between the 2 groups (16.5% vs 21.4%, P=0.14).

Conclusions: Presentation to ED with AKI is independently associated with inpatient deaths as well as overall mortality and morbidity.

Funding: Government Support - Non-U.S.

TH-PO085

Renal Failure After Knee Arthroplasty and Antibiotic Cement: Role of Dialysis

Pradeep Vaitla,1 Swetha Rani Kanduri,1 Prakrati C. Acharaya,2 Karthik Kovuru,2 Rachana Marathi,1 Nephrology, University of Mississippi, Jackson, MS; 2University of Mississippi Medical Center, Ridgeland, MS.

Background: Incidence of AKI after total hip (THA) and total knee arthroplasty (THA-R) is accepted, but data on risk factors is limited. We aimed to determine risk factors associated with AKI and to determine the effect of dialysis and antibiotic impregnated cement on AKI.

Methods: Using the orthopedic and transplant databases, we designed a case-control study of 102 patients undergoing a total of 141 THA and THA-R between 2000 and 2018 at Mayo Clinic. Variables of interest not available in the databases were obtained through chart review. AKI was defined per the current KDIGO guideline.

Results: The average age at surgery was 59 years (range 27-82); with 58% male and 96% white. The most common surgical indications for THA were degenerative joint disease (57%), avascular necrosis (27%), and fractures (12%); and for THA-R, loosening (28%), dislocation (22.7%), and infection (9%). The incidence of AKI was 10.4% and 17% in THA and THA-R, respectively (p=0.36). All AKI were stage 1 per AKIN criteria. Anesthesia time was longer in patients with AKI (232 vs 196 min, p = 0.055) and in those undergoing THA-R compared to THA (256 vs 182 min <0.001). The length

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
of hospitalization for those with AKI was 5.1 vs. 4.3 days for those without AKI (p = 0.03). There was no significant difference in blood loss, need for transfusion, crystalloid or colloid administration between the AKI and non-AKI groups. At one year, mean change in eGFR was not different between the two groups (AKI: -1.7 mEq/l; Non-AKI: -2.6 mEq/l; p = 0.7). 

22% of patients who underwent kidney biopsy to investigate their renal disease, particularly glomerulonephritis, were male. The overall results of kidney biopsy were, 70.5% of patients had glomerulonephritis, 16.5% had interstitial nephritis, and 13% had other diagnoses.

Results: The incidence of AKI after total hip arthroplasty in KTAs was 10.4% (17% after revision arthroplasty) and associated with longer hospitalization. However, all cases of AKI were mild, resolved by hospital discharge and did not affect allograft function (17% after revision arthroplasty) and associated with longer hospitalization. However, all cases of AKI were mild, resolved by hospital discharge and did not affect allograft function.

Background: Obstruction to urine flow occurs at any site in the urinary tract and development of postrenal acute kidney injury (AKI) depends on whether it is acute or chronic, unilateral or bilateral and presence of combined sepsis. However, incidence, etiologies, risk factors or prognosis of postrenal AKI in urinary tract obstruction are largely unknown due to paucity of extensive epidemiologic data.

Methods: We conducted a retrospective analysis of 1,784 patients who received percutaneous nephrostomy (PCN) due to upper urinary tract obstruction in 3 university hospitals in Korea from January 1, 2002 to August 16, 2018. AKI was diagnosed according to KDIGO AKI criteria and analyzed risk factors of AKI using multivariate logistic regression analysis.

Results: AKI developed in 79.9% of patients who underwent PCN. Patients with postrenal AKI were more likely to be male (50.4 vs. 51.1%, p<0.01), older (64 years vs 57.5 years, p<0.01) and associated with decreased baseline renal function (eGFR 72.88 vs 90.79 mEq/l, p<0.01). Prevalence of hypertension (47.5 vs 35.5%, p<0.01), ischemic heart disease (5.4 vs 2.3%, p=0.013), peripheral arterial occlusive disease (7.1 vs 3.9%, p=0.003), heart failure (4.5 vs 1.1%, p<0.01) or cancer (68.5 vs 53%, p<0.01) was significantly higher in patients with AKI compared with those without AKI. Mean hemoglobin level, protein, albumin and CO2 level were significantly lower while uric acid, blood urea nitrogen and creatinine levels were significantly higher in patients with AKI compared with those without AKI. Mean hospitalization days for those with AKI was 5.1 vs. 4.3 days for those without AKI (p = 0.03). There was no significant difference in blood loss, need for transfusion, crystalloid or colloid administration between the AKI and non-AKI groups. At one year, mean change in eGFR was not different between the two groups (AKI: -1.7 mEq/l; Non-AKI: -2.6 mEq/l; p = 0.7). 

Conclusions: The incidence of AKI was very high (79.7%) in patients who underwent PCN due to upper urinary tract obstruction. Anemia, leukocytosis, hyperuricemia, and underlying hypertension are found to be independent risk factors for AKI with male predominancy.

Risk Factors of AKI in Patients with Decompensated Cirrhosis

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

TH-PO087 Risk Factors of AKI in Upper Urinary Tract Obstruction

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Background: Nephrotoxicity of bortezomib, a proteasome inhibitor, has not been described frequently, while tumor lysis syndrome (TLS) associated with multiple myeloma (MM) has been increased after introduction of the drug. This study compared the incidence and risk factors of acute kidney injury (AKI) and TLS in patients with MM after bortezomib-based chemotherapy to investigate the drug-related nephrotoxicity.

Methods: From 2006 to 2017, 276 patients who underwent first cycle of bortezomib-based chemotherapy for MM were identified in single tertiary hospital. Laboratory TLS was defined according to the Cairo-Bishop definition. Development of AKI was assessed by AKI Network criteria within 7 days after first chemotherapy.

Results: The age was 65 [56-72] years old, and 47% (n=131) of participants were female and baseline estimated glomerular filtration rate (eGFR) was 61.2 [34.8-91.1] mEq/l, 177 of 276 patients (64%) developed AKI. Multivariate analyses showed that lower eGFR category (30~59, odds ratio [OR]=3.063 [1.278-7.339]; 15~29, OR=3.417 [1.088-10.726]; <15, OR=10.080 [2.677-37.951] vs 60), lower serum albumin level (OR=0.491 [0.278-0.868], P=0.0144) and renal amyloidosis (OR=11.174 [3.974-31.420], P<0.0001) were predictors of development of AKI. MM stages and β2-microglobulin were not associated with AKI occurrence. Regarding laboratory TLS, MM stage and β2-microglobulin were higher in those with TLS. In multivariate analyses, β2-microglobulin levels (OR=1.194 [1.066-1.337], P=0.0021) and any chromosomes abnormalities at high risk (OR=0.115 [0.026-0.503], P=0.0041) were associated with higher risk of TLS.

Conclusions: Development of AKI was often observed without being accompanied by TLS in patients with MM after treatment of bortezomib. In addition, risk factors of AKI and TLS were widely different. These findings implicated the potential nephrotoxicity of bortezomib besides TLS in patients with decreased kidney function. The efforts to prevent the development of AKI are needed in patients with risk factors, when initiating bortezomib treatment.

TH-PO091 Clinical Significance of AKI in Lung Cancer Patients

Sung-eun Cho, Eunjung Kang,1 Dong Ki Kim,1 Kwon Wook Joo,1 Yon Su Kim,1 Haejung Lee,1 Eunjeong Cho,1 Seungmin Park,1 Kyungho Jang,1 Min Young-Bin Kim,1 Kwon Wook Joo,1 Seul National University College of Medicine, Jongno-gu, Seoul, Republic of Korea;1 Seoul National University College of Medicine, Jongno-gu, Seou, Republic of Korea.

Background: Acute kidney injury (AKI) in cancer patients is related to increased morbidity and mortality. Previous our exploration of AKI in cancer patients showed unexpectedly a higher incidence of AKI in lung cancer patients than those with other malignancy. This study aimed to evaluate the clinical significance of AKI in lung cancer patients.

Methods: The patients diagnosed as lung cancer from 2004 to 2013 in Seoul National University Hospital were enrolled. They were categorized into two groups by an occurrence of AKI, and the patients with AKI were categorized into three groups by AKI stage. AKI was defined based on KDIGO-AKI guideline. Demographic factors, co-morbidities, laboratory findings, count of contrast-enhanced computed tomography (CE-CT), pathologic types, and treatment options such as surgery and chemotherapy were included as covariates. We performed Cox proportional hazard modeling for mortality among patients who survived more than 1 year after cancer diagnosis.

Results: A total of 3,202 patients were included in the final analysis. Mean age was 63.8±10.34 years and 68.6% were male. AKI occurred in 1,783 (55.7%) patients during the follow-up period. Most AKI was mild with stage 1 (75.8%). We found that development of AKI were independently associated with older age, higher systolic blood pressure, diabetes mellitus, high initial serum creatinine, anemia, hyperkalemia,
AKI: Epidemiology, Risk Factors, Prevention - I

Background: Hawaii has the highest rate of homeless population per capita. Homeless people are a vulnerable group and prone to multiple health problems, including kidney diseases. Little is known about the characteristics and outcomes of acute kidney injury (AKI) in this population.

Methods: This is a retrospective study of homeless and domiciled patients who were admitted to a tertiary medical center in Honolulu, Hawaii between 2015-2016, with AKI diagnosis present on admission by ICD10 code and meeting 2012 KDIGO criteria for AKI.

Results: Between 2015 and 2016, we identified 324 patients who were admitted with AKI of which 6.48 % were homeless. Mean age of homeless patients was 56.9±8.75 compared to 66.9±15.75 in domiciled patients (p<0.01). Homeless patients tended to be female (80.85%) compared to domiciled patients (52.81%), p<0.01. Caucasian race was a majority of homeless patients, 47.62%, compared to 21.45% in domiciled patients. 71.43% of the homeless patients had a pre-renal cause of AKI compared to 38.61% in domiciled patients, p=0.06. There was no difference in percentage of underlying chronic kidney disease between homeless and domiciled patients, p=0.89. 38.10% of homeless patients visited the emergency room within 1 month prior to an index admission compared to 17.49% in domiciled patients, p<0.02. Homeless patients were more likely to be a substance user, current smoker, and alcohol abuser compared to domiciled patients, all p<0.01. Homeless patients were more likely to be discharged with a lower serum creatinine, p<0.01, and significantly shorter hospital stay, p=0.04.

Conclusions: Homeless AKI patients tended to be younger, more likely a substance user, current smoker, alcohol abuser, and with liver disease than domiciled patients. Caucasian race was the majority of homeless patients, whereas Asian race was the majority of domiciled patients. Although pre-renal cause was the most common cause of AKI in both groups, the rate of pre-renal cause in homeless patients was almost twice that of domiciled patients. There was no difference in admission serum creatinine, but the homeless were discharged with lower serum creatinine likely due to a higher rate of reversible kidney injury. There was no difference in mortality or dialysis rate.

TH-PO094
Community-Acquired AKI in Older Adults Admitted to the Emergency Medical Service: At 1-Year Follow-Up
Diego F Argudo Sanchez, I. M. Perez-Navarro, Ivan Rosero, Maria F Garcia-Guevara, Rafael Valdez-Ortiz. Hospital General de México Dr. Eduardo Liceaga, México, Mexico.

Background: Community acquired acute kidney injury (AKI-CA)is defined in patients who, at the time of admission to the hospital, present criteria for acute kidney injury diagnosis. Older adults are recognized as a vulnerable population for the development of AKI. The objective of this study was to determine the risk factors and the prognosis at one year follow-up of older adult AKI-CA. Methods: Cohort study in patients with ≥65 years old admitted in the emergency room, from March to May of 2018. The AKI-CA was according to the criteria of KDIGO 2012. The groups were compared using the Student’s t-distribution or the X2 distribution depending on the type of variable, logistic regression was performed for OR, and a Cox regression for HR and survival with IC 95% and p>0.05.

Results: A total of 221 patients that satisfied the inclusion criteria, the average age was 75.1±7.6, the 44% (97) were men. The incidence of the AKI-CA was 58.8% being more common in patients with sepsis (p< 0.001), this was the principal associated factor with the development AKI-CA (OR: 3.52, IC95% 1.6-7.1). It was noticed that the highest stage of the AKI occurs in patients with previous chronic kidney disease (AKI1: 6.4% AKI2: 5.7% AKI 3: 41.2 % p< 0.001), or presence of sepsis (AKI1: 50.7% AKI2: 55.9% AKI 3: 57.1 % p= 0.009). It was not identified increase in risk of inpatient’s mortality in patients with AKI-CA. In contrast, a relation between them was noticed after one year follow-up (Figure 1).

Conclusions: Older adults patients that suffer AKI-CA exhibit worst outcomes after one year follow up.
TH-PO095
Differences on Outcomes Between AKI and AKI on CKD in Community-Acquired AKI
Rolando Claver-Del Granado,1 Susana G. Ramirez-Yapura,3 Emmanuel A. Burdman,4 Luis Yu,5 Mauricio Younes-Itatim,6 Alejandro Ferreiro,5 Guillermo J. Rosa diez,6 Raúl Lombardi,5 On behalf of EPILAT-IRA group. AKI Committee of the Latin American Society of Nephrology and Hypertension (SLANH) 1Hospital Obervo #2 - C.N.S., 2University of San Juan, School of Medicine, Cochabamba, Bolivia, Plurinational State of; 2Servicio Medico Integral, Montevideo, Uruguay; 3Hospital Obervo #2 - C.N.S., Cochabamba, Bolivia, Plurinational State of; 4University of Sao Paulo Medical School, Sao Paulo, Brazil; 5University of Sao Paulo School of Medicine, Sao Paulo, Brazil; 6School of Medicine, Montevideo, Uruguay; 7Hospital Italiano de Buenos Aires, Argentina; 8University of Rio de Janeiro, Rio de Janeiro, Brazil.

Background: AKI is a frequent disorder in community-based populations. Most studies have focused on hospital-acquired AKI and very few have explored characteristics and outcomes of patients with community-acquired AKI (CA-AKI). CKD may adversely affect kidney repair and recovery from AKI. We therefore aimed to explore characteristics and outcomes of CA-AKI in patients with and without CKD.

Methods: We conducted a prospective observational study (EPILAT-IRA) within the ER of a University Hospital, screening for any patient ≥16 years. We included patients meeting ≥2 KDIGO AKI definition over a 9-month period and designated as community acquired. De-identified clinical and lab data was entered in a specifically designed on-line platform. Co-variables potentially linked to AKI were recorded and we analyzed if these were differences in short and long-term outcomes between patients with and without CKD.

Results: During study period we screened 1,210 patients, CA-AKI incidence was 11.65% (n = 141) most patients were male (55.32%) and the mean age was 67.9 years. There were no differences in risk factors between patients with AKI and AKI on CKD. Inpatient nephrotoxic drugs were the most common cause of CA-AKI in both groups (AKI 92.2% vs. AKI on CKD 87.2%; p = 0.72) followed by dehydration (AKI 81.3% vs AKI on CKD 76.9%; p = 0.65) and systemic disease (AKI 81.3% vs. AKI on CKD 82.0%; p = 0.64). Different outcomes are reported in table.

Conclusions: CA-AKI in developing countries is common and potentially preventable since the main etiology factors were dehydration and nephrotoxins. Hospital, 90-day and one year mortality were not different between AKI and AKI on CKD; however, RRT requirement was higher and partial recovery of renal function was lower in patients with AKI on CKD which indicates that CKD may adversely affect kidney repair and recovery. Our study provides important information that contributes to a better knowledge of CA-AKI.

TH-PO096
Comparison of Urinary Biomarkers in Critically Ill Children: Early Detection of AKI, Prediction of Mortality, and Confounding Factors
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Background: Most AKI biomarkers are susceptible to confounding factors in the prediction. We aimed to compare the performance of urinary biomarkers for early detection of AKI and the prediction of PICU mortality, and investigate the impact of confounding factors on these biomarkers in critically ill children.

Methods: Urine samples were serially collected in 123 children during the first 7 d of PICU stay for measurement of NGAL, KIM-1, TIMP2, IGBP7, L-FABP, TIMP1, Renin, trefoil factor 3 (TFF-3), interferon-inducible protein-10 (IP-10). AKI diagnosis was based on KDIGO classification.

Results: Of the children, 35 developed AKI, including 12 with stage 1, 14 with stage 2 and 9 with stage 3, and 15 died during PICU stay (1). The initial urinary biomarkers, associated with AKI stage 3 in univariate analysis, were TIMP1, KIM-1, NGAL, TIMP2, Renin and L-FABP, and achieved AUC of 0.75, 0.74, 0.71, 0.70, and 0.68 for early detection of AKI stage 3. The initial TIMP1, TIMP2, NGAL, IP-10, KIM-1, L-FABP, TFF-3, Renin and IGBP7 achieved AUC of 0.84, 0.79, 0.78, 0.77, 0.76, 0.74, 0.73, 0.67 and 0.65 for predicting mortality. However, only initial TIMP1 remained associated with AKI stage 3 (<0.016) and mortality (<0.038) after adjustment for age, body weight and illness severity. (2). Peak urinary KIM-1 and TIMP2 remained associated with AKI stage 3, and peak NGAL, L-FABP, IP-10, NGAL, L-FABP, IP-10 remained associated with mortality after adjustment. (3). Illness severity assessed by PRISM III was identified as an independent factor associated with all the initial and peak urinary biomarkers. Sepsis had an impact on initial and peak levels of NGAL, KIM-1 and IP-10 and peak Renin levels. Furosemide use was independently associated with peak levels of NGAL, L-FABP, TIMP1 and Renin and peak KIM-1, TIMP2 and TFF3 levels.

Conclusions: Although a higher initial urinary level of TIMP1, NGAL, KIM-1, TIMP2, Renin or L-FABP is predictive of severe AKI and mortality in critically ill children, the urinary biomarkers are significantly associated with illness severity and influenced by confounding factors. Sepsis has an impact on levels of NGAL, KIM-1, Renin and IP-10. Furosemide affects NGAL, FABP-1, TIMP1 and Renin. Sepsis appeared not to have impact on urinary TIMP1 and TIMP2, in contrast to NGAL and KIM-1, in critically ill children.

TH-PO097
Biomarkers in the Prediction of Contrast Media Induced Nephropathy: The BITCOIN Study
Felix S. Seibert, Nikolaos Pagonas, Timm H. Westhoff. University Hospital Marien Hospital Herne, Herne, Germany.

Background: Subjects with chronic kidney disease (CKD) are at increased risk for the development of contrast-induced acute kidney injury (CI-AKI). It remains elusive, whether urinary biomarkers are able to identify subjects at increased risk as well. The present prospective trial examines the predictive value of urinary neutrophil gelatinase-associated lipocanil (NGAL), kidney injury molecule-1 (KIM-1), calprotectin, and Dickkopf-3 (DKK3) for the development of CI-AKI.

Methods: We enrolled 489 patients undergoing coronary angiography, 137 subjects had a CKD. An increase of serum creatinine concentration ≥0.3 mg/dl from baseline to day 2-3 was defined as CI-AKI and primary endpoint. Urinary calprotectin, NGAL, KIM-1 and DKK3 concentrations were assessed ≥24h before coronary angiography.

Results: We enrolled 489 patients undergoing coronary angiography, 137 subjects had a CKD. An increase of serum creatinine concentration ≥0.3 mg/dl from baseline to day 2-3 was defined as CI-AKI and primary endpoint. Urinary calprotectin, NGAL, KIM-1 and DKK3 concentrations were assessed ≥24h before coronary angiography.

Conclusions: Although a higher initial urinary level of TIMP1, NGAL, KIM-1, TIMP2, Renin or L-FABP is predictive of severe AKI and mortality in critically ill children, the urinary biomarkers are significantly associated with illness severity and influenced by confounding factors. Sepsis has an impact on levels of NGAL, KIM-1, Renin and IP-10. Furosemide affects NGAL, FABP-1, TIMP1 and Renin. Sepsis appeared not to have impact on urinary TIMP1 and TIMP2, in contrast to NGAL and KIM-1, in critically ill children.

TH-PO098
Admission Plasma Uromodulin and the Risk of AKI in Hospitalized Patients with Cirrhosis
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Background: Acute kidney injury (AKI) is a common complication in patients hospitalized with decompensated cirrhosis. Current methods for identifying patients at risk for AKI are suboptimal. Uromodulin, a protein uniquely produced by the kidney and released both in the urine and circulation, has been shown to regulate AKI and is linked to tubular reserve. Although low levels of urine uromodulin are associated with an increased risk of AKI after cardiac surgery, it is unclear whether circulating uromodulin can stratify the risk of AKI, particularly in a susceptible population such as patients with cirrhosis.

Methods: Patients admitted with cirrhosis were monitored for subsequent hospital-acquired AKI (defined by a rise in serum creatinine >0.3 mg/dl within 48 hours or >1.5 fold increase compared to baseline). Plasma levels of uromodulin were measured at the time of hospital admission. Multivariable logistic regression adjusted for significant clinical variables was used to evaluate the associations between admission uromodulin and odds of developing AKI.

Results: 698 patients [mean age 54 years, Model for Endstage Liver Disease Sodium score (MELD-Na) 19, and baseline creatinine of 0.95 mg/dl] were included, of which 13% (n=13) developed AKI. Median uromodulin levels were significantly lower in patients who developed AKI compared to patients who did not (9.30 vs. 13.53 mg/mL, p<0.02). Age, adjusting for age, sex, BMI, and baseline albumin, and MELD-Na score (which includes kidney function) as co-variates, uromodulin was independently associated with AKI OR of 1.19 (95% CI 1.02, 1.37; p=0.02).

Conclusions: Lower uromodulin levels on admission are associated with increased odds of developing AKI in patients with cirrhosis. To our knowledge, this is the first study linking plasma uromodulin with AKI development, albeit in a unique population of patients with cirrhosis. If validated in larger studies, the measurement of circulating uromodulin on admission could enhance our clinical decision making for risk assessment of AKI in patients with liver disease.

Funding: NIDDK Support, Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
TH-PO100

**Cell Cycle Biomarkers and Soluble Urokinase-Type Plasminogen Activator Receiver for the Prediction of Septic AKI Courses Requiring Renal Replacement Therapy: An Explorative Study**

**Poster/Thursday**

**Background**: Sepsis-induced acute kidney injury (AKI) is the dominant AKI etiology in critically ill patients and is often associated with the need for renal replacement therapy (RRT). The timing of RRT is an ongoing controversy. A major issue that persists is the early differentiation of patients with progressive AKI and need for RRT from those with spontaneous renal recovery. We hypothesized, that the product of the two cell cycle arrest and tubular injury biomarkers Cystatin C (CysC) and urokinase-type plasminogen activator (suPAR) are of diagnostic value for the prediction of septic AKI courses requiring RRT.

**Methods**: 100 critically ill patients were enrolled prospectively after the fulfillment of Sepsis-3 criteria. Urinary [TIMP-2]*[IGFBP7] levels over time and serum suPAR levels once at inclusion were measured. The primary clinical endpoint was the occurrence of need for RRT within 7 days. Area under the receiver-operating characteristic curves (AUC-ROC), deLong’s tests and logistic regression models were calculated.

**Results**: Nineteen patients developed need for RRT. Diagnostic performance of urinary [TIMP-2]*[IGFBP7] improved significantly over time with the highest AUC of 0.89 (95%CI 0.80-0.98) at 24h after study inclusion. SuPAR levels at inclusion showed an AUC of 0.83 (0.75-0.92). The best discrimination ability for the primary outcome was achieved for [TIMP-2]*[IGFBP7]24h by applying a cut-off value of a0.6 (mg/ml)/1000 (sensitivity 90.9, specificity 67.1). SuPAR at inclusion performed best by using a cut-off value of ≥8.53 mg/l (sensitivity 84.2, specificity 72.7). The combination of newly tested biomarkers with Cystatin C (CysC) resulted in a significantly improved diagnostic accuracy. CysC in combination with [TIMP-2]*[IGFBP7]24h outperformed all present standard renal parameters (AUC 0.95 [0.86-1.00]).

**Conclusions**: [TIMP-2]*[IGFBP7] levels after the initiation of therapeutic measures and suPAR levels at baseline are promising biomarker candidates for the risk stratification of septic AKI patients with the need for RRT.

TH-PO101

**Assessment of Urinary Biomarkers for AKI in Major Elective Nonvascular Abdominal Surgeries**

**Poster/Thursday**

**Background**: Sepsis-induced acute kidney injury (AKI) is the dominant AKI etiology in critically ill patients and is often associated with the need for renal replacement therapy (RRT). The timing of RRT is an ongoing controversy. A major issue that persists is the early differentiation of patients with progressive AKI and need for RRT from those with spontaneous renal recovery. We hypothesized, that the product of the two cell cycle arrest and tubular injury biomarkers Cystatin C (CysC) and urokinase-type plasminogen activator (suPAR) are of diagnostic value for the prediction of septic AKI courses requiring RRT.

**Methods**: A total of 298 pts submitted to MENVAS were prospectively assessed and evaluated, pre, peri-operatively and from the ICU admission up to 7 days. Serum creatinine (Scr) was assessed before surgery and once a day up to 7d or until ICU discharge. Hourly urinary output (UO) (ml/kg/h) was measured. AKI was diagnosed by either Scr or/and UO (KDIGO definitions). Urine was collected 1d before surgery (baseline), 30 min, 12 and 24h after ICU admission. Monocyte chemotactic protein 1 (MCP-1), interleukin 1α (IL-1α), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), urine inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 ([TIMP-2]*[IGFBP7]) were assessed by Luminex x-MAP. Data are median (1st quartile to 3rd quartile) or mean ± SD. A total of 298 pts submitted to MENVAS were prospectively assessed and evaluated, pre, peri-operatively and from the ICU admission up to 7 days. Serum creatinine (Scr) was assessed before surgery and once a day up to 7d or until ICU discharge. Hourly urinary output (UO) (ml/kg/h) was measured. AKI was diagnosed by either Scr or/and UO (KDIGO definitions). Urine was collected 1d before surgery (baseline), 30 min, 12 and 24h after ICU admission. Monocyte chemotactic protein 1 (MCP-1), interleukin 1α (IL-1α), kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), urine inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 ([TIMP-2]*[IGFBP7]) were assessed by Luminex x-MAP. Data are median (1st quartile to 3rd quartile) or mean ± SD.

**Results**: Overall, age was 56±15, 59±1% were female, hospital LOS was 17±7±16.2d, ICU LOS was 3±1±2±4d and 90±1% mortality was 6.4%. A total of 197 pts (60±1%) developed AKI, mostly KDIGO I (118 pts, 59±9%). The uBMs combination with the higher AUC was [TIMP-2]*[IGFBP7] vs. NGAL vs [TIMP-2]*[IGFBP7] (baseline: 0.65; 30min: 0.72; 12h: 0.79; 24h: 0.72), which was better than any of the uBMs alone, or other combinations, including the product [TIMP-2]*[IGFBP7](baseline: 0.62; 30min: 0.65; 12h: 0.75; 24h: 0.72).

**Conclusions**: We found a strikingly high incidence of MENVAS-associated AKI diagnosed by KDIGO criteria in patients admitted at the ICU. The uBMs with the better performance to diagnose moderate and severe AKI was the combinations of KIM-1 vs. NGAL vs. [TIMP-2]*[IGFBP7] 12h after ICU admission.

**Funding**: Government Support - Non-U.S.
TH-PO103
Low Fractional Excretion of Urinary Sodium Is a Common Finding During Acute Tubular Injury Presenting with Abundant Muddy Brown Granular Casts
Maria Soledad Rivera,1,2 Juan Carlos Q. Velez,1,2 Ochsner Clinical School, The University of Queensland, New Orleans, LA; Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.

Background: Fractional excretion of urinary sodium (FENa) remains the most widely utilized diagnostic test in clinical practice for the evaluation of acute kidney injury (AKI). A low FENa (<1%) is considered consistent with prerenal azotemia and not due to overt tubular injury. However, presence of muddy brown granular casts (MBGCs) during microscopic examination of the urinary sediment (MicrExUrSed) are deemed pathognomonic of AT.

Methods: We conducted a prospective observational study in patients seen in the inpatient nephrology consultation team with AKI stage ≥ 1 (AKIN) over a 1.5-yr period.

On the day of the consult and 48 hrs later, MicrExUrSed was performed to determine the percentage of low power fields (lpf) containing MBGCs. FENa was calculated on the same day to compare it with MBGCs abundance. Outcome measure was a 50% increase from baseline serum creatinine to the maximum value within the AKI.

Results: Both FENa and presence of MBGCs by MicrExUrSed was completed in 135 patients, 57 (42%) were female, median age was 59 (25-88). The median FENa at the time of AKI was 3.2 (2.5 - 4.6) mg/dL. The urinary MBGCs of AKI (pure de novo AKI 57%, AKI on CKD 43%) was ischemic AT (40%), toxic AT (15%), ischemic/toxic AT (19%) and others (27%). MBGCs were found in 71 patients (53%) in our cohort. Among those, 56 (42%) and 32 (24%) had >10% and ≤50% lpf with MBGCs, respectively. FENa was ≤1% in 24/56 (44%) and 13/32 (41%) of those with >10% and ≤50% lpf with MBGCs, respectively. Thus, the concordance between FENa and MicrExUrSed for ATI diagnosis was 56 (42%) and 32 (24%) had >10% and ≤50% lpf with MBGCs, respectively.

Conclusions: Close to half of the patients in our cohort who exhibited abundant amounts of TECs compared to the AKI cohort (pTECs: p=0.0001; dTECs: p=0.0003; Mann-Whitney-U: 0.0001; Student’s t test: p=0.0001).

TH-PO104
Urinary Tubular Epithelial Cells as a Tool for Diagnosis and Prognosis Estimation in AKI
Jacob Kujat, Christopher Skopnik, Paul Freund, Diana Metzke, Philipp Enghard, Charité Universitätsmedizin Berlin, Berlin, Germany.

Background: Acute kidney injury (AKI) is a common clinical condition with serious short- and long-term consequences. Present classification focuses on serum creatinine (SCr) and urine output, though these are functional damage markers and only allow indirect examination of the cellular damage during AKI. Tubular injury (ATI) provides prognostic information.

Methods: We conducted a prospective observational study in patients seen in the inpatient nephrology consultation team with AKI stage ≥ 1 (AKIN) over a 1.5-yr period.

On the day of the consult, MicrExUrSed was performed to determine the percentage of low power fields (lpf) containing MBGCs and to assess a validated score for ATI based on granular casts and tubular epithelial cells per lpf [Perazaella score (PS): score ≥ 2 consistent with ATI]. The primary outcome measure was need for dialysis at 3 days (RRT).

Results: Urine specimens from 167 patients [median age 58 (25–88), 43% women] were assessed. The etiology of AKI (pure de novo AKI 56%, AKI on CKD 44%) was ischemic AT (41%), toxic AT (14%), ischemic/toxic AT (17%) and others (28%). WxCs were found in 47 patients (28%), 33 (70%) of which had pure de novo AKI. Median serum creatinine for those with WxCs was 3.7 (2.8–4.9) mg/dL compared to 3.1 (2.4–4.6) mg/dL for those without WxCs (p = 0.087). Having >10% lpf w/ ≥ 1 WxCs was associated with greater risk for RRT [relative risk (RR): 2.3, CI 1.4–3.5, p = 0.0003]. As reported by others, PS ≥ 2 was associated with increased risk for RRT (RR: 2.6, CI 1.1–6.6, p = 0.04). When presence of WxCs was added to a PS ≥ 2, the RR for need for RRT became stronger (PS w/ WxCs: p = 0.0176; dTECs: p=0.0282; Spearman).

Conclusions: Results show that WxCs can be found in a significant proportion of patients with AKI, even among those without preexisting CKD. Among patients with ATI, the presence and abundance of WxCs are associated with a greater risk for need for RRT, suggesting that WxCs carry similar and potentially additive prognostic value to that of granular casts.

TH-PO105
Urinary Waxy Casts Are Associated with Greater Severity of Acute Tubular Injury
Maria Soledad Rivera,1,2 Juan Carlos Q. Velez,1,2 Ochsner Clinical School, The University of Queensland, New Orleans, LA; Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.

Background: Waxy casts (WxCs) constitute a recognized finding during microscopic examination of the urinary sediment (MicrExUrSed) and they are classically linked to chronic kidney disease (CKD). It is less clear whether WxCs are a relevant finding in acute kidney injury (AKI). We hypothesized that identification of WxCs in AKI due to acute tubular injury (ATI) provides prognostic information.

Methods: We conducted a prospective observational study in patients seen in the inpatient nephrology consultation team with AKI stage ≥ 1 (AKIN) over a 1.5-yr period. On the day of the consult, MicrExUrSed was performed to determine the percentage of low power fields (lpf) containing MBGCs and to assess a validated score for ATI based on granular casts and tubular epithelial cells per lpf [Perazaella score (PS): score ≥ 2 consistent with ATI]. The primary outcome measure was need for dialysis at 3 days (RRT).

Results: Urine specimens from 167 patients [median age 58 (25–88), 43% women] were assessed. The etiology of AKI (pure de novo AKI 56%, AKI on CKD 44%) was ischemic AT (41%), toxic AT (14%), ischemic/toxic AT (17%) and others (28%). WxCs were found in 47 patients (28%), 33 (70%) of which had pure de novo AKI. Median serum creatinine for those with WxCs was 3.7 (2.8–4.9) mg/dL compared to 3.1 (2.4–4.6) mg/dL for those without WxCs (p = 0.087). Having >10% lpf w/ ≥ 1 WxCs was associated with greater risk for RRT [relative risk (RR): 2.3, CI 1.4–3.5, p = 0.0003]. As reported by others, PS ≥ 2 was associated with increased risk for RRT (RR: 2.6, CI 1.1–6.6, p = 0.04). When presence of WxCs was added to a PS ≥ 2, the RR for need for RRT became stronger (PS w/ WxCs: p = 0.0176; dTECs: p=0.0282; Spearman).

Conclusions: Results show that WxCs can be found in a significant proportion of patients with AKI, even among those without preexisting CKD. Among patients with ATI, the presence and abundance of WxCs are associated with a greater risk for need for RRT, suggesting that WxCs carry similar and potentially additive prognostic value to that of granular casts.
Difference in AUC of absolute and normalized uBMs concentrations

<table>
<thead>
<tr>
<th>uBM</th>
<th>Absolute</th>
<th>30 min-ICU</th>
<th>12h ICU</th>
<th>24h ICU</th>
<th>48h ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP-5</td>
<td>0.60</td>
<td>0.60</td>
<td>0.67</td>
<td>0.64</td>
<td>0.60</td>
</tr>
<tr>
<td>IL-10</td>
<td>0.63</td>
<td>0.57</td>
<td>0.54</td>
<td>0.55</td>
<td>0.65</td>
</tr>
<tr>
<td>IL-18</td>
<td>0.60</td>
<td>0.64</td>
<td>0.70</td>
<td>0.72</td>
<td>0.67</td>
</tr>
<tr>
<td>OPN</td>
<td>0.59</td>
<td>0.59</td>
<td>0.64</td>
<td>0.64</td>
<td>0.66</td>
</tr>
<tr>
<td>NGAL</td>
<td>0.58</td>
<td>0.53</td>
<td>0.64</td>
<td>0.61</td>
<td>0.71</td>
</tr>
<tr>
<td>TIMP-2</td>
<td>0.56</td>
<td>0.56</td>
<td>0.60</td>
<td>0.59</td>
<td>0.70</td>
</tr>
<tr>
<td>TIMP-3</td>
<td>0.56</td>
<td>0.56</td>
<td>0.60</td>
<td>0.59</td>
<td>0.70</td>
</tr>
</tbody>
</table>

ns AUC not significant

TH-PO107

Prognostic Biomarkers of Kidney Function and Steroid Responsiveness After Acute Interstitial Nephritis

Dennis G. Moledina,1 Francis P. Wilson,1 Mark A. Perazella,1 Gilbert W. Moeckel,2 Lloyd G. Cantley,1 Chirag R. Parikh.3 Yale School of Medicine, New Haven, CT; 2Johns Hopkins University, Baltimore, MD; 3Yale University School of Medicine, New Haven, CT.

Background: Predictors of kidney injury, inflammation and function after AIN can guide therapeutic strategies.

Methods: In participants with adjudicated AIN, we examined the relationship of conventional and novel biomarkers of kidney structure and function (glomerular filtration rate [eGFR] before biopsy, histology, injury (urine uromodulin, NGAL, KIM-1, IL-18, microscopy) and inflammation (TNFa, IFNg, IL4, IL5, IL6, IL9, IL13) with eGFR measured 6 months (6m) after biopsy controlling for eGFR before biopsy and albuminuria. We also evaluated the impact of steroids on 6m eGFR.

Results: We ascertained 6m eGFR in 51 (93%) out of 55 participants. Mean (SD) eGFR before, during, and 6m after AIN was 41.6 (26.3), 15.6 (10.5), and 33.4 (24.3) ml/min, respectively. Urine uromodulin at time of AIN diagnosis was independently associated with 6m eGFR (Figure), whereas other novel biomarkers were not associated with 6m eGFR. Among the histological features, higher interstitial fibrosis/tubular atrophy (IF/TA) was associated with lower 6m eGFR, whereas other novel biomarkers were not associated with 6m eGFR before, during, and 6m after AIN was 41.6 (26.3), 15.6 (10.5), and 33.4 (24.3) ml/min, respectively. Urine uromodulin at time of AIN diagnosis was independently associated with 6m eGFR (Figure), whereas other novel biomarkers were not associated with 6m eGFR. Among the histological features, higher interstitial fibrosis/tubular atrophy (IF/TA) was associated with lower 6m eGFR, whereas other novel biomarkers were not associated with 6m eGFR independent of prebiopsy eGFR and albuminuria. Steroid use was associated with higher 6m eGFR in those with ≥25% involvement, and in those with urine IL-9 level above the median (0.75 ng/ml versus no IL-9 involvement p=0.01) and in those with <25% involvement, and in those with urine IL-9 level above the median (0.75 ng/ml versus no IL-9 involvement p=0.01) but not in those with IL-9 levels below the median.

Conclusions: Higher urine uromodulin level at the time of AIN diagnosis was associated with higher 6m eGFR independent of prebiopsy eGFR and albuminuria. Steroid use was associated with higher 6m eGFR in those with active inflammation at the time of biopsy. These findings could help prognosticate kidney function after AIN and guide the initiation of steroid therapy.

Funding: NIDDK Support

TH-PO108

Risk Factors and Outcomes of AKI Subphenotypes Based on Serum Creatinine Trajectory After Vancomycin Exposure

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Background: Vancomycin-associated (VA) acute kidney injury (AKI) is poorly characterized. We hypothesized that the phenotyping of VA-AKI according to the time course of changes in serum creatinine (sCr ‘trajectory’) could identify different risk factors and prognosis.

Methods: Cohort study. We included all subjects (2017 to 2019) admitted to a tertiary referral hospital exposed to vancomycin IV ≥4 days without CKD G5 or dialysis treatment. We collected daily sCr and vancomycin serum concentrations, calculated the area under the concentration-time curve (AUC24h), and eGFR 30 days after hospital discharge.

Results: We included 361 subjects. In survivors (332/361, 91.9%), we identified 4 phenotypes based on sCr trajectory: 1) No AKI-VA (n=229, 67%): subjects without AKI who did not have sCr changes during exposure; 2) Severe AKI-VA (n=19, 6%): subjects with an accelerated rise in sCr not related to other clinical factors, with a median time of vancomycin exposure 10 days (IQR: 7-18) with tubular injury (biopsy in 2 cases); 3) non-severe AKI-VA (n=55, 17%): subjects who at the beginning of vancomycin prescription had AKI, which was improving but had slight and slow sCr increases during treatment, usually in context of other AKI risk factors (sepsis relapsed, nephrotoxic drugs, bleeding); 4) recovery of AKI (n=29, 9%): subjects with sepsis induced AKI who had improvement with VA during treatment. In a multivariate analysis, risk factors for group 2 were the slope of the initial day 2-4 vancomycin drug levels (OR:2.1 95%CI 1.4-3.1) and baseline sCr (OR:1.7 95%CI 1.2-2.7) and baseline sCr. Risk factors for group 3 non-severe AKI-VA were vancomycin drug levels >15 mg/L (OR 1.6 per each 10 mg/L, 95%CI 1.1-3.5) and 24h target of a 600 mg*6h/L (OR 2.9 95%CI 1.6-5.9). After 30-d of discharge, severe AKI-VA was usually reversible (12% had CKD G3A1). Group 3 had a higher frequency of CKD (78% CKD G3) compared to other groups. Total daily vancomycin dose, accumulated dose, and duration of therapy were not risk factor for any group.

Conclusions: VA-AKI occurs in different clinical presentations. Acute and severe AKI-VA can be predicted according to slope change in first doses of vancomycin levels. Non-severe AKI-VA was multifactorial, had a higher risk of CKD, and had pre-AKI high vancomycin trough levels.

TH-PO109

Plasma Neutrophil Gelatinase Associated Lipocalin (NGAL) and the Prediction of Sustained AKI and Worsening Renal Function in Hospitalized Kidney Transplant Recipients

Jutta S. Swolinsky,1 Ricardo M. Hinz,1 Carolin E. Markus,1 Eugenia Singer,1 Klemens Budan,1 Kai-Uwe Eckardt,1 Timm H. Westhoff,1 Kai M. Schmidt-Ott,12 Charité-Universitätsmedizin, Berlin, Germany; 2Berlin Institute of Health, Berlin, Germany; 3Ruhr Universität Bochum, Bochum, Germany.

Background: Neutrophil gelatinase-associated lipocolin (NGAL) and Calprotectin (CPT) have been validated as biomarkers of acute kidney injury (AKI) in multiple clinical settings. The utility of these biomarkers in post-transplant care of kidney transplant recipients (KTR) remains largely unclear. We hypothesized that NGAL and CPT levels, measured at the time of any unscheduled hospital admission after kidney transplantation, would be associated with episodes of sustained AKI (sAKI) and worsening renal function (WRF).

Methods: As part of a monocentric cohort study of 709 KTR, plasma and urinary NGAL and CPT levels were measured in 164 KTR at the time of hospital admission for any non-elective cause. sAKI was defined as an increase in creatinine by ≥0.3 mg/dl or by ≥1.5-fold compared to outpatient baseline that did not normalize within 72 hours (h). WRF was defined as an increase in creatinine by ≥0.5 mg/dl within 72 h after admission. ROC analyses, univariable and multivariable logistic regression analyses and net reclassification improvement (NRI) were assessed for the biomarkers in predicting sAKI and WRF.

Results: 33 KTR developed sAKI, 12 developed WRF. Plasma NGAL (pNGAL) had the highest diagnostic accuracy compared to urinary NGAL, urinary and plasma CPT. Median pNGAL levels at admission were significantly higher in patients with sAKI (332 [IQR 243-563] ng/ml vs no sAKI 275 [IQR 193-363] ng/ml, p=0.00). For WRF (395 [IQR 305-639] ng/ml vs no WRF 278.5 [IQR 193-378.8] ng/ml, p=0.05). ROC analyses for pNGAL showed an AUC ROC of 0.66 for sAKI and of 0.75 for WRF. A pNGAL level ≥410 ng/ml had positive likelihood ratios of 2.3 (95% CI 1.3-8.3) for sAKI and 2.0 (95% CI 1.1-3.4) for WRF. In multivariable logistic regression, pNGAL was an independent predictor of sAKI when combined with other predictors (serum creatinine, coronary artery disease, congestive heart failure, p<0.05). Adding pNGAL to conventional predictors of sAKI resulted in an NRI of 20.5% (p=0.01).

Conclusions: Elevated pNGAL at the time of hospital admission may be useful in identifying KTR at risk of sustained or progressive acute kidney injury. Although test characteristics speak against its use as a single biomarker, it may contribute to prognostication.

Funding: Private Foundation Support
TH-PO110

Urinary Exosomal MicroRNA-21 as a Marker of Scrub Typhus-Associated AKI

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Background: Extracellular vesicles contain various molecules including DNA, mRNA, and microRNA (miRNA), and are involved in cell-to-cell communication. MiRNA-21 is reported to be a biomarker for detection of acute kidney injury (AKI). The aim of this study is to investigate the clinical significance of urinary exosomal miRNA-21 for AKI in patients with scrub typhus.

Methods: In a cross-sectional study, we collected 138 urine samples at the time of admission from 145 patients with scrub typhus. For 25 patients with scrub typhus-associated AKI and 25 age, sex-matched patient without AKI, we measured miRNA-21 in urinary exosomal fraction. Then, we investigated correlation between urinary exosomal miRNA-21 and clinical parameters.

Results: Compared with patients in the non-AKI group, patients in the AKI group had worse renal function (30 ± 13 vs. 56 ± 20 mL/min/1.73m², P=0.01) at admission and higher total leukocyte counts (10.4 ± 269 vs. 104 ± 51 ng/mL, P<0.01) and urine NGAL/creatinine values (371 ± 57 ng/mg, P<0.01) were higher in the AKI group than in the non-AKI group. The levels of urinary exosomal miRNA-21 (17.8 ± 1.8 vs. 20.1 ± 1.2 ΔCt value of miRNA-21, P<0.01) were higher in the AKI group than in the non-AKI group, while those levels in urinary supernatant were not different between two groups. Urinary exosomal miRNA-21 levels correlated directly with total leukocyte counts and serum NGAL values and inversely with estimated glomerular filtration rate. The receiver operator characteristics curve analysis for urinary exosomal miRNA-21 showed good discriminative power for detecting scrub typhus-associated AKI, with area under the curved value of 0.887.

Conclusions: Urinary exosomal miRNA-21 could be a surrogate markers for the diagnosis of scrub typhus-associated AKI.

TH-PO111

Impact of Elevated Echocardiographic Index of Left Ventricular Filling Pressure on AKI After Aortic Valve Replacement

Soo Young Lee, Jae young Kang. Sejong General Hospital, Bucheon, Republic of Korea.

Background: Increased LV filling pressure was found to be associated with deterioration of renal function in patients with congestive heart failure. However, it remains unclear how to contribute to cardio-renal interaction in patients who undergo aortic valve replacement (AVR). We sought to evaluate the association between preoperative echocardiographic index of left ventricular (LV) filling pressure and postoperative acute kidney injury (AKI), and impact of AKI on clinical adverse outcomes after surgical AVR.

Methods: We conducted a retrospective study of 576 patients (292 males, mean age 68±10 years) who underwent surgical AVR. Patients were stratified according to E/e' ratio above and less than 15, and assessed for AKI using the KDIGO criteria, defined as either a serum creatinine rise >0.3 mg/dL, or an increase in serum creatinine ≥1.5 times baseline within 7 days after AVR. The clinical adverse outcomes were early and long-term mortality, and hospitalization due to heart failure.

Results: Patients with E/e' ratio ≥15 had more AKI complication after surgical AVR (odd ratio [OR] 1.05; 95% confidence interval [CI], 1.17–2.34 p<0.005). The Cox hazard model reveals that AKI (hazard ratio [HR], 2.07; 95% CI, 1.17–3.69, p=0.012) was an independent predictor for AKI after surgical AVR, while high LV filling pressure (E/e', HR 1.29; 95% CI, 1.01–2.00, p=0.04) was an independent risk factor for AKI. The Cox hazard model reveals that AKI (hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.17–2.34, p=0.005). The Cox hazard model reveals that AKI (hazard ratio [HR], 2.07; 95% CI, 1.17–3.69, p=0.012) was an independent predictor for AKI after surgical AVR, while high LV filling pressure (E/e', HR 1.29; 95% CI, 1.01–2.00, p=0.04) was an independent risk factor for AKI. Further research in other and larger cohorts is needed and planned. We propose that Syn-1 may be a mechanistic biomarker for AKI.

Conclusions: Among patients who undergoing surgical AVR, preoperative elevated LV filling pressure is associated with increased risk for AKI, and AKI is related to postoperative adverse clinical outcomes.

TH-PO112

Endothelial Glycocalyx Shedding and Microcirculatory Impairment in Traumatic Haemorrhagic Shock Are Early Markers of AKI

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1Renal Sciences, King’s College London, London, United Kingdom; 2University of Birmingham, Birmingham, United Kingdom; 3King’s College Hospital, London, United Kingdom.

Background: Microcirculatory disruption is evident in the pathogenesis of many acute kidney injury (AKI) causes, and regulation of microvascular perfusion is dependent on the integrity of the endothelial glycocalyx (Glx). We hypothesised that systemic Glx shedding and microcirculatory impairment are associated with AKI. The MICROSHOCK study reported on multiple organ dysfunction syndrome; we report the association with Glx and microcirculatory changes and AKI outcomes for the first time.

Methods: Patients with traumatic haemorrhagic shock from two UK Major Trauma Centres underwent plasma sampling for Syndecan-1 (Syn-1, Glx constituent) and sublingual Incident Dark Field (IDF) microscopy on admission. IDF videos were analysed to quantify perfused vessel index (PVD) and microvascular flow index (MFI). Presence and stage of AKI within 7 days were recorded.

Results: 45 patients were included; 10 (22%) female and 35 (78%) male. Mean age was 45 (SD 26) years. 34 of 45 (76%) developed AKI within 7 days; 15 (44%) stage 1; 12 (33%) stage 2; and 7 (21%) stage 3. Syn-1 results were available for 17 patients. Admission Syn-1 concentration was significantly higher (representing increased Glx shedding) in patients who did (n=11) than did not develop AKI within 7 days, p = 0.0183 (Figure 1). PVD and MFI results were available in all 45 patients. Both PVD and MFI were significantly lower (representing impaired microcirculatory perfusion) in patients who went on to develop stage 2 or 3 AKI (Table 1).

Conclusions: This novel study provides preliminary evidence that Glx shedding and impaired microcirculatory perfusion parameters can predict AKI. Further research in other and larger cohorts is needed and planned. We propose that Syn-1 may be a mechanistic biomarker for AKI.

Table 1: PVD and MFI in patients who did and did not develop AKI

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>PVD (percentage)</th>
<th>MFI</th>
<th>Syn-1 (ng/ml)</th>
<th>AKI</th>
<th>No AKI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>451 (355, 885)</td>
<td>2.81</td>
<td>51 ng/ml</td>
<td>6</td>
<td>15</td>
<td>0.0012</td>
</tr>
<tr>
<td>Stage 2</td>
<td>32 (27, 37)</td>
<td>2.62</td>
<td>2.5</td>
<td>3</td>
<td>5</td>
<td>0.0023</td>
</tr>
<tr>
<td>Stage 3</td>
<td>2.53</td>
<td>3.2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0.0020</td>
</tr>
</tbody>
</table>

Figure 1: Syn-1 concentration in patients who did and did not develop AKI
TH-PO113 Serum α1-Antitrypsin Predicts Severe AKI After Cardiac Surgery
Jin Aj, Zhixwen Xiao, Jianwei Tian. State Key Laboratory of Organ Failure Research, National Clinical Research Center of Kidney Disease, Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China.

Background: Human α1-antitrypsin (A1AT), a binding protein with affinity to hemin, is an acute phase glycoprotein with broad anti-inflammatory properties. It is involved in the pathophysiologic processes underlying ischemic AKI and could exert dramatic renoprotective effects. Our objective is to assess the ability of serum A1AT (sA1AT) to predict AKI in adults undergoing heart surgery.

Methods: We conducted a prospective, single-center, cohort study in 201 patients undergoing cardiac surgery in our center since 1 July to 31 December 2017. We analyzed levels of sA1AT and other injury biomarkers during the perioperative period. Severe AKI was defined as Kidney Disease Improving Global Outcomes (KDIGO) stage 2 or 3. Overall AKI was defined as KDIGO stage 1.

Results: Of the 201 patients entered the final analysis, 69 (34.3%) developed mild AKI, and 22 (10.9%) developed severe AKI. sA1AT level increased immediately 1h after operation, maintained at the peak for 12 hours, and subsequently decreased in patients who developed severe AKI. After multivariate adjustment, sA1AT 1h after CPB independently associated with the development of severe AKI (OR, 1.46; 95% CI, 1.10-1.95; P=0.009) compared with mild AKI and no AKI, and the highest quartile of MMP-7 level associated with 23-fold higher odds of severe AKI compared with the lowest quartile. For predicting severe AKI, sA1AT had an area under the receiver operating characteristic curve of 0.814, outperforming uTIM-1 and the clinical model. Elevated sA1AT level associated with longer stay in the intensive care unit and hospital.

Conclusions: sA1AT is a valuable potential predictor for severe AKI and poor hospital outcomes in patients after cardiac surgery.

TH-PO115 A Modified Renal Angina Index Predicts Poor Outcomes After Pediatric Cardiac Surgery
Katja M. Gist,1 Megan Soohoo,1 Catherine Krawczeski,1 David S. Cooper,4 Emily Mack,2 David M. Kwiatkowski,2 Jeffrey Alten,4 Stuart Goldstein,4 Rajit K. Basu.2 1University of Colorado, Children’s Hospital Colorado, Aurora, CO; 2Children’s Healthcare of Atlanta, Atlanta, GA; 3Nationwide Children’s Hospital, Columbus, OH; 4Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 5Children’s Hospital Colorado, Arvada, CO; 6Stanford University School of Medicine, Palo Alto, CA.

Background: Children undergoing congenital cardiac surgery are at high risk for poor outcomes including those related to acute kidney injury (AKI), prolonged mechanical ventilation and death. Early adjudication of risk for poor outcome may identify opportunities for early mitigative or preventative actions. We hypothesized modification of the renal angina index (RAI), a composite score of patient risk and early signs of renal dysfunction, for use in patients following cardiac surgery would predict AKI related poor patient outcomes.

Methods: The cRAI, combining risk factors and clinical signs of kidney dysfunction [Figure] was studied in a multicenter derivation analysis to compare predictive performance for poor outcome to prediction by the individual cRAI terms. Poor outcome was defined as Day 3 AKI or ≥5 days of mechanical ventilation or death.

Results: Of 308 patients (64% male, age 37 days [IQR:5-152] days) were analyzed. Half had single ventricle heart disease. The cRAI ≥10 outperformed individual and combination risk and injury factors for prediction of the composite outcome and demonstrated the optimal balance of sensitivity and specificity (AUC=0.77) [Table].

Conclusions: Derivation data indicates the cRAI, assessed soon after surgery, may optimize prediction for poor outcomes in children undergoing cardiac surgery. Future prospective studies are needed to validate the cRAI encompassing factors that may enhance its performance.

Table. Sensitivity analysis for individual and combination risk and injury factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive Value (95% CI)</th>
<th>Negative Predictive Value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Society of Thoracic Surgeons-European Association for Cardio Thoracic Surgery - standardized score STS (Society of Thoracic Surgeons-European Association for Cardio Thoracic Surgery - standardized score STS)</td>
<td>0.275 (0.197-0.354)</td>
<td>0.574 (0.548-0.599)</td>
<td>0.405 (0.356-0.455)</td>
<td>0.595 (0.574-0.615)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass (CPB) &gt; 180 minutes</td>
<td>0.225 (0.133-0.318)</td>
<td>0.605 (0.578-0.632)</td>
<td>0.303 (0.258-0.351)</td>
<td>0.697 (0.662-0.732)</td>
</tr>
<tr>
<td>Urea output &gt; 1.0 mL kg bodymass 1 day</td>
<td>0.306 (0.197-0.415)</td>
<td>0.330 (0.305-0.355)</td>
<td>0.720 (0.688-0.752)</td>
<td>0.580 (0.544-0.616)</td>
</tr>
<tr>
<td>Urea output &gt; 1.5 mL kg bodymass 1 day</td>
<td>0.286 (0.178-0.394)</td>
<td>0.330 (0.305-0.355)</td>
<td>0.720 (0.688-0.752)</td>
<td>0.580 (0.544-0.616)</td>
</tr>
<tr>
<td>Creatinine-cystatin C ratio &gt; 0.08</td>
<td>0.500 (0.392-0.608)</td>
<td>0.522 (0.498-0.546)</td>
<td>0.662 (0.630-0.694)</td>
<td>0.538 (0.507-0.569)</td>
</tr>
<tr>
<td>Admission sCr &gt; 3 mg/dL</td>
<td>0.500 (0.392-0.608)</td>
<td>0.522 (0.498-0.546)</td>
<td>0.662 (0.630-0.694)</td>
<td>0.538 (0.507-0.569)</td>
</tr>
</tbody>
</table>

TH-PO116 Creatinine-Cystatin C Ratio Is Associated with Mortality in ICU Patients Undergoing Continuous Renal Replacement Therapy

Background: Development of acute kidney injury (AKI) in intensive care patients considerably increases the risk of mortality. Although several factors that are related to outcome have been recognized in this patient group, stratifying mortality risk still remains

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
a challenge. While serum creatinine levels are confounded by muscle wasting in critical illness, the less modulated changes in cystatin C reflect muscle mass in critically ill AKI patients, we evaluated the association between creatinine-cystatin C ratio and mortality in patients requiring continuous renal replacement therapy (CRRT) in the intensive care unit (ICU).

Methods: Retrospective analyses were conducted on 443 ICU patients who underwent CRRT between August 2009 and October 2016 at Severance Hospital of Yonsei University Health System, Seoul, South Korea. The patients were divided into four groups based on the creatinine-cystatin C ratio at the time of CRRT commencement. The primary outcome was 90-day mortality after CRRT initiation.

Results: The mean age was 64 ± 15 years, and 57.3% of patients were male. The most common cause of AKI was sepsis. The median and range of the creatinine-cystatin C ratio was 0.33 (0.13-2.0). The 90-day mortality rate for each creatinine-cystatin C ratio quartiles 1, 2, 3, and 4 were 76.6%, 73.9%, 61.3%, and 51.8%, respectively. Multiple Cox proportional hazard models revealed that the creatinine-cystatin C ratio was an independent predictor of 90-day mortality even after adjusting for confounding factors (Hazard ratio, 0.97; 95% confidence interval, 0.95-0.99; P <0.01). The prediction of mortality was significantly improved when creatinine-cystatin C ratio was considered compared to the Apache-II or SOFA scores alone.

Conclusions: Creatinine-cystatin C ratio is associated with mortality in ICU patients undergoing CRRT, and may be a practical marker in predicting survival among ICU patients with AKI.
Use of Caplacizumab in Germany to Treat Acquired Thrombotic Thrombocytopenic Purpura in a Real-World Setting

**Lucas A. Volke**, 1, 2 Jessica K. Kaufeld, 1 Paul T. Brinkkotter, 3 Jan Menne, 4 1CECAD, University of Cologne, Cologne, Germany; 2Medical School of Hannover, Hannover, Germany; 3University Hospital Cologne, Cologne, Germany; 4Medical School Hannover, Hannover, Germany.

**Background:** Acquired thrombotic thrombocytopenic purpura (aTTP), a form of thrombocytopenic microangiopathy, is a rare but life-threatening disease, which is characterized by microangiopathic hemolysis and thrombocytopenia with and without end-organ damage. It results from an autoantibody mediated inhibition of the metalloproteinase ADAMTS13 that is required for the degradation of ultra-large von-Willebrand-factor multimers. Two recent seminal trials (HERCULES and TITAN) demonstrate the efficacy of the new nanobody caplacizumab for the treatment of this condition. To assess the utility and role of caplacizumab in the treatment of aTTP patients, we analyzed the first 22 German patients that had been treated with the new drug since May 2018.

**Methods:** Retrospective analysis of epidemiologic and treatment related data of the first 23 German aTTP patients undergoing caplacizumab treatment in 12 German medical institutions between May 2018 and April 2019.

**Results:** Between May 2018 and April 2019, 22 patients (age range 26–83 years) were treated with caplacizumab in addition to pulsed steroids, plasma exchange and rituximab. On average, patients received 32 daily doses of caplacizumab, and treatment was initiated on day 7 after disease onset. Patients received an average of 12 plasma exchanges. 36 percent of all patients relapsed, however, most patients received caplacizumab only as treatment of refractory disease or relapse and not as front-line therapy. This resulted in only 20% of patients being treated strictly according to the HERCULES trial protocol. One patient died from microangiopathic complications despite early caplacizumab treatment. One patient suffered major bleeding complications, one patient an allergic reaction to the drug; in general, minor bleeding complications were reported but scarce.

**Conclusions:** Caplacizumab appears to be efficacious and reduced the time to platelet normalization in a real-world setting. Caplacizumab augments therapy options for patients with aTTP. The data presented here and future experience will help address pending questions about patient selection for caplacizumab treatment, therapy monitoring, timing of treatment cessation, and drug safety.

**TH-PO123**

Incidence and Risk Factors of AKI in Cancer Patients with Multi-Drug-Resistant Infections Treated with Colistin

**Ayesha Bhihkar, Dr Junaid Iqbal, Umm-e-Rubab Syeda, Aun Raza, Muhammad Abu bakar, Faisal Sultan. Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan.**

**Background:** Developing countries have seen a resurgence in the use of Colistin in recent years, for treatment of multidrug resistant (MDR) gram-negative bacterial infections. Colistin is associated with increased risk of nephrotoxicity and consequently poor outcomes in high-risk patients. We studied cancer patients at our centre to determine incidence, risk factors and outcomes of acute kidney injury (AKI) associated with use of Colistin.

**Methods:** We reviewed patient medical records using electronic information system (eHIS), from January 2015 to December 2018, in this single centre cross-sectional study using secondary data analysis. Adults with solid organ or hematological malignancies with confirmed or suspected multi drug resistant gram-negative infections, who received colistin for at least 48 hours, were included. Outcomes of AKI including need for renal replacement therapy (intermittent or continuous), length of hospital stay and mortality were studied. Patients were followed for 3-6 months following an episode of AKI to review development of chronic kidney disease (CKD). AKI was defined according to Kidney Disease Improving Global Outcomes (KDIGO).

**Results:** A total of 115 patients were studied. Mean age was 42.6 ± 15.4 years and Mean weight was 60.3 ± 14 kilograms. Majority (68.7%) were male. In multivariable analysis, three independent variables including weight (adjusted odds ratio [AOR] 1.43; 95% confidence interval [CI] 1.01-1.10), underlying malignancy (solid versus hematological [AOR 3.39; 95% CI (1.15-9.98), 0.02) and need for admission to intensive care unit (ICU) (AOR 2.75; 95% CI (1.00-7.82), 0.05) were identified as significant independent risk factors for nephrotoxicity. In patients who had AKI (n=75, 65.2%), mean length of hospital stay was 21.7 ± 13.7 days, 20% required renal replacement therapy (RRT), 10.4% developed residual CKD and 60% died.

**Conclusions:** Increased weight, solid organ malignancy and ICU admission were significantly associated with increased risk of AKI in this cohort. Patients who required RRT had worse outcomes.

**TH-PO124**

A Case of Steroid-Dependent Interstitial Nephritis Related to Pembrolizumab Use

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**Introduction:** Pembrolizumab is a humanized monoclonal antibody belong to class of Immune check point inhibitors (IC) used in cancer immunotherapy which targets the programmed cell death protein 1 receptor of lymphocytes. Ever since the FDA approval of Iplimumab in 2011 for Metastatic melanoma, there has been a rapid advancement in the use of IC in various forms of cancer. Every year the use of IC is rising so do adverse events related to the use of Immune check point inhibitors

**Case Description:** 77 y/o female with h/o metastatic lung cancer, on chemotherapy, transferred to ER from clinic after labs showed Creatinine of 8.95 and potassium: 7.4 compared to a baseline creatinine of 1.1 six weeks prior. Her Urinalysis showed 62 wbc's with rest of the labs unremarkable except for metabolic acidosis with a bicarbonate level of 16. She was managed supportively and subsequently a renal biopsy was done which showed diffuse severe acute tubulointerstitial nephritis with eosinophils consistent with a hypersensitivity reaction, marked interstitial fibrosis, marked arteriolesclerosis and mild arteriolosclerosis. Her history is significant for biopsy proven adenocarcinaoma of the lung diagnosed in June 2017 Started on chemotherapy with Carboplatin, pemetrexed initially. She had Left upper lobectomy and wedge resection in Oct 2017, followed by maintenance immunotherapy with Pembrolizumab only since December 2017. Considering the pathology finding patient was started on high dose prednisone for AIN. Even though creatinine improved to 1.71 on follow up visit she remained steroid dependent and her AKI progressed to CKD IV with recent EGRF of 27.

**Discussion:** The presence of Acute interstitial nephritis (AIN) secondary to Immune check point inhibitors has been described before but usually with the cessation of drug and with high dose prednisonne therapy for few weeks renal function improves. We present a case of Acute interstitial nephritis related to pembrolizumab use which presented a year after initiation of therapy and despite early initiation of steroids, she remained steroid dependent with progression of Acute kidney injury (AKI) to Chronic kidney disease (CKD). Our case emphasis on keeping AIN on top of differential diagnosis in patients treated with IC even if IC use is not recent and patient can develop steroid dependency with progression of AKI to CKD.
TH-PO125
Spontaneous Late Acute Cholesterol Emboli with Acute Hydrophilic-Polymer Kidney Injury in a Renal Allograft
Asad Riaz,1 Olwafisayo O. Adebiyi,1 Muhammad S. Yaqub,2 Tim E. Taber,1 Asif A. Sharfuddin.1 Indiana University School of Medicine, Indianapolis, IN; 2Indiana University, Indianapolis, IN.

Introduction: Hydrophobic coatings are used on intravascular devices to avoid thrombosis, and vasospasm during endovascular procedures. We report a very rare case of Acute Kidney Injury caused by this coating.

Case Description: 58 year old male underwent his second left renal transplant in March 2017. Prior to transplant he has mild- to moderate aortic stenosis. However subsequent to his transplant in October 2017 he was found to have critical aortic stenosis. For which he underwent a transcatheter -aortic valve replacement via right transfemoral percutaneous approach with the insertion of a bioprosthetic aortic valve. His renal function function remained stable at 1.4mg/dl range at the time of the aortic valve replacement. Three months in January 2018 later he presented with oliguric acute kidney injury with a creatinine of 5mg/dl. Urinalysis revealed microscopic hematuria and 1+ proteinuria. Doppler evaluation revealed elevated velocities within the proximal, midportion, the renal artery. with features suggestive of renal artery stenosis. The biopsy showed Acute tubular necrosis; Arteriole with isolated cholesterol embolus; Glomerular capillaries with intraluminal embolic material which was not palpable which appeared weakly eosinophilic, periodic acid-Schiff (PAS)-negative, largely silver-negative with speckled granular positivity, and slight blue-gray on trichrome stain. This was consistent with hydrophilic-polymer emboli prior case reports. The biopsy was complicated by acute hemorrhage and the patient had to have angiogram showing a severe 90% stenosis at the origin of the renal transplant artery. The lower pole segmental artery had to be embozled along with a 5 mm self-expanding bare-metal stent with resultant brisk flow through the stent to the transplant kidney. After 6 weeks of needing dialysis he recovered from his acute kidney injury with a creatinine back down to 1.6mg/dl.

Discussion: To date, only 4 cases of hydrophilic polymer emboli have been reported to involve the kidneys, of which 2 were in a renal allograft.(Chen et al NEJM 2015). This case provides evidence that renal lesions may be induced by hydrophilic-polymer emboli due to the transcatheter aortic valve procedures in conjunction with spontaneous acute atherosclerotic cholesterol embolism.

TH-PO126
Focus on POCUS: Do Not Blindly Trust the Bladder Scanner in Patients with Ascites
Harini Bejanki,1 Abhabish Koratala.1,2 1University of Florida, Gainesville, FL; 2University of Texas Health Science Center, San Antonio, TX.

Introduction: Urethral catheterization, an invasive procedure with infection risk, was regarded as gold standard for measuring residual urine volume(UVoI). It has now been superseded by portable automated bladder scanners(BS) performed by nurses at the patient’s bedside. The benefits include fewer invasive catheterizations and increased patient comfort. However, caution has to be exercised when using BS to identify UVoI in complex cases such as patients with ascites or other pelvic pathology. We report a case of pelvic ascites, where nephrologist-performed point-of-care ultrasonography (POCUS) has facilitated the correct diagnosis.

Case Description: A 45-year-old woman with history of liver cirrhosis was admitted for failure to thrive. Hospital course was complicated by decompensated cirrhosis, septic shock, and Acute Kidney Injury requiring renal replacement therapy. A routine BS to monitor renal recovery revealed UVoI of ~800ml. However, there was no urine return on insertion of a urethral catheter. Urology consult was requested to assist with the catheter insertion of a urethral catheter. Urology consult was requested to assist with the catheter.

Discussion: The blind nature of BS measurement does not allow differentation of bladder from other fluid collections. Hence, nephrologists should perform POCUS and need to be aware of the pelvic anatomy in patients prone to ascites, which likely avoids unnecessary consultations and catheterizations.

TH-PO127
Acute Interstitial Nephritis Presenting with Isolated Glycosuria
Benjamin Schwartz,1 Jason M. Kido.2 1Virginia Commonwealth University, Richmond, VA; 2VCU Medical Center, Richmond, VA.

Introduction: Acute Interstitial Nephritis (AIN) is often induced by drugs and is a common cause of acute kidney injury. The classical triad of AIN consists of eosinophilia, rash, and fever. However, clinically diagnosing AIN can often be challenging as these signs and symptoms rarely present in concert. The inflammatory pathology of AIN leads to renal tubule dysregulation which can be clinically observed as glycosuria, eosinophilia, leukocytosis or white blood cell casts and proteinuria. We present a case of AIN presenting with acute kidney injury and isolated glycosuria without pyuria.

Case Description: A 34-year-old female presented to our institution with nausea, vomiting and abdominal pain. She had been treated for tonsillitis with amoxicillin a month prior to presentation. She had a blood pressure of 160/104 mmHg without antecedent history of hypertension. She was afebrile. Her physical exam was significant for trace lower extremity edema. She had no rashes. On admission, her serum creatinine was 7.7 mg/dL with a potassium of 3.1 mmol/L, and hemoglobin of 11.7 g/dL. Her white blood cell count was 10.2 without eosinophilia. Urinalysis was significant only for glycosuria of over 500 mg/dL with a serum glucose of 119 mg/dL. Urine sediment examination was unremarkable. Hepatitis and HIV serologies were negative, complement levels were normal, and urine immunofixation was negative. Ultrasound of kidneys was normal. Throughout admission she sustained glycosuria with normoglycemia. She underwent renal biopsy which demonstrated acute interstitial nephritis. She was started on high dose prednisone that was tapered over the course of three months. Two months following presentation her glycosuria resolved, and four months following presentation her serum creatinine was 1.2 mg/dL.

Discussion: This patient had an atypical presentation of AIN that lacked classical diagnostic lab features and has been rarely reported. She had profound glycosuria in setting of normoglycemia, which resolved following a course of corticosteroids. Glycosuria was most likely due to proximal tubule damage from AIN. This case supports previous hypotheses that drug-induced AIN can cause SGLT dysfunction resulting in glycosuria in the absence of other identifiable proximal tubule dysregulations. We propose that resolution of AIN involves the repair and restoration of SGLT function.

TH-PO128
Sizzurp Joins the List: AKI from Recreational Drug Use
Cecille Marie C. Sales,1 Farida Migally,2 Roger A. Rodby.1 1Rush University Medical Center, Chicago, IL; 2Nephrology Associates of Northern Illinois and Indiana, Chicago, IL.

Introduction: Synthetic cannabinoids and bath salts, both popular for their psychoactive effects have been associated with acute kidney injury (AKI). Another recreational drug “sizzurp” (also known as “purple drank” and “lean”) was first used in the 1960s and made popular in the 1990s by the hip hop community. It consists of the antihistamine promethazine +/- codeine, typically mixed with a sweet soft drink, and ingested in higher than prescribed doses. Promethazine causes CNS depression, cholestatic jaundice and hypotension. Codeine can cause behavioral changes, respiratory depression, and cardiac arrest. Promethazine induces codeine metabolism to morphine via CYP2D6, potentiating a “high” and intensifying the sedative effects. Sizzurp is desired for creating euphoria accompanied by a “disassociative feeling”. Often ingested with alcohol, its risk profile is magnified.

Case Description: We have a 39-/+0 man with no PMH, who presented with abdominal pain after taking sizzurp for several days. He had scleral icterus and a BP of 150/96. Labs: WBC 25.4, Hgb 13.2 g/dL, Pt 367k, BUN 80 mg/dL, Cr 8.3 mg/dL. Total drug levels revealed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
bilkubin was 12 mg/dl with a mild transaminitis and a CK of 1500 units/L. The UA showed mild hematuria and proteinuria with urine P/C ratio of 1.2 g/g. The urine drug screen was positive for cannabinoids. Serologies, SREP and UREP were negative. The kidneys were normal in size and echogenicity and without hydronephrosis. Liver US showed fatty infiltration and liver biopsy revealed drug induced injury. A renal biopsy had 11 nl glomeruli with diffuse ATN, focal interstitial nephritis and a negative bile stain. It was negative. He was oliguric and required dialysis for one month but had eventual renal recovery with a Cr of 1.3 mg/dl.

**Discussion:** Little is known about the mechanism of AKI in many recreational street drugs including sizzurp. It may be directly toxic (nephrotoxic ATN) or it may be associated with hyperperfusion leading to ischemic ATN. Sizzurp should be added to the list of recreational drugs associated with AKI.

**Figure 1.** ATN with focal interstitial nephritis.

**TH-PO129**

**An Unusual Case of Atypical Hemolytic Uremic Syndrome Triggered by Acute Infectious Mononucleosis Infection Presenting Without Thrombocytopenia**

University of Alabama at Birmingham, Birmingham, AL.

**Introduction:** Atypical hemolytic uremic syndrome (aHUS) is characterized by abnormal clotting with features of intravascular hemolysis, thrombocytopenia, and acute kidney injury. A proportion of cases of aHUS are related to defects in the coagulation pathway. Due to absence of causal relationships, these findings have not been widely appreciated. Genetic testing has mainly been helpful in research settings. Given the paucity of evidence, an update on the management of aHUS is warranted.

**Case Description:** A 26-year-old female with acute infectious mononucleosis diagnosed a week before, presented with malaise, hypertension (148/98 mm) and oliguria. Laboratory data revealed hemoglobin 7.9 gm/dl, BUN 123 mg/dl, creatinine 11.3 mg/dl, UPCR of 5.6 mg/mg with a nephritic sediment. Moderate schistocytes were seen in the peripheral smear but platelets were normal. ADAMTS13 was normal. Renal biopsy showed acute and subacute tubular microangiopathy. Other than a recent positive IgM Monospot, autoimmune and other infectious studies were unremarkable. She had elevated Ba fragment, Bb fragment and soluble level sMAC/C5b-9. Genetic panel found a likely pathogenic variant in the CFH gene and a novel variant of unknown significance in the PLG (plasminogen) gene. Treatment with eculizumab resulted in discontinuation of dialysis after 4 weeks. Follow up at 6 months showed improved UPCR to 1.5 mg/mg.

**Discussion:** aHUS is characterized by uncontrolled activation of the alternate pathway of complement and coagulation pathways. Disease pathogenesis and coagulation pathway genetic variants have been associated. Our patient’s finding of EBV-triggered aHUS has been rarely reported and even less commonly in association with aHUS. The patient has a likely described combination of a likely pathogenic variant in the complement pathway CFH gene and a variant in the coagulation pathway PLG gene. Due to absence of causal relationships, these findings may be coincidental in this patient with EBV-triggered aHUS. Further research is needed to elucidate the pathophysiology of aHUS.

**TH-PO130**

**Diagnosing Atypical HUS in the Setting of Complement Amplifying Conditions (CAC): A Case Series**

Karthik Kovvuru, Maria Lourdes Gonzalez Suarez, Swetha Rani Kanduri.
University of Mississippi Medical Center, Jackson, MS.

**Introduction:** Detecting aHUS in the setting of complement amplification conditions (CACs) is challenging. We report 2 cases of aHUS which presented as treatment resistant Lupus, and unresolving sepsis from infection in post partum period.

**Case Description:** Case 1: A 20 year old African American woman with Lupus, diagnosed at age 16, chronically low complements, partially controlled with Azathioprine, Rituximab, Mycophenolate and recently started on Cyclophosphamide (CYC) for class IV lupus nephritis, received 3 doses) presented to hospital for confusion and seizures. She was diagnosed with lupus and cerebritis. Labs were significant for microangiopathic hemolytic anemia, thrombocytopenia and low complements. Considering her resistant lupus despite outpatient CYC and inpatient pulse dose steroids, she was started on plasmapheresis (PTE) after sending ADAMTS13 and genetic panel for aHUS. No clinical or lab improvement was noted after 5 sessions of PTE. Genetic panel for aHUS resulted equivocal with heterozygous missense mutations in CFI, CFHR1-3, CFIH, CFH genes. Started on Eculizumab (ECU) for aHUS (900 mg/week for 4 weeks). Serum creatinine and hemolysis labs improved significantly. She was maintained on ECU (1200mg/week) for 8 months after which she suffered sudden death. Case 2: A 38 year old African American woman with hypertension presented with headaches in her 3rd trimester (first pregnancy); underwent C-section at 27 weeks due to pre-eclampsia. Post-op she was transferred to ICU for hypoxic respiratory failure (ARDS) and sepsis. She was treated with antibiotics initially and changed to Oseltamivir due to positive Influenza PCR. She developed AKI requiring CRRT. Due to lack of clinical response, low complements and slowly declining platelet counts, further workup showed microangiopathic hemolytic anemia. APLA was started after sending ADAMTS13 and genetic panel for aHUS. Hemolysis labs and platelet levels partially improved after 10 sessions of PTE. aHUS genetic panel showed heterozygous missense mutation for CFIH. Started on ECU 900 mg/week for 4 weeks, followed by 1200 mg/week for 2 doses. Her renal function and other lab parameters returned to normal, and remained stable for past 18 months.

**Discussion:** Clinicians should have threshold for suspecting aHUS if CAC’s do not respond to appropriate therapy.

**TH-PO131**

Don't Judge a Book by Its Cover: The Challenges of Diagnosing Nondilated Obstructive Uropathy

Muhammad A. Shalhazd, Pravir V. Baxi, Roger A. Rodhy.
 Rush University Medical Center, Chicago, IL; Louis Weiss Memorial Hospital, Chicago, IL.

**Introduction:** Nondilated obstructive uropathy (NDOU) is a rare and elusive cause of AKI since the diagnosis of obstructive uropathy (OU) depends on the demonstration of a dilated collecting system while the lack of rules it out. Reported in <5% of OU, NDOU has been associated with retroperitoneal malignancy, lymphadenopathy and fibrosis. The diagnosis requires a high index of suspicion and intervention despite normal radiographic screening studies. We present a case of AKI thought to be ATN where recognition and treatment of NDOU prevented irreversible IRSDP.

**Case Description:** A 60-y/o woman with breast cancer complicated by metastasis to the retroperitoneal lymph nodes with a baseline serum creatinine (sCr) of 0.6 mg/dl was given zoladex and one month later had a sCr of 1.3. She had decreased urine output and abdominal pain. Ultrasound and CT imaging showed no evidence of hydronephrosis. Her UA was benign. She became anuric and HD was initiated. Her AKI was postulated to be ATN from biphosphonate use. A renal biopsy could not be performed because of DVT’s requiring anticoagulation. She was discharged on HD. Despite normal imaging and a possible diagnosis, her AKI remained a clinical concern for NDOU. Bilateral retrograde pyelogram performed two weeks post-discharge showed no hydronephrosis. There were questionable areas of mild ureteral segmental narrowing and because her clinical course suggested obstruction, bilateral stents were placed. There was an immediate diuresis with an average output of about 300 ml/hr. Her sCr improved from 8.6 mg/dl to 0.8 mg/dl over the next 24 hrs (Fig.1).

**Discussion:** NDOU is a rare diagnosis that requires a high level of clinical suspicion. The lack of dilatation in NDOU has many pathophysiologic explanations, but is felt mainly to be secondary to the encasement of the collecting system. Direct visualization via retrograde or antegrade pyelography with empiric stent or nephrostomy tubes placement may be necessary when the concern for NDOU is high despite imaging lacking evidence of hydronephrosis.
2.7 mg/dL, and she developed oliguric AKI. Renal US with Doppler was consistent with bilateral RAS (Table 1). Right RA stenting was performed, with immediate improvement in UO and Scr (F1g A&B). At 6-mo fu, her Scr is 3.3 mg/dL with BP of 114/62 mmHg on 3 meds, incl ACEI. **Case 2:** A 72-year-old WF with hx of uncontrolled HTN, CKD (baseline Scr 1.8-2.5 mg/dL) and recurrent hospitalizations for vol overload, presented with SOB and oliguric AKI. Renal US with Doppler revealed L RAS (Table 1). She developed oliguric AKI and left RA stenting was performed (Fig 1), with prompt improvement in renal function. At 5-mo fu, her BP is 138/64 mmHg on 3 meds, including an ARB, and her Scr was 1.62mg/dL. She has not had any further hospitalizations for vol overload.

**Discussion:** After publication of 2 large RCTs (ASTRAL & CORAL), RA stenting has fallen out of favor in tx of RAS. However, it is important to note that these studies excluded patients with severe disease, pulm edema and renal failure. Thus, determination for risks and potential benefits of RA stenting needs to be individualized high-risk pts.

**Table 1**

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<th>Antihypertensive</th>
<th>BP on admission</th>
<th>Admission Scr</th>
<th>Peak Scr</th>
<th>Renal artery US</th>
<th>Renal artery Doppler</th>
<th>Discharge Scr</th>
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<td>F</td>
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<td>3 yrs</td>
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<td>0</td>
<td>100 mg/dL</td>
<td>170/110</td>
<td>2.7 mg/dL</td>
<td>5.0/0.7</td>
<td>L RAS</td>
<td>No</td>
<td>2.15</td>
</tr>
</tbody>
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**Case 2:** A 72-year-old WF with history of uncontrolled HTN, CKD (baseline Scr 1.8-2.5 mg/dL) and recurrent hospitalizations for vol overload presented with SOB and oliguric AKI. Renal US with Doppler revealed L RAS (Table 1). She developed oliguric AKI and left RA stenting was performed (Fig 1), with prompt improvement in renal function. At 5-mo fu, her BP is 138/64 mmHg on 3 meds, including an ARB, and her Scr was 1.62mg/dL. She has not had any further hospitalizations for vol overload.

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**Table 2**

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<th>Antihypertensive</th>
<th>BP on admission</th>
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<th>Peak Scr</th>
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<td>170/110</td>
<td>2.7 mg/dL</td>
<td>5.0/0.7</td>
<td>L RAS</td>
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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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**TH-PO133**

**Renal Amyloidosis and Intracranial Mucormycosis in an Intravenous Drug User**

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**Introduction:** Mucormycosis is a rare but fatal fungal infection commonly seen in immunocompromised patients such as end-stage kidney disease and post-renal transplantation. Here we report a unique case of invasive mucormycosis associated with severe amyloidosis in a patient with impaired renal function and AA amyloidosis.

**Case Description:** A 37-year-old Caucasian man with a history of active intravenous drug use including heroin was admitted for one week of slurred speech, right-sided weakness and right facial drop. CTH showed a 2x3 cm lesion in the left deep frontal white matter with surrounding vasogenic edema. His labs showed a serum creatinine (Scr) of 15.04 mg/dL (estimated GFR: 4 mL/min/1.73m2), BUN of 120 mg/dL, and bicanecitaine of 10 mmol/L. The pH and pCO2 of the first venous gas were 7.14 and 28 mmHg respectively. His urinalysis was positive for 3+ glucose with a pH of 8.0. A spot urine protein/creatinine ratio was 6.87. A brain biopsy confirmed the diagnosis of mucormycosis and a renal biopsy was subsequently performed. Outcomes: The patient received maintenance isotonic bicarbonate fluid with daily urine output about 3-4L. His Scr improved but plateaued at 7 mg/dL. A course of IV amphotericin B, IV micafungin, and oral posaconazole were implemented. Renal biopsy (Fig 1) demonstrated AA amyloidosis, with greater than 90% of glomeruli showing mostly global involvement by amyloid. There was also vascular and tubulointerstitial involvement, and approximately 70-80% interstitial fibrosis and tubular atrophy were noted. He was eventually started on peritoneal dialysis and remains on posaconazole.

**Discussion:** Invasive intracranial mucormycosis can occur in patients with profound acidemia. Therefore, aggressive bicarbonate repletion is essential to control the infection in addition to appropriate antibiotic treatment. Glucosuria and bicarbonate wasting in our patient may suggest potential tubular injury from AA amyloidosis. A comprehensive history taking is pivotal to diagnose heroin-related AA amyloidosis, which results from chronic subcutaneous injections.

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**TH-PO134**

**Silicone Implant-Induced Granulomatosis and IgA Nephropathy in a Male-to-Female Transgender Person**

Karina P. Verma,1 Christina Irene Mejia,2 Muhammad O. Hanif,3 Suzanne Boyle,1 Drexel University College of Medicine, Panetueek, RI; 2Drexel University Section of Nephrology/Hahnemann University Hospital, Philadelphia, PA; 3Drexel University, Philadelphia, PA

**Introduction:** Silicone implants, used in cosmetic procedures, induce local and systemic inflammatory reactions. We describe a case of silicone implant-induced granulomatosis (SIG) presenting with hypercalcemia and AKI.

**Case Description:** A 58-year-old male-to-female transgender was referred to nephrology for symptomatic hypercalcemia (11.7 mg/dL) and AKI (Cr 1.46 mg/dL; baseline 0.88 mg/dL). Her history included well-controlled HTN, HTN, gender reassignment surgery, breast augmentation, perineal/gluteal silicone implantation in the 1990s. Evaluation of hypercalcemia revealed a suppressed PTH (12 pg/mL), normal PTHrP and SPEP, and high ACE and 1,25 vitamin D levels, suggestive of granulomatous disease. There was no evidence of TB. Urine protein/Cr was 0.360 mg/mg and urinalysis was bland. Other studies showed the following: CT scan, calcified granulomas on breasts and gluteal areas with portacaval and retroperitoneal lymphadenopathy; renal ultrasound, increased cortical echogenicity and non-obstructing renal calculi; inguinal node biopsy, granulomatous inflammation and non-polarizable injectable material consistent with silicone implant. Renal biopsy showed acute mild tubular injury, mild focal interstitial calcification without significant scarring or granulomas; 2-3+ mesangial IgA deposits with 30% foot process effacement. Resection of the granulomas was impossible. Low-dose prednisone was initiated for chronic management of hypercalcemia with normalization of serum calcium (9.6 mg/dL) and Cr (0.9 mg/dL).

**Discussion:** Bioimplants, like silicone, trigger local and systemic immune reactions by acting as T-cell-directed antigens or as adjuvants—substances that enhance the antigen-specific immune response. The systemic inflammatory responses that ensue have been labeled autoimmune/inflammatory syndrome induced by adjuvants (ASIA). ASIA can present as granulomatous disease, lupus-like syndromes, or vasculitis weeks to decades following receipt of the bioimplant. Our patient presented with hypercalcemia mediated by SIG an unanticipated finding of IgA nephropathy on biopsy, but no evidence of renal granulomatous disease. It is unknown if IgA nephropathy is a manifestation of ASIA or a coincidental diagnosis in this case. With increasing prevalence of cosmetic procedures, nephrologists should be aware of potential latent complications of bioimplants.

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**TH-PO135**

**First Case of Leptotrichia goodfellowii Endocarditis-Associated Glomerulonephritis**

Guneet S. Kocher, Ann Herron, Anna M. Burgner. Vanderbilt University Medical Center, Nashville, TN

**Introduction:** Infective endocarditis is a well described cause of glomerulonephritis (GN), but can be difficult to diagnose. We present the first case of ANCA-associated immune complex GN from Leptotrichia goodfellowii endocarditis with initial diagnosis made by kidney biopsy.

**Case Description:** A 57 year old male with hypertrophic cardiomyopathy with an ICD was found to have an acute rise of his creatinine to 3.4 mg/dL from a baseline of 1.1 mg/dL prior to his left heart catheterization in preparation for a septal myotomy. He noted two weeks of lower extremity edema, chills, subjective fevers, and poor oral intake. Workup notable for a UPCR 1.9 mg/mg, 415 RBC/HFP with dysmorphic RBCs, low C3 and C4 at 35 and 8 mg/dL respectively, atypical ANCA staining with positive MPO and PR3, and type II cryoglobulinemia. Remainer of serologic workup was negative. Creatinine worsened so methylprednisolone 1 gram daily was started and a renal biopsy was performed.
was performed showing IgM dominant, predominantly mesangipathic immune complex and necrotizing crescentic glomerulonephritis suggestive of endocarditis, as well as diffuse tubular injury. He developed acute severe mitral valve regurgitation due to a torn chordal tissue with vegetation seen on the mitral valve and an ICD lead. He was started on broad spectrum antibiotics and steroids stopped. Blood cultures grew Leptotrichia goodfellowii, a gram negative fusiform bacteria found in oral flora. It highlights the importance of considering indolent infectious etiologies in patients with acute renal failure. Clues suggesting subacute endocarditis-associated GN include presence of cardiac devices, low C3 and C4, and ANCA positivity, though kidney biopsy is key in confirming the diagnosis. While the role of immunosuppression in these patients is unclear, renal recovery can be seen with antimicrobial therapy alone, underscoring the need for isolation of the pathogen.

**TH-POI36**

**Bilateral Renal Infarction: An Uncommon Presentation of Multiple Myeloma**

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**Introduction:** We report on a case of bilateral renal infarction from disseminated intravascular coagulation, secondary to a previously undiagnosed multiple myeloma. This case of acute renal infarction is uncommon and may have a misleading presentation, leading to diagnostic delays/misdiagnosis, reason for us highlighting it here.

**Case Description:** A 70-year-old male with coronary disease, hypertension, repaired abdominal aortic aneurysm, presented with acute onset severe abdominal pain, nausea and a 2.1 L blood loss (in 6 months). Blood pressure was 185/90 mm Hg. He had abdominal tenderness. Labs showed hyperuricemia, normal plasma osmolality and creatinine was 1.43. CBC showed leukocytosis, anemia and thrombocytopenia. Peripheral smear showed Rouleaux formation and plasma cells (plasma cell count was 1239/mm3). Also, there was an elevated LDH, D-Dimer, and low fibrinogen, haptoglobin. He had an elevated bilirubin, alkaline phosphatase and AST with normal ALT. Prothrombin time and INR were elevated. A CT scan showed wedge-shaped opacifications within the right kidney and the left renal cortex without thrombi. Procalcitonin was normal and factor 5 Leiden mutation was absent. A 2-D echo was negative for any valvular disease. EKG showed sinus rhythm. With concerns for multiple myeloma (age, creatinine, rouleaux formation, increased plasma cells), we observed a monoclonal protein in SPEP SIFE showed monoclonal IgG-Lambda protein. Kappa/Lambda free light chain ratio was 0.01. Bone marrow biopsy revealed 20% plasma cells. FISH showed an IgH/MAF rearrangement (seen in plasma cell disorders). Carfilzomib, cyclophosphamide and dexamethasone as a predominance of CD4-positive T cells in the interstitium. Finally, a drug lymphocyte stimulation test was positive, and the patient was started on broad spectrum antibiotics and steroids stopped. Blood cultures grew Leptotrichia goodfellowii, a gram negative fusiform bacteria found in oral flora. It highlights the importance of considering indolent infectious etiologies in patients with acute renal failure. Clues suggesting subacute endocarditis-associated GN include presence of cardiac devices, low C3 and C4, and ANCA positivity, though kidney biopsy is key in confirming the diagnosis. While the role of immunosuppression in these patients is unclear, renal recovery can be seen with antimicrobial therapy alone, underscoring the need for isolation of the pathogen.

CT scan of Abdomen showing bilateral renal infarction

**TH-POI37**

**Acute Tubulointerstitial Nephritis Associated with a Vaccination of Japanese Encephalitis Virus: A Case Study**

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**Introduction:** Common causes of acute tubulointerstitial nephritis (ATIN) include infections diseases, collagen diseases, sarcoidosis, or a reaction to certain drugs (e.g., nonsteroidal anti-inflammatory drugs, antibiotics, lithium, anticonvulsants, and gout). Several studies have shown that acute kidney injury (AKI) is a frequent complication of dengue fever. In this case, we report a patient with AKI following vaccination with Japanese encephalitis virus (JEV). JEV is a flavivirus that is transmitted by mosquito bite and is endemic in Southeast Asia, the western Pacific, and China. The virus can cause both a mild form of the disease and severe encephalitis. Infection with JEV can be asymptomatic or cause a mild febrile illness with headache, myalgia, gastrointestinal symptoms, and rash. In severe cases, JEV can cause acute encephalitis, which may progress to acute respiratory distress syndrome (ARDS) and death. The virus can also cause other complications, such as hepatitis, myocarditis, and pancreatitis. A 52-year-old male, admitted due to chronic cough. He was incidentally found to be Human Immunodeficiency Virus (HIV) positive with CD4 254 cells/µL and was empirically treated for possible Pulmonary Tuberculosis (PTB) reactivation and Pneumocystis pneumonia (PCP). During his hospital stay, his serum creatinine (Cr) was noted to be increased reaching level of 3.82 mg/dL (from baseline of 0.82 mg/dL one year prior). He was then dialyzed and underwent kidney biopsy which showed minor glomerular abnormalities, acute interstitial nephritis with acute tubular injury, mild interstitial fibrosis and tubular atrophy with 20% global glomerulosclerosis.

CT scan of Abdomen showing bilateral renal infarction

**Discussion:** JEV vaccination, in addition to other well-known side effect, such as acute disseminated encephalomyelitis.

**TH-POI38**

**A Case of Severe AKI from Cutaneous Contact with Cresol**

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**Introduction:** Cresol is a hydroxytoluene of ortho-, meta-, and para-isomers that are precursors to various compounds including household pesticides, disinfectants, and dyes. Although cresol is harmless in low concentrations in the environment, it can be inadvertently absorbed through intact skin, respiratory, and gastrointestinal tracts causing multiple organ dysfunction.

Cresol exposure is a rare cause of acute kidney injury. Previous cases of cresol toxicity have focused on ingestions that report multi-organ dysfunction with a high prevalence of liver dysfunction. Only a handful of cases describe cutaneous absorption of cresol, usually associated with severe acute kidney injury without evidence of significant liver injury. This observation is likely because cutaneous cresol absorption bypasses the portal venous system and reduces the liver’s exposure to the toxin. The cause of acute kidney injury in cases of cresol intoxication is acute tubular necrosis based on a limited number of biopsy and autopsy case studies. Treatment is supportive with the potential for requiring prolonged hemodialysis depending on extent of exposure.

**TH-POI39**

**A Case of BK Nephropathy in a Newly Diagnosed HIV Patient**

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**Introduction:** BK virus-related nephropathy has been reported more among post transplant patients with immunosuppressive therapy but is less identified among non-transplant and HIV patients.

**Case Description:** We report at 52-year-old male, admitted due to chronic cough. He was incidentally found to be Human Immunodeficiency Virus (HIV) positive with CD4 254 cells/µL and was empirically treated for possible Pulmonary Tuberculosis (PTB) reactivation and Pneumocystis pneumonia (PCP). During his hospital stay, his serum creatinine (Cr) was noted to be increased reaching level of 3.82 mg/dL (from baseline of 0.82 mg/dL one year prior). He was then dialyzed and underwent kidney biopsy which showed minor glomerular abnormalities, acute interstitial nephritis with acute tubular injury, mild interstitial fibrosis and tubular atrophy with 20% global glomerulosclerosis. Clinical Nephrology and Rheumatology, Niigata University, Niigata, Japan

**Discussion:** We report a 52-year-old male, admitted due to chronic cough. He was incidentally found to be Human Immunodeficiency Virus (HIV) positive with CD4 254 cells/µL and was empirically treated for possible Pulmonary Tuberculosis (PTB) reactivation and Pneumocystis pneumonia (PCP). During his hospital stay, his serum creatinine (Cr) was noted to be increased reaching level of 3.82 mg/dL (from baseline of 0.82 mg/dL one year prior). He was then dialyzed and underwent kidney biopsy which showed minor glomerular abnormalities, acute interstitial nephritis with acute tubular injury, mild interstitial fibrosis and tubular atrophy with 20% global glomerulosclerosis. Clinical Nephrology and Rheumatology, Niigata University, Niigata, Japan

This is an interesting case of a biopsy-proven BK nephropathy in a native kidney of a newly diagnosed HIV patient with a CD4 count of more than 200 cells/µL. Most published data on BK nephropathy in HIV patients have CD4 of less than 50 cells/µL.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
BKN may be considered as a diagnostic dilemma in HIV or immunocompromised patients with progressive renal failure.

TH-PO140
AKI Secondary to Thrombotic Microangiopathy (TMA) in a Myeloma Patient: Scleroderma Renal Crisis (SRC), A Paraneoplastic Phenomenon
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Introduction: AKI due to TMA in a myeloma patient is an uncommon presentation. Rheumatologic paraneoplastic syndromes have atypical presentations and are typically a result of anti-tumor immune responses. These subsets of diseases occur simultaneously or in close temporal relation to the diagnosis of an underlying malignancy. Our case report describes scleroderma as a likely cause of AKI/TMA and a paraneoplastic manifestation of multi-organ myeloma.

Case Description: A 47-year-old man with no prior renal disease presented with peripheral neuropathy, hypertensive urgency, seizures, microangiopathic hemolytic anemia (MAHA), and acute renal failure. AKI work-up revealed paraproteinaemia and subsequent bone marrow biopsy confirmed multiple myeloma (MM). On examination, he was found to have findings suspicious for scleroderma including telangiectasia, limited cutaneous thickening, salt-and-pepper skin changes, and abnormal nailfold capillaroscopy. CT Abdomen revealed distal esophageal and rectal thickening and esophagram showed esophageal dysmotility. Worsening kidney function, new skin findings, and MAHA lead to a kidney biopsy, which demonstrated findings of severe thrombotic microangiopathy (TMA) with no evidence of cast nephropathy. CK 41.1°C was compatible with papillary and mid dermal sclerosis. Although autoantibodies were negative, patient was diagnosed clinically with scleroderma with scleroderma renal crisis (SRC) which appeared to be a paraneoplastic presentation of MM. Patient was treated with corticosteroids initially for SRC and subsequently Eculizumab. Interestingly, his kidney findings have not progressed after treatment for MM but remains dialysis dependent.

Discussion: AKI due to TMA in a patient with MM and SRC is a diagnostic dilemma. Paraproteins are associated with mimics of rheumatic diseases; however, there are rare reports of anti-tumor autoimmunity and paraneoplastic scleroderma. TMA known to be associated with both MM and SRC, and although the clinical presentation was suggestive of scleroderma, the negative serologies challenged the diagnosis. Further studies are required to determine whether MM can induce SRC and if chemotherapy can improve scleroderma outcomes in these patients.

TH-PO141
Rhabdomyolysis Associated with Aspirin-Mediated Hyperthermia
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Introduction: Salicylate toxicity and rhabdomyolysis are both potentially life-threatening conditions. Only 2 reports have previously described an association between salicylate toxicity and rhabdomyolysis. We present a case of non-traumatic rhabdomyolysis occurring after aspirin overdose.

Case Description: A 36-year-old male with a history of chronic aspirin use (~2,600 mg/day) presented to the emergency department with severe headache. A few hours prior, he had taken approximately 20 tablets of aspirin (325 mg each) to treat a headache. He denied trauma. Within an hour, he developed hypoxic respiratory failure requiring intubation and mechanical ventilation. His initial salicylate level was 76.1 mg/dL. Other laboratory values on presentation included serum creatinine 2.7 mg/dL, total CO2 18 mmol/L, arterial pH 7.72, and creatine kinase (CK) 436 U/L. Pressures were initiated for worsening hypotension. The patient became hyperthermic to 41.7°C. The aspirin overdose was initially treated with intravenous sodium bicarbonate, but when the patient became anuric the following day, renal replacement therapy was initiated. The patient had a stage 3 acute kidney injury (AKI) revealed that CK increased to 28,880 U/L by hospital day 3, and then slowly returned to normal limits over the next 2 weeks. Kidney function recovered sufficiently to stop hemodialysis on hospital day 27.

Discussion: Salicylate toxicity has been described in 1989 and 1994, describe rhabdomyolysis and AKI in patients presenting with acute aspirin overdose. Both cases described patients with hyperthermia, attributed to aspirin-mediated mitochondrial toxicity, followed by rhabdomyolysis. A case report from 2016 describes a young patient presenting with temperature 41.1°C, CK 2424 (604-1618) with IgG4-1117 (382-929) and IgG4-338 (4-86). Liver biopsy revealed minimal plasma cell infiltrate with negative IgG4 staining and no sscloising cholangitis. CT revealed increased retroperitoneal and inguinal lymphadenopathy. Prednisone 60 mg was initiated. He was subsequently readmitted for brawny LE edema and SOB. Repeat CT demonstrated bilateral cavitary lung lesions and increased retroperitoneal/pelvic lymphadenopathy. Blood cultures were positive for MSSA, TEE revealed normal leaflets and no vegetations. Repeat kidney biopsy again revealed plasma rich interstitial infiltrate (~30 IgG4+ cells/HPF) and diabetic kidney disease. Lyme nephropathy was denied but patient left prior to procedure.

Discussion: IgG4 is challenging to diagnose due to multiple disease manifestations. In our patient, findings consistent with IgG4 include those on kidney biopsy along with retroperitoneal lymphadenopathy and possible fibrosis. However, not all diagnostic criteria were met and he did not respond to a course of steroids. Other diseases potentially associated with IgG4 plasma cells within tissues (drugs, sarcoidosis, syphilis, GPA) were excluded in our patient. Our case may represent an atypical case of IgG4 or manifestation of a yet to be diagnosed disease.

TH-PO143
Urinary Arstics from Spontaneous Bladder Rupture: Rare Cause for Pseudo AKI
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Introduction: Spontaneous intraperitoneal bladder rupture is a rare entity. Diagnosis can be challenging. Symptoms are non-specific and misleading which delays the diagnosis and treatment. Life-threatening complications such as hypovolemic shock, hemodynamic instability, shock, and even death has been reported. We present a case of an unusual presentation of pseudo AKI due to TMA in a myeloma patient is an uncommon presentation. Rheumatologic paraneoplastic syndromes have atypical presentations and are typically a result of anti-tumor immune responses. These subsets of diseases occur simultaneously or in close temporal relation to the diagnosis of an underlying malignancy. Our case report describes scleroderma as a likely cause of AKI/TMA and a paraneoplastic manifestation of multi-organ myeloma.

Case Description: A 38yo male with urachal cyst excision 6 years ago, presented with abdominal pain and elevated creatinine. Imaging studies revealed mild ascites. Liver morphology was reported normal. Elevation in creatinine was attributed to pre-renal etiology and was encouraged hydration. He presented back 3 months later with increasing abdominal distension and discomfort, rapid elevation of the creatinine with hematuria. With rapid rise in creatinine and positive urinary sediment, renal biopsy was done. Biopsy was suggestive of MPGN with faint IgM and C3 deposits. He was started on urgent dialysis for elevated creatinine and steroids initiated. Peritoneal fluid creatinine was reported high consistent with urine leak in the peritoneum. CT Cystogram confirmed urinary leak. He was emergently taken up by urology for cystostomy.

Discussion: This case highlights phenomena of bladder rupture, urinary ascites and pseudo AKI. Bladder rupture occurs following blunt or penetrating trauma or spontaneous. Pseudo renal failure is the elevation of the creatinine from the resorption of the peritoneal fluid from urinary leak. If the ascitic fluid creatinine is significantly higher than serum levels, one should consider spontaneous bladder perforation as the etiology for the urinary ascites. CT cystogram is the gold standard imaging technique for diagnosis.

TH-PO144
Cocaine-Associated Atypical Haemolytic Anaemia Syndrome in a Genetically Susceptible Individual
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Introduction: Atypical haemolytic uraemic syndrome (aHUS) is characterised by thrombocytopenia, renal impairment and non-autoimmune haemolytic anaemia that requires early recognition and urgent treatment. Genetic variants predispose to this condition when a trigger, or ‘complement amplifying condition’, is supplied. Identification of such genetic variants and of lesser known complement amplifying conditions are crucial for furthering the understanding of this serious condition.

Case Description: A forty-seven-year-old man presented to the emergency department and was found to have an acute renal injury, thrombocytopenia, thrombocytopenia, non-immune haemolytic anaemia and hypertension (205/150mmHg). He had smoked cocaine for the first time two weeks prior. The patient was taken to the intensive care unit for urgent plasma exchange with fresh frozen plasma. An urgent ADAMTS13 demonstrated normal level (44.1% [40-130]). Treatment with eculizumab was commenced and the patient responded well. Six months following his initial presentation, the patient was stable. The patient was heterozygous for the c.268C>A-p (Ala423Glu) variant in the CFI gene.

Discussion: This case highlighted several important points. Firstly, our patient was found to be heterozygous for a rare gene variant previously detected in only two aHUS
mg and the dose was increased as tolerated. His proteinuria and hematuria improved with this new regimen. Four weeks after 2 months a repeat urinalysis showed 0.3 g of proteinuria and absence of microhematuria. This is only the third known case of biopsy proven FSGS reported with Infliximab use.

**Discussion:** Our case highlights an uncommon adverse effect of a commonly used medication. Contrary to the other two cases, which reported renal effects within first 6 months of infliximab therapy, we found renal involvement even after 20 months of infliximab suggesting possibility of delayed effects on kidneys. The possible mechanism responsible for the development of renal complications during anti-TNFα infliximab administration implicates an interaction of anti-TNFα antibodies with TNFα receptors on glomerular visceral epithelial cells. These effects of the TNFα inhibitors should trigger screening urinalysis in patients on these medications for early diagnosis and management of renal effects. Future research should elucidate the links behind the renal effects of infliximab.

**TH-PO147**

Membranous Glomerulonephritis as an Immune-Related Adverse Effect of Checkpoint Blockade Therapy

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**Introduction:** Immune checkpoint inhibitors are being used more frequently to treat various cancers, leading to immune related adverse effects (irAE). Although data on checkpoint inhibitor-induced nephrotoxicity is limited, a link to tubulointerstitial nephritis has been previously documented. We present a case of a patient who received ipilimumab and nivolumab, who developed membranous glomerulonephritis (MGN).

**Case Description:** A 20-year old Caucasian male with fibrolamellar-variant hepatocellular carcinoma (HCC) treated with nivolumab for the prior 2 years and additional plimulimumab for the prior 2 months presented with shortness of breath and pedal edema. Vital signs were notable for a heart rate of 100. Exam revealed tachycardia with no murmurs, lungs had inspiratory crackles bilaterally at the bases, and abdomen was soft, non-tender, and non-distended. On initial labs, albumin was 1.2 g/dL. Urinalysis demonstrated 4+ protein, and urine protein/creatinine (UPC) ratio was 14. He was found to have bilateral pleural effusions. Kidney biopsy demonstrated membranous glomerulonephritis negative for staining with PLA2R and THSD7A. Immune checkpoint inhibitors were discontinued and tacrolimus 2mg twice daily and prednisone 60mg daily were initiated. The patient was discharged home on lisinopril, rosvastatin, and bumetanide. UPC ratio was 6.5 at discharge and 0.7 a month after discharge.

**Discussion:** This is a case of a patient with HCC on immune checkpoint blockade therapy developing membranous nephropathy. Although HCC may also cause MGN, the rapid improvement of MGN with cessation of therapy more strongly suggests that this was an irAE. Given the increased use of checkpoint inhibitors, nephrologists should be mindful of this complication.

**TH-PO148**

Tocilizumab-Induced Complex Glomerulonephritis in a Patient with Rheumatoid Arthritis

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**Introduction:** Anti-TNF-α inhibitors used in the treatment of rheumatoid arthritis (RA) often cause immune complex glomerulonephritis (IC-GN) as part of biologics-induced immune renal disorders. However, similar effects due to anti-IL6 receptor inhibitors are very rare. Here, we report a case of tocilizumab (TCZ)-induced IC-GN in a patient with RA.

**Case Description:** A 70-year-old Japanese man was admitted to our hospital due to acute nephritic syndrome. He was diagnosed with RA 14 years previously and had received methotrexate (MTX) and biologics. Three years ago, the biologic was switched from adalimumab to TCZ. RA had been in remission, and his serum creatinine (Cr) was 0.8 mg/dL. One month ago, after showing flu-like symptoms, he developed bilateral lower leg edema, renal dysfunction (Cr 1.3 mg/dL), hematuria, and proteinuria, indicating acute nephritic syndrome. On admission, renal dysfunction (Cr 1.77 mg/dL, eGFR 30.7 ml/ min/1.73 m²), urinary protein 0.75 g/Cr, urinary red blood cells 50–99/high power field, and
and hypoalbuminemia (C3, 24 mg/dL; C4, 1 mg/dL; CH50, 0 IU/L) were found. Anti-nuclear antibody, anti-dsDNA antibody, parvoviral B19DNA, and anti-streptolysin O were negative, whereas cryoglobulin was weakly positive. Renal biopsy revealed mesangial cell proliferation and endocapillary hypercellularity with partial crescent formation. Immunofluorescence analysis indicated IgG, IgA, IgM, C3, and C4q deposition in the mesangium, so a diagnosis of IC-GN was made. After discontinuing TCZ and MTX, intravenous methylprednisolone was administered at a dose of 500 mg/day for three days and then prednisolone (PSL) was initiated at 60 mg/day. His renal function and urinary abnormalities improved, and serum complement levels increased. After 5 months of treatment, his renal function has been maintained using PSL 10 mg/day.

Discussion: The anti-IL-6 receptor antibody, TCZ, may lead to the development of IC-GN, similar to anti-TNFα inhibitor. The mechanism remains unknown because only one case of TCZ-induced IC-GN has been reported to date. Rheumatologists and nephrologists should be aware of this lesion and similar cases should be collected in future.

TH-PO149
DAMPaned Methotrexate Levels: A Case Report of Acute Methotrexate Toxicity
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Introduction: New guidelines exist on the management of methotrexate-induced nephrotoxicity, focusing on the use of glucarpidase (Voraxaze®). We describe an application of these guidelines and highlight nuances around drug procurement and post-intervention laboratory monitoring.

Case Description: A 61-year old male with diffuse large B-cell lymphoma (DLBCL) with cerebral involvement was admitted for his first cycle of high-dose methotrexate (HD MTX). He previously received two cycles of R-CHOP chemotherapy. Baseline serum creatinine (Scr) was 63 µmol/L. Following HD MTX, his methotrexate level was 175 µmol/L. Despite extracellular volume expansion, urinary alkalization, and leucovorin rescue, he developed severe acute kidney injury (Scr 374 µmol/L) and subsequently went into status epilepticus. He was given glucarpidase at 52-hours post-HD MTX. Methotrexate level 8 hours after glucarpidase was 7.26 µmol/L by immunoassay, but <0.05 µmol/L by mass spectrometry. Interference due to the DAMPA metabolite resulted in falsely elevated levels by immunoassay for > 5 days after glucarpidase administration. He remained non-oliguric. Serum creatinine peaked at 608 µmol/L then trended down. He ultimately avoided the need for dialysis and had full renal and neurologic recovery.

Discussion: Glucarpidase is an effective option for non-renal elimination of toxic methotrexate concentrations in patients with nephrotoxicity. Awareness of how to access the drug, protocolization of monitoring including specific laboratory requirements, and knowledge of alternative treatments is necessary for centres where HD MTX therapy is used.

TH-PO150
Azacitidine Indition of Creatinine Tubular Secretion: A Case Report
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Introduction: It is well documented that a number of medications lead to mild to moderate and reversible elevations of serum creatinine (Scr) without affecting glomerular filtration rate. In many instances, the discovery of this effect is a result of clinical observation with high index of suspicion. Such as an observation is also illustrated in our case report on a patient who has been receiving azacitidine.

Case Description: A 63-y/o male with PMI of FLX3+ AML in remission and stage 4 CKD was referred for episodic worsening of Scr. The initial presentation of AML was with a blastic crisis and AKI due to tumor lysis syndrome requiring urgent hemodialysis (HD). He was continued on intermittent HD for an additional 2 months and was able to come off HD with a new baseline Scr of 2.5 mg/dL. Around the same time, he was initiated on chemotherapy with azacitidine 75 mg/m² of body surface area subcutaneously daily for 7 days every 4 weeks. Upon evaluation of the patient in our Clinic 9 months after his AML diagnosis, transient elevations in Scr were noted, as illustrated in figure 1. The sharp rise in Scr was noted at the dates during which azacitidine was administered. Following careful review of history, which was uneventful as to the cause of fluctuating Scr, decision was made to monitor Scr concurrently with serum cystatin C during and after administration of azacitidine. Serum cystatin C did not follow the same trend, raising suspicion for inhibition of creatinine tubular secretion by azacitidine without affecting renal function per se.

Discussion: The current drug label for azacitidine recommends that if unexplained elevations of Scr occur, the next cycle of therapy to be delayed until values return to normal or baseline and the dose to be reduced by 50%. To our knowledge, inhibition of creatinine tubular secretion by azacitidine was not previously reported. This case calls for the need of azacitidine on renal proximal tubular transporters to be defined with physiologic studies, as this would have important implications on the underlying diseases being treated.

TH-PO151
Membranous Nephropathy Associated with Immune Checkpoint Inhibitors: A Report of Two Cases
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Introduction: Immune checkpoint inhibitors (ICI) are novel cancer immunotherapies with recognized nephrotoxicities. The most common toxicity is acute tubulointerstitial nephritis, but cases of glomerular injury have been reported. We describe 2 patients with membranous nephropathy (MN) associated with pembrolizumab.

Case Description: Case 1: 52-year-old woman with stage III ovarian cancer, treated with pembrolizumab. She presented with frothy urin and edema. Urine sediment was bland. Investigations demonstrated albumin 3 g/dL, proteinuria 12 g/dL and serum creatinine (sCr) 0.7 mg/dL. A biopsy showed thickened glomerular capillary walls. Immunofluorescence showed staining for IgG(3+), Anti-Phospholipase-A2-Receptor antibody [PLA2R(-)] and Thrombospondin Type-1 Domain Containing 7A antibody [THSD7A(+)]. Electron microscopy (EM) showed subepithelial immune-type electron-dense deposits with diffuse effacement of the podocyte foot processes consistent with MN. Pembozirumab was held and she received prednisone 1 mg/kg in remission of proteinuria. She was re-challenged with pembrolizumab with recurrence of proteinuria. Pembrolizumab was stopped and she received prednisone with resolution of proteinuria. Case 2: 39-year-old man with stage IV colon cancer, treated with pembrolizumab. He presented with proteinuria 2.2 g/dL, sCr 1.1 mg/dL, albumin 3.3 g/dL and bland urine sediment. Biopsy revealed staining for IgG(3+), Anti-PLA2R(-) and anti-THSD7A(+). EM showed subepithelial immune-type electron-dense deposits with diffuse podocyte effacement. The findings were consistent with MN. He received prednisone and pembrolizumab was held with resolution of proteinuria (0.3 g/dL).

Discussion: These are the first reported cases describing the association of MN and pembrolizumab. Although MN is well-described in solid tumors, the timing of onset and remission of proteinuria in these cases is suggestive of immunotherapy-related glomerular
Bevacizumab-Associated Thrombotic Microangiopathy Treated with Eculizumab


Introduction: Bevacizumab is a recombinant monoclonal antibody neutralizing VEGF-A that has demonstrated efficacy as an anti-angiogenic agent. Thrombotic microangiopathy (TMA) is a well-described complication of VEGF inhibitors. A previous case series described treatment of VEGF inhibitor-associated TMA with eculizumab. Here, we present two cases of bevacizumab-associated TMA with biopsy-proven kidney involvement who were treated with eculizumab.

Case Description: Case 1: A 68 yo woman with recurrent, metastatic ovarian high-grade serous carcinoma received pegylated liposomal doxorubicin (PLD) and bevacizumab. She developed new onset HTN, proteinuria (UPCR 0.6 from 0.1 g/dL) and AKI (Scr 1.5 from 0.9 mg/dL). Her HTN and AKI improved with holding bevacizumab. Bevacizumab was restarted and she again developed HTN, proteinuria (UPCR 3.1 g/dL) and AKI (1.5 mg/dL). Despite drug discontinuation for over two months, she developed hypertensive emergency, reduced urine output, and increased creatinine. Eculizumab was continued and she improved.

Discussion: We present two cases of severe bevacizumab-associated TMA with renal involvement who had evidence of disease progression or stabilization with eculizumab treatment. Thrombotic microangiopathy is a potential complication of VEGF inhibitor therapy and should be considered in patients with acute kidney injury.

TH-PO153
Nivolumab-Related ANCA-Negative Focal Necrotizing Glomerulonephritis

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Introduction: Immune checkpoint (ICP) inhibitors have revolutionized treatment options for many types of cancers. Adverse events associated with ICP inhibitors are mainly due to uninhibited immune response to tumor cells. Acute tubulointerstitial nephritis (ATIN) is the most commonly described kidney injury secondary to ICP inhibitors. Few case reports also identified glomerulonephritis (GN) induced by ICP inhibitors. Here we present a case of ICP associated focal necrotizing pauci-immune GN.

Case Description: Patient, 65-year-old man with aortic valve replacement, prior embolic stroke, was diagnosed with left lower quadrant de-differentiated liposarcoma on 7/21/2018, and treated with nivolumab on 9/6/2018. A month later he underwent excision of tumors, resection and anastomosis of small intestine and revascularization of femoral popliteal/iac arteries. His baseline GFR was 1.12 mg/dL. His course was complicated by infections and was treated with ciprofloxacin and developed an allergic reaction with a rash. Thereafter, he started having increase in creatinine with a peak of 7.53 mg/dL on 12/16/2018. His urine analysis was significant for hematuria and proteinuria of 2 grams. Renal ultrasound did not show hydronephrosis. ANA, dsDNAAb, c-p-ANCA, anti-CLAD Ab, C4, and hepatitis A/B/C and HIV1/2 were all negative. Patient underwent a renal biopsy that revealed pauci-immune vasculitis with minor mesangial IgA and C3 positive staining. Patient was started on prednisone, Rituximab, and plasmapheresis with improvement in renal function and finally came off dialysis and creatinine stabilized at 2.0 mg/dL two months later.

Discussion: Use of ICP have resulted in improvement in patient survival compared to standard chemotherapy; however, there has been increasing appreciation for the adverse events associated. Therefore, obtaining a kidney biopsy and early recognition of ICP associated renal toxicity is essential to further optimize cancer patient’s morbidity and mortality.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO156
Dasatinib Induced Thrombotic Microangiopathy
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Introduction: Treatment of chronic myeloid leukemia (CML) is complex. With the development of tyrosine kinase inhibitors (TKI), disease control is now possible. Dasatinib, a second-generation TKI, has proven to be effective for the long-term treatment of CML. Nephrotic range proteinuria has been reported with this agent, however a kidney biopsy is rarely performed. We present a case of a patient with CML who developed nephrotic-range proteinuria after initiation of dasatinib therapy that resolved after changing treatment to Imatinib.

Case Description: A 48-year-old female with CML was started on dasatinib. Three months into her treatment, her dose was increased. Two months later, she developed worsening hypertension, nephrotic range proteinuria (6gm/24 hours) and hypoalbuminemia (2.4g/dl). Her urinalysis was otherwise unremarkable. She had no laboratory signs of microangiopathic hemolytic anemia. She had not been on any other chemotherapy or targeted therapy. A kidney biopsy was performed. Pathological findings of kidney biopsy specimen by light microscopy and electron microscopy were consistent with acute and chronic thrombotic microangiopathy. There were no signs of podocyte injury. These pathological findings were compatible with renal-limited thrombotic microangiopathy induced by dasatinib. After change of treatment to imatinib (Gleevec), levels of proteinuria dropped to less than 1gm/24 hours and she was taken off her blood pressure medications. Her CML is responding to Imatinib.

Discussion: We present a case of acute kidney injury, hypertension and proteinuria that developed during treatment with dasatinib for CML. Pathological findings revealed endothelial injury consistent with a renal-limited thrombotic microangiopathy. Patient’s proteinuria and hypertension resolved after changing therapy from dasatinib to imatinib. These pathological findings were suggestive of dasatinib as the culprit drug. We should be aware of this off-target adverse effects of dasatinib on the kidney.

TH-PO157
Bevacizumab-Associated IgA-Dominant Membranoproliferative Glomerulonephritis
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Introduction: Bevacizumab, a recombinant monoclonal antibody that blocks the vascular endothelial growth factor A (VEGF-A), is known to induce a renal-limited thrombotic microangiopathy (TMA), hypertonsemia and proteinuria. Acronic bevacizumab-associated TMA can eventually lead to a glomerulopathy with membranoproliferative glomerulonephritis (MPGN) histology. We describe the unique case of IgA-dominant MPGN induced by bevacizumab in the absence of TMA.

Case Description: A 29-year-old male patient, with a history of neurofibromatosis type II and bilateral vestibular schwannomas treated with bevacizumab, is evaluated for nephrotic range proteinuria with preserved renal function eight months after initiation of therapy. Bevacizumab was initially held and the serologic evaluation for proteinuria worsening (24h-urine protein: 6460 mg/24h) despite cessation of bevacizumab for 9 months and treatment with ACE Inhibitor eventually leading to a kidney biopsy. The kidney biopsy showed segmental endocapillary hypercellularity with thickening of the glomerular capillary walls and segmental double contours. The immunofluorescence was positive for IgG, IgM, IgA, Kappa and Lambda with IgA dominant pattern. The electron microscopy showed subendothelial and mesangial deposits. No TMA was seen. The final diagnosis was MPGN with IgA-dominant immune complex deposition. The patient was treated with Mycophenolate Mofetil with poor response after 4 months of therapy.

Discussion: VEGF-A secretion by the podocytes is essential in maintaining a healthy glomerular capillary endothelium. Disruption of this interaction by bevacizumab leads to a renal-limited TMA that is reversible after stopping the medication. Few previous case reports described IgA deposits in patients with bevacizumab-induced TMA. Previous reports of bevacizumab-associated TMA are well described, and a link between these two differing lesions may be possible but presently remain speculative. As the use of these agents is becoming more prevalent, further studies are needed to identify the mechanism and potential risk factors for renal disease to help guide treatment.

TH-PO158
Immune Checkpoint Inhibitor Use in a Patient with a History of Familial Anti-GBM Disease: A Clinical Dilemma
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Introduction: Immune checkpoint inhibitors (ICIs) have gained increasing use for the treatment of lung adenocarcinoma. Its utilization in patients with underlying autoimmune diseases is a challenge due to the fear of disease relapse or flare. Here, we present the case of a familial anti-GBM disease that received pembrolizumab for lung cancer.

Case Description: 71-year-old lady was evaluated 6 years ago for worsening kidney function. A kidney biopsy led to a diagnosis of anti-GBM disease. Her creatinine peaked at 2.7 mg/dl and with treatment remained at 1.2-1.3 mg/dl, with anti-GBM undetectable after therapy. Three years later, she was diagnosed with left lung adenocarcinoma and underwent surgical resection, followed by external beam radiation and chemotherapy (carboplatin and paclitaxel). Unfortunately, her disease progressed and since she had positive Programmed Death-Ligand (PD-L1) staining of her tumor cells; she was considered for starting on immunotherapy with pembrolizumab as a second line. She was evaluated by nephrology prior to initiation. Her baseline anti-GBM antibodies, ANCA antibodies and Anti-nuclear antibodies (ANA) were negative. Mutual decision with the patient was made to proceed with pembrolizumab with close monitoring of these target antigens and serum creatinine. Seven months after treatment, her creatinine remains stable at 1.2-1.3 mg/dl, with undetectable Anti-GBM, ANCA and ANA antibody titers.

Discussion: Checkpoint inhibitors are agents that unleash the immune system against cancer cells. Its use in patients with pre-existing autoimmune diseases pose a major clinical challenge. With cautious monitoring patients can use checkpoint inhibitors as a therapeutic option.

TH-PO159
Checkpoint Inhibitors: The Double-Edged Sword in Kidney Transplant Patients
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Introduction: Immuno therapy in the form of Checkpoint inhibitors (CPI) has significantly improved outcome and survival in patients with melanoma and its use has extended to multiple malignancies with good outcome. However around 50% allograft rejection is reported in patients with renal transplant who were treated with CPI with median time of 21 days from initiation of therapy.

Case Description: 40-year-old man with deceased donor kidney transplantation 7 years ago was diagnosed with metastatic melanoma of the right scalp and underwent wide excision followed by Dabrafenib and Trametinib and then switched to Ipilimumab and nivolumab. His baseline creatinine was 1.8 mg/dl. After 2 cycles of immunotherapy, he was noted to have severe acute kidney injury with Creatinine of 8.5 mg/dl. Renal biopsy showed acute T cell mediated rejection Banff grade IIA and suspicion for acute antibody mediated rejection in addition to positive peritubular capillaries for C4d. patient was treated for acute rejection with IV Methylprednisolone, rituximab, plasmapheresis (3 sessions) and intravenous immunoglobulin. Patient didn’t have renal recovery and a decision was taken to sacrifice the allograft and continue immuno therapy for Melanoma.

Discussion: The complex mechanism for acute rejection in renal transplant patient with use of CPI is still under investigation. One suggested mechanism is related to the inhibition of programmed death ligand 1 (PD1/L) that involved in increasing graft tolerance by increasing T regulatory (Treg) cells and limiting the function of effectors T cells. The current recommendation for treatment of malignancy in patients with renal transplant is to reduce the immunosuppression by stopping the anti-metabolites and possibly switching to mTOR inhibitors. However, these guidelines predated the era of immunotherapy for metastatic malignancy and need to be reevaluated. Currently there are no established guidelines to help guide the prevention and treatment of acute reaction in this population and no clear studies about the safety of anti-rejection therapy on tumor progression. With the reported high probability of graft loss, the nephrologist and oncologist should have an extensive discussion with the patient prior to starting CPI to guide with treatment decision that will impact patient lifestyle and cancer response.

TH-PO160
Intravitreal Injection of Avastin over Time Can Be Associated with Thrombotic Microangiopathy in the Native Kidney
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Introduction: Avastin, an inhibitor of vascular endothelial growth factor, has been used for treating various metastatic cancers. Its side effects relating to renal thrombotic microangiopathy (TMA) has been well known. Intravitreal injection of Avastin (IAA) has been used to treat macular proliferation or degeneration in patients. A recent study of 69 patients with IAA showed no side effects, while there were two case reports suggested a link between IAA and native renal failure in 5 patients without proven biopsies. Whether IAA over time can lead to renal TMA in diabetic patients remain controversial. This case reports the presence of renal TMA after months of IAA in a diabetic patient.

Case Description: A 56 years old diabetic man received IAA for macular edema and proliferative retinopathy over the past few months was found to have decreased creatinine clearance and rising creatinine. Upon further examination, serum creatinine up to 2.47 mg/dl with a nephrotic range of proteinuria (protein/creatinine ratio 4.7). All his serology tests were negative. A renal biopsy was performed to evaluate pathologic changes in the kidneys (Light microscopy revealed mesangial nodular expansion, characteristic for diabetic nephropathy, with additional segmental subendothelial expansion and lamination around the diabetic nodules. The acute tubular injury was present on PAS-stained sections. No thrombi formation was noted in glomeruli or vessels.
Immunofluorescent studies reveal moderate nearly linear IgM staining around diabetic nodules with positive IgG staining. Electron microscopy showed double constituted glomerular basement membranes with subendothelial edema causing detachment of glomerular endothelial cells. Overall findings supported a diagnosis of chronic active TMA on top of diabetic nephropathy background and secondary acute tubular injury.

Phenotypic analysis was informed of the result. A follow-up will be conducted (IAA may be discontinued). The finding of this case suggest the link between repeat IIA and renal TMA, where a small leakage of Avastin from repeat IIA could be a thread to interact with glomerular podocytes and endothelial cells leading to chronic active TMA in the kidney, resulting in renal failure and proteinuria.

**TH-PO161**

Wiedemann-Steiner Syndrome Presenting as Bladder Outlet Obstruction

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**Introduction:** Wiedemann-Steiner syndrome is a rare autosomal dominant disorder associated with pathogenic variants in the KMT2A (Ewing Methyltransferase 2A) gene, which encodes a histone methyltransferase thought to regulate transcription via methylation of histone H3K4. This gene has targets in many human tissues, including multiple HOX and WNT genes. The disorder classically presents as prenatal and postnatal growth restriction with atypical facial features. While renal involvement has been seen in some cases, this has never been described as a presenting feature, as in this case.

**Case Description:** This late-preterm SGA newborn boy presented with anuria for the first 2 days of life and a distended bladder. There was a prenatal diagnosis of hydronephrosis later described as bilateral grade IV hydronephrosis with hydroureter on US and isolated left grade 3 hydronephrosis on VCUG, not due to PUV or ureteroceles. SCr on DOL 2 was 1.9 with improvement to 1.2 after a suprapubic tube was placed for urine output. He was evaluated by genetics in the early newborn stage who appreciated hypertichosis, upslanted palpebral fissures, and clinodactyly. After recurrent UTIs, a voiding cystourethrogram was performed and showed a severely distorted left upper tract collecting system. A skeletal survey showed no signs of skeletal dysplasia and a chromosome microarray was normal. Endocrine evaluation for his short stature (height and weight below the 3rd percentile) revealed no obvious hormone-mediated disease process. Whole Exome Sequencing (WES) identified a de novo autosomal dominant pathogenic variant in the KMT2A gene (p.R1151*, c. 3451 C>T), consistent with the diagnosis of Wiedemann-Steiner syndrome.

He went on to develop stage III chronic kidney disease within his first year of life, and is expected to require kidney transplant by the age of 5 after vesicostomy closure and self-catheterization for renal protection.

**Discussion:** This case illustrates an atypical presentation of a rare genetic disorder and adds to the phenotype of Wiedemann-Steiner syndrome.

**TH-PO162**

Unraveling the Genotype to Phenotype Correlation: A Child with PH1 and a Novel Mutation Responsive to Pyridoxine Therapy

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**Introduction:** Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disorder, caused by a mutation in the AGXT gene, and characterized by an accumulation of calcium oxalate in various body tissues, particularly the kidney. Disease expression is variable, ranging from nephrocalcinosis during infancy to recurrent or infrequent nephrolithiasis in childhood or adulthood and renal failure in 20-50% of patients. Over 175 mutations have been identified to date. About 10 to 30% of patients with PH1, particularly those with p.Gly170Arg or p.Phe152Le mutations, respond to pyridoxine therapy with a significant reduction of urinary oxalate excretion. We present a patient with PH1, found to have a previously undescribed mutation in the AGXT gene, who showed excellent response to pyridoxine therapy.

**Case Description:** AS, a nine year old male, born in Afghanistan to consanguineous parents, initially presented with a history of flank pain, failure to thrive and bilateral nephrolithiasis at the age of five years. He underwent several rounds of extracorporeal shock wave lithotripsy, and at a year of age, established care with nephrology in the U.S., his workup revealed hypocitraturia, elevated 24 hour oxalate level at 127mg/day (normal range 20-40) and a urine glycolate level of 249mg/day (normal range <80) raising concern for PH1. He was empirically started on vitamin B6, potassium citrate and advised to increase hydration. Genetic testing confirmed PH1 with a homozygous mutation in AGXT (c.552C>T; p.Arg185Cys), reported as a variant of uncertain significance. Follow up urine testing at 3 and 7 months showed a reduction in oxalate levels by 35% and 58%, respectively. He remains asymptomatic, has normal GFR, with no evidence of systemic oxalosis and stable right sided nephrolithiasis since last ESWL in 2017.

**Discussion:** We conclude that in this patient with classic PH1 phenotype, the finding of a homozygous variant in AGXT is not only pathogenic, but also responsive to pyridoxine therapy. We hope this case will add to the knowledge base of PH1 and help guide management in patients with a similar genotype. Pyridoxine therapy has been life changing for AS and his family.

**TH-PO163**

A Case of Childhood Bilateral Renal Artery Stenosis Not Seen on Angiography

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**Introduction:** Renovascular hypertension (HTN) is an important cause of secondary HTN in children. Multiple imaging modalities are considered for detection of renal artery stenosis (RAS) such as: duplex ultrasound, CTA, and MRA. However, the gold standard for detection is conventional angiography. We present a case of bilateral RAS that was undetected by angiography.

**Case Description:** A 12 year old previously healthy female presented to a well-child exam with a BP 180/111 mmHg. Her BMP was remarkable for a serum K+ of 3.2 mmol/L and normal eGFR. Renal US was unremarkable and UA demonstrated microprecipitation (5-10 RBCs/hpf). She also had left ventricular hypertrophy on echocardiogram. Hypertension work up included: plasma aldosterone, serum free metanephrines, ACTH, monogenic HTN panel, and serum cortisol levels. Work up was negative other than an elevated aldosterone. A CTA demonstrated “string of beads appearance of the bilateral renal arteries and lobar segments suggestive of bilateral fibromuscular dysplasia and focal moderate-severe stenosis of the proximal left renal artery.” Angiography did not demonstrate RAS. She was started on captopril and elevation in creatinine was noted. She was then sent to a vascular surgeon for a second opinion. At that time, angiography was repeated and bilateral renal vein renin measurements were elevated. Via imaging, she had ostial left RAS and mid-right RAS. She is currently managed on clonidine, HCTZ, and lisinopril. She is scheduled for bilateral renal revascularization.

**Discussion:** This case illustrates the importance of multiple imaging modalities in the work up of renovascular HTN. Our patient underwent angiography by a skilled radiologist and bilateral RAS was not detected, thus we highlight the value of specialized vascular surgery centers for cases with a high index of suspicion.
Discussion: Pipecaldine is excreted by the kidney; therefore, elimination is prolonged in patients with chronic kidney disease (CKD). The mean clearance of this drug by HD is 32%. Interestingly, the QRS was narrow during HD even though the serum pipecaldine level was high. The volume of distribution of this medication is 1.7-L/kg in CKD patients; most of the drug is distributed in the tissue. We infer that the drug in the tissue was re-distributed after HD. Pipecaldine should be administered cautiously to elderly patients even if the serum creatinine is normal. Serum pipecaldine level may not correlate with EKG findings.

TH-PO165
Vedolizumab, a Monoclonal Antibody for Treating Crohn Disease, Can Cause T-Cell-Mediated Interstitial Nephritis and CKD
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Introduction: Vedolizumab (Vedo), a gut-selective humanized monoclonal antibody, binds specifically to the a4/β7 integrin as a lymphocyte homing antagonist. Previously, Bailly et al have reported the first case of Vedo induced acute interstitial nephritis (AIN) (Am J Kid Dis 2017), with good renal recovery after the standard steroid treatment. Here, we report another case of Vedo associated AIN which resulted in CKD despite the standard steroid treatment. She was subsequently received steroid treatment without significant improvement of renal function (serum creatinine 1.8 mg/dl at the 3rd month follow-up following the biopsy). The case indicates that Vedo associated T cell mediated AIN can lead to a substantial CKD.

Case Description: A 33 years old woman with Crohn’s disease involving her small bowel and colon developed acute kidney injury with rising serum creatinine (from 0.7 to more than 2.0 mg/dl) after her receiving 3 standard doses of Vedo infusions over 2 months. Without signs of recovery after stopping the Vedo treatment, a renal biopsy was performed to evaluate her renal pathology. Light microscopy revealed AIN with only 10% of B lymphocytes, 10% of CD8 positive macrophages, but 80% of T lymphocytes in the interstitium and mild tubulitis. Further stains showed 60%CD4 regulatory T lymphocytes and 40% of CD8 positive cytotoxic T lymphocytes. No eosinophils, neutrophils or granulomas were present. Kidney injury molecule-1 staining was positive in proximal tubules, consistent with an acute tubular injury secondary to AIN. Trichrome stained sections showed moderate interstitial fibrosis and tubular atrophy. Immunofluorescent studies and electron microscopy did not reveal additional specific findings.

Discussion: She has subsequently received steroid treatment without significant improvement of renal function (serum creatinine 1.8 mg/dl at the 3rd month follow-up following the biopsy). The case indicates that Vedo associated T cell mediated AIN can lead to a substantial CKD.

TH-PO166
Cefepime-Induced Neurotoxicity in a Patient with ESRD
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Introduction: Cefepime causes neurotoxicity with an increased risk in patients with renal dysfunction.

Case Description: A 59-year-old male with ESRD on hemodialysis (HD) on Tuesday/Thursday/Saturday, hypertension and peripheral arterial disease was admitted with altered mental status of 2 days duration. Patient was admitted 1 month prior to presentation for elective placement of an iliofemoral vein graft.
DRESS to Impres: Unusual Case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) due to Epoetin Alfa

**Introduction:** DRESS syndrome is a severe life-threatening hypersensitivity reaction to medication or its active metabolites. It manifests with fever, rash & organ involvement, kidneys & liver most commonly. It has a 10% mortality rate. More frequently associated with DRESS are sulfonamides, anti-inflammatory medications & anticonvulsants. There is only one case report of epoetin alfa related DRESS syndrome in the literature, and herein we present the second.

**Case Description:** 92 y/o man with hypertension, A. fib. & CKD IIIa arrived at ED due to generalized pruritic skin eruption since 7 days ago. Physical exam: generalized non-blanching erythematous patches on lower extremities, torso & upper extremities. Few violaceous purpuric patches on extremities, petechiae on palms & feet. Labs: WBC: 17.9 x10^3/U.L, PtH: 270 10^3/U.L, Eosinophil: 895. BUN: 50.7 mg/dl & Cr.: 1.8 mg/dl (base:1.2), ALT: 39, AST: 23 & CRP: 127.3. He was started on eopetin alfa 8 days prior, which was discontinued upon admission. Dermatology biopsied a lesion & recommended methylprednisolone (MP) IV for 2 days. Rash, eosinophils & creatinine improved. MP was discontinued as per derm. rec. but rash, eosinophils & creatinine again worsened. Biopsy: spongiotic dermatitis w/papkeratosis, pustules in stratum corneum, dermal perivascular lymphocytic infiltrate & scanty eosinophils. Allergist recc. restart MP for epoetin alfa related DRESS. See Fig 1 for data on MP, creatinine & eosinophils. He improved & was discharged on a steroid tapering.

**Discussion:** The European Registry of severe cutaneous adverse reactions is a scoring system to help yield the diagnosis of DRESS, a score of 6 makes it definitive, as presented in this case. Only ~11% of patients with DRESS manifest with renal disease. After literature review, this is only the second case of epoetin alfa associated DRESS. Epoetin alfa is a commonly used drug in patients with CKD & physicians should be aware of this potentially fatal adverse effect.

**Comparison of ATZV nephropathy case reports**

**TH-PO170**

**Fanconi Syndrome in an Elderly Patient with Membranous Nephropathy During Treatment with Immunosuppressant Mizoribine**

**Sho Nishikawa, Naoki Takahashi, Yudai Nishikawa, Sayu Morita, Kazushisa Nishimori, Mami Kobayashi, Sachiko Fukushima, Seiji Yokoi, Daisuke Mikami, Hideki Kimura, Kenji Kasuno, Masayuki Iwano. Nephrology, University of Fukui, Fukui, Japan.**

**Introduction:** Acquired Fanconi syndrome (FS) is often caused by drugs (antibacterial drugs, antiviral agents and anticanicar agents), is sometimes caused by autoimmune diseases, monoclonal light chain associated diseases and heavy metal poisoning. Mizoribine (MZR) is an oral immunosuppressant inhibiting inosine monophosphate dehydrogenase, widely used in Japan for treatment of autoimmune diseases, nephrotic syndrome and renal transplantation. Recently several studies have shown that a combination of steroids and MZR is effective in patients with membranous nephropathy (MN). Furthermore, there is an interesting report that the addition of steroid after MZR monotherapy for two or three months may be beneficial for patients with MN.

**Case Description:** An 80-year-old man was referred to our hospital with FS, acute kidney injury (AKI) and severe proteinuria (15 g/gCr). Two months before this admission, he was diagnosed with primary MN by his renal biopsy. He and his wife chose outpatient treatment because of his mild dementia due to ageing. Oral administration of MZR was started prior to prednisolone administration. One month later, serum creatinine was rapidly increased from 1.9 to 2.7 mg/dl with nephrotic-range proteinuria. In addition, serum albumin was decreased to 1.1 g/dl, and various abnormalities of laboratory data including glucosuria, hypokalemia, hypophosphatemia and hypouricemia were newly recognized. He had no history of exposure to heavy metals or administration of any other additional drug, including Chinese medicines. Hypokalemia, hypophosphatemia, glucosuria, hypouricemia and severe proteinuria were gradually improved by discontinued administration of MZR, additional oral administration of prednisolone followed by single intravenous injection of rituximab. He was finally diagnosed with MZR-induced FS from this clinical course and his typical laboratory data except proximal tubular acidosis.

**Discussion:** To the best of our knowledge, this is the first report demonstrating FS induced by MZR. Although the mechanisms induced proximal tubular dysfunction with MZR are unknown, nephrologists should pay attention to the onset of FS during treatment with MZR.

**TH-PO171**

**Atazanavir Crystal-Induced Chronic Granulomatous Interstitial Nephritis**

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**Introduction:** Atazanavir (ATZV) is a protease inhibitor used in the treatment of human immunodeficiency virus (HIV) infection. Highly active antiretroviral therapy (HARRT)-related nephrotoxicity is primarily linked to tenofovir (TFV) or to the non-older generation protease inhibitor. We describe a unique case of biopsy-proven ATZV-induced chronic granulomatous interstitial nephritis (CGIN) and review previously reported cases.

**Case Description:** A 51-year-old black man with HIV infection presented to renal clinic for evaluation of worsening kidney function. He was asymptomatic. He denied NSAID use and was on ritonavir (RTV), ATZV, abacavir and lamivudine. Physical examination was unremarkable. Laboratory data showed a serum creatinine (Cr) 2.7 mg/dL (3 months prior 1.7 mg/dL; 9 months prior 1.2 mg/dL). CD4 count was 327 and HIV-1 viral load was undetectable. Hepatitis B and C were negative. Complement, lupus serology and serum protein electrophoresis were within normal limits. Urinalysis showed 20-30 white blood cells/bpf. Urine protein-creatinine ratio (UPCR) was 450 mg/g. Urine culture was negative. Renal ultrasound was normal. One month later, sCr rose to 3.3 mg/dL. A kidney biopsy was performed and the specimen showed: interstitial mononuclear cell infiltrate containing granulomas, a granulomatous process with central necrosis, crystal-like material and neutrophils, moderate interstitial fibrosis, and 9/15 obsolescent glomeruli. ATZV was stopped and prednisone was begun. After 8 months, sCr gradually improved to a new baseline of 2.0 mg/dL. Our case is only the 10th reported (see Table TH-PO171).

**Comparison of ATZV nephropathy case reports**

**TH-PO172**

**Successful Treatment of Chronic Osteomyelitis with Avoidance of Amputation During PCSK9-inhibitor Treatment for Cardiovascular Diseases in Patients with Diabetes Mellitus and CKD**

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**Introduction:** Management of DM patients with chronic osteomyelitis (OM) of the foot is a challenging. Even with targeted antimicrobial therapy tailored to culture and sensitivity results, due to micro- and macromicrobial ischemia, patient's conditions usually deteriorate leading to subsequent amputation. We present a case series of 5 patients whose chronic OM recovered during treatment with PCSK9/Propionate Convertase Subtilisin/Kexin type 9) inhibitor to reduce the risk of myocardial infarction, stroke, and coronary revascularization.

**Case Description:** The patients (age 65-91 years) have a common history of chronic DM-2 (20-35 years) and multiple comorbidities such as coronary artery disease, CKD, obesity and diabetic nephropathy. A 77-year-old patient presented with fever, non-healing OM of the foot ulcer began as a minor injury, precipitated by DM peripheral neuropathy and 20-30 white blood cells/bpf. Imaging studies of the foot revealed OM. Patients underwent revascularization. We present a case series of 5 patients whose chronic OM recovered during treatment with PCSK9/Propionate Convertase Subtilisin/Kexin type 9) inhibitor to reduce the risk of myocardial infarction, stroke, and coronary revascularization.

**Comparison of ATZV nephropathy case reports**
nonhealing wounds as prevention of future amputation. It may also be advantageous to initiate PKCS-Inhibitor in all DM foot ulcer patients during treatment of chronic OM or even before the development of cellulitis or OM.

### TH-PO173

**Far Infrared Therapy May Improve Arterial Insufficiency and Joint Inflammation in CKD Stage 5 Patients**

**Siddique Akbar,** Christina Irene Mejia, Rudava Ullah, Sayeda Huimaira, Ziauddin Ahmed, Ridwan Faruq, Hasan Arif

**Introduction:** Far infrared (FIR) induces expression of endothelial heme oxygenase-1, reduces monocyte adhesion to endothelial cells, and provides a strong anti-inflammatory benefit to the vascular endothelium. It has been shown that FIR therapy improves dialysis fistula flow, maturation, and patency and leads to decreased pain and hematoma formation with needling in CKD stage 5 and 5d patients. It is also effective in relieving pain in patients with chronic pancreatitis syndrome like fibromyalgia and phantom limb after amputation through thermal and non-thermal effects. In the past we reported an improvement in graft survival and resolution of internal jugular vein thromboses associated with tunneled catheter insertion in two dialysis patients with FIR therapy. Now we report 3 CKD stage 5 patients with improvement of arterial insufficiency, frozen shoulder and partial rotator cuff injury using FIR therapy.

**Case Description:** Case 1. A 68-year-old man with CKD 5 due to FSGS and HTN developed significant claudication on his right leg and dislocation of his second toe. An arteriogram showed substantial small arterial disease not amenable to bypass and below knee amputation was recommended by his surgeon. A trial of FIR therapy on his leg was done for 5 minutes 3 times a week during dialysis and his dislocation resolved. FIR therapy was stopped and he remained pain free after 2 years of follow-up. Case 2. A 67-year-old man with CKD 5d due to HTN developed left shoulder pain with restricted range of motion. Analgesics and 3 weeks of physical therapy (PT) did not provide relief. A trial of 40 minutes of FIR therapy 3 times a week during dialysis was done. After 3 weeks, his frozen shoulder improved completely. Case 3. A 75-year-old woman with CKD 5 developed right partial rotator cuff tear after a fall. Diagnosis was confirmed by MRI and surgery was recommended. She refused surgery and tried 2 months of PT, which did not provide relief. Trial of FIR therapy was completely resoluated of pain and stiffness after 8 weeks of therapy. FIR therapy may have beneficial effect on arterial insufficiency and joint injury and inflammation and should be considered in CKD 5 patients suffering from these conditions. It is non-invasive and can be easily done as 40-minute sessions in the clinic or during dialysis treatments.

### TH-PO174

**Denosumab-Induced Severe Hypocalcemia and Hyperparathyroidism in a Peritoneal Dialysis Patient**

**Akintunde M. Akinjero, Chelsea C. Estrada, Hecscueh Suh. Stony Brook University Medical Center, Stony Brook, NY.**

**Introduction:** Denosumab is increasingly used in the treatment of osteoporosis in patients with End Stage Renal Disease (ESRD). The safety of Denosumab in ESRD is unproven. We report a case of severe hypocalcemia and hyperparathyroidism after Denosumab use in ESRD.

**Case Description:** A 56-year-old woman with history of osteoporosis, secondary hyperparathyroidism, and ESRD related hypocalcemia for the past eight years presented to clinic with complaint of paresthesias of hands and feet for two weeks. Vital signs and physical exam were unremarkable. Laboratory work-up showed profound hypocalcemia (corrected calcium of 6.8 mg/dL) and markedly high intact PTH (iPTH) of 3448 pg/mL (Table 1), with normal phosphate (5.1 mg/dL) and alkaline phosphatase (193 U/L). Upon medication review, we noted that the patient had been documented to receive denosumab 60 mg subcutaneously for the first time, two weeks prior to her visit. Before the use of denosumab, calcium, phosphorus, and 25-vitamin D were normal, with mildly high iPTH (Table 1). We noted that the patient had a history of 3,000 mg oral calcium and 4,000 mg Renvela. With these drugs, her hypocalcemia resolved. The laboratory workup improved after 3 weeks of treatment with normalization of serum calcium levels. The patient was discharged home on day 6. She was started on Repaglinide 0.5mg TID and asked to avoid metformin for the rest of her life.

**Discussion:** Denosumab is a monoclonal antibody used to treat osteoporosis; it binds to receptor activator of nuclear factor-kappa B ligand, an osteoclast differentiating factor, to inhibit bone resorption and increase bone mineral density. Bisphosphonates are first line treatment for osteoporosis. However, bisphosphonates are contraindicated in ESRD due to impaired clearance. Denosumab is not renally cleared, hence seen as an alternative for treating osteoporosis in ESRD. Decreased phosphate clearance, reduced production of 1α hydroxylation, and elevated fibrinolysis and bone mineral density. Denosumab further increases this risk by downregulating osteoclast activity. Denosumab continues to be used in ESRD, with increasing reports of hypocalcemia. Our case outlines the life-threatening hypocalcemia that may occur, and highlight the need for closer monitoring in ESRD patients receiving denosumab.

### Table 1. Changes in Calcium and iPTH levels after Denosumab.

<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Calcium (mg/dL)</th>
<th>iPTH (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Denosumab</td>
<td>Current Calcium</td>
<td>3.7</td>
</tr>
<tr>
<td>2 weeks after Denosumab</td>
<td>4.8</td>
<td>444</td>
</tr>
<tr>
<td>9 weeks after Denosumab</td>
<td>3.8</td>
<td>548</td>
</tr>
<tr>
<td>10 weeks after Denosumab</td>
<td>3.76</td>
<td>390</td>
</tr>
</tbody>
</table>

### Key

**TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only**

**Underline represents presenting author.**

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a creatinine kinase > 50,000 µ/L, hyperkalemia, hypercalcemia, and hyperphosphatemia. On arrival, the patient became non-oliguric and his calcium began gradually rising to peak- ionized calcium of 1.91 mmol/L requiring multiple sessions of hemodialysis. Workup demonstrated depressed intact parathyroid hormone, Vitamin D 25-OH and 1-25(OH)2, Vitamin D as well as ongoing hyperphosphatemia and a marginally elevated 24-hour urine calcium. Comparison of the two CT scans obtained during the oliguric/hypercalcemic and non-oliguric/hypercalcemic phases of AKI demonstrated a clear reduction in intramuscular calcification. Calcium levels improved spontaneously after 11 days along with complete renal recovery.

Discussion: Sudden onset of severe hypercalcemia during the non-oliguric phase of AKI in the setting of rhabdomyolysis is due to mobilization of intramural calcium as evidenced by decreased intramuscular calcification observed on CT scan, a novel finding. Previous cases have described secondary hyperparathyroidism as the driving cause of hypercalcemia, although PTH was appropriately suppressed in this case, which is a unique finding. The temporal relationship between renal recovery and hypercalcemia could be explained by contemporaneous recovery of renal and skeletal tissue. Nephrologists must remain vigilant during the recovery phase of rhabdomyolysis and monitor for potentially life-threatening hypercalcemia.

CT abdomen on days 14 (L) and 29 (R) during the oliguric and non-oliguric phases of rhabdomyolysis induced AKI with improving intramural calcification

TH-PO178

Survival After Severe Metformin-Associated Lactic Acidosis (MALA) with Aggressive Dialysis and Massive Bicarbonate Administration

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Introduction: MALA is a severe condition affecting fewer than 1 in 10,000 people. Mortality is often above 20%. We present a case of intentional metformin overdose surviving after the combined dialysis modality use and massive parenteral sodium bicarbonate (NaHCO3) administration.

Case Description: 52-year-old male with PMH: HIV on HAART, DM, HTN, Hep C and cocaine use who intentionally ingested 60g Metformin in the ED without staff knowledge. 12 hours later, patient was found lethargic with a blood glucose of >10 mg/dL. Arterial blood gas: pH 7.02, PaCO2, 23.3mmHg, PaO2, 128mmHg. Serum chemistry: Na 144mmol/L, K 3.8mmol/L, CI 98mmol/L, Cr 1.57mg/dL, HCO3 12mmol/L, ALT 64unit/L, AST 74unit/L, AG 32, lactate acid >25.0 mmol/L. Patient was intubated, hyperventilated and begun on 3 vasopressors for hypotension. No GI lavage performed. Next, simultaneously started 150meq NaHCO3 was added to each dialysate bag. The patient’s pH remained <7.2 throughout NaHCO3 infusion was increased to 600mL/hr due to persistent pH <7.2. An additional 50meq NaHCO3 infusion at 125 mL/hr. However, over the next 12 hours, urine output continued to decline with serum [Na] decreased to as low as 107 mg/dL with serum [Cr] 4.90 mg/dL. Though serum osmolality decreased to 296 mg/dL, serum OG remained 60 mOsm/kg. Given progressive oliguria, azotemia, and hyperkalemia, emergent HD was performed with repeat serum [Na] 117 mg/dL, serum OG 31 mOsm/kg, and improved urine output. After repeat HD, serum [Na] increased to 129 mg/dL with a normal OG. Oliguria resolved and mental status improved.

Discussion: Metformin can be used to manage elevated IOP but high and frequent dosing can lead to oliguric renal failure with profound hyperosmolar hyponatremia, particularly in elderly patients with CKD. Our case highlights the importance of recognizing hyperosmolar hyponatremia as a distinct clinical entity and emphasizes reversibility of renal failure with early HD. It also raises thoughts regarding alternative therapies for elderly patients with CKD and increased IOP.

TH-PO180

A Case of Hyperosmolar Hyponatremia from Polyethylene Glycol (PEG)

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Introduction: N/A

Case Description: 69 year old man with pulmonary sarcoidosis presented to the ER with shortness of breath, diagnosed with acute pneumonia and treated with antibiotics, with gradual improvement in dyspnea. Hospital course was complicated by an ileus, for which increasing amounts of polyethylene glycol (PEG) was prescribed. On hospital day 10 the laboratory data revealed acute worsening of hyponatremia (123mmol/L), hyperkalemia (5.5mmol/l), and a mild non-oliguric AKI, prompting nephrology consultation.

Discussion: The measured serum osmolality of our patient was normal (277 mOsm/kg), and a low whole blood sodium (127mmol/L) ruled out pseudohyponatremia. The serum osmol gap was elevated at nearly 20 mOsm/kg, indicating the presence of an unmeasured osmolyte. A negative correlation between the patient’s serum sodium and potassium was observed, such that when [Na+] decreased, [K+] increased (Image 1). Searching the chart for known etiological agents that may act as an effective osmole and produce these series of events was unsuccessful. Our attention was focused on PEG, which was being administered in high doses (170 grams cumulatively) in the absence of a bowel movement. A dose-dependent temporal relationship between PEG administration and non-oliguric AKI was observed, supporting the diagnosis of PEG-induced hyponatremia. A proposed mechanism is outlined and illustrated in Image 2. When PEG was discontinued by Nephrology, the electrolyte abnormalities corrected rapidly.
**TH-PO181**

Severe Hypermagnesemia-Induced Ischemic Colitis in a Patient with AKI

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**Introduction:** Severe hypermagnesemia is a rare complication seen with laxative/antacid overdose, usually in patients with acute kidney injury (AKI). We present a case of marked hypermagnesemia leading to ischemic colitis with perforation, pancreatitis and multi-system organ failure in a patient with AKI.

**Case Description:** A 54 year old female with hypertension, asthma, and chronic neurogenic bladder presented with abdominal pain and vomiting for one day. She was taking magnesium hydroxide 1200mg four times a day for constipation. She was hypotensive on arrival with blood pressure of 70/50mmHg. Labs were remarkable for AKI with serum creatinine of 6.89mg/dl (baseline 0.9mg/dl) and severe hypermagnesemia (>10mg/dl, baseline of 2.2mg/dl about one month ago). Other significant lab findings were microangiopathic hemolytic anemia (MAHA) and lactic acidosis. She was intubated, started on vasopressors and admitted to the intensive care unit. CT abdomen revealed free air suggestive of perforation, reactive pancreatitis and ischemic colitis. Emergent exploratory laparotomy was performed which showed cecal ischemia. She also received plasma exchange for for MAHA which was stopped after three treatments given normal ADAMTS13 activity. Continuous renal replacement therapy (CRRT) was started for hypermagnesemia and oliguria. Her renal function and hypermagnesemia improved and she was weaned off CRRT. The etiology of AKI was presumed to be multifactorial in the setting of obstructive uropathy from neurogenic bladder, acute tubular necrosis from hemodialysis, and thrombotic microangiopathy. Severe hypermagnesemia was attributed to high dose oral magnesium supplementation in the setting of AKI. She showed significant improvement in her follow up labs in renal clinic two months later with magnesium level of 2.2mg/dl and serum creatinine of 0.9mg/dl.

**Discussion:** Hypermagnesemia is known to induce hypomotility of gut leading to ileus, colitis, intestinal perforation and toxic megacolon, especially in the setting of AKI. Our patient developed severe refractory hypermagnesemia requiring CRRT complicated by ischemic colitis, bowel perforation and reactive pancreatitis. High index of suspicion for bowel complications is warranted if patients present with hypermagnesemia and abdominal symptoms.

**TH-PO182**

Noninvasive Left Ventricular End-Diastolic Pressure (LVEDP): A Novel Volume Assessment Tool

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**Background:** Objective assessment of volume is a major barrier to improving volume management in dialysis patients. The Valsalva maneuver is a well-recognized bedside marker of central volume overload. We tested a novel non-invasive handheld device that combines Valsalva maneuver with finger photoplethysmography to reliably estimate LVEDP. The goal of our pilot study was to determine the associations of non-invasive LVEDP measurements with common volume-related hemodialysis parameters.

**Methods:** We assessed predialysis LVEDP in 67 patients undergoing maintenance hemodialysis at two dialysis units in Baltimore. Patients also underwent extracellular water measurement by bioimpedance (BA), in addition to routine dialysis parameters. We assessed the association of these parameters with changes in systolic blood pressure during dialysis.

**Results:** Mean age of the participants was 57 years, 63% were male, and 76% black. Predialysis LVEDP was 16 ± 6 mmHg (normal: <12 mmHg) with a range of 5 mmHg to 33 mmHg. Among the parameters assessed, only LVEDP was associated with a significant fall in systolic blood pressure (SBP) during dialysis (Table). However, this was not associated with any of the commonly used definitions of intradialytic hypotension. R² was 47% for a model of change in SBP that included predialysis SBP, LVEDP, intradialytic weight gain (IDWG), extracellular water, ultrafiltration (UF) volume, UF rate, and treatment time, suggesting that >50% of the variability in the change in SBP during dialysis remains unaccounted for by these variables.

**Conclusions:** Non-invasive LVEDP is a novel parameter that can provide additional information to guide volume management in hemodialysis patients. However, 50% of the variability in the change in SBP remained unexplained, pointing to the need to fully understand the pathophysiology of fall in SBP during hemodialysis.

**Funding:** NIDDK Support

Predictors of change in SBP (adjusted for age, sex, and race)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Mean ± SD</th>
<th>Change to SBP (Post - Pred) per 1 SD increase in predictor (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP, mmHg</td>
<td>16.1 ± 5.6</td>
<td>0.52 ± 0.26 (0.04)</td>
</tr>
<tr>
<td>IDWG, kg</td>
<td>2.3 ± 1.1</td>
<td>2.7 ± 1.3 (0.57)</td>
</tr>
<tr>
<td>Extracellular water (mL)</td>
<td>20.3 ± 1.8</td>
<td>0.32 ± 0.15 (0.03)</td>
</tr>
<tr>
<td>Ultrafiltration (UF) volume, L</td>
<td>2.1 ± 1.4</td>
<td>0.31 ± 0.19 (0.03)</td>
</tr>
<tr>
<td>UF rate, mL/hr</td>
<td>7.9 ± 8.8</td>
<td>2.2 ± 2.8 (0.01)</td>
</tr>
</tbody>
</table>

**SD, standard deviation; SE, standard error**

**TH-PO184**

Calculation of Extracellular Fluid Volume from Regular Blood Test Results of Patients Undergoing Hemodialysis

Shigeru Nakai,1 Kazuhiko Shibata,4 Ikuto Masakane,2 Takahito Ito,2 Teppei Matsuoka,2 Takeshi Aoki,2 Takahiro Shinzato,3 Hiroki Hayashi,1 Naotake Tsuibo,1 Midori Hasegawa,1 Daiju Inaguma,1 Yukio Yuzawa,1 Shinjiro Tokiyokawa.4 1Fuji Health University School of Health Sciences, Toyooka, Aichi, Japan; 2Katagayu Medical Center, Shibata, Japan; 3Honcho-Tabuki Clinic, Yamagata, Japan; 4Yokohama Minami Clinic, Yokohama, Japan; 5taiseikai medical corporation, ogaki-city Gifu pref., Japan; 6Nagoya Municipal Industrial Research Institute, Iwakura-shi, Aichi-ken, Japan; 7Fujita Health University School of Medicine, Aichi, Japan; 8Saitama Medical Center, Jichi Medical University, Saitama-city, Japan; 9Daiko Medical Engineering Research Institute, Nagoya-shi, Japan.

**Background:** Urine osmolality (UA) is a solute that cannot cross cell membranes in the general tissues via simple diffusion, facilitated diffusion, or active transport, indicating that the UA distribution volume (UDiV) is equal to the extracellular fluid volume (ECFV). At ASN 2018, we reported that UDiV is closely correlated with ECFV predicted using the UA distribution volume (UDiV) is equal to the extracellular fluid volume (ECFV). At ASN 2018, we reported that UDiV is closely correlated with ECFV predicted using NAIDDK Support.

**Methods:** Fluid volume overload (FO) and vascular stiffness are prominent features of end-stage renal disease patients. Although both are risk factors for cardiovascular events, the relationship between these two factors has not yet been fully elucidated. We hypothesized that FO is associated with high vascular stiffness which can only be partly corrected by ultrafiltration (UF) of fluid during the hemodialysis (HD). We aimed to determine whether vascular stiffness is higher in fluid overload (FO) vs. non-fluid overloaded (non-FO) HD patients. Also, we investigated the effect of fluid removal on vascular stiffness of a single HD run.

**Results:** Fluid status and arterial stiffness were tested in 20 FO and 19 non-FO HD patients. 26 healthy subjects were evaluated as controls. Fluid status was assessed by bioimpedance spectroscopy device. Pulse wave velocity (PWV) and augmentation index (AIx), as markers of vascular stiffness, were measured using ArteriographTM. The PWV and AIx were performed for 5 hours, starting 30 minutes before and ending 30 minutes after the HD run. All measurements were done during the mid-week HD session. In healthy controls, 5-hour measurement of PWV and AIx was performed as time control. HD subjects were divided into three tertiles according to the baseline PWV measurement.

**Results:** The median age of HD patients was 60 (29-56) and 49 (29-56) years in healthy subjects. Fluid status in healthy controls, FO and non-FO HD patients was 0.05 (0.0-0.5), 2.9 (1.7-5.2), and 0.3 (0.3-0.6), respectively. As anticipated, PWV and AIx were higher in HD patients vs. healthy controls. FO was not associated with a higher PWV (m/s) in FO 10.0 (9.2-11.1) vs non-FO 10.0 (8.8-11.4) HD groups. A significant positive linear relationship was observed between dialysis UF (L) and intradialytic PWV changes in the upper tertile group (r²=0.233; P=0.05). The latter group showed significant changes in AIx (%): 20.00±5.55 compared to the lower-tertile group 15.7±2.71 (P<0.005).

**Conclusions:** The PWV and AIx were higher in HD patients compared to healthy subjects. Strangely, there was no difference in PWV/AIx between the two HD groups. Dialysis treatment appears to be a detrimental factor in improving the vascular status of patients with higher PWV and/or AIx. However, an additional interventional study would be needed to further delineate the relationship between fluid status and arterial stiffness.

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The bioimpedance method (BIA-ECVF), however, whether UDV is a useful tool for distinguishing different hydration statuses remains unclear.

Methods: We compared UDV calculated from regular blood test results with BIA-ECVF of 53 patients undergoing hemodialysis (HD) predicted using BCM (Fresenius Medical Care). Further, we compared UDV normalized with the post-HD body weight (nUDV) in nine patients with pedal edema (overhydrated patients), five with intradialytic hypotension (underhydrated patients), and 24 without any clinical symptoms relating to hydration status (symptom-free patients).

Results: We observed a significant correlation between UDV (r) and BIA-ECVF (r) = 0.69, 0.25, respectively. The regression line substantially coincided with the line of identity. Bland–Altman analysis showed a systematic error for UDV versus BIA-ECVF. In addition, we found a significant difference between UDV and BIA-ECVF (mean difference = 0.94 L, 95% CI = 0.37–1.52 L). As shown in the figure, the nUDV could help distinguish different hydration statuses.

Conclusions: UDV is a plausible alternative marker of BIA-ECVF for the assessment of the hydration statuses of HD patients.

TH-PO186
Thoracic Electrical Bioimpedance Measurement in Monitoring Cardiac Index and Thoracic Fluid Content During Hemodialysis
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Background: Hemodynamic stress during hemodialysis (HD) results in recurrent segmental ischemic injury that drives cumulative cardiac damage. Thoracic electrical bioimpedance (TEB) has been shown to provide accurate, noninvasive, continuous, measurements of cardiac index (CI) and thoracic fluid content (TFC). We performed this study to evaluate the changes in TFC in comparison with fluid removal (FR) and to understand the trends in CI changes in HD patients.

Methods: In this observational study, we enrolled 114 patients from a single hemodialysis unit. Minute-by-minute changes in TFC and CI were collected using the TEB (BioZ) in HD patients. Change in body weight (DW) and amount of FR were measured.

Results: The TFC decreased in all patients by an average of 4.6±2.4 l/kg, weight decreased by 2.05±1.2 kg, and FR averaged 2.5±0.9 l/kg in HD session. There were significant correlations between changes in TFC and CI (R=0.74, P<0.001) and FR (R=0.82, P<0.001). A 1 l/kg change of TFC correlates with an 150 mL change in total body water. The change in CI (-0.42±0.51 l/min/m²) during HD did not correlate with FR (R=0.14, P=NS). Changes in TFC represented the monitored variable most closely related to FR. Interestingly, during the first 5 mins of HD, CI and stroke volume index reduced obviously compared to the base level before dialysis.

Conclusions: It suggested that thoracic electrical bioimpedance could monitor the acute cardiac effects of dialysis during hemodialysis treatment.

Funding: Government Support - Non-U.S.

TH-PO187
Change in Extracellular Fluid Volume (ECV) Calculated with a Plasma Uric Acid Kinetic Model May Reflect True ECV Better Than That With Body Weight in Hemodialysis Patients
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Background: In Kidney Week 2018 (SA-PO-867 and 868), we reported a novel method to calculate extra-cellular fluid volume (ECV) of hemodialysis (HD) patients, which is based on a kinetic model for plasma uric acid concentration. In this study, we compared annual change of clinically adjusted dry weight (DW) with that of ECV calculated by our method.

Methods: Among 79 Japanese HD outpatients who were enrolled in the previous study, 53 patients maintaining stable blood flow and ultrafiltration rates on the days of blood sampling both at April 2018 and at April 2019 were included in this analysis (64.8 ± 10.5 y, male 69.8%). They had no cardiac event at least for two years. DW of each patient had been adjusted throughout the period by a nephrologist-in-charge using cardiac-thorax ratio and blood pressure. ECV values at post-HD were calculated by our method and were standardized by the body surface area (BSA). Demographic and biochemical data used below were obtained at April 2018. An annual increment is designated as Δ.

Results: DW and ECV/BSA values decreased during the period (-0.51 ± 1.71 kg and -0.42 ± 1.22 l/m²), paired Wilcoxon P=0.0377 and 0.0078, respectively. Both were not associated with age, sex, total protein, albumin, creatinine, corrected-calcium, phosphate, urea nitrogen, hemoglobin, nPCR, and diabetic history. ΔECV/BSA was not associated with ΔDW at all (R=0.141, P=0.3133) (Fig). ΔECV/BSA correlated positively with dialysis vintage (R=0.307, P=0.0251) and negatively with Δalbumin (R=-0.402, P=0.0029), but ΔDW did not. AECV/BSA showed better correlation with plasma atrial natriuretic peptide concentration measured in 2018 (R= -0.420, 0.0018) than ΔDW (R=0.356, 0.0088) (Fig).

Conclusions: AECV, which is calculated with our plasma UA kinetic model, was consistent with clinical data better than ΔDW. Our results suggest that AECV/BSA rather than ΔDW reflects true change of ECV in HD patients.

Funding: Clinical Revenue Support

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Oxidative Stress Is Associated with Overhydration and Sarcopenia in Hemodialysis Patients

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Hallym University Sacred Heart Hospital, Anyang, Republic of Korea; Hallym University, Anyang, Republic of Korea.

Methods: In this longitudinal observational study, serum protein carbonyl levels were measured in 88 stable HD patients. Additionally, multifrequency body composition analysis and handgrip strength (HGS) and nutritional assessments were performed and followed prospectively for up to 6 years.

Results: The mean patient age was 60.6 ± 13.5 years, and the mean HD duration was 30.8 ± 41.3 months. In total, 16 patients (18.2%) were overhydrated, 49 (55.7%) had low HGS and 36 (40.9%) had low muscle mass. Serum protein carbonyl levels were associated with serum levels of albumin, prealbumin and transferrin, hydration status and low HGS. Overhydration, prealbumin, subjective global assessment score and sarcopenia were significant predictors for serum protein carbonyl levels in the highest quartile. Multivariate analysis showed that the serum levels of protein carbonyl, albumin, prealbumin, overhydration and sarcopenia were independent determinants of all-cause and cardiovascular mortality. (Figure 1.)

Conclusions: Serum protein carbonyl was significantly associated with overhydration, nutritional status and sarcopenia and could be an important predictor of long-term outcomes in patients undergoing HD.

Lung Ultrasound for Fluid Status Assessment in Dialysis Patients: An Option to Consider

Martta Arias, Jose J. Broseta Monzo, Elena Guillen, Gastón J. Piñeiro, Lida M. Rodas Marin, Miquel G. Umbert, Francisco Maduell. Hospital Clinic de Barcelona, Barcelona, Spain.

Methods: The maintenance hemodialysis patients of the First Affiliated Hospital of Zhengzhou University, Henan, China, Zhengzhou, China.

Background: sCD146 is a marker of endothelial cell injury and also a biomarker of systemic circulation congestion. There is no study on the relationship between sCD146 and total body extracellular resistance (TBE) and interdialytic weight gain (WG) in routine hemodialysis (HD). The aim of this study was to evaluate the relationship between interdialytic changes in whole body extracellular resistance (Re) and interdialytic weight gain (WG) to facilitate prescription of ultrafiltration volumes (UFV) and rate (URF).

Methods: Ambulant patients were studied at 4±2 successive HD sessions. Whole body and calf bioimpedance were measured pre- and post-HD to obtain whole body extracellular resistance (Re) and calf normalized resistivity (CNR). Interdialytic weight change (ΔW), change in Re (ΔRe), and CNR (ΔCNR) between pre- and post-HD (calculated as pre-HD minus post-HD of the preceding HD session), UFR, and UFV were recorded per HD session. Simple and multiple regression analysis were used to determine the relationship between ΔW and ΔRe.

Results: Thirty-eight patients (age 54.3±14 years, 17 females, BMI 26.4±7.4 kg/m2) were studied. We collected 387 measurements (10.2±6 per patient; table 1). UFR and UFV were 2.98±0.9 L and 0.75±0.24 L respectively. ΔW correlated inversely with ΔRe (average R=0.71; range 0.44 to 0.91) with a slope of -53.3 (range -182 to -18) kg/ΔW and an intercept of -12.9 (range -110 to -18) kg. As an example, Fig 1 and 2 show the relationship between ΔRe with ΔW1 and to ΔCNR in the same patient. Multiple regression analysis indicated that the slope was determined by UFR (p<0.01) and pre-HD CNR (p<0.05).

Conclusions: This study demonstrates that interdialytic weight gain can be predicted in individuals by whole body extracellular resistance. This method may be useful in patients who cannot be weighed. Using ΔRe to predict fluid gain is based on the high correlation between extracellular resistance and extracellular volume. Once corroborated in an elderly, non-ambulant population, this method may provide guidance for UFR prescription, a problem encountered occasionally in patients undergoing dialysis at home or - more frequently - in nursing homes.

Conclusions: Serum protein carbonyl was significantly associated with overhydration, nutritional status and sarcopenia and could be an important predictor of long-term outcomes in patients undergoing HD.
Conclusions: Strengthen nephrologists’ lung ultrasound skills could be appropriate for optimizing fluid status in patients with high PSAP in those departments with US device and the right probe available, since its predictive mortality value has been demonstrated even in patients with a low LC number.

TH-PO193
Lung Ultrasonography in the Assessment of Volume Overload: An Extra Tool to Improve Patient Care and Clinical Skills in Nephrology Fellows
Karla G. Caras martinez, Gerardo Zablah, Saul N. Gonzalez Montalvo, Naveen Punchayil narayankuttty, Vasuki N. Venkat, Daniel J. Soberon, Marco A. Ladino Avellaneda. "University of Miami, Miami, FL; "Jackson Memorial Hospital, Miami, FL; "Bruce W. Carter VA Medical Center Hialeah, FL; "Miami VA Medical Center/University of Miami/ Jackson Memorial Hospital, Plantation, FL; "Jackson Health System, Miami, FL.

Background: Estimating euveloemia in patients with end stage renal disease (ESRD) is critical in their management. Nephrologists use their clinical judgment and skills to estimate the volume status. Lung ultrasonography (LU) is a tool that allows clinicians to have an objective evaluation of volume status. B-lines on lung ultrasound have been validated as a sign of pulmonary congestion and volume overload. This study evaluates the use of LU in the clinical assessment of volume status in the patient that is admitted to the hospital with ESRD.

Methods: Twenty patients with ESRD, admitted with volume overload were evaluated on admission with LU. Physical exam on all the patients didn’t show physical signs of volume overload, on 9 patients the chest X-ray was clear, on 8 patients the CXR showed signs of congestion and on 3 patients the CXR showed mild-moderate pulmonary edema. A LU using a GE Vscan portable ultrasound was done on all the patients.

Results: B-lines were found in the 20 patients, LU was suggestive of volume overload (B-lines present). Hemodialysis/Ultrafiltration was provided for all the patients, 10 patients needed extra ultrafiltration sessions in the following days for a complete resolution of the B-lines which was evidenced with subsequent use of LU.

Conclusions: LU guided fluid management protocol improves the clinical evaluation in ESRD patients. Clinical judgment and integrated lung ultrasonography for management of volume in hemodialysis patients improves outcomes and facilities the clinical management of hypervolemia. LU is an objective tool to assess volume overload in this patient population.

TH-PO194
Seeing the Volume for the Bs: Longitudinal Variation in Ultra-sound-Guided Volume Assessment in Hemodialysis Patients

Background: Ultrasound (US) studies in hemodialysis (HD) patients have demonstrated improvements in lung water from the beginning to the completion of HD. These studies, however, have focused primarily on the pre-, intra-, and immediate post-dialytic periods. There are no published studies examining how fluid shifts between the intravascular and interstitial compartments in the post-dialysis period. This study aimed to characterize this phenomenon.

Methods: In this single-center, prospective observational study, patients with acute kidney injury and end-stage renal disease receiving HD in an inpatient HD unit at an urban academic medical center were recruited to receive three US volume assessments: first within two hours before HD, second within an hour following HD conclusion, and third four hours

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after HD conclusion. US volume assessment consisted of assessment of inferior vena cava (IVC) variability and 28-point lung ultrasound (LUS) with B-line scoring per zone (BLZ).

**Results:** In a preliminary analysis, IVC variability increased a mean of 21.1% in three of the four subjects (range 29.9 to 23.2%) between the pre-HD and post-HD period. At the extended post-HD period, the same three subjects demonstrated a mean decrease in IVC variability of 19.1% (range 10.9 to 23.2%), whereas a fourth subject experienced an increase in IVC variability of 19.9%. The BLZ results were mixed, without clear signal across the four patients.

**Conclusions:** In preliminary analysis, IVC variability appeared to decrease in the extended post-HD period compared to the immediate post-HD period. BLZ did not show a signal for increase or decrease in the same period. The study is continuing to recruit patients for further analysis.

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**Unilateral Pulmonary Edema in Dialysis Patients**

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**Introduction:** Unilateral pulmonary edema (UPE) usually affects right upper lobe & is seen in less than 2% cases of cardiac failure. Severe mitral regurgitation (MR) is the commonest underlying cause. We report 4 cases of UPE in Hemodialysis (HD) patients which resolved following dialysis.

**Case Description:** Four cases of Diabetic Nephropathy on MHD, presented with breathlessness. There was no preceding H/O chest pain/fever/hemoptysis. ECHO showed moderate MR in 2, mild & severe MR in one each. All had hypoalbuminemia (2.8-3.6 gm/dl). In view of Unilateral opacities on chest X-ray (Fig 1-4), patients were started on broad spectrum antibiotics. Following dialysis surprisingly there was clearance of opacities in all of them.(Fig 5-8)

**Discussion:** UPE is a rare manifestation of cardiogenic pulmonary edema. Severe MR associated regurgitant blood in right pulmonary vein, poor lymphatic drainage of the right lung & hypoalbuminemia are the main contributing factors. Our cases show that UPE can affect any zone of right lung. We feel that, in fluid overloaded dialysis patients even mild/moderate MR is enough to cause UPE of any zone. High index of suspicion for UPE and impressive clinical response following dialysis warrants repeat chest skiagram. Clearance on X-ray gives diagnosis avoids antibiotic therapy.

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**Lung Ventilation Abnormalities in Chronic Hemodialysis Patients with Hyperpolarized $^{129}$Xe Gas Magnetic Resonance Imaging**

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**Background:** Shortness of breath is common among chronic HD patients, usually attributed to congestive heart failure and volume overload. However, it may be the hallmark of an underlying lung airway disease, such as asthma or COPD, which are often undiagnosed and there may be unique pathomechanisms in dialysis patients (e.g. salt loading). In this study, we used inhaled hyperpolarized xenon-129 ($^{129}$Xe) gas magnetic resonance imaging (MRI) to directly measure lung ventilation abnormalities in prevalent HD patients.

**Methods:** Ten chronic HD patients underwent $^1$H and $^{129}$Xe lung MRI on a non-HD day. $^{129}$Xe MRI was acquired during breath-hold at end-inspiration, after inhalation of a fixed volume of hyperpolarized $^{129}$Xe, and co-registered with proton images with matching lung volumes. Patients were scanned before and after administration of salbutamol to evaluate reversibility. Static ventilation $^{129}$Xe images were analyzed with a semiautomated software pipeline implemented in Matlab (2018b; Mathworks, Natwick MA) to calculate the ventilation defect percent (VDP).
Results: In the study sample, three main ventilation patterns were identified: Normal, Single Defect, Multiple Defects (Figure 1A). Partial ventilation improvement after salbutamol administration was also observed (Figure 1B).

Conclusions: Underlying lung airway diseases as detected by $^{129}$Xe lung MRI are common and may help explain the pathophysiology of shortness of breath in prevalent HD patients.

Figure 1. (A) $^{129}$Xe MRI ventilation images showing three ventilation patterns: Normal, Single Defect and Multiple Defects. (B) $^{129}$Xe MRI ventilation images showing partial improvement after salbutamol administration.

TH-PO197

Changes in Ultrafiltration Rate (UFR) with Relative Blood Volume Monitoring (RBV-M)

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Background: High UFRs during hemodialysis (HD) have been linked to increased risk of mortality, and avoidance of UFR ≥13 mL/kg/h has been advised. However, limiting UFR may lead to volume overload. We examined the changes in UFR and related parameters among patients who were part of a one-year fluid management QI project with RBV-M at 20 Renal Research Institute clinics.

Methods: Patients included in the analysis were receiving HD at Baseline (BL; month before QI project) and at Month 12 of the QI project (M12). Crit-Line monitor (CLM-III, CLM-IV, or CLiC) was used to monitor relative blood volume during the QI project. All available data on ultrafiltration volume (UFV), HD treatment duration (TD), UFR, interdialytic wt gain (IDWG), and post-HD body weight (wt) were averaged monthly for each patient. Paired t-tests and McNemar’s tests were used to test for differences between BL and QI month 12 (M12).

Results: Treatment parameters at BL and M12 stratified by BL UFR are shown in Table. Patients with UFR>10 mL/kg/h experienced an increase in UFR by M12 (0.43 mL/kg/h) along with decreases in Post-HD wt of -1.1 kg and -1.0 kg in pre-HD wt. Patients with UFR<10 mL/kg/h at baseline experienced an average decrease in UFR of -2.34 mL/kg/h accompanied by a decrease in IDWG with no change in post-HD wt or TD. A similar, but less pronounced, pattern was observed for pts with UFR 10-13 mL/kg/h.

Conclusions: During a one-year fluid management QI project utilizing RBV-M, pts with UFR<10 mL/kg/h at baseline experienced an increase in UFR accompanied by improvements in IDWG with stable post-HD wts. Treatment duration remained unchanged for all groups.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

TH-PO198

Decline in Hemodialysis Ultrafiltration Rate (UFR), 2012-2018

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Background: UFR has received heightened attention due in part to several observational studies that reported higher mortality at UFRs above 13 mL/kg/hour. Several organizations have proposed quality measures to discourage high UFR. We examined national UFR trends for US patients.

Methods: We evaluated trends in UFR and its components (pre- and post-dialysis weight, dialysis session time) from 2012-18 as reported by dialysis facilities through the CROWNWeb system. Medicare-certified dialysis facilities began reporting UFR data for the last hemodialysis session of each month in 2012, and for a full week of sessions in 2018 in accordance with the ESRD Risk Incentive Program.

Results: Data for monthly UFR were submitted for 88-98% of patients. Average UFR declined steadily from 9.3 to 7.8 mL/kg/hour between 2012 and 2018. The percent of dialysis sessions with a UFR>13 mL/kg/hour declined from 19% to 10%. The percent of dialysis sessions with a UFR>10 mL/kg/hour fell from 39% to 26%. The decline in UFR was largely driven by interdialytic weight gain, which fell from approximately 3.3% to 2.8% of body weight (~2.6 to 2.2 kg). Dialysis treatment time and patient weight trended upward, but these made a relatively small contribution to the decline in average UFR.

Conclusions: The average UFR has declined from 2012 to 2018, largely driven by lower interdialytic weight gain. One possible explanation is that dialysis facilities provide patients with better education about fluid and dietary intake and patients follow such advice more carefully. However, we believe a more likely explanation comes from other studies reporting a secular decline in the average dialysate sodium concentration, which suppresses thirst and fluid intake. Although the strength of current evidence has not supported specific UFR guidelines, the changes responsible for the declining UFR were potentially motivated by published studies and expectations of forthcoming guidelines and incentives related to UFR management.

Funding: Other U.S. Government Support

TH-PO199

Electronic Health Record-Based E-Alerts for Ultrafiltration Rate in Prevalent Dialysis Patients: A Quality Improvement Project

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Background: Studies have shown an association between higher ultrafiltration rate and mortality in prevalent dialysis patients. Ultrafiltration rate exceeding 10 mL/kg per hour has been associated with greater mortality even when calculations are normalized to various anthropometric measurements.

Methods: We recorded interdialytic weight gain (IDWG) for one week of thrice a week prevalent dialysis patients. Also baseline characteristics of study population were recorded. Various ultrafiltration data is recorded in AXIS renal data solution (electronic health record designed and conceptualized by Nephrologist). IDWG was calculated by dividing the ultrafiltration volume (ml) by the target dry weight (kg) and duration of time of the dialysis session (hours). Average ultrafiltration rate for all 3 sessions of hemodialysis and percentages of dialysis session where UF rate exceeded 10mL/kg per hour were calculated. After preliminary data collection, we are planning to introduce electronic alert (e alert) within AXIS system whenever ultrafiltration rate exceeds 10mL/kg per hour. This e alert will be sent to patient’s caregiver as well as will serve as a teaching tool for dialysis nurse.

Results: Of the 387 subjects, 62% were males. The average age was 53.1±3.6 years. The average dialysis vintage was 4.0±3.4 years. 33.6% had diabetes, 85.5% had hypertension and 10.0% had history of ischemic heart disease. Average UF rate of first session of week (after weekend) was 13.8±5.7 mL/kg per hour. Average UF rates of mid week and last session of week were 10.5±10.5 and 10.0±4.5 mL/kg per hour respectively. About 75.7% of HD sessions after weekend had UF rate more than 10mL/kg per kg per hour whereas 48.3% and 47.8% of sessions of remaining week exceeded safe UF rate limit.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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Conclusions: About 75% of dialysis sessions after weekend gap exceeded safe limits for ultradialysis rates in prevalent dialysis patients. This calls for quality improvement initiative to improve knowledge and to monitor in change in behavior among dialysis patients, caregivers and providers regarding safe limits of UF rate.

TH-P0200

Ultrafiltration Does Not Correlate with the Difference Between Pre-dialysis and Post-Dialysis Blood Pressure

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Background: Hypervolemia contributes to blood pressure (BP) elevations in hemodialysis (HD) patients and is addressed with ultrafiltration (UF). However, high UF rates (UFR) are generally avoided as it is associated with intradialytic hypertension. It is unknown whether the amount of UF or volume removed actually correlates with the change between pre and post dialysis BPs. We hypothesize that there is an inverse correlation, with higher UF resulting in larger decreases in post HD BP.

Methods: We reviewed the records of 24 ESRD patients receiving HD in a single outpatient center in Philadelphia over a 2 month period. Patients on midodrine were excluded, and treatments with missing pre and post HD BPs and without UF were not analyzed. Using Pearson r, we correlated intradialytic weight change (pre minus post HD weight) and achieved UF rate (UFR, ml/kg/hr) with changes in systolic BP, diastolic BP and mean arterial pressure during HD (post minus pre HD SBP, DBP and MAP). Patients were further stratified into those who received UFR < vs ≥ 10 ml/kg/hr and with intradialytic weight (IDW) changes < vs ≥ 3 kg.

Results: Individual intermittent HD treatments were analyzed (n=363). We found no significant correlation between IDW change and change in SBP (r= -0.024), DBP (r= -0.012) and MAP (r= -0.019). IDW change ≥ 3 kg correlated better with a decrease in SBP post HD, although it did not reach statistical significance (r= -0.24, p=0.08). There was no correlation between achieved UFR and change in SBP (r= -0.061), DBP (r= -0.021) and MAP (r= -0.04). There was still no significant correlation even in patients who received high UFRs (a 10 ml/kg/hr).

Conclusions: Our study showed that UFR and IDW change did not correlate with the difference in pre and post dialysis BPs. This suggests that other factors, in addition to volume, play important roles in intradialytic BP regulation and should be explored. To our knowledge, only one other similar study looked at similar parameters and reported a significant but weak correlation between UF and change in MAP (r=0.17, p=0.045, 136 treatments) (Kovacic, et al, 2003). Larger studies are necessary.

TH-P0201

Prevalence of Body Weight Variations in the Pre-Dialysis Period and the Effect of Hemodialysis Initiation: A Single-Centre Retrospective Observational Study


Background: Body weight(BW) changes rapidly during pre-dialysis(pre-D) period and in regular monitored during pre-D clinics but less utilised as an indication for RRT initiation in isolation. Hemodialysis(HD) provides a target weight (TW). Aims:To 1) Assess prevalence and magnitude of BW changes during pre-D 2) Measure the effect of RRT initiation on BW 3 month(s) post HD

Methods: We retrospectively examined BW changes of a large cohort of incident HD patients who attended Pre-D clinics between 2012-2016 (n=103). Excluded:Those with missing BW between 2-5 m in pre-D and 2-5 m after RRT initiation, previous PD, HD or fluid overload as indication for RRT initiation (n=38). W0,W1,W2 are the corresponding BW at ≤ 3 months before (PD), pre-weight at 1st HD initiation and post-HD TW after ≥ 3 m. Delta BW is calculated as absolute and % change for Pre-D(W0-W1) and Post-HD(W1-W2).

Results: n= 65, mean age 68±12 yr, M:F 44:21. HD was RRT in all. Pre-D and HD intervals were similar 99 ± 29 Vs. 92 ± 13.6 days. Post-weight and BW were within 0.5±0.4 Kg. Weight loss seen in both pre-D and HD; it slowed modestly after HD initiation (66.4% to 56.9%) mainly in 0-5% (40% Vs. 26%) (Fig 1). Weight gain was mostly 0 - 9.9% on HD as compared to pre-D (38.4 Vs 27.7). High weight gainers of >10% BW reduced from 165 to 77 Vs. 92 Kg. Weight loss seen in both pre-D and HD; it slowed modestly after HD initiation (66.4% to 56.9%) mainly in 0-5% (40% Vs. 26%) (Fig 1). Weight gain was mostly 0 - 9.9% on HD as compared to pre-D (38.4 Vs 27.7). High weight gainers of >10% BW reduced from 165 to 77 Vs. 92 Kg. Weight loss seen in both pre-D and HD; it slowed modestly after HD initiation (66.4% to 56.9%) mainly in 0-5% (40% Vs. 26%) (Fig 1). Weight gain was mostly 0 - 9.9% on HD as compared to pre-D (38.4 Vs 27.7). High weight gainers of >10% BW reduced from 165 to 77 Vs. 92 Kg.

Conclusions: Our study showed that UFR and IDW change did not correlate with significant but weak correlation between UF and change in MAP (r=0.17, p=0.045, 136 treatments) (Kovacic, et al, 2003). Larger studies are necessary.

TH-P0202

Impact of Extracellular Volume Overload on Ambulatory Blood Pressure in Hemodialysis Patients with and Without Intradialytic Hypertension

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Background: Hemodialysis (HD) patients with recurrent intradialytic hypertension (IH) have higher ambulatory blood pressure (BP) and atypical ambulatory BP patterns compared to HD controls. Recurrent IH is also associated with increased extracellular volume (ECV) and intradialytic vasoconstriction surges. We examined how these variables influence ambulatory BP in HD patients with and without IH.

Methods: In a case-control study of recurrent IH patients (systolic pre to post-HD BP increase ≥10 mmHg in 4/6 treatments) and hypertensive HD controls we obtained pre and post-HD ECV/weight with impedance spectroscopy and total peripheral resistance index (TPRI) with a cardiac output monitor. Linear regression measured associations of peridialytic variables on 44-hr ambulatory BP measurements.

Results: There were 18 IH subjects and 57 controls. Those with IH had higher ECV compared to controls (0.27±0.04 L/kg vs. 0.23±0.04, p=0.002) and different intradialytic TPRI changes than controls (385±58 dyn/sec/cm²/m² vs.-478±700, p<0.001). Ambulatory BP was nonsignificantly higher in IH subjects (147±13 mmHg vs 142±14, p=0.1), and BP slopes were different in hours 1-24 (-0.14±0.9 mmHg/hr vs. 0.4±0.9, p=0.04) but not hours 1-44. ECV/weight was associated with mean ambulatory BP in IH subjects and ambulatory BP slope in controls (Table). Post-HD BP associated with ambulatory BP in both groups.

Conclusions: Chronic ECV overload is a primary factor associated with ambulatory BP in IH patients, but interdialytic weight gain and intradialytic vasoconstriction surges are not. In controls, ECV overload is associated with a blunted ambulatory BP rise. Intra- and interdialytic BP patterns may help guide diagnosis and management strategies of ECV in HD patients.

Funding: NIDDK Support, Veterans Affairs Support

TH-P0203

Aquapheresis: An Institutional Experience at Lenox Hill Hospital

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Background: Aquapheresis (AQ) is the extracorporeal extraction of plasma water from the vascular space across a semipermeable membrane in response to a transmembrane pressure gradient, which efficiently removes extravascular fluid from the patient without compromising electrolytes. It is primarily used in the management of patients (pts) with diuretic resistant heart failure (CHF). AQ is comparable to isolated ultrafiltration (UF) performed on those pts requiring dialysis, but utilizes a machine that is smaller, and easier to operate compared to traditional dialysis equipment. Three major
studies on the use of AQ compared to diuretics have shown mixed results: UNLOAD (2013), a randomized controlled trial of greater reduction and achievement of target weight 2-day rehospitalization; in contrast, in CARRRESS-HF (2012), the use of AQ did not relieve CHF and caused worsening of renal function; AVOID (2016), supported the use of AQ to lower rehospitalization rates in CHF pts. There are no reports of the use of AQ in clinical studies outside of patients with CHF.

Methods: A retrospective study of AQ utilization at Lenox Hill Hospital, a tertiary care hospital in NYC. Records of pts who received AQ therapy were reviewed. The patient list was generated by searching for keyword “Aquaph in” our EMR. Pts were categorized by indication for AQ and hospital location. Additional information includes duration of treatment (days), changes in creatinine, and total volume removed.

Results: The search generated 28 pts, 5 were excluded as they never actually received AQ, Indications for AQ went into 5 categories: cardiogenic shock including post cardiac surgery (5), right heart failure (11), renal failure (5), pre-dialysis volume overload (4); 8 pts had bridge ultrafiltration during hemodialysis treatments (2); post-op volume overload (2). There were 16 pts from Cardiothoracic ICU, 5 pts from CCU, 1 pt from the Medical ICU and 1 pt from the Surgical ICU. The average duration per patient was 4.26 days. The mean aquapheresis volume per day was 1954 mls, and per encounter was 8323 mls with no significant change in creatinine.

Conclusions: We found that aquapheresis can be safely utilized in situations other than diuretic resistant heart failure. Also to consider, is the ease in which this less complicated aquapheresis machine can be operated compared to the more complex hemodialysis equipment.

TH-PO204
Over Ultrafiltration May Increase the Risk of Ischemic Cerebral Small Vessel Disease in Hemodialysis Patients
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Background: Cerebral small vessel disease (CSVD) is an important cause and risk factor of stroke and dementia. Recently, CSVD in patients with end-stage renal disease and undergoing dialysis had attracted great attention. A higher prevalence of CSVD in hemodialysis patients had been shown in others’ and our previous studies. Hemodialysis is a complicated procedure with multiple factors that could affect cerebrovascular disease. Ultrafiltration could bring hemodynamic instability during the hemodialysis. The aim of this study is to discover the relationship between ultrafiltration and ischemic CSVD.

Methods: In this retrospective study, we collected a whole year’s ultrafiltration information before the brain MRI scan of the HD participants in our dialysis cohort of 2013–2014 CSVD/CI study in which the CSVD were assessed by magnetic resonance imaging. We analyzed average ultrafiltration volume (UV mean), fluctuation of ultrafiltration volume (UV CV) and ultrafiltration volume over 6% dry weight (UV CV 6%) in 2011-2014. In addition, we assessed whether CSVD/CI and CSVD/CI + CI were associated with the baseline characteristics.

Results: In our 2013–2014 dialysis CSVD/CI cohort, 119 participants were on HD, and among them, 59.9% were male. The average age was 56.6±7 years, average dialysis vintage was 58 months. Median UV mean was 2.3 (0.2–4.6) L, UV CV was 21.4 (0.0–78.1) mL and “UV mean - 6%W” was -1.3 (-4.6 – 1.4) kg. The prevalence of lacune in MRI was 28.6% and WMH was 38.7%. By multivariable analysis, we found that UV mean, UV CV, UV CV6%, and UV CV 6% were related to increased risks for lacune and WMH with OR1.94 (95% CI 1.03, 3.70), or relative risk increase defined as the ratio of the risk of the treatment to the risk of the comparator group, divided by the risk of the comparator group (r=(1-R1)/R0) was significantly higher in HHD as compared to SHD (+42.9% vs. +17.2%; P=0.021). The total amount of shed syndecan-1 was higher during HHD than during SHD, albeit borderline significance (P=0.05). Lower plasma albumin and osmolality during HD were independent predictors of syndecan-1 increase during dialysis (P=0.001 for both groups). In HHD, a higher cumulative UF volume was independently associated with more intradialytic syndecan-1 shedding (P<0.001).

Conclusions: Over ultrafiltration during hemodialysis procedure could increase the risk of ischemic CSVD, especially the risk of subcortical white matter lacune and periventricular white matter hyperintensities (PVWMH) in MRI. Multivariable analysis was used to explore the relevance between ultrafiltration parameters and CSVD.

TH-PO205
Ultrafiltration Rate Correlates Better with Intradialytic Weight Change Indexed to Body Weight Than Absolute Weight Change
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Background: Intradialytic weight change (IDW change), ultrafiltration rate (UFR), and total ultrafiltration (UF) are used to quantify volume removal during hemodialysis (HD) treatments. These parameters are frequently used in clinical research to find associations between volume removal and outcomes like mortality and intradialytic complications. IDW change is a measure of the difference in body weight and it has a 53% variation of bias that is used both in the clinics and research. The objective of this study is to explore how indexed weight change correlates with the commonly used volume parameters during HD.

Methods: We reviewed records of 28 ESRD patients receiving HD in a single outpatient center in Philadelphia over a 2 month period. Treatments without UF were excluded from analysis. Correlations between absolute IDW change (pre minus post HD weight), achieved UFR (ml/kg/hour), and indexed weight change (IDW change divided by pre HD weight) were calculated using Pearson r. Range and mean of indexed weight change was also calculated and expressed as a percent of body weight lost (indexed weight change multiplied by 100).

Results: Individual intermittent HD treatments were analyzed (n=422). Absolute IDW change was not a significant impact on change weight (r=0.08, p=0.0001). Interestingly, UFR correlated strongly and better with indexed weight change than absolute IDW change. Indexed weight change takes into account differences in body habitus of individual patients, differences in their body surface area and total body water. Indexed weight change may be an important clinical parameter that could be used to guide UF prescriptions and more studies are needed to look into its association with hemodynamic changes during hemodialysis.

TH-PO206
Rise of Plasma Sodium Levels Is Followed by an Increase of Plasma Syndecan-1 in Hemodialysis Patients
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Background: In hemodialysis (HD) patients, endothelial dysfunction (ED) contributes to atherosclerosis. A major hallmark of ED is loss of glycoxylin evidenced by shedding of syndecan-1 into the blood stream. Release of syndecan-1 is seen in pro-inflammatory and pro-oxidative conditions such as in HD patients. HD by the Hemocontrol biofeedback system (HCB) is characterized by initially higher dialysate and plasma sodium levels. Using HHD as a model for an acute increase in plasma sodium, we investigated associations between courses of plasma sodium and syndecan-1 during HD and standard HD (SHD).

Methods: Plasma syndecan-1 was measured by ELISA in blood samples obtained from a group of 29 prevalent HD patients before, during, and after HD and SHD (randomized sequence). Wilcoxon signed-rank test or paired student’s t-test was used to compare syndecan-1 levels between SHD and HHD. Intradialytic shedding of syndecan-1 was determined by area under the curve analyses. Associations with the intradialytic course of syndecan-1 were analyzed with a mixed effects repeated-measures model.

Results: During HDH, plasma sodium increased early after the start of HD (predialysis 139.1 mmol/L; at 30 minutes of HD 142.3 mmol/L; P=0.0001) whereas sodium did not increase significantly during SHD. During HDH, plasma syndecan-1 increased after 1 hour of HD (P=0.025). Plasma syndecan-1 also increased significantly during SHD (within 120 minutes; P<0.0001) but at 120 minutes, the rise in syndecan-1 levels was significantly higher in HHD as compared to SHD (+42.9% vs. +17.2%; P=0.021). The total amount of shed syndecan-1 was higher during HDH than during SHD, albeit at borderline significance (P=0.05). Lower plasma sodium and osmolality during HDH were independent predictors of syndecan-1 increase during dialysis (P=0.001 for both groups). In HHD, a higher cumulative UF volume was independently associated with more intradialytic syndecan-1 shedding (P<0.001).

Conclusions: Plasma syndecan-1 levels increased significantly during both HDH and SHD. Furthermore, this rise was greater and occurred earlier as compared to SHD. This may reflect IDW change from increased sodium load. Further research to assess long term effects and clinical implications of high salt exposure is needed.

TH-PO207
Home vs. In-Center BP in Hypertensive Hemodialysis Patients
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Background: In hemodialysis (HD) patients, home blood pressures (HBP) are stronger than dialysis unit BP as predictors of adverse outcomes. In the HD pilot study, we assessed safety and feasibility of treating hypertensive HD patients to a standardized predialysis systolic BP (SBP) of 110-140 mm Hg vs. 155-165 mm Hg. Participants measured HBP according to American Heart Association guidelines twice on the day after the midweek HD. We assessed left ventricular mass index (LVMi) using MRI at baseline and midweek of the 1-year follow-up of the study. The present study assessed the differences between HBP and SDUPB within individuals.

Methods: To be included patients had to have a 6 pairs of standardized predialysis BPs from a midweek HD and a time-matched HBP the following day. Patients were assigned to one of 3 clusters, based on the average SDUBP to HBP differences and the variability of the difference within an individual, using cluster analysis in R.

Results: There were 97 patients with an average of 26 pairs of SDUBP and HBP who were included in the cluster analysis. This resulted in three clusters, (1) SDUBP > HBP (n=24); (2) SDUBP = HBP (n=20); and (3) SDUBP < HBP (n=53) where significant difference in body weight was not used both in the clinics and research. The objective of this study is to explore how indexed weight change correlates with the commonly used volume parameters during HD.

Conclusions: Patients in Cluster 3 (HBP higher than SDUBP) had higher LVMi at baseline and after the 12-month intervention than those in Clusters 1 and 2. Patients

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
in Cluster 3 frequently had an increase in SBP during HD. Monitoring home BP measurements may improve care of HD patients.

**Funding:** NIDDK Support, Commercial Support - Dialysis Clinic, Inc.

**Methods:** HD patients were consented and interviewed using a standardized cross-sectional survey, consisting of questions on fluid and BP management. Patients were paid $10 for their participation. Six months of retrospective data was collected from medical records.

**Results:** Ninety-two patients completed the survey, and 38/92 were not aware of the last time their dry weight (DW) was changed. Patients reported their last DW change was 5.93 ± 15.3 months ago on average. Of the 54 patients who reported their last DW change, 7/54 reported it was changed, 13/54 reported it was raised, 17 lowered, and 6 were not sure what changes were made. Medical records indicated that patients were not aware of the majority of DW changes. Over 3 months, DWs were changed an average of 2.54 ± 2.18 times. Twenty-four patients (26%) could not list their previous DWs, while those who listed their DW were on average 3.73 ± 10.16 kg away from the DW listed within their medical record.

Forty-six patients were currently on 1 or more AHT medications. Of these, the average time since AHT medications were last changed was 15.22 ± 16.4 months. The majority of patients (78/92) patients were interested in (or already) measuring their BP at home. Figure 1 shows how patients rated the likelihood of a direct relationship of their interdialytic fluid gains and BP.

**Conclusions:** Despite a desire to learn, most HD patients lack an understanding of the basic principles of fluid & BP management. There is a need for a structured education program for those initiating dialysis that encompasses fluid and BP management.

**Funding:** Private Foundation Support

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**TH-PO208**

**Patient Engagement with a Digital Health Intervention (patientMpower) to Optimise Interdialytic Fluid Management in Ambulatory Hemodialysis Patients**

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**Background:** Many aspects of a chronic illness rely heavily on patient self-care and engagement. While promising, studies on the use of digital medicine platforms to empower patients to self-manage have suffered from low patient engagement. This pilot-scale study (NCT03403491) evaluated a mobile digital health intervention+weighing scales+blood pressure (BP) meter [patientMpower intervention (pMp)] in ambulatory hemodialysis patients treated in a clinical setting. Patient-reported weight and BP were captured by wireless connection to pMp (cellular or Bluetooth).

**Methods:** 43 patients (28M/15F; age 51 ± 14y) entered an open-label, randomised, random-order, 2 x 28-day crossover comparison of pMp vs. a sham intervention. Patients were asked to record weight, BP symptoms, fluid intake & medicines adherence every day during the pMp period. pMp calculated and displayed weight gain relative to individualised target (dry) weight to each patient. An algorithm within pMp delivered tailored feedback messages (dependent on actual weight gain) to optimise fluid intake between dialysis sessions. Primary endpoint was patient engagement with pMp.

**Results:** Engagement was high. 35 patients (81%) recorded weight on ≥21 days of the pMp period. Engagement metrics in the 28-day pMp period are shown below. However, only 2 patients recorded medicines adherence on pMp. Patients were asked to complete an online survey to feed back opinion of pMp. 23 gave feedback. 198 (93%) reported pMp gave them a greater sense of control & had positive impact on their well-being. 187 (89%) wished to continue using pMp after study, 21 (91%) rated pMp as easy to use and 15 (65%) liked using pMp (score ≥8/10 on rating scale).

**Conclusions:** This study demonstrated that ambulatory hemodialysis patients are willing and engaged in using a mobile digital health intervention with connected devices to regularly monitor body weight and BP to help them optimise fluid intake. The high engagement by these patients suggests that this methodological approach could be useful in future studies of optimisation of dry weight estimation and/or fluid intake.

**Funding:** Commercial Support - patientMpower Ltd., Government Support - Non-U.S.

**TH-PO209**

**Assessment of Hemodialysis Patients’ Knowledge of Fluid and Blood Pressure Management**

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**Background:** Hemodialysis (HD) patients are expected to minimize interdialytic fluid gains and manage their blood pressure (BP) with antihypertensive (AHT) medications. Due to a paucity of data reporting patients’ knowledge and understanding of fluid and BP management, we conducted a prospective cross-sectional survey with retrospective medical record review at three HD clinics in Illinois.

**Methods:** HD patients were consented and interviewed using a standardized cross-sectional survey consisting of questions on fluid and BP management. Patients were paid $10 for their participation. Six months of retrospective data was collected from medical records.

**Results:** Ninety-two patients completed the survey, and 38/92 were not aware of the last time their dry weight (DW) was changed. Patients reported their last DW change was 5.93 ± 15.3 months ago on average. Of the 54 patients who reported their last DW change, 7/54 reported it was changed, 13/54 reported it was raised, 17 lowered, and 6 were not sure what changes were made. Medical records indicated that patients were not aware of the majority of DW changes. Over 3 months, DWs were changed an average of 2.54 ± 2.18 times. Twenty-four patients (26%) could not list their previous DWs, while those who listed their DW were on average 3.73 ± 10.16 kg away from the DW listed within their medical record.

Forty-six patients were currently on 1 or more AHT medications. Of these, the average time since AHT medications were last changed was 15.22 ± 16.4 months. The majority of patients (78/92) patients were interested in (or already) measuring their BP at home. Figure 1 shows how patients rated the likelihood of a direct relationship of their interdialytic fluid gains and BP.

**Conclusions:** Despite a desire to learn, most HD patients lack an understanding of the basic principles of fluid & BP management. There is a need for a structured education program for those initiating dialysis that encompasses fluid and BP management.

**Funding:** Private Foundation Support

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**TH-PO210**

**Factors Influencing Hourly Hemodynamic Changes During Hemodialysis**

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**Background:** The cardiovascular system adapts to maintain blood pressure during hemodialysis primarily by altering cardiac output and systemic vascular resistance. However, many dialysis patients develop intradialytic hypotension (IDH) or hypertension, both having serious consequences. While blood pressure is consistently monitored during dialysis, other hemodynamic variables are not. The purpose of our study is to examine changes in total peripheral resistance index (TPRI) and cardiac power index (CPI) during each hour of dialysis to determine the primary factors causing IDH and intradialytic hypertension throughout a dialysis session.

**Methods:** Intradialytic systolic blood pressure (SBP), mean arterial blood pressure (MAP), CPI and TPRI were evaluated hourly using peripheral bioimpedance (NCAs, Inc) in 27 HD patients. Measurements were taken at baseline and after each hour of dialysis for a total of 198 hourly measurements. IDH was defined as a drop of hourly SBP ≥ 20 mmHg or drop of hourly MAP ≥ 10 mmHg. Intradialytic hypertension was defined as a rise in hourly BP ≥ 15 mmHg. Measurements of blood pressure not meeting the definitions were defined as non-IDH or non-intradialytic hypertension time periods. Hourly changes in CPI and TPRI were compared.

**Results:** During the 1st hour of dialysis, neither SBP, CPI nor TPRI changed significantly. During the 2nd hour of dialysis, the average hourly TPRI changes in IDH and non-IDH groups were -211.5 ± 480.6 and 145.6 ± 572.1 (p=0.03). During the 3rd hour, the hourly CPI change was 0.12 ± 0.1 in the intradialytic hypertensive and -0.04 ± 0.1 in non-hypertensive groups (p=0.02) whereas the average TPRI change was -476.6 ± 701.7 in IDH and 168.4 ± 812.5 in non-IDH groups (p=0.008). During the 4th hour, the hourly CPI change was -0.06 ± 0.07 in the intradialytic hypertensive group and 0.04 ± 0.1 in intradialytic non-hypertensive group (p=0.03).

**Conclusions:** The predominant change responsible for IDH in the 2nd and 3rd hour of dialysis appears to be reduction in TPRI. By contrast, intradialytic hypertension in the 3rd hour appears to be primarily mediated by increases in CPI. In the 4th hour, there was a paradoxical reduction in CPI in the intradialytic hypertensive group. More closely monitoring hemodynamic changes during dialysis may provide information that could be used to intervene medically to prevent this dialysis-associated complications.

**Funding:** Commercial Support - RRI
Background: Published clinical studies on the use of blood volume monitoring to guide ultrafiltration in hemodialysis (HD) have had mixed results. We conducted a continuous quality improvement (CQI) project to assess the impact of Crit-Line monitoring on the overall care in a chronic HD population managed by a large, nonprofit dialysis provider. We postulated that Crit-Line monitoring would decrease intradialytic hypotension & hospitalization due to fluid overload.

Methods: A 6-month baseline period, we conducted 1 month staff training on Crit-Line followed by a 26-month period with Crit-Line monitoring with each HD. A total of 209 HD patients contributed a mean of 62 & 61 treatments to the baseline & Crit-Line periods, respectively. Mean & 95% confidence intervals (95% CI) for age & vintage were 62.6 (57.6, 67.6) & 4.7 (2.2, 7.2) years, respectively. Males & diabetics comprised 72% & 38% of the patients, respectively. Hypotension was defined as systolic blood pressure (BP) < 100 mmHg or symptoms associated with a drop in BP. Dialysate temperature & Crit-Line use, followed by a 2nd 6-month period with Crit-Line monitoring with each HD. Background: As the prognostic value of blood pressure variability (BPV) in hemodialysis patients has previously been inconclusive, this work performed a systematic review and meta-analysis to assess the association between BPV and clinical outcomes in hemodialysis patients.

Methods: Pubmed/Medline, EMBASE, Ovid, the Cochrane Library, and the Web of Science databases were searched through March 5, 2019 for full text articles in English. Cohort studies on the association between BPV and prognosis in hemodialysis patients were selected. Study selection and data extraction were performed by two reviewers independently, with adjudication by a third reviewer. Hazard ratios and 95% confidence interval were pooled in a random-effects model for the primary outcomes of all-cause and cardiovascular mortality. Statistical analysis was performed using STATA 14.0 (STATA Corp., Texas, USA).

Results: A total of 13 studies (37,827 patients) were eligible. Systolic BPV was associated with higher all-cause mortality (HR: 1.12, 95% CI: 1.06-1.19, P < 0.001) and cardiovascular mortality (HR: 1.16, 95% CI: 1.10-1.22, P < 0.001), while diastolic BPV was not associated with them (P = 0.14, 0.56). Long-term systolic BPV (inter-dialytic or inter-visit BPV) was shown to be a risk factor for all-cause mortality (HR: 1.11, 95% CI: 1.05-1.17, P < 0.001) and cardiovascular mortality (HR: 1.14, 95% CI: 1.06-1.22, P < 0.001) mortality, but short-term systolic BPV (intra-dialytic or ambulatory) was only associated with cardiovascular mortality (HR: 1.19, 95% CI: 1.09-1.29, P < 0.001). The associations between systolic BPV and mortality events were not affected by region (North America vs. Europe vs. Asia), follow-up time (≥2.5 years vs. >2.5 years) or variable type (BPV as a categorical vs. continuous variable). Among the different BPV metrics, the coefficient of variation of systolic blood pressure was identified as predictor of both all-cause (P=0.012) and cardiovascular (P=0.002) death.

Conclusions: In the hemodialysis population, systolic BPV was associated with both increased all-cause and cardiovascular mortality, while diastolic BPV was not associated with the clinical outcomes. CV of systolic blood pressure was identified as a predictor for both all-cause and cardiovascular mortality, while the utility of other BPV metrics requires further investigation.

Funding: Government Support - Non-U.S.

Background: Chronic kidney disease (CKD) is associated with progressive arteriolar and increased arterial stiffness (AS) – expressed as higher measured aortic pulse wave velocity (aPWV) – has been frequently described in dialysis patients. However, the intrinsic physiologic relationship between aPWV and prevailing arterial pressure complicates the direct comparison of aPWV values between different collectives. An individual pressure-independent expression of aPWV could be a possible solution.

Methods: Hemodialysis patients were age- and sex-matched with patients with preserved kidney function. Long-term measurements (24 hours for patients with preserved kidney function and 44 hours for hemodialysis patients) of blood pressure (BP) and aPWV were obtained. aPWV was then adjusted to 120 mmHg central systolic BP (PWV120) based on individually determined relationship and mean PWV120 was compared between the two collectives.

Results: 45 patients were included in each group. Haemodialysis group had significantly higher prevalence of diabetes mellitus and significantly more patients with hyperlipoproteinemia, history of coronary heart disease, stroke and peripheral artery disease, while patients with preserved renal function had significantly higher systolic and diastolic BP. PWV120 did not differ between the groups.

Conclusions: In our study, we used BP-adjustment for pressure-independent expression of aPWV. Our results show that pressure-independent aPWV did not differ between patients on haemodialysis and with preserved kidney function. This finding is in contrast to previous reports and prompts questions about association between AS and CKD. However, more data are needed to reproduce the results for further assessment.

Funding: Commercial Support - Dialysis Clinic, Inc.
TH-PO215

Body Composition Analyzer Monitoring Improves Dialysis in Maintenance Hemodialysis Patients Role in Hypotension
Jun Yin, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

Background: Exploring the role of body composition analyzer (BCM) monitoring in improving dialysis hypotension in patients undergoing maintenance hemodialysis (MHD)

Methods: 51 patients with dialysis hypotension in our center, 27 males and 24 females, with an average age of (55.8±7.3) years old, were monitored and adjusted by BCM. The patients were re-evaluated and adjusted for 1 month before and after BCM monitoring.

Results: The average dry weight before BCM monitoring was (53.2±7.9) kg, and the average dry weight after BCM monitoring was (55.8±8.1) kg. The incidence of dialysis hypotension before BCM monitoring was 38%, and the incidence after monitoring was significantly reduced to 14%. The incidence of dialysis hypotension was significantly reduced after BCM was monitored and up-regulated (P<0.05). There was no significant change in the mean arterial pressure after BCM monitoring and up-regulation of dry weight (P>0.05).

Conclusions: BCM monitoring can improve the dialysis hypotension of patients with MHD without increasing the patient’s water and sodium retention, and does not increase the blood pressure before transfusion. It can quickly and accurately regulate the patient’s dry weight.

TH-PO216

Standing Blood Pressure Differentiates True and Pseudo Intradialytic Hypertension
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Background: Intradialytic hypertension (IH) is a blood pressure (BP) increase from pre to post-hemodialysis (HD). While IH occurs sporadically in nearly all HD patients, recurrent IH is clinically significant and associated with extracellular volume (ECV) excess, intradialytic vasoconstriction and mortality. We investigated if standing BP measurements from a single HD treatment with seated IH could distinguish patients with recurrent vs sporadic IH.

Methods: Among HD patients with increases in seated systolic BP from pre to post-HD in a single treatment, we compared ECV-weight (biompedance spectroscopy) and cardiac hemodynamics from that treatment and intradialytic BP trends in the prior 6 months between those with increases (true IH) or decreases (pseudo IH) in standing BP from pre to post-HD.

Results: There were 18 subjects with true IH and 7 with pseudo-IH with no differences in age or demographics. True IH subjects had higher post-HD ECV-weight, intradialytic TPRI increases, and more IH episodes in the past 6 months compared to pseudo IH (Table).

The intradialytic BP patterns (excluding pre and post-HD seated measurements) are shown (Figure).

Conclusions: Patients with seated, but not standing, IH in a single treatment have a different physiologic phenotype than those with true-IH. The clinical significance of IH is the intradialytic BP patterns (excluding pre and post-HD seated measurements) are shown (Figure).

TH-PO217

Effect of Sodium and Ultrafiltration Modeling vs. Low-Temperature Dialysate on Prevention of Intradialytic Hypotension: Single-Center Study from India
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Background: Symptomatic intradialytic hypertension is the most frequent complication in patients receiving hemodialysis. It complicates 5 to 30 percent of all dialysis treatments. In our study, we aimed to compare the effect of sodium and ultrafiltration modeling versus low-temperature dialysate on the occurrence of intradialytic hypertensive episodes.

Methods: A total of 320 patients with chronic kidney disease (CKD) stage V on conventional hemodialysis (HD) for at least twice weekly for a minimum of 3 months were observed for the occurrence of ≥1 intradialytic hypertensive episodes per month. After full filling the inclusion and exclusion criteria, 60 patients were randomized into two groups based on computer-generated randomization numbers allotted to them by the dialysis coordinator. Group 1: Underwent dialysis with sodium and Ultrafiltration modeling (Linearly decreasing dialysate sodium from 141 mmol/L to 128 mmol/L and linearly decreasing ultrafiltration rate). Group 2: Underwent dialysis with low-temperature dialysate (36 degrees Celsius). Both groups underwent 240 sessions of hemodialysis.

Results: Intradialytic hypotension was found in 18.75% of patients. Diabetic nephropathy (61.66%) was the leading cause of end-stage renal disease in these patients. There was no significant difference between the two groups in mean arterial blood pressure, hemoglobin, cardiac status, and serum albumin before dialysis. Both groups had a similar incidence of intradialytic hypertensive episodes (P >0.05). Intradialytic weight gain and ultrafiltration volume removed per session were also similar in both groups.

Conclusions: Sodium and ultrafiltration modeling and low-temperature dialysate were both equally effective in the prevention of intradialytic hypertensive episodes.

TH-PO218

True Arterial Stiffness Does Not Change Between Dialysis Sessions During 1 Week in Outpatients on Intermittent Hemodialysis
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Background: End-stage renal disease (ESRD) is associated with exponentially elevated cardiovascular mortality. Higher pulse wave velocity (PWV) values are frequently observed in patients with ESRD. However, the intrinsic physiologic relationship between PWV and prevailing arterial pressure can deteriorate its cardiovascular predictive value making an individual pressure-independent expression of PWV essential.

Methods: Dialysis patients from a single outpatient unit obtained repeated measurements of blood pressure (BP) and pulse wave analysis during each dialysis session of one week. Aortic PWV was then adjusted to 120 mmHg central systolic BP based on individually determined relationship.

Results: 54 subjects were included. The median age was 75.5 years. Mean systolic/diastolic BP was 121.4/70.5 mmHg and the median heart rate was 64.6 beats/min. Mean PWV was 10.9 m/s and mean PWV120 was 11.3 m/s. PWV120 did not change across single dialysis session during one week, while systolic, diastolic BP, PWV and ultrafiltration volume differed significantly.

Conclusions: Our data suggest that true AS does not change in the short-term course in dialysis patients and observed changes in PWV are rather associated with BP change due to intrinsic pressure-dependence. Our analytical approach represents a novel method for this purpose, which is easy in performance and also applicable for large interventional trials and clinical practice.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Change in A- systolic, diastolic, central systolic blood pressure (BP) and B- pulse wave velocity (PWV) and PWV adjusted to 120 mmHg central systolic blood pressure (PWV120) between the dialysis days of one week.

**TH-PO219**

Serum Fibroblast Growth Factor 21 Level Is a Risk Factor for Central Arterial Stiffness in Maintenance Hemodialysis Patients

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**Background:** Fibroblast growth factor 21 (FGF21) is a hepatic hormone in the regulation of glucose and lipid metabolism. Serum FGF21 levels were higher in patients with carotid atherosclerosis and in patients with coronary artery disease. The aim of this study was to evaluate the relationship between serum FGF21 levels and carotid-femoral pulse wave velocity (cPWV) values in patients on hemodialysis (HD).

**Methods:** Among 130 HD patients, 54 patients (41.5%) were in the central arterial stiffness group. When compared to those in control group, the central arterial stiffness group had high prevalence of diabetes mellitus (P < 0.001), hypertension (P = 0.026), and older age (P = 0.036), higher body weight (P = 0.027), body mass index (P = 0.048), systolic blood pressure (P = 0.044), C-reactive protein (P = 0.040), and higher serum FGF21 level (P < 0.001). Multivariable logistic regression analysis of the factors significantly associated with central arterial stiffness revealed that FGF21 levels (odds ratio (OR): 1.001, 95% confidence interval (CI): 1.000-1.001, P = 0.001), age (OR: 1.043, 95% CI: 1.002-1.085, P = 0.042), and diabetes mellitus (OR: 4.495, 95% CI: 1.703-11.867, P = 0.002) were the independent predictors of central arterial stiffness in HD patients. Multivariable forward stepwise linear regression analysis also showed that logarithmically transformed FGF21 level (log-FGF21, β = 0.301, adjusted R ² change = 0.301) was an independent predictor of cPWV values in HD patients. The area under the receiver-operating characteristic (ROC) curve predicting central arterial stiffness by serum FGF21 level in HD patients was 0.693 (95% CI: 0.606-0.771, P < 0.001).

**Conclusions:** Serum FGF21 level positively correlated with cPWV values and is also the independent predictor of central arterial stiffness among HD patients.

**TH-PO220**

Correlation Between Arterial Stiffness and Body Fat in Hemodialysis Patients

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**Background:** Arterial stiffness is common in chronic kidney disease. It has been known that the traditional risk factors such as ageing, hypertension and diabetes are linked to aortic elasticity. Few studies have focused on peripheral arterial elasticity. Some clinical trials have found a nonlinear relationship between body fat percentage and atherosclerosis in general population. Here, we explore the correlation between body fat and arterial elasticity in hemodialysis patients by measuring a variety of body fat indexes.

**Methods:** Blood samples and baseline characteristics were obtained from 130 HD patients. Patients underwent arterial elasticity examination and body fat assessment. Basic elasticity in hemodialysis patients by measuring a variety of body fat indexes.

**Results:** Among 130 HD patients, 54 patients (41.5%) were in the central arterial stiffness group. Compared to those in control group, the central arterial stiffness group had high prevalence of diabetes mellitus (P < 0.001), hypertension (P = 0.026), and older age (P = 0.036), higher body weight (P = 0.027), body mass index (P = 0.048), systolic blood pressure (P = 0.044), C-reactive protein (P = 0.040), and higher serum FGF21 level (P < 0.001). Multivariable logistic regression analysis showed the factors significantly associated with central arterial stiffness revealed that FGF21 levels (odds ratio (OR): 1.001, 95% confidence interval (CI): 1.000-1.001, P = 0.001) was an independent predictor of central arterial stiffness in HD patients. Multivariable forward stepwise linear regression analysis also showed that logarithmically transformed FGF21 level (log-FGF21, β = 0.301, adjusted R ² change = 0.301) was an independent predictor of cPWV values in HD patients. The area under the receiver-operating characteristic (ROC) curve predicting central arterial stiffness by serum FGF21 level in HD patients was 0.693 (95% CI: 0.606-0.771, P < 0.001).

**Conclusions:** Serum FGF21 level positively correlated with cPWV values and is also the independent predictor of central arterial stiffness among HD patients.

**TH-PO221**

Post-Dialysis Orthostatic Blood Pressure Is Not Associated with Extracellular Volume in Hemodialysis Patients

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**Background:** Blood pressure (BP) measurements are obtained before, during, and after hemodialysis (HD) for safety monitoring. The pattern of intradialytic seat BP changes is becoming recognized as an extracellular volume (ECV) assessment tool. It is unknown if orthostatic BP changes after HD provide information on ECV.

**Methods:** In a cohort of 55 hypertensive HD patients, we identified those with and without orthostatic BP decreases, defined as a ≥10 mmHg decrease in systolic BP from seated to standing position (both post-HD). We compared post-HD ECV/body weight using bioimpedance spectroscopy between the groups. We also compared orthostatic BP changes among tertiles of post-HD ECV/b weight.

**Results:** Compared to those with orthostatic decreases (n=26), those without orthostatic decreases (n=29) were more likely to be African American. There were no differences in presence of diabetes or distribution of antihypertensive drug class. There were no differences in ECV/b weight or cardiac hemodynamics between the groups (Table). There were no differences in orthostatic BP changes among tertiles of ECV/b weight (Figure).

**Conclusions:** We found no associations between ECV/b weight and post-HD orthostatic BP changes. Seated to standing BP changes should not be used to diagnose post-HD ECV overload or depletion in HD patients.

**Funding:** NIDDK Support, Veterans Affairs Support

**TH-PO222**

Oxygen Extraction Ratio (OER) and Intradialytic Hypotension

Silverio Rotondi, Lida Tartaglione, Sandro Mazzaffer. Sapienza University of Rome, Roma, Italy.

**Background:** Intradialytic hypotension (IDH) worsens treatment tolerance, and outcome of hemodialysis (HD) patients. Attention has been given to the role of HD-induced hypoxia, evaluated by measuring arterial oxygen saturation (SaO2) and central venous saturation (ScvO2), in IDH prone patients. Oxygen Extraction Ratio (OER), the ratio between SaO2 and ScvO2, better than the two parameters alone theoretically describes intra-HD hypoxia. OER basal values and its changes occurring during HD (deltaOER) have been associated with mortality in HD patients. A delta OER~40% seems to identify patients experiencing sub-clinical hypoxia and parenchymal stress. Aim of our study was to evaluate if delta OER could help identify patients at higher risk of IDH.

**Methods:** We enrolled clinically stable patients on HD since 3 months, with Central Venous Catheter. We sampled arterial SO2 (oxymer) and ScvO2 (blood gas analysis) to calculate OER basally and at the end of HD, for three consecutive HD sessions. Average individual measurements were obtained to divide patients into two groups with delta OER > or ≤40%. We recorded IDH in each subject, during a 24-months follow-up period.

**Results:** We divided patients into two group according to delta OER (threshold 40%). The group were not different for age, HD vintage, systolic (SBP) and diastolic blood pressure (DBP) and pulse rate. The group with delta OER ~40% had a number of
IDH significantly higher than delta OER<40% group (30±20vs.10±20;p= .011), which was associated with lower pre-HD OER (30±4v.36±5;p=0.025) and similar post HD OER values.

**Conclusions:** Our study indicates that in HD patients, delta OER associate with IDH, with a threshold value set at ~40% the basal value. We suggest that we could use OER to identify patients at higher risk of IDH, deserving more intensive intradialytic monitoring. Repetitively, it is applicable only in patients with CVC.

**Methods:** This is a retrospective cohort study, 922 HD patients were enrolled from 10 HD facilities in China. The patients were categorized into hypercalcemia group and hypocalcemia group according whether the serum corrected calcium levels is a 8.67mg/dl (the median of serum corrected calcium in all patients), which were further categorized into high PTH (serum intact PTH>300pg/ml) and low PTH (serum intact PTH<300pg/ml) groups. Not only the clinic characters, especially the pre and post dialysis blood pressure measurements were analyzed between the four groups, but also the risk factors of IDH were studied by multiple logistic regression in all HD patients.

**Results:** The prevalence of IDH was much higher in patients of hypercalcemia and high PTH than those of hypocalcemia and low PTH (21.1% vs. 9.6%, p=0.001). Adjusted with age, dialysis vintage, gender, diabetes mellitus, BMI, Kt/V, serum albumin, and hemoglobin, logistic multiple regression analysis determined that hypercalcemia and iPTH with intradialytic hypotension (IDH) is unclear.

**Background:** High Serum Calcium and Parathyroid Hormone Are Risk Factors of Intradialytic Hypotension in Hemodialysis Patients

**Methods:** This is a retrospective cohort study, 922 HD patients were enrolled from 10 HD facilities in China. The patients were categorized into hypercalcemia group and hypocalcemia group according whether the serum corrected calcium levels is a 8.67mg/dl (the median of serum corrected calcium in all patients), which were further categorized into high PTH (serum intact PTH>300pg/ml) and low PTH (serum intact PTH<300pg/ml) groups. Not only the clinic characters, especially the pre and post dialysis blood pressure measurements were analyzed between the four groups, but also the risk factors of IDH were studied by multiple logistic regression in all HD patients.

**Results:** The prevalence of IDH was much higher in patients of hypercalcemia and high PTH than those of hypocalcemia and low PTH (21.1% vs. 9.6%, p=0.001). Adjusted with age, dialysis vintage, gender, diabetes mellitus, BMI, Kt/V, serum albumin, and hemoglobin, logistic multiple regression analysis determined that hypercalcemia (OR:2.477, 95%CI: 1.632-2.758, P<0.001) (Model1), and hypercalcemia accompany with high PTH (OR:2.634, 95%CI: 1.378-5.031, P=0.003) (Model2) were risk factors of IDH. Furthermore, increasing ultrafiltration was also risk factor of IDH (Model1 OR:1.409, 95%CI: 1.072-1.851, P=0.014; Model2 OR:1.397, 95%CI: 1.061-1.839, P=0.017). However, hemodialfiltration (HDF) was a protective factor of IDH in the patients (Model1 OR:0.441, 95%CI: 0.281-0.693, P=0.001; Model2 OR:0.442, 95%CI: 0.281-0.694, P=0.001).

**Conclusions:** Not only increasing ultrafiltration, but also high serum calcium and PTH are the risk factors of IDH. Furthermore, the hemodialfiltration will lower the risk of IDH compared with hemodialysis.

**Funding:** Other U.S. Government Support

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underline represents presenting author.**
the predicting model. The data showed that the connections of BG-MTG and Amyg-FuG is stronger than other regions in predicting systolic orthostatic blood pressure reduction, while the connections strength in Amyg-pST5 holds the major contribution in predicting diastolic reduction.

**Conclusions:** Our analysis suggests that impaired orthostatic BP homeostasis has a significant effect on brain network in dialysis patients. These results provide further insight into the association between orthostatic hypotension and cognitive impairment and indicate that maintaining orthostatic homeostasis might be an effective strategy for the prevention of cognitive decline in the patients.

**Funding:** Government Support - Non-U.S.

**TH-PO226**

**Pilot Study to Measure Indicators of Blood Flow in the External Auditory Meatus During Haemodialysis**

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**Background:** Intradialytic hypotension remains the most common complication of outpatient haemodialysis (HD) sessions. As such, there is a need to develop non-invasive monitoring devices, which would then allow for therapeutic interventions to prevent hypotension. We report on a pilot study monitoring indicators of blood flow in the external auditory meatus.

**Methods:** We measured the maximum pulse wave amplitude and indicators of blood flow by red and green pixel values in the outer auditory meatus from video recordings made using an otoscope fitted with a digital camera in adult patients undergoing haemodialysis treatments.

**Results:** We studied 61 patients, 43 (71.5%) male, mean age 64.9±12.7 years during their dialysis session. Weight fell from 72.8±22.1 kg post-dialysis (p<0.001). Blood pressure did not significantly change (pre-dialysis 142±17 mmHg to 141±17 mmHg, respectively) and remained low thereafter, and the change at the end of the dialysis session was associated with percentage weight loss (r=−0.37, p=0.003). Green and red pixel values did not change (pre-dialysis 0.339 (0.333-0.345) to 0.302 (0.291-0.33) post, and 0.301 (0.293-0.326) pre-dialysis to 0.339 (0.334-0.347), respectively).

**Conclusions:** This pilot study showed that the maximum pulse wave amplitude measured in the external auditory meatus fell during the dialysis session, and that the fall was associated with fluid removal. This could potentially lead to the development of a monitoring device which could fit in the ear and record during the dialysis session.

**Funding:** Private Foundation Support

**TH-PO227**

**Uric Acid Distribution Adjusted by Urea Distribution Volume Is a Promising Marker of Hydration Status in Hemodialysis Patients**

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**Background:** Hemodialysis (HD) patients are prone to developing volume disturbance. Bioelectrical impedance analysis (BIA) provides indices for evaluating volume status, although this requires a dedicated machine, which precludes it from other general clinical use. Uric acid (UA) barely crosses the cell membrane, while urea does so readily. The volume of distribution (Vd) of UA and urea can be considered markers of extracellular water (ECW) and total body water (TBW), respectively. We investigated whether the ratio of the Vd of UA and urea (VUA/VUN) can be a surrogate marker of ECW/TBW measured by BIA.

**Methods:** In total, 108 patients who were receiving HD at our facility and who underwent BIA in 2018 were included in this study. VUA/VUN was calculated using the single-pool model. We compared ECW/TBW values after dialysis measured by BIA (InBody S10; InBody, Tokyo, Japan). We investigated factors associated with residuals from regression. We also evaluated the predictive ability of overhydration (ECW/TBW 0.4) or dehydration (ECW/TBW <0.38) in two randomly selected groups, the training group and the validation group.

**Results:** VUA/VUN and ECW/TBW were 0.646±0.062 and 0.393±0.014, respectively. ECW/TBW was highly correlated with VUA/VUN (ECW/TBW = 0.274 + 0.184·VUA/VUN). Multivariate analysis demonstrated that only creatinine and ECW/TBW were significantly associated with the regression residuals. The cut-off values of VUA/VUN for overhydration and dehydration were 0.666 and 0.579, respectively, in the training group. The corresponding area under the receiver operating characteristic curves were 0.872 and 0.896, respectively. The sensitivity and specificity values in the validation group were 0.571 and 0.968 for overhydration and 0.444 and 0.953 for dehydration, respectively.

**Conclusions:** VUA/VUN was not only associated with ECW/TBW but was also highly predictive of hydration status evaluated by BIA. We need only blood tests before and after the dialysis session for estimating VUA/VUN, so this measure is widely applicable, even in epidemiological studies, without the need for dedicated devices.

**TH-PO228**

**Ambulatory Blood Pressure Monitoring and Other Blood Pressure Measures in the BID (Blood Pressure in Dialysis) Pilot Study**

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**Background:** Ambulatory blood pressure monitoring (ABPM) is the gold standard for diagnosis and management of hypertension. However, poor adherence limits its use in clinical practice. In the BID pilot, we used predialysis standardized dialysis unit systolic blood pressure (SDUSBP) to drive BP management. We also compared this measure to ABPM, standardized home SBP (SHSBP), intradialysis SBP (IDSBP), and postdialysis SBP (PDSBP).

**Methods:** The BID protocol called for a 44-hour ABPM after the mid-week dialysis at baseline and quarterly in 5 geographic hubs, SDUSBP before each dialysis, SHSBP weekly the day after the mid-week HD treatment and also IDSBP and PDSBP with each treatment. Outcomes included the quantitative differences between these measures and their ability to predict left ventricular hypertrophy (LVH) on cardiac MRI at baseline and quarter four by analyzing the area under receiver operator characteristic (ROC) curves (AUC).

**Results:** Ninety-four out of 95 patients and 53 out of 84 patients eligible for ABPM, had both an ABPM and cardiac MRI at baseline and in quarter 4 respectively. The differences between average daytime SBP on ABPM vs. other measures in quarter 4 were as follows 1) SDUSBP – 3.36 (95% CI -8.72, 2.00) mm Hg; 2) IDSBP 1.63 (95% CI -2.73, 5.99) mm Hg and 3) PDSBP 1.40 (95% CI -2.90, 5.71) mm Hg. Forty-four patients in quarter 4 had ABPMS in addition to SHSBP measurement. Mean difference between average day SBP on ABPM vs. SHSBP was 0.35 (95% CI -5.45, 6.16) mm Hg. The AUCs used to compare the ability of the different BP measures to predict LVH are shown.

**Conclusions:** Although difference between daytime SBP on ABPM and SDUSBP were higher than the other measures, the differences were modest. HSBP, IDSBP and PDSBP demonstrated similar values when compared to ABPM. ABPM was the strongest and SDUSBP the weakest predictor of LVH. Dialysis units should encourage adherence with ABPM and HBP measurements.

**Funding:** NIDDK Support, Commercial Support - Dialysis Clinic, Inc
Higher Dialysis Dose and Less Intradialytic Hypotension Are Associated with Improvements in Longitudinal Changes in Dialysis Recovery Time

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Background: We studied if higher hemodialysis (HD) dose and less intradialytic hypotension (IDH) would associate with longitudinal improvements in dialysis recovery time (DRT).

Methods: We used data from adult HD patients at a large dialysis organization who responded to DRT survey ≤180 days from first date of dialysis (FDD) during 2014 to 2017. DRT survey asks: “How long does it take you to be able to return to your normal activities before/after 1200 hours.” Answers are: <0.5, 0.5-1, 1-2, 2-4, or >4 hours. A logistic regression model computed odds ratio for increased/maintained longer DRT (increase above DRT >2 hours) in reference to decreased/maintained shorter DRT (decrease below DRT <2 hours, or from DRT >4 hours). Changes in DRT were calculated from incident (≤180 days FDD) to prevalent (>365-to-≤545 days FDD) year. Model included/adjusted for incident DRT, age, comorbidities, HD with IDH episodes/month, Kt/V, and HD start time (DRT).

Results: Among 98616 incident HD patients (age 62.6 ± 14.4 years), higher incident spKt/V associated with 13.5% (OR=0.865; 95%CI 0.801-to-0.935) lower odds of increased/maintained longer DRT in the prevalent year (Figure 1). A higher incident number of HD sessions with IDH episodes/month and change to a higher number associated with 0.8% (OR=1.008; 95%CI 1.001-to-1.015) and 2.2% (OR=1.022; 95%CI 1.015-to-1.028) higher odds of increased/maintained longer DRT in the prevalent year, respectively.

Conclusions: Incident patients who had higher spKt/V with a low number of HD sessions were less likely to have incident IDH episodes had a lower likelihood of increased/maintained longer DRT in first year of HD. Dose optimization strategies with cardiac stability in fluid removal should be tested.

Funding: Commercial Support - Fresenius Medical Care North America.
Patient-Reported Quality of Life in Dialysis Compared with Non-Dialysis

CKD Patients with Hyperkalemia in the United States and European Union: Results from the KDQOL

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Background: Patients with chronic kidney disease (CKD) have an increased risk of hyperkalemia (HK), which increases with CKD progression. Patients in longitudinal study report negative impact on quality of life (QoL), though evidence is limited. The increased risk of HK and associated morbidity and mortality may further add to patient burden.

Methods: Data from the 2015 and 2018 Adelphi CKD Disease Specific Programmes were merged to create a longitudinal dataset. Patients, including data from physicians, and their CKD patients across France, Germany, Italy, Spain, the UK and USA. Patients completed the KDQOL, a measure targeted at specific concerns of individuals with CKD. A multiple linear regression was performed, for each of the 5 KDQOL domains, to study the association between non-dialysis dependent (NDD) patients with HK (K+ >5.0 mmol/L), DD patients without HK (K: 5.5-5.0 mmol/L) and DD patients with HK to a reference group of NDD patients without HK (and their interaction), adjusting for age, sex, eGFR level, and presence of heart failure and diabetes.

Results: Results: From 1,242 participants, we measured an incremental decrease in QoL across each patient group for 2 of the 5 KDQOL domains. When compared to the reference group, NDD patients with HK experienced significantly poorer QoL across all 5 of the KDQOL domains. However, DD patients with HK experienced an additional significant deterioration in QoL across 4 of the 5 domains, compared with NDD patients without HK (Table 1).

Conclusions: This study highlights the negative impact that HK contributes to CKD patients, leading to further decrements in QoL, particularly among DD CKD patients. Innovative HK treatment approaches should be an important consideration by physicians to improve QoL in this patient population.

Funding: Commercial Support - AstraZeneca

<table>
<thead>
<tr>
<th>Table 1: KDQOL values vs. CKD and Hyperkalemia Status</th>
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<tbody>
<tr>
<td>KDQOL domains, mean (SD)</td>
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<tr>
<td>----------------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Dialysis need status</td>
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<tr>
<td>Effect of kidney disease</td>
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<tr>
<td>Effect of hypertension</td>
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<tr>
<td>Mean change in a year</td>
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<tr>
<td>SF 12 physical summary score</td>
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<td>SF 12 mental summary score</td>
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Quality of Life in Caregivers of Patients Receiving Standard vs. Extended Hours Hemodialysis: The Co-ACTIVE Substudy of the ACTIVE Dialysis Trial

Melissa S. Natsatmadju,1,2 Rathiha Krishnasamy,1,2 Li Zhuo,1 Daqing Hong,3,4 Brendan Smyth,1,5 Min Jun,1 Janak de Zoya,5 Kirsten Howard,1 Lu Chunlai,1 Vladko Perkovic,1 Meg J. Jardine,1,2 Nicholas A. Gray,1,2 Department of Nephrology, Sun Yat-sen University, China; 3Department of Nephrology,.TabIndex Biritania, QLD; 4School of Medicine, The University of Queensland, Herston, QLD, Australia; 5Peking University People's Hospital, Beijing, China; 6Sichuan Provincial People's Hospital, Chengdu, China; 7The George Institute for Global Health, Sydney, NSW, Australia; 8Renal Service, Wataimata District Health Board, Auckland, New Zealand; 9Department of Medicine, University of Auckland, Auckland, New Zealand; 10Department of Medicine, University of Public Health, Sydney, NSW, Australia; 11Department of Nephrology, Shanghai 8th Hospital, Shanghai, China; 12Department of Renal Medicine, Concord Repatriation General Hospital, Sydney, NSW, Australia.

Background: Caregivers of dialysis patients experience significant burden and lower quality of life (QOL) compared to the general population. Extended hours dialysis has benefits for the patient, however little is known about its effects on caregivers.

Methods: We evaluated QOL amongst caregivers of the ACTIVE Dialysis trial participants who were randomised for 12 months to receive extended (median 24 hours/ week) or standard (12 hours/week) hemodialysis. Caregivers completed the EuroQOL-5 Dimension-3 Level (EQ5D-3L), Short Form-36 (SF-36) physical component summary (PCS), mental component summary (MCS) and SF-6D, and Personal Wellbeing Index (PWI). We measured outcome change in QOL scores from study entry to follow-up.

Results: A total of 40 participated in this longitudinal study. Most caregivers were female (64%) and Asian (94%). At baseline, QOL scores in caregivers of patients randomised to standard and extended hours hemodialysis were similar (Table 1). At follow-up, there was a significant difference in the mean change in EQ5D-3L between those allocated to standard versus extended hours dialysis (+0.029±0.16 vs. -0.197±0.30, p=0.04). There were no differences between standard and extended hours groups in mean change in PCS (-5.9±8.9 vs. -1.2±9.8, p=0.02), MCS (-5.5±7.1 vs. -4.1±11.2, p=0.4), SF-6D (-0.04±0.1 vs. 0.03±0.1, p=0.8) and PWI (0.00±0.04 vs. -2.3±17.6, p=0.9).

Conclusions: Our study found significantly poorer health utility amongst caregivers of patients randomised to extended hours dialysis, but no differences in QOL measures. This suggests extended hours dialysis may have a negative impact on caregivers, although our study has a number of limitations including small sample size and short follow-up, and the results should be regarded as exploratory. Further studies are needed to better understand the impact of dialysis on caregivers to inform the provision of support services.

Table 1. Baseline characteristics of caregivers in the Co-ACTIVE study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard (n=16)</th>
<th>Extended (n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>54.4 (10.3)</td>
<td>54.3 (11.0)</td>
<td>0.9</td>
</tr>
<tr>
<td>Sex, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31.4</td>
<td>28.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Female</td>
<td>68.6</td>
<td>71.4</td>
<td></td>
</tr>
<tr>
<td>Marital status, %</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>52.9</td>
<td>7.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Married</td>
<td>100</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>0</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Non-Chinese</td>
<td>100</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Travel Arrangements in In-Center Hemodialysis: A Qualitative Study

Jane Wat, Wongboonsin, Joseph R. Merighi, Paul E. Drewz. University of Minnesota, Minneapolis, MN.

Background: For people with end-stage renal disease, “travel” and “independence” are rated as 2 of the top 5 factors that inform their treatment modality choice. The limits imposed by in-center hemodialysis treatment can present a variety of challenges for patients who wish to travel. This exploratory study investigated how IHD patients managed their travel and the role of dialysis social workers in executing travel arrangements for patients.

Methods: An interview-based, qualitative study was conducted with IHD patients being treated at a University-affiliated hospital and community-based dialysis social workers. Patients were screened from an inpatient nephrology consult panel and, after enrolling in the study, provided contact information for their dialysis social workers. Two coders used a grounded theory (constant comparative) approach to analyze the data fromverbatim transcriptions.

Results: Sixteen patients and eight social workers were enrolled in the study. The patient sample included 8 women (50%), 13 whites (81.3%), and a mean dialysis vintage of 5 years. The social worker were all women and had a mean of 6 years of practice experience. Three overarching themes emerged from the interviews: the process, barriers, and facilitators of travel. The travel process subthemes included communication, dialysis schedule, and travel itinerary. The barrier and facilitator subthemes were categorized into patient, dialysis facility, and supporting factors. These subthemes addressed caregiver roles, being flexible, staff professionalism, and managing unanticipated situations. Overall, there was lack of uniform infrastructure and understanding regarding the travel process at the patient level, provider level, and system level.

Conclusions: This study identified multiple perspectives surrounding travel arrangements in chronic IHD patients. There is limited research on travel issues for chronic IHD patients and this investigation is among the first to articulate barriers and facilitators associated with travel from the perspective of patients and social workers.

Promoting and supporting travel for IHD patients can serve to increase their sense of autonomy and provide opportunities to improve their quality of life.

86.46%, for PVT, MCR and MCD, respectively (P<0.01). The average compliance of patients randomised to extended hours dialysis, but no difference in QOL measures. This suggests extended hours dialysis may have a negative impact on caregivers, although our study has a number of limitations including small sample size and short follow-up, and the results should be regarded as exploratory. Further studies are needed to better understand the impact of dialysis on caregivers to inform the provision of support services.

| Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only |
|-----------------|-----------------|-----------|
| TH-PO231 | Patient-Reported Quality of Life in Dialysis Compared with Non-Dialysis CKD Patients with Hyperkalemia in the United States and European Union: Results from the KDQOL |
| TH-PO232 | Quality of Life in Caregivers of Patients Receiving Standard vs. Extended Hours Hemodialysis: The Co-ACTIVE Substudy of the ACTIVE Dialysis Trial |
| TH-PO233 | Travel Arrangements in In-Center Hemodialysis: A Qualitative Study |
Conclusions: Our findings suggest that health insurance and transportation modality play a significant role in hemodialysis treatment compliance. Transportation modality also plays a significant role in the mental health component of the KDQOL survey. Further prospective studies are required to confirm these relationships.

TH-PO235
Assessing the Impact of Hyperkalemia on the Quality of Life of Dialysis Patients Compared with Non-Dialysis Patients: Results from a Real-World Study in the United States and European Union 5
Esinder Tafesse,1 Jackson,2 Rebecca Moon,3 Gary R. Milligan,3 Jennifer Kim,1 Adelphi Real World, Macclesfield, United Kingdom; 2AstraZeneca, Gaithersburg, MD.

Background: Patients with chronic kidney disease (CKD) are at increased risk for hyperkalemia (HK), which increases with CKD disease severity. Quality of life (QoL) may be impacted by the presence of HK, which is associated with greater risk of sudden cardiac death and hospitalization among hemodialysis patients. Only limited data exists on the impact of HK on the QoL of CKD patients who are dialysis dependent (DD) compared with non-dialysis dependent (NDD) patients, with and without HK.

Methods: Data from the 2015 and 2018 Adelphi CKD Disease Specific Programmes were pooled and analyzed. These real-world surveys collected data from physicians and patients with CKD in France, Germany, Italy, Spain, the UK and the USA. Patients completed the EuroQol-5D-3L (EQ-5D) questionnaire and the EuroQol visual analog scale (EQ-VAS). Physicians provided data on patient demographics, disease characteristics and comorbidities. A multiple linear regression was performed for EQ-5D utility and EQ-VAS to assess the association between NDD patients with HK (K⁺ >5.0 mmol/L), DD patients without HK (K⁺ 3.5-5.0 mmol/L), and DD patients with HK to a reference group of NDD patients without HK (and their interaction), adjusting for age, sex, eGFR level, HF and diabetes.

Results: NDD patients with HK (n=176) had a significantly lower mean EQ-5D utility score than NDD patients without HK (n=766) (0.788 vs. 0.825; p=0.039). DD patients with HK (n=10) reported an additional deterioration in mean EQ-5D utility scores compared with NDD patients without HK (0.755; p=0.090) indicating poorer health status among this cohort. EQ-VAS mean scores also showed a significantly poorer QoL for DD patients with HK (n=175) compared to NDD patients without HK (n=766; 64.7 vs. 67.5; p=0.048). Further reduction in QoL was observed for DD patients with HK (n=100) (62.3 vs. 67.5; p=0.015), compared with NDD patients without HK.

Conclusions: HK is associated with reduced EQ-5D health state utility scores in CKD patients. DD patients with HK experienced significantly greater negative impact on their QoL compared with NDD patients without HK. New therapeutic options and effective management of HK in DD CKD patients may positively improve QoL in this population.

Funding: Commercial Support - AstraZeneca

TH-PO236
How Does Starting Dialysis Impact Quality of Life in Patients and Their Partners? A Longitudinal Study
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Background: For patients and their families, quality of life (QOL) while on dialysis is of central importance. Despite this, limited research exists on how (QOL) changes as patients transition from pre-dialysis to dialysis. The present study aimed to investigate changes in QOL in renal patients and their partners (spouses or significant others) during the critical period of preparing for dialysis and over the first 12 weeks on dialysis. We also aimed to determine whether psychosocial factors measured during pre-dialysis can predict QOL outcomes 12 weeks after starting dialysis.

Methods: 10 renal units in England took part in this observational, longitudinal study. 88 couples completed baseline questionnaires during pre-dialysis; 50 couples completed follow-up questionnaires at 6 weeks after starting dialysis; and 40 couples completed further follow-up questionnaires at 12 weeks after starting dialysis. At each time point patients and their partners completed a QOL questionnaire (WHOQOL-BREF), study specific questionnaires on psychosocial factors (Expectations, Accepting Dialysis, and Patient-Partner Relationship Characteristics), affect (HADS), and symptoms (POMS, POS Renal or Generic).

Results: Preliminary analyses show significant positive changes in QOL in patients from pre-dialysis to 6 weeks (b=0.3, p <0.001, 95% CI 0.17, 0.45). No significant differences were found in changes in partners’ scores over this time period (b=0.2, p=0.134, 95% CI -0.1, 0.49). QOL remained steady over the subsequent 6-week period (patients b=0.2, p=0.357; 95% CI (0.2, 0.5); partners b=-0.1, p=-0.793, 95% CI (-0.9, 0.5); p=0.043). Further analyses will be conducted once data collection concludes in June 2019. Multi-level modelling will be used to estimate the changes in QOL between patients and partners. Baseline scores on the psychosocial factor scales will then be tested as predictors of QOL outcomes at 12 weeks.

Conclusions: This research is one of the first to investigate QOL in patients and their partners as they transition on dialysis and to explore the impact of psychosocial variables on QOL. These findings could assist renal clinicians in targeting couples who may need support and may suggest the key psychosocial and relationship factors which will facilitate better QOL during this stressful period.

Funding: Government Support - Non-U.S.

TH-PO237
Effectiveness of Decision Aids in Promoting Knowledge and Shared Decision Around Treatment for ESRD: A Systematic Review and Meta-Analysis
Bioerq Thorsteinsdottir,1 Aditya S. Pawar,2 LaTonya J. Hickson,3 Cristina Wirtz,4 Navdeep Tangri,4 Nilay D. Shah,1 Mayo Clinic, Rochester, MN; 2Department of Medicine, Seven Oaks General Hospital, University of Manitoba, Winnipeg, MB, Canada.

Background: Renal replacement therapy (RRT) for end stage renal disease (ESRD) is a preference-sensitive decision yet patients do not perceive they have a choice. Guidelines have called for increased shared decision making in this space especially for higher risk patients for whom there is equipoise regarding the balance of benefits and harms. Decision aids have been proposed to ensure goal concordant care. We systematically reviewed the performance of decision aids for ESRD treatment choice.

Methods: Multiple databases were searched for comparative studies of using decision aids to help advanced kidney failure patients choose between different types of RRT from inception to January 30, 2018. PRISMA guidelines were followed with two reviewers independently screening abstracts, performing full text assessment of inclusion criteria and extracting study design, outcomes and risk of bias.

Results: Of 1083 articles screened and 90 reviewed in full text, 10 were included, tested in a total of 1114 patients (range 35-569). There was great heterogeneity of measured and reported outcomes and few validated tools. Pre-planned meta-analyses of knowledge showed significant increase in standardized mean difference of 0.598 but with high heterogeneity I² 61%.

Conclusions: Decision aids appear to increase patient knowledge in ESRD but their outcome reporting is heterogeneous which limits the strength of inferences. To move the field forward, international consensus is needed on the most meaningful outcome measures and best practices in future decision aid research.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging K23AG051679 (B.T); and National Institutes of Health National Institute of Diabetes and Digestive and Kidney Diseases grant K23 DK109134 (L.J.H.).

TH-PO238
Week-to-Week Variability of Dialysis Recovery Time
Wael F. Hussein,1 Vishal Duggal,2 Sumi J. Sun,1 Brigitte Schiller,1 1Satellite Healthcare, San Jose, CA; 2Department of Medicine, Division of Nephrology, Stanford University School of Medicine, Palo Alto, CA.

Background: Fatigue is identified by patients as a priority for research. Post-dialysis fatigue is common and associated with poor outcomes. Unpredictability of symptoms was the main impact of these symptoms on patients. In a previous study, we prospectively recorded weekly dialysis recovery time (DRT) for four weeks in patients with prolonged DRT at baseline [Duggal et al. HDI 2019]. Here, we report on the weekly variability of DRT in these patients.

Methods: Patients with DRT data from all four weeks were included in this study. We hypothesized that a change in DRT of four hours or more from the previous week was a significant fluctuation to impact symptom predictability and patient’s ability to plan activities after dialysis. We report on the proportion of patients who had at least two such fluctuations during the follow-up period. In addition, we report on within-patient week-to-week variability using within-patient ranges, standard deviations (SD), coefficients of variation and mean absolute differences (MAD).

Results: Seventy-four patients were included in this analysis; median age 64 years (IQR: 59 - 75), 32% female. During the follow-up period, 26% of patients had at least two recorded DRTs that were four hours or more different from the prior week. Median within-patient week-to-week DRT range, SD and MAD were 525 (180-960), 230 (77 – 446) and 209 (80 – 440) minutes respectively, and the coefficient of variation was 0.48 (0.22 – 0.87).

Conclusions: Among patients with long recovery time at baseline, we report substantial variability in week-to-week DRT. These fluctuations in symptoms increase the burden on hemodialysis patients. More attention is needed to study the variability of symptoms and its burden in terms of extent and effect.

Funding: Government Support - Non-U.S.
TH-PO239
The Impact of Extended Hours Haemodialysis on Quality of Life, Vascular Access, Mortality, and Residual Renal Function: Systematic Review and Meta-Analysis
Katherine E. Hull,1,2 Daniel S. March,2 Darren R. Churchward,2 Matthew P. Graham-Brown,1,3 James Burton,1,3 1John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; 2Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom.

Background: Patients with end-stage renal failure on conventional haemodialysis (CHD) experience significant morbidity and mortality. There is increasing evidence that extending weekly haemodialysis (HD) time is associated with improvements in quality of life (QoL), biochemical and cardiovascular parameters, and mortality. However, there is concern that increasing HD duration or frequency accelerates the loss of residual renal function (RRF) and increases vascular access adverse events. This systematic review aims to determine the impact of extended HD in comparison to CHD on QoL, vascular access events, mortality and RRF.

Methods: Randomised and non-randomised controlled trials of adult prevalent HD patients comparing extended hours HD (> 12 hours of HD in 1 week) to CHD were eligible. Outcomes of interest were quantitative measures of QoL, vascular access adverse events, all-cause mortality and RRF. Data from randomised and non-randomised trials were pooled separately using a random-effects model.

Results: 476 patients from 6 trials were eligible. The number of trials available for meta-analysis varied for each outcome. There was no significant change in QoL when comparing extended HD to CHD (SF-36 PCS standardised mean difference 0.61, 95% CI -0.10 to 1.31, P = 0.09, SF-36 MCS standardised mean difference -0.04, 95% CI -0.61 to 0.54, P = 0.84). There was no significant change in vascular access adverse events (relative risk ratio 1.25, 95% CI 0.88 to 1.77, P = 0.21) or mortality (relative risk ratio 2.29, 95% CI 0.60 to 8.71, P = 0.22). RRF was only assessed in one report which demonstrated a potential reduction over 12 months with extended HD, however, RRF was not a pre-specified secondary outcome. All trials had a high risk of bias.

Conclusions: In this systematic review, we demonstrated no significant difference between extended HD and CHD on QoL, adverse vascular access events and mortality. There was only a single trial with data regarding the changes in RRF. The majority of the included trials were either low or very low in quality. This supports the need for further adequately powered randomised controlled trials.

Funding: Government Support - Non-U.S.

TH-PO240
Comparison of Approaches to the Identification of Symptom Burden in Hemodialysis Patients Utilizing Electronic Health Records
Lili Chan, Kelly H. Beers, Kinsuk Chauhan, Neha Deb Nath, Pattharawin Pattharantinmita, Steven G. Coca, Tielman T. Van Vleck, Girish N. Nadkarni. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Symptoms are common in patients on maintenance hemodialysis (HD), however identification within the electronic medical record (EMR) is challenging. Natural language processing (NLP) can be utilized to identify symptoms from narrative clinical documentation by physicians and other providers.

Methods: We utilized NLP to identify 7 patient symptoms from clinical notes of HD patients from the BioMe Biobank and validated our findings using the MIMIC-III database. We compared NLP performance with ICD codes and the performance of NLP and ICD codes vs. manual chart review.

Results: We identified 1034 and 519 HD patients from BioMe Biobank and validated our findings using the MIMIC-III database. We compared NLP performance with ICD codes and validated our findings using the MIMIC-III database. We compared NLP performance with ICD codes and the performance of NLP and ICD codes vs. manual chart review.

Results: We identified 1034 and 519 HD patients from BioMe and MIMIC-III, respectively. In BioMe, the most frequent symptoms identified were pain (NLP 93% vs. ICD 40%, P = 0.001), fatigue (NLP 84% vs. ICD 41%, P = 0.001), and nausea and/or vomiting (NLP 74% vs. ICD 19%, P = 0.001). Sensitivity for NLP ranged from 0.85 (95% CI 0.65-0.96) for depression to 0.99 (95% CI 0.93-1) for fatigue while sensitivity for ICD ranged from 0.59 (95% CI 0.43-0.73) for fatigue. Results were similar in MIMIC-III. ICD codes were significantly more specific for nausea and/or vomiting in BioMe and for fatigue, depression, and pain in MIMIC-III. A majority of patients in both cohorts had 4 symptoms. Patients with more symptoms identified by NLP, ICD, and chart review had more clinical encounters. Results were similar in MIMIC-III and for fatigue, depression, and pain in MIMIC-III. A majority of patients in both cohorts had 4 symptoms. Patients with more symptoms identified by NLP, ICD, and chart review had more clinical encounters. Results were similar in MIMIC-III.

Conclusions: Identification within the EMR is challenging. NLP can be utilized to identify symptoms from narrative clinical documentation by physicians and other providers.

Funding: NIDDK Support

TH-PO241
Symptom Burden in Renal Patients Under the Care of Single United Kingdom Center
Venkata R. Guillapudi, Komal Chauhan, Hari Dukka. University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom.

Background: Renal patients suffer from a high and variable symptom burden, irrespective of the standard of care provided. We assessed the symptom burden of a cohort of renal patients under our care to understand the extent of the problem in our center.

Methods: NHS England health survey questionnaire was used to evaluate symptoms suffered by patients with chronic kidney disease (CKD) stage 4/5 and those receiving renal replacement therapy (RRT). Age, Urea clearances, Charlson comorbidity index (CCI), eGFR and RRT vintage were noted.

Results: 290 patients completed the questionnaire. Median age was 64.5 (IQR: 21), 60.3% were males with median CCI of 3.5 (IQR: 6). The whole cohort experienced a median of 3.5/17 symptoms (IQR: 6). Weakness (53.4%), poor mobility (40.6%) and difficulty sleeping (33.96%) were the top 3 symptoms complained. Table 1 summaries the distribution and top 3 symptoms suffered by patients with CKD and those on RRT. Symptom burden was significantly less in the transplant cohort. Age, renal clearances (eGFR in CKD and transplant cohorts; Kt/V in dialysis cohorts) did not correlate with symptom burden, however CCI score statistically (r=0.193, p=0.001) correlated to the symptom burden.

Conclusions: Renal patients experience multitude of symptoms and symptom burden is similar in CKD and those on RRT. The standards of care provided to renal patients should include symptom assessment and management where possible.

Table 1

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CKD Stage 4/5</th>
<th>CKD Transplant</th>
<th>RRT Stage 4/5</th>
<th>RRT Transplant</th>
</tr>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Weakness</td>
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<td>Weakness</td>
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<td>Difficulty sleeping</td>
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<tr>
<td>Nausea</td>
<td>Fatigue</td>
<td>Difficulty sleeping</td>
<td>Difficulty sleeping</td>
<td>Difficulty sleeping</td>
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</tbody>
</table>

*Questionnaire explored 17 symptoms in total
Symptom Burden with Calcium Carbonate Compared to Sevelamer in Hemodialysis Patients

Methods:
Prevalent haemodialysis (HD) patients were recruited into a randomised study (n=37). Total study duration was 37 weeks, including 1 week of PB ‘washout’. Participants were randomised to either i) 36 weeks of CC therapy or ii) 12 weeks of CC followed by 24 weeks of sevelamer therapy. Patient symptoms were assessed with the Palliative Care Outcome Scale-Renal Version (POS) and analysed according to total scores and individual scores for specific GIT symptoms.

Results:
Participants completed the study, and were analysed according to intention-to-treat analysis. 10 patients were randomised to the CC only arm, whilst 16 to the CC/sevelamer arm. There were no statistically significant differences in baseline demographics or co-morbidities between the groups. At baseline, median total POS scores were 12 for the CC 3-17 for sevelamer arm. At study completion, median POS scores were 12 for the CC (7-13) in the CC/sevelamer arm, with no statistically significant differences between groups at any timepoint. In regards to GIT symptoms, the proportion of patients experiencing improvement in nausea from baseline to study end were 39% and 44% in the CC only and CC/sevelamer arms respectively, and for vomiting 10% vs 25% experienced improvement in the respective groups. 20% of CC only patients had more severe constipation at study end vs 31% in the CC/sevelamer group; and for diarrhoea, 30% of CC only vs 35% of CC/sevelamer patients reported increased symptoms. No differences in changes in specific GIT symptoms were noted between the sevelamer, PB therapy with those on sevelamer in a clinical trial.

Conclusions:
Symptom burden of patients on HD did not change significantly with different PB therapy in our study, with similar changes in GIT symptoms over time comparing CC and sevelamer therapy.

Funding:
Commercial Support - Sanofi

Pruritus and Mortality in Hemodialysis Patients: Results from the International DOPPS

Methods:
We analyzed 5418 HD patients from 17 countries in phase 5 (2013) of the Dialysis Outcomes and Practice Patterns Study (DOPPS) who self-reported being bothered by itchy skin (yes/no). ‘No’ responses were assigned a Skindex-10 (SK-10) score of 0. Patients responding ‘Yes’ then answered 10 questions about the frequency (0-6 scale) they were distressed by various aspects of CKD-aP. We investigated the association between SK-10 score (0-60 range; higher = more bothered) and 4 outcomes: (1) Physical and (2) Mental Health, (3) Quality of life, and (4) Sleep quality.

Results:
Patients who responded ‘Yes’ to being bothered by pruritus had higher total MHI score (indicative of depressive symptoms), and were more likely to report sleep disturbances and impaired sleep quality (as indicated by Akebia Therapeutics, AstraZeneca, European Renal Association-European Dialysis Association (ERA-EDTA), Fibogen, Fresenius Medical Care Canada Ltd, German Society of Nephrology (DGN), Italian Society of Nephrology (SIN), Janssen, Japanese Society for Peritoneal Dialysis (JSPD), Kidney Care UK, MEDICE Arzneimittel Pütter GmbH & Co KG, Otsuka America, Proteon Therapeutics, the Association of German Nephrology Centres, and Vifor Fresenius Medical Care Renal Pharma. Public funding and support is provided for specific DOPPS projects, ancillary studies, or affiliated research projects by National Health & Medical Research Council (NHMRC) in Australia, Belgian Federal Public Service of Public Health in Belgium, Canadian Cancer Care Ontario (CCO) through the Ontario Renal Network (ORN), in Canada, French National Institute of Health and Medical Research (INSERM) in France, Thailand Research Foundation (TRF), Chulalongkorn University Matching Fund, King Chulalongkorn Memorial Hospital Matching Fund, and the National Research Council of Thailand (NRCT) in Thailand, National Institute for Health Research (NIHR) via the Comprehensive Clinical Research Network (CCRN), and Kidney Research UK (KRUK) in the United Kingdom, and the Agency for Healthcare Research and Quality (AHRQ) and National Institutes of Health (NIH) in the US. All support is provided without restrictions on publications. All grants are made to Arbor Research Collaborative for Health., Private Foundation Support, Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Hemodialysis and Frequent Dialysis - II
Difelikefalin Improved Quality of Life (5-D Itch Scale-Domains) in Hemodialysis Patients with Pruritus in an 8-Week Phase 2 Randomized, Placebo-Controlled Study

Patients treated with DFK 0.5 mcg/kg (n=44) exhibited a clinically meaningful improvement in 5-D itch total scores vs PBO (n=45) at Wk 8 (-5.7 vs -2.8 LS mean [p=0.003 vs PBO]), with a significant correlation between WCSC and 5-D total scores (r= 0.71, p<0.001). Except for Duration (0.6 vs 0.4 [p=0.368]), significant improvements from baseline were reported across all subdomains in DFK vs PBO groups at the end of Wk 8. Degree: -1.1 vs -0.5 [p<0.001 vs PBO]; Duration: -1.2 vs -0.5 [p=0.001]; Disability: -1.2 vs -0.5 [p=0.004].

Conclusions: This analysis further characterized the impact of itch severity reduction with DFK indicating significant improvement in QoL as measured by the 5-D Itch multidimensional questionnaire. Results demonstrate itch intensity reduction with DFK is associated with improved QoL.

Funding: Commercial Support - Cara Therapeutics, Inc.

Difelikefalin Significantly Reduced Sleep Disturbance in Hemodialysis Patients with Moderate-to-Severe Pruritus in an 8-Week Phase 2, Randomized, Placebo-Controlled Study

Background: Patients with chronic kidney disease (CKD) undergoing hemodialysis (HD) have moderate-to-severe pruritus, which is associated with poor quality of life (QoL). Difelikefalin (DFK, CR845) is a selective kappa opioid receptor agonist that acts peripherally with a dual anti-inflammatory/antipruritic effect and to date has negligible abuse potential. In a Phase 2 study of HD patients with CKD associated pruritus, it was previously reported that DFK significantly reduced itch intensity. ICH reduction, assessed by the Worst Itching Intensity Numerical Rating Scale (WI-NRS) score correlated with significant improvements in itch-related QoL measures, as measured by the Skindex-10 and 5-D Itch scales. To further characterize the impact of itch reduction on patient QoL, we present results using the 5-D Itch scale domains.

Methods: Patients were randomized 1:1:1:1 to receive an IV bolus of DFK 1.5, 1.0, 0.5 mcg/kg or placebo (PBO), at the end of each dialysis over an 8-week (Wk) treatment period. The 5-D Itch scale domains were used to measure Degree, Duration, Direction [change over time of itch], Disability [sleep, leisure/social, housework/errands, work/school], and Distribution [bodily location of itch] – each ranked on a 5-point increasing severity scale. This analysis focused on the 0.5 mcg/kg dose that was advanced into Phase 3 studies.

Results: Patients treated with DFK 0.5 mcg/kg (n=44) exhibited a clinically meaningful improvement in 5-D itch total scores vs PBO (n=45) at Wk 8 (-5.7 vs -2.8 LS mean [p=0.003 vs PBO]), with a significant correlation between WCSC and 5-D total scores (r= 0.71, p<0.001). Except for Duration (0.6 vs 0.4 [p=0.368]), significant improvements from baseline were reported across all subdomains in DFK vs PBO groups at the end of Wk 8. Degree: -1.1 vs -0.5 [p<0.001 vs PBO]; Duration: -1.2 vs -0.5 [p=0.001]; Disability: -1.2 vs -0.5 [p=0.004].

Conclusions: This analysis further characterized the impact of itch severity reduction with DFK indicating significant improvement in QoL as measured by the 5-D Itch multidimensional questionnaire. Results demonstrate itch intensity reduction with DFK is associated with improved QoL.
Patients treated with DFK exhibited a significant reduction in sleep disturbance compared with PBO, with a mean change from baseline in DFK 0.5 mcg/kg (n=44) and PBO (n=45) groups, respectively, of -8.6 ±2.2 vs P=0.013 at Wk 4, -9.8 ±2.2 vs P=0.077 at Wk 8, -13.8 ±1.3 vs P=0.006 at EOT.

Conclusions: Significantly improved MOS-S sleep disturbance scores were obtained after DFK therapy, indicating a clinically sustained improvement in sleep through Wk 8 that was associated with a robust and sustained reduction in itch intensity. The effects of DFK on sleep, as well as long-term efficacy and safety of DFK, are currently under investigation in patients with CKD-aP in ongoing Phase 3 studies. Reference: Shrir azan S et al. J Nephrol Renovasc Dis 2017;10:11. 1Benz R et al. Am J Kidney Dis 2000;35:1052

Funding: Commercial Support - Cara Therapeutics, Inc.

TH-PO248
Arterial Pulse Enhancement Technology (A-PE T) Therapy Using VascuPump for Relief of Symptoms in Restless Legs Syndrome (RLS) in Patients on Dialysis
Anil Bhalla,1 Ravi K. Singh,1 Devinder S. Rana,1 Ashwani Gupta,1 Anurag Gupta,2 Vinant Bhargava,1 1Sir Ganga Ram Hospital, New Delhi, India; 2Synergy Hospital, Utkhahand, India.

Background: Restless legs syndrome (RLS) occurs in 25% to 40% patients on hemodialysis. In patients on dialysis poly-pharmacy and pill burden is a significant risk factor and there is a need for treatment which is noninvasive, non-pharmacologic, time efficient and has long lasting response. Arterial Pulse Enhancement Technology (A-PE T) therapy delivered using VascuPump is noninvasive, non-pharmacologic treatment given during dialysis for 15 min on both legs (no extra visit). VascuPump device uses inflatable cuffs, placed around calf, to rhythmically compress the limb with each heartbeat to enhance blood flow down the limb.

Methods: Open labelled treatment for patients on maintenance hemodialysis thrice per week. Six treatments were given during consecutive dialysis sessions. Patients with DVT, aortic insufficiency, leg wound or ulcer, acute thrombophlebitis and medically unstable patients were excluded. Baseline Doppler study was done to exclude DVT. To assess RLS, International RLS Study Group Rating Scale (IRLS) was used, range 1-40.

Results: Patients on dialysis poly-pharmacy and pill burden is a significant risk factor and there is a need for treatment which is noninvasive, non-pharmacologic, time efficient and has long lasting response. Arterial Pulse Enhancement Technology (A-PE T) therapy delivered using VascuPump is noninvasive, non-pharmacologic treatment given during dialysis for 15 min on both legs (no extra visit). VascuPump device uses inflatable cuffs, placed around calf, to rhythmically compress the limb with each heartbeat to enhance blood flow down the limb.

Methods: Open labelled treatment for patients on maintenance hemodialysis thrice per week. Six treatments were given during consecutive dialysis sessions. Patients with DVT, aortic insufficiency, leg wound or ulcer, acute thrombophlebitis and medically unstable patients were excluded. Baseline Doppler study was done to exclude DVT.

To assess RLS, International RLS Study Group Rating Scale (IRLS) was used, range 1-40. Wong Baker Pain Scale (WBPS) was used before and after treatment, range 0-10.

Results: 52 patients with mean age 58.4 yr (range 26-77), male 52 (62%), diabetes 40 (77%). RLS score at start of the treatment was 27.1 (17-39) which dropped to 20 (14-34) at the end of the last treatment. WBPS before and after treatment was 7.6 (2-10) and 3.3 (2-8) respectively. The acute response after cumulative 270 treatments was a 41% decrease in pain. There was a trend towards consistent decrease in the baseline WBPS of individual patients with multiple treatments. Average Relief lasted for an average of 55 hours (range 0-172 hrs) after individual treatment. A total of 14 patients did not complete the six treatments due to unstable clinical condition or no response. One patient had worsening cramps in the legs. There were no other complications observed after 270 cumulative treatments in these patients on dialysis. A total of 73% (38/52) patients benefited from the treatment.

Conclusions: A-PE T therapy during dialysis is an effective non pharmacologic therapy for RLS patients on maintenance hemodialysis. Further randomized controlled studies are needed in larger population.

TH-PO250
Frailty, Age, and Post-Dialysis Recovery Time in an Incident Hemodialysis Population
Jessica Fitzpatrick,1 Stephen M. Sozio,1 Bernard G. Jaar,1 Michelle M. Estrella,2 Dorry L. Segev,1 Jose Monroy-Trujillo,1 Rulan S. Parekh,1 Mara McAdams-DeMarco.2 1The Hospital for Sick Children, Toronto, ON, Canada; 2University of California, San Francisco and San Francisco VA Medical Center, San Francisco, CA; 2Johns Hopkins University, Baltimore, MD.

Background: Frailty, a phenotype characterized by an inability to recover from a stressor, may help identify incident hemodialysis patients at risk for longer recovery time. Recovery time has been associated with downstream outcomes including quality of life and mortality. We characterize post-dialysis recovery times in incident in-center hemodialysis patients and quantify the association of frailty and recovery time.

Methods: In 285 incident hemodialysis patients enrolled in the Predictors of Arhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE) study, frailty was classified by the Fried phenotype as non-frail, intermittently frail, or frail. Post-dialysis recovery time was assessed by asking, "How long does it take you to recover from a dialysis session?" We estimated the association of frailty and post-dialysis self-reported recovery time using negative binomial regression after adjusting for clinical confounders.

Results: Mean age was 55 years, 24% were ≥65 years, and 73% were African American. Median recovery time was 20 min (IQR: 10, 120). Age ≥65 was independently associated with longer recovery time (IRR 2.36; 95%CI: 1.44-3.85). Intermediate frailty and frailty were associated with 2.56-fold (95%CI: 1.45-4.52) and 1.72-fold (95%CI: 1.03-2.89) longer recovery times. In particular, frail participants <65 were more likely to report longer recovery times (IRR 2.55; 95%CI: 1.46-4.43) [Figure] In non-frail participants, however, age was not associated with recovery time.

Conclusions: In adults initiating hemodialysis, frailty was independently associated with prolonged post-dialysis recovery. Future studies should assess the impact of frailty-targeted interventions on recovery time to improve clinical outcomes.

Funding: NIDDK Support
Fall Risks in Chronic Hemodialysis and Peritoneal Dialysis Patients in the United States (2006-2016)

Xinju Fall, Astrid and Depression

Background: People with end-stage kidney disease (ESKD) have a substantially higher risk of falls, but the burden of fall events has not been sufficiently characterized in this population. We compared trends in minor and major fall rates in both hemodialysis (HD) and peritoneal dialysis (PD) patients in the US between 2006 and 2016.

Methods: Analysis included 4,766,341 dialysis patients (HD: 4,343,752; PD: 422,589) in the US Renal Data System database (2006-2016). ICD-CM diagnosis codes were used to identify major and minor falls. Major falls included those in combination with fractures, brain injuries, or joint and ligament dislocation. Minor falls included falls without these complications. Fall rates expressed per 1000 patient-years (py) were calculated and patient characteristics compared for both types of falls by dialysis modality.

Results: Overall, HD patients were older and more likely to be male compared with PD patients (mean age: 63.6 vs 57.5 years, male: 56.3% vs 54.7%). Over the past decade, patients on HD experienced higher rates of both major and minor falls than those on PD (Figure 1). The rate of major falls gradually decreased from 2006-2014, and grew substantially after 2014 among both populations (HD vs PD: 227 vs 157 per 1000 py in 2016). There was a notable increase in the rate of minor falls among both populations during the period from 2006-2016 (HD: 125 to 190 per 1000 py; PD: 66 to 119 per 1000 py). Patients who were female, white, age >45 years and prevalent dialysis patients had a higher risk of falls than their counterparts who were male, other ethnicity origins, age ≤45 and incident dialysis patients.

Conclusions: Fall risk is high for the ESKD population, especially among those undergoing HD, aged >45years, white, female and prevalent dialysis. Falls are a safety issue can cause serious injuries with resultant complications along with increased resource utilization. Further research and implementation projects designed to lower fall risk among ESKD patients are urgently warranted.

Funding: NIDDK, Support

TH-PO253

Physical Activity in Patients on Hemodialysis and Its Relation to Fatigue and Depression

Astrid Brva, Maurizio Bossola, Bert Lentaert, Filippo Bianmonte, Giovanni Gambardo, Enrico Di stasio. 

Department of Nephrology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Rome, Italy; 2Department of Neuropsychology and Psychopharmacology, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, Netherlands; 3UCO Chimica, Biochimica e Biologia Molecolare Clinica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Rome, Italy.

Background: Hemodialysis (HD) patients are less active than healthy sedentary adults. Fatigue and depression are considered main reasons for physical inactivity in HD patients and are associated with impaired quality of life (QoL). A better understanding of the relation between fatigue, depression and physical activity (PA) is crucial in order to develop effective therapies and improve QOL. Measurement of PA is however challenging, as it is usually assessed by subjective self-report questionnaires. Recently, objective assessment of PA with motion sensors has gained interest. Therefore, we aimed to objectively measure HD patients’ daily PA and to explore its relation with fatigue and depression.

Methods: PA was assessed in 37 HD patients (mean age 61 years) based on the daily step count measured with the SenseWear20 Armband for 7 days. The Fatigue Severity Scale (FSS) and Beck Depression Inventory-II (BDI) were administered to evaluate fatigue and depressive mood.

Results: Median physical activity was 2247 steps a day, [IQR:614-4363], and no significant differences in PA were observed between treatment and non-treatment days. PA per measurement day did not correlate with fatigue experience (r=0.04, p=0.499), and did not significantly differ between patients that were categorized as fatigued (n=23, FSS≥4) or not (n=14, FSS<4) (Fig.1a: p’s 0.745-0.988; Cohen’s d’s <0.20). In contrast, PA measurement day significantly though inversely correlated with depressive mood (r=-0.22, p=0.001) and significantly differed between high-depressed (n=18, BDI>13) and low-depressed subjects (n=19, BDI≤13) (p=0.004), who made on average 1.7 times more steps a day than their high-depressed counterparts. The main differences in PA were observed on non-treatment days (Fig.1b: p’s 0.017-0.105; Cohen’s d’s 0.57-0.90).

Conclusions: Objective assessment of PA with motion sensors is feasible in HD patients. Depressive mood, in contrast to fatigue experience, seems to be associated with PA. These findings may help to increase awareness about the need for intervention trials to affect the effect on PA in HD patients by improving their mood, or vice versa.

TH-PO254

Psychosocial Interventions for Preventing and Treating Depression in Dialysis Patients: A Cochrane Review and Meta-Analysis

Patrizia Natale,1 Suetonia Palmer,2 Mariella Ruossop, Jorgen B. Hegbrant,3 Giovanni F. Strippoli,2 D’Avernum, Lund, Sweden; 2University of Bari, Bari, Italy; 3University of Otago, Christchurch, New Zealand.

Background: People with end-stage kidney disease treated with dialysis are frequently affected by major depression. Psychological and social support are potential treatments for depression, although a Cochrane review in 2005 identified zero eligible studies. This is an update of the Cochrane review published in 2005 to evaluate the available evidence for using psychosocial interventions to prevent and treat depression in patients treated with dialysis for end-stage kidney disease (ESKD).

Methods: The specialized register of Cochrane Kidney and Transplant was searched for randomized trials (RCTs) reporting psychosocial interventions for prevention and treatment of depression among adults treated with long-term dialysis. Two authors independently screened citations for eligibility, extracted data, and assessed risk of bias using the Cochrane tool. Evidence certainty was evaluated using GRADE.

Results: Thirty-one studies (1820 participants) were eligible. Twenty-four new studies were added to this 2018 update. Seven studies originally excluded from the 2005 review were included as they met updated review eligibility criteria. Trial duration ranged between three weeks and one year. Median study age was 50.8 years. Methodological reporting was incomplete for most studies. Cognitive-behavioural therapy probably improves depression symptoms (mean difference [MD] -6.10, 95% confidence interval [CI] -8.63 to -3.57; moderate certainty) and health-related quality of life (standardized MD [SMD] 0.51%, CI 0.19 to 0.83; moderate certainty). Exercise probably improves depressive symptoms (MD -7.61, 95% CI -9.59 to -5.63; moderate certainty) and health-related quality of life (MD 3.06, 95% CI 2.29 to 3.83; moderate certainty). Counselling and relaxation techniques probably reduce depressive symptoms (MD -3.84, 95% CI -6.14 to -1.54; moderate certainty and MD -5.77, 95% CI -8.76 to -2.78; moderate certainty, respectively). In very low certainty evidence, the effects of acupressure, telephone support, and meditation were uncertain. Data on adverse events were sparse.

Conclusions: Cognitive-behavioural therapy, exercise, counselling, or relaxation techniques probably reduce depressive symptoms for adults with ESKD treated with dialysis. Evidence for other psychosocial interventions is uncertain.

TH-PO255

Effects of Intravenous L-Carnitine (LC) Administration in Improving Muscle Strength in Hemodialysis (HD) Patients

Takashi Miyamoto,1 Satoshi Funakoshi,2 Jyunichiro Hashiguchi,1 Kenji Sawase,1 Tayo Kawazu,1 Takuya Kubara,1 Sayaka Miyazaki,1 Masatoshi Hayashida,2 Mashumi Ide,1 Tomoya Nishino,2 Takashi Harada.1

1Nagasaki Kidney Center, Nagasaki, Japan; 2Nagasaki Renal Center, Nagasaki, Japan; 3Nagasaki University School of Medicine, Nagasaki, Japan.

Background: Several clinical studies have suggested that LC, a naturally occurring compound involved in bioenergetic processes, may improve muscle function of HD patients. This is an update of the Cochrane review published in 2005 that identified zero eligible studies. LC is an essential nutrient for bioenergetic processes. This is an update of the Cochrane review published in 2005 to evaluate the available evidence for using LC to improve muscle function of HD patients. Two authors independently screened citations for eligibility, extracted data, and assessed risk of bias using the Cochrane tool. Evidence certainty was evaluated using GRADE.

Methods: After appropriate IC 172 HD patients on HD were enrolled in this study. Intravenous L-carnitine (1000 mg) was administered after each HD session. HGS was measured using a dynamometer before and after LC administration in female
n=56 and male (n=116) patients of different ages (median age: 68.2±33.3 years) as well as various clinical parameters were determined. Using the Asian Working Group for Sarcopenia criteria the subjects were divided into 2 groups by initial HGS: cut-off score of 18 kilograms (kg) for female and 26 kg for male.

**Results:** As shown in Figure, significant increase was obtained both in female and male among weaker HGS groups, but not normal HGS groups. There was no significant difference in nutrition parameters such as serum albumin or cholinesterase between weaker and normal HGS groups in females or males.

**Conclusions:** In our study the administration of intravenous LC has potentially contributes to muscle strength in patients on maintenance HD. LC can be one of the candidates for improving sarcopenia in patients on HD.

**Funding:** Private Foundation Support

### Effects of intravenous LC administration on handgrip strength

**TH-PO256**

A 6-Month Program of Intradialytic Cycling Results in a Reduction in Associated Healthcare Costs in Patients Receiving Prevalent Hemodialysis

**Daniel S. March,1 Adam W. Hurt,2 Alice C. Smith,3 James Burton,1,2** University of Leicester, Leicester, United Kingdom; 2Loughborough University, Loughborough, United Kingdom.

**Background:** Individuals receiving hemodialysis have complex medical needs. Interventions that reduce health care utilization can improve patient outcomes, and therefore decrease the financial burden. The aim of this health economic analysis is to investigate the effect of a 6-month program of intra-dialytic cycling exercise (IDE) on health care costs.

**Methods:** This is a retrospective complete case analysis of a 100 participants enrolled in CYCLE-HD, an open-label, blinded end-point, cluster randomised control trial investigating the benefit of IDE. Participants were randomised to either a 6-month progressive program of IDE (30 minutes of thrice weekly, moderate intensity cycling at RPE: 12-14) or standard care (control). Data on hospital admissions, length of stay, clinic appointments, A&E attendances, primary care appointments and prescribed medications were extracted from medical records for the 6-months before, during and after the IDE intervention. Costs of healthcare utilization were calculated using the National Health Insurance National Tariff Payment System, and prescribed medications were calculated using the British National Formulary. Data are presented as mean difference (95% confidence interval) or mean (95% confidence interval).

**Results:** Data from a 100 participants (control n=49 and IDE n=51) were included in our complete case analysis. Time-series with incomplete data sets were excluded. There was no difference between groups for the before (228.30 ±£4550.24 to £5118.83, p=0.9075) or during (-£2124.67 (-£6466.69 to £2217.35), p=0.3342) periods. However following the IDE program there was a significant reduction in cost of -£8199.438 (-£15137.43 to -£715.4473, p<0.001) or during (-£2124.67 (-£6466.69 to £2217.35), p=0.3342) periods. However

**Conclusions:** These data show a 6-month of program IDE can reduce associated health economic costs. The overall reduction appears to be driven by a reduction in hospital admissions and length of stay. These results strengthen the argument that IDE programs should be routinely offered and are of crucial importance to commissioners of dialysis care.

**TH-PO257**

Intradialytic Isometric Handgrip Training Seems to Be Safe: A Pilot Study on Hemodialysis Patients

**Heitor S. Ribeiro,1 Vinícius A. Cunha,2 Victor M. Bialão,3 Marvery P. Duarte,4 Helton L. Carvalho,5 Gustavo D. França,2 Renato N. Ferreira,1 Lucas D. Almeida,2 Antonio Jose Inda-Filho,1 Aparecido P. Ferreira,1 Grupo of Studies in Exercise Physiology and Health (GEFES)1, University Center ICESP,2 Universidade Federal de São Carlos,3 Universidade Federal de Rondônia,4 Universidade Federal de Minas Gerais,5 Universidade de Brasília, Brazil.

**Background:** Cardiovascular capacity of chronic kidney disease (CKD) patients tends to decline with the natural progression of the disease. In this sense, resistance training is an important non-pharmacological tool in the control of cardiovascular (CDV) parameters. However, there is no evidence of isometric handgrip training (IHT) protocols in this population. Thus, the aim of this study was to verify the safety of two isometric RT protocols on CDV variables in hemodialysis (HD) patients.

**Methods:** This was an experimental study, with acute intervention, cross-over design and sample of 8 patients, mean age 56.63 ± 12.66 years, who undergo HD at a private clinic in the city of Brasília – DF. The participants were randomly assigned to three different moments to analyze the response of the variables heart rate variability (HRV) and blood pressure (BP), being: 1) control; 2) low-intensity; 3) moderate-intensity. Variables were collected at the beginning of session 5, 15, 30, 40, 60 minutes and immediately after the end.

**Results:** IHT protocols, regardless of intensity, did not show a significant change for both HRV and BP variables during their performances, nor when compared to the control moment. When the moments immediately before and after exercise were analyzed, a significant increase was observed for SBP (120.5 ±4.6 vs 126.7±4.6, p<0.05) and DP (6364.5±398.5 vs 9419.1±545.3, p<0.05) in the protocol of moderate-intensity, but returning to normal values 10 minutes later.

**Conclusions:** Therefore, we conclude that the intradialytic IHT seems to be a safe therapeutic tool for the intradialytic control of cardiovascular parameters in this population.

**Funding:** Government Support - Non-U.S.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.”

Figure 1. BP during HD with and without isometric handgrip training

**TH-PO258**

L-Carnitine Supplementation Enhances Physical Activity and Improves Muscle Quality in Hemodialysis Patients

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**Background:** Carnitine plays a central role in the activation of fatty acid b-oxidation and energy production by transporting long-chain fatty acids from the cytoplasm to mitochondria. We previously reported that serum carnitine levels are significantly decreased in hemodialysis (HD) patients and thereby involved in muscle atrophy and decreased quality of life. Moreover, recent evidence has suggested that ergometer exercise can be effective against sarcopenia and frailty in HD patients. However, whether L-carnitine supplementation or ergometer exercise can improve HD-related impairment of physiological activity and muscle quality is yet to be elucidated. Here we prospectively examined this issue.

**Methods:** Twenty patients undergoing HD were divided into two groups: L-carnitine group (n = 10) and exercise group (n = 10). Patients were treated with L-carnitine supplementation (1000 mg intravenously) for 3 months. Muscle and fat mass were measured using impedance methods. Physical activity was evaluated using indices, including grip strength, lower limb extension strength, chair stand up time, 10 m walking times (10 mWT), functional reach test, time up & go test, and the Borg Scale. We further evaluated muscle mass quality using magnetic resonance imaging.

**Results:** Total and free carnitine levels in the serum significantly decreased in HD patients than in healthy subjects (both p < 0.001). At baseline, muscle mass and the Borg scale were positively associated with free carnitine levels; however, the other variables were not. L-carnitine supplementation significantly increased muscle mass (p = 0.023) and thigh circumference (p = 0.019), decreased fat mass (p = 0.007), and improved chair stand up time (p = 0.03) and 10 mWT (p = 0.004). Ergometer exercise did not improve any physical activity. Notably, the intramuscular fat fraction significantly decreased with L-carnitine supplementation (p = 0.023), suggesting the improvement of muscle quality.

**Conclusions:** Compared with ergometer exercise, L-carnitine supplementation had superior effects on physical activity and muscle quality in HD patients. These observations suggest that L-carnitine supplementation may be a novel therapeutic strategy for HD-related sarcopenia and frailty.
TH-PO259

Use of a Wrist-Based Monitoring Device Among Hemodialysis (HD) Patients: A Feasibility Study

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Background: Pervasive sensing technologies allow healthcare providers to gain insights into patients’ status outside the clinical setting. To adopt widespread use of remote monitoring devices we must first study their feasibility. We aim to quantify how long patients will use a wearable device before requiring an intervention to maintain use of the device.

Methods: HD patients were enrolled from 3 clinics in New York City starting in May 2019. Patients ≥18 years, on HD ≥3 months, able to walk, owning a smartphone, tablet or PC were enrolled and provided with a wrist-based monitoring device (Fitbit Charge 2). Participants were instructed on how to use the device. If a patient failed to sync data for 7 consecutive days, a text message or email reminder was sent. We evaluated time to first notification using Kaplan Meier analysis. Patients were censored at 515/19.

Results: 89 patients were enrolled into our study with 6 patients screen-failed. At enrollment patients were 55±12 years old with a dialysis vintage of 5.8±6.3 years. 36% lived alone, 54% were single, 57% unemployed, 68% were African-American, and 49% had an education level of some college or higher. 61% of the patients required a notification to continue using the device. Mean and median time to first notification were 95 days (95%CI 66 to 125) and 44 days (95%CI 32 to 70 days), respectively. The probability of being on the study without intervention is shown in Figure 1.

Conclusions: We found that most patients will require some counseling to maintain the use of a wrist-based wearable device for remote monitoring. While most patients require an intervention before 90 days into wear, the patients who can maintain use independently after that point are likely to do so for longer.

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TH-PO260

The Relationship Between the Patient Activation Measure and Changes in Patient Self-Efficacy on In-Center Hemodialysis

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Background: The patient activation measure (PAM) assesses the knowledge, skills and confidence to manage their health condition. Low PAM is associated with worse outcomes and increased healthcare cost, and is increasingly seen as an endpoint for outcomes and increased healthcare cost, and is increasingly seen as an endpoint for complex interventions in chronic diseases. PAM includes many domains applicable to in-center (ICH) and home (HHD) hemodialysis but its sensitivity to change in more complex interventions is unknown. PAM and how many of 15 objective measures of self-efficacy in ICHD and HHD patients is unknown.

Methods: A stepped wedge randomised trial involving 12 centers supported patients to learn and undertake ICHD-related tasks over 18 months. PAM and how many of 15 ICHD tasks patients were undertaking was measured on 4 occasions. The relationship between within-patient changes in PAM (scored 0-100%) and the endpoints of numbers of ICHD tasks and moving to HHD were assessed using mixed-effects linear regression models, adjusting for patient characteristics.

Results: 534 patients completed 1611 PAM questionnaires during the study. The proportion of patients doing ≥ 5+ tasks increased from 44.3% to 52.3% (P<0.01), with 10.3% performing HHD or ICHD independently by the end of the study. At baseline (left figure) performing ≥ 5+ tasks was associated with a 10.7% difference in PAM score (95% CI 16.8 – 14.6%). During the study (right figure) moving from <5 to ≥ 5+ tasks was associated with a 4.3% change in PAM (95% CI 2.3 – 6.4%) and 4.8% (95% CI 0.4 – 9.2%) moving to independent ICHD or HHD.

Conclusions: This supported learning intervention was effective at increasing patient participation in ICHD-related tasks. Despite a strong baseline relationship between PAM and ICHD tasks, the longitudinal change in PAM with increased ICHD tasks, independent ICHD and HHD only just exceed the minimum clinically meaningful difference (4%). The relationship between PAM and self-efficacy is complex and greater understanding of measurement is needed to avoid potential underestimation of benefits of complex interventions.

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TH-PO261

Natural Killer Cell Activity Contributes to Development of Sarcopenia in Hemodialysis Patients

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Background: Sarcopenia, a syndrome of reduced skeletal muscle mass and function, is associated with decreased immune system responsiveness. Decreased natural killer (NK) cell activities have been suggested in hemodialysis (HD) patients. The aim of this study is to determine the relationship between NK cell activity and sarcopenia in HD patients.

Methods: We enrolled 116 clinically stable HD patients (62 male) and clinical data such as age, sex, height, weight, dialysis duration, and comorbidities were collected. Biochemical parameters, including white blood count, hemoglobin, albumin, C-reactive protein, and iron profiles were determined before the dialysis session. Muscle mass was evaluated by bioimpedance analysis (Inbody S10, Biospace Co., Korea) and hand grip strength was assessed using digital hand grip dynamometer. The diagnosis of sarcopenia was made according to the guidelines of Asian Working Group for Sarcopenia. Cytotoxic activity of NK cells was determined using commercial blood test assay (NK Vue, ATGen, Seongnam, Korea) that uses serum of ex vivo stimulated whole blood to detect interferon (IFN)γ secreted from NK cells as an indicator of NK cell activity. IFNγ levels were further quantified by ELISA. Univariate and multivariate binominal logistic regression analyses were used to determine the association between clinical variables including NK cell activity and sarcopenia in HD patients.

Results: A total of 29 patients (25%) were diagnosed as sarcopenia among 116 HD patients. The sarcopenic HD patients were significantly older (70.1 ± 8.1 vs. 61.1 ± 11.3 years, P<0.001) and had longer HD vintage (63.1 ± 54.0 vs. 38.5 ± 38.9 months, P<0.029), whereas showed lower body mass index (BMI) (20.7 ± 3.8 vs. 23.4 ± 6.2 kg/m², P<0.01), lower percentage lean muscle mass (ALM, K.26 ± 2.8 vs. 9.83 ± 4.5 kg/m², P<0.01), and lower activity of NK cell (392 ± 517 vs. 876 ± 667 pg/mL, P<0.001). Low NK cell activity had a very significant correlation with sarcopenia, and the statistical significance was maintained even after adjustment for age, sex, BMI, ALM in multivariate regression analysis (OR=1.004[0.104/0.033, 0.324], P=0.001).

Conclusions: Our results show that the NK cell activity of sarcopenic HD patients is significantly decreased and such low NK cell activity may contribute to development of sarcopenia in HD patients.

TH-PO262

Skeletal Muscle Chaperone and Co-Chaperone Proteins Are Elevated in Maintenance Hemodialysis Patients

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Background: Various chaperone and co-chaperone proteins are required for the assembly and maintenance of the sarcoprote to allow for maintenance of muscle tissue. We have previously established that both myofibrillar protein synthesis rates and markers of proteolysis are elevated in patients on maintenance hemodialysis (HD) when compared to BMI-matched controls. This result potentially underpins poor structural integrity that ultimately leads to poor physical performance in HD patients. Therefore, we aimed to determine whether HD patients have a higher abundance of chaperone and co-chaperone proteins involved in sarcrome integrity as compared to age- and BMI-matched controls.

Methods: Six HD patients (sex: 83.3% male; age: 58±13 y; BMI: 32.7 ± 4 kg/m²) and six controls (sex: 66.7% male; age: 51±7 y; BMI: 31±4 kg/m²) received biopsies from the
Reliability of Appendicular Muscle Mass Assessment by Bioelectrical Impedance Analysis vs. Dual-Energy X-Ray Absorptiometry in Hemodialysis Patients

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Background: Loss of skeletal muscle mass (MM) increases the risk for morbidity and mortality in hemodialysis (HD) patients. Dual energy X-ray absorptiometry (DXA) is a valid tool for assessing skeletal MM but limited by cost and radiation exposure. In contrast, bioelectrical impedance analysis (BIA) is cheap and has no radiation exposure risk. Aim of this study was to assess the concordance between MM measured by BIA and DXA in HD patients.

Methods: We enrolled 55 clinically stable HD patients. Body composition, including appendicular lean muscle mass (ALM), was evaluated by BIA (Inbody S10) and whole body DXA (Hologic®). Hand grip strength (HGS) was performed to evaluate muscle performance. Agreement between tools was assessed by means of the Bland-Altman method. Multiple linear regression was used to develop an ALM value by BIA close to that by DXA.

Results: The mean age was 63.4±11.29 years (range 39 to 88 years) and 65.5% were men. The prevalence of diabetes and hypertension was 54.5% and 94.5%, respectively. There was a significant association between muscle mass index which determined via body DXA and BIA. The mean value of ALM divided by the height3 (AMMI) was found to be 5.98±0.90 kg/m2 and 7.90±1.39 kg/m2 by DXA and by BIA, respectively, indicating overestimation of ALM in BIA method. BIA underestimated total body lean mass in 98% of participants. Bland-Altman plots for differences in AMMI between BIA and DXA showed large bias (Mean difference=1.95±0.7 kg/m2), with significant mean differences (0.29, 3.55) (P<0.001). After adjusting for sex, age and BMI, AMMI by BIA was significantly correlated with those measure by DXA (R2=0.643, P<0.001). Using the formula, we can estimate the overestimated in HD patients. Further refinement of adaptation formula for use BIA is needed to obtain accurate measurement of AMMI close to that measured by DXA.

Conclusions: Only the 48 patients who had at least a month of step-count data available were included in the analysis. The cohort consisted of 51% women, 40% African Americans and 47% were diabetic. Patients who reported recovery time of <15 minutes walked 5376 (±427) steps per day in comparison to patients who reported recovery time of >12 hours and walked 3260 (±573) steps. After adjustment, compared with patients in the recovery time group, those in the 15 min-2 hr group took 271 fewer steps (95% CI, -1038 to 496), 2-6 hours recovery took 1635 fewer steps (95% CI, -2456 to -812), 6-12 hours recovery time group took 2129 fewer steps (95% CI, -4417 to 170) and >12 hours recovery time took 2267 fewer steps (95% CI, -3397 to -1356). In comparison, 10 years older HD patients were associated with 737 (±710) steps per day. Diabetes, gender, race and ultrafiltration amount were not associated with step counts.

Conclusions: Longer recovery time after dialysis is associated with lower physical activity level. This is not explained by the amount of ultrafiltration. Studies should examine the effectiveness of increasing physical activity to improve outcomes in these patients.
Conclusions: Step count monitoring using a wearable device identifies changes in activity that are associated with increased risk of hospitalization or ED visit. Future studies should examine whether this approach could provide a real-time prediction of adverse events.

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TH-PO267

Dialysis Recovery Time as a Predictor of Hospitalization Among Incident Hemodialysis Patients

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Background: Dialysis recovery time (DRT) is the perceived time it takes patients to recover their ability to undertake daily activities after hemodialysis (HD). DRT is a meaningful variable to assess health related quality of life (HRQOL) in HD patients. As such, DRT as a predictor of hospitalization could be looked at as an early indicator of treatment success or impending morbidity. We characterized the hospital admission rates based on DRT categories among incident HD patients treated at a large dialysis organization (LDO).

Methods: We used data at an LDO during 2014 through 2017 for patients who completed a DRT survey ≥180 from first date of HD. DRT survey was administered as part of KDQOL questionnaire. DRT survey asks: “How long does it take you to be able to return to your normal activities after your dialysis treatment?”. Categorical answers were: ≤0.5, 0.5-1, 1-2, 2-4, >4 hours. Hospital admission rates were compared by DRT category (DRT ≤0.5 hour reference) via unadjusted Poisson models.

Results: We included data from 98616 incident HD patients (age 62.6±14.4 years; 57.8% male). There were 25.2%, 19.1%, 17.3%, 15.5%, and 22.9% of HD patients reporting a DRT of ≤0.5, 0.5-1, 1-2, 2-4, >4 hours, respectively. We observed 6-, 12-, and 24-month crude admission rates of patients rose with each longer DRT category (all p<0.001), as compared to patients with a DRT ≤0.5 hour (Figure 1).

Conclusions: Finding suggest longer DRTs in incident HD may associate with progressive increases in crude short- and long-term admission rates. DRT is an important marker of how well the patient feels and tolerates HD therapy. Optimizing the HD treatment around DRT in the incident period may have the ability to improve HRQOL and outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO268

Perspectives of Pakistani Patients Receiving Maintenance Dialysis on End-of-Life and Dialysis Decision-Making

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Background: There is a paucity of literature on end-of-life care (EoLC) and treatment preferences of Pakistani patients receiving maintenance dialysis. Most of the literature on these issues report beliefs of Western dialysis patients; however, both patient populations may differ in their cultural and religious beliefs about EoLC issues.

Methods: Using a convenient sampling method, we surveyed 522 dialysis adult patients from 7 different dialysis units across 4 cities of Pakistan from March through June 2015. The survey was adapted from the previous literature and translated in the Urdu language.

Results: The majority of the patients wanted detailed information about their disease (67.6%), and prognosis (54.4%). However, 81% reported not having prognostic discussions with their nephrologists. Only a small percentage of patients’ self-reported knowledge about services such as hospice (5%) and palliative care (8%). Nearly forty-seven percent of the respondents said that they would choose a course of treatment focused on relieving pain rather than extending life (19%). The decision to initiate dialysis over conservative management was made by doctors in 54% of the respondents. Almost 35% of the patients were not satisfied with their decision to start dialysis.

Conclusions: Pakistani patients receiving maintenance dialysis wish to receive better education on their prognosis and end-of-life care issues. Interventions to improve dialysis decision-making processes and uptake of hospice and palliative care services are needed in this population.

Funding: Governmental Support - Non-U.S.

Table 1: Main reasons not to have a certain treatment

<table>
<thead>
<tr>
<th>Reason</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not feeling ready (29%)</td>
<td></td>
</tr>
<tr>
<td>Emotional/Religious reasons (28%)</td>
<td></td>
</tr>
<tr>
<td>Cared for by family (28%)</td>
<td></td>
</tr>
<tr>
<td>Inadequate treatment at home (15%)</td>
<td></td>
</tr>
<tr>
<td>Fear of surgery (19%)</td>
<td></td>
</tr>
<tr>
<td>Dying in hospital (17%)</td>
<td></td>
</tr>
<tr>
<td>Other reasons that were not listed (16%)</td>
<td></td>
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</tbody>
</table>

TH-PO269

The EDITH Kidney Patient Survey on Modality Choice Among More Than 8000 European Dialysis and Transplant Patients

Rianne W. de Jong,1 Vianda S. Stel,1 Raymond C. Vanholder,2 Ziad Massy,1 Kitty J. Jager,1 ‘Ambroise Pare University Hospital and Inserm U1018 Ep5, Boulogne Billancourt, Paris cedex, France; 2ERA-EDTA Registry, Department of Medical Informatics, Amsterdam Public Health Research Institute, Amsterdam, UMCP, Amsterdam, Amsterdam, The Netherlands, Amsterdam, Netherlands; 3University Hospital Gent, Gent, Belgium.

Background: Renal replacement therapy (RRT) modality selection may be challenging for both patients and nephrologists. Within the EDITH project we surveyed adult European dialysis and kidney transplant patients on factors influencing modality choice and their satisfaction with the modality choice made.

Methods: The EDITH kidney patient survey (online and on paper) was translated into 30 languages. European adults with end-stage kidney disease treated by dialysis or kidney transplantation were eligible to participate between November 2017 and November 2018.

Results: 8133 patients from 40 European countries participated. Age, gender and modality characteristics (56% male, mean age 59 years (SD 14), 66% on haemodialysis (HD), 6% on peritoneal dialysis (PD), 29% on transplantation (Tx)) reflected the European RRT population in the ERA-EDTA Registry. A quarter of the patients did not receive any information on any modality before the start of RRT. 44% received no information on home haemodialysis (HHI), 24% nothing on PD and resp. 23% and 20% nothing on living and deceased kidney donor Tx. The majority of those who received information, were (very) satisfied with the information (range 57% for HHD to 86% for deceased kidney donor Tx). Two-thirds of the patients reported that decision making was shared with their doctor and most patients (83%) were satisfied with way the decision was made. The main reasons for patients not having a particular treatment are listed in Table 1. Most important factors influencing modality choice were quality of life, survival and safety (resp. 97.3%, 96.6% and. 92.2% rated as (very) important). Results were similar by age group, sex, educational level and start of RRT time period.

Conclusions: Though most patients seem to be satisfied with the information provision and modality choice, there remains room for improvement as a quarter of all patients did not receive any information on treatment modalities before start of RRT. Better education may also influence patients to choose a home-based form of dialysis or empower them to find a living donor.

Funding: Governmental Support - Non-U.S.

TH-PO270

Functional Status Index Directed Care in the Patient-Centered Supportive Care (PCSC) Pilot Study

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Background: A large dialysis organization (LDO) developed a functional status index (FSI) that can identify hemodialysis (HD) patients who are experiencing a lower level of functional status. The LDO performed Patient Centered Supportive Care (PCSC) pilot that identified HD patients with a decreasing/diminished FSI and provided targeted interventions based on identified barriers. We assessed if the FSI-directed intervention was associated with improvements in the FSI score.

Methods: We used data from 8 PCSC pilot clinics between 04/13/2018 to 10/30/2018. The FSI uses an array of clinical data and is computed via Z scores and weighted assignments of parameters. In the PCSC pilot, FSI-directed intervention was provided over 28 weeks to patients with a low and decreasing trend in their FSI score. This intervention included targeted clinical recommendations related to treatment adherence, weight management, nutrition, financial assistance, medications and comorbidities, as well as, external referrals to specialists. We calculated the percent of patients who had an increase in their FSI score from baseline in the FSI-directed intervention (FSI positive) versus standard of care (SOC) group who did not have an intervention (FSI negative).

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Results: We analyzed data from 497 HD patients at the 8 PCSC pilot clinics. FSI- directed intervention reduced 42% of participants. Patients with a low/decreasing FSI score had a higher mortality rate (14% FSI positive and 6% FSI negative SOC). Over the course of the pilot, 58% of the survivors with FSI-directed intervention had an increase in their FSI score compared to baseline. In the SOC group, 47% of survivors without the intervention had an increase in their FSI score.

Conclusions: The FSI-directed intervention was associated with >10% higher proportion of patients having an improvement in their FSI score. As anticipated, the FSI score identifies patients with higher mortality rates. Additional testing of the FSI-directed intervention needs to be confirmed to further evaluate its effectiveness.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO271

“I Didn’t Know Better”: Family Members’ Unexpected Negative Experiences with ESKD Treatments

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Background: Understanding the extent to which family members feel prepared for what to expect from patients’ end-stage kidney disease (ESKD) treatment could guide the development of family-centered interventions that enhance their treatment preparedness. We examined unexpected negative experiences with ESKD treatments among family members of dialysis and post-transplant patients to inform family-centered research and clinical care.

Methods: Forty-nine family members of patients receiving medical care in the Baltimore/Linthicum/Hopkins area participated in eight focus groups stratified by their self-reported race (African American or non-African American) and patients’ treatment experience in the past year (in-center hemodialysis, home hemodialysis, peritoneal dialysis, or live donor kidney transplantation). Focus group discussions were analyzed thematically.

Themes present in discussions from multiple treatment groups were highlighted to provide insight into common experiences. Exemplar quotes are provided for each theme.

Results: Four themes were identified. Becoming a caregiver reflected family members’ unpreparedness for caregiving responsibilities (“I didn’t expect to have to be involved”) and related consequences (“I couldn’t even sleep”). Psychological repercussions captured family members’ negative reactions to treatment (“The anxiety”) as well as their perceptions of patients’ reactions (“I think he’s depressed”). Treatment delivery and logistics depicted treatment situations family members considered problematic (“Why can’t he do this on his own?”), challenges they had managing their health and constantly juggling that), and inconvenience (“The space it takes to store 3,000 cases of stuff is unbelievable”) for themselves and patients alike. Morbidity encompassed family members’ perceptions of patients’ experiences with dialysis-related health problems (“More illnesses since dialysis”) and fatigue (“My son was so tired”). Finances pertained to treatment-related expenses, financial strain from unemployment, and hiring caregivers to assist with treatment delivery.

Conclusions: Patients felt unprepared for non-clinical, logistical, and clinical aspects of ESKD treatments. Findings underscore the need for pre-treatment interventions to help patients know what to expect from and feel psychologically prepared for ESKD treatment.

Funding: NIDDK Support

TH-PO272

Patients’ Unexpected Adverse Experiences with Dialysis and Transplantation

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Background: Patients with end-stage kidney disease (ESKD) desire better education about what to expect from treatment, and preparatory information is associated with positive outcomes for chronic disease patients. Yet, knowledge about the unexpected experiences of ESKD patients’ treatment experiences is limited. We studied unexpected adverse treatment experiences among dialysis patients and transplant recipients to understand how providers and pre-treatment interventions can better prepare ESKD patients for treatment experiences.

Methods: Fifty-five patients receiving medical care in Baltimore, Maryland participated in focus groups stratified by their treatment in the past year (in-center hemodialysis, home hemodialysis, peritoneal dialysis, or live donor kidney transplantation) and race (African American or non-African American). Discussions were analyzed thematically. Themes present in discussions from multiple groups were highlighted; exemplar quotes are provided.

Results: We identified five themes. Psychological responses reflected patients’ negative psychological reactions to treatment, which ranged from feeling different from healthy peers (“I want to be like everybody else who’s not on dialysis”) to feeling suicidal (“I’m going to kill myself”). Constrained freedom of choice captured losses or limitations in recreational (“The only thing I can get on now is the treadmill”) and work (“I can’t work”). Work and treatment delivery (logistics characterized patients’ perceptions of painful (“I dislike sticking needles in my arm”), problematic (“I felt like a number in the center”), challenging (“It was hard for me to stay focused on the diet plan”), and inconvenient (“it’s not always convenient to dialyze five days a week”) treatment situations. Morbidity described patients’ experiences with treatment complications (“I’ve had so many operations”) and comorbidity (“I’ve had two asthma attacks”). Finances pertained to treatment-related expenses, financial strain from unemployment, and hiring caregivers to assist with treatment delivery.

Conclusions: Patients felt unprepared for non-clinical, logistical, and clinical aspects of ESKD treatments. Findings underscore the need for pre-treatment interventions to help patients know what to expect from and feel psychologically prepared for ESKD treatment.

Funding: NIDDK Support

TH-PO273

Patient and Caregiver Experiences and Perspectives on Access to Kidney Replacement Therapy in Rural and Remote Communities: Thematic Synthesis of Qualitative Studies

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Background: Patients with chronic kidney disease requiring kidney replacement therapy in rural and remote communities are at higher risk of mortality when compared with those in urban areas, and encounter many barriers in accessing care. We aimed to describe patient/caregiver perspectives on access to dialysis and kidney transplantation in rural/remote communities. Access is defined as the opportunity to reach and obtain appropriate health care services and includes the right to seek information concerning health issues and treatment options.

Methods: Medline, Embase, PsycINFO and CINAHL were searched to February 2019. Studies that where qualitative in nature, provided perspectives of patient and/or caregivers who resided in rural/remote communities, patients over 18 years of age and requiring kidney replacement therapy were included. Thematic synthesis was used to analyze the findings.

Results: From 18 studies (n= 540 participants) conducted across 8 countries (Australia, Canada, United Kingdom, New Zealand, Ghana, United States, Tanzania, and India), we identified six themes: uncertainty in navigating healthcare services (inadequacy of absorbing information, without familiarity and exposure to options, lacking trust in clinicians and yearning for cultural safety at a local level); fearing separation from family and country (devastating homesickness, unable to fulfill family roles, preserving social relationships, managing in community and grieving former roles); intense burden of travel and cost (poverty of time, exposure to risks and hazards, taking a financial toll and tedious pre-transplant testing processes and workup expenses); suffering hardship and loss (making life changing sacrifices, relocation with no return and inadequacy of transitional arrangements, challenges with receiving care (shame in resource usage and harboring concerns for living donor) and coping and managing in isolation (hesitation about capacity to do home dialysis).

Conclusions: Patients with CKD in rural/remote areas face profound challenges of distance, financial burden, separation from family in accessing kidney replacement therapy, which can have severe consequences on wellbeing and outcomes. Strategies are needed to improve access for those patients in rural/remote communities.

TH-PO274

Patient Driven Video-Educational Tool in ESRD

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Background: Each year, of the ~ 110,000 incident incident end stage renal disease (ESRD) patients in the U.S., ~ 46% have not received pre-ESRD nephrology care. Pre-ESRD patient education improves outcomes and quality of life. There are limited options to incorporate patient experience into pre-ESRD education.

Methods: In a large academic program we designed a educational tool comprised of a patient interview video, in a patients-teaching-patients model. A planning committee (trainees, physicians, nurse educator and patient surveys) determined the components of this tool. The open-ended patient interviews focused on domains pertaining to experience with dialysis modality, preparation towards dialysis/transplant, lifestyle changes, and journey of accepting life after ESRD. After obtaining informed consent patients were interviewed for ~ 4 hours, edited by three reviewers into a 50 min video, and viewed by faculty and trainees to obtain feedback.

Results: There were 6 patients with ESRD (3 Women; 1 White and 5 Black); [3 hemodialysis (HD), 2 home dialysis (HD) and peritoneal dialysis, and 1 transplant recipient]. Patients had varying degrees of pre-ESRD education, and had different pre-treatment intervention. Most (80%) patients described a lack of available flexibility of dialysis care which may allow them to travel, continue employment, and maintain quality of life. As for provider feedback, 100% found this video to be a critically important educational tool. A shorter shorter duration and including more discussion on transplantation was recommended. Interestingly, patients felt that although they preferred a peer-driven educational component, it cannot replace the healthcare professionals education.

Conclusions: We successfully demonstrated that patient experience can be incorporated into a succinct video-based educational tool. Key peer-driven components may allay fears of dialysis, improve adherence to dietary and lifestyle changes, and

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compliment provider education. Future steps include incorporating this tool prospectively, and assessing its effectiveness in pre-ESRD educational programs.

**Funding:** Clinical Revenue Support

**TH-PO275**

**Shared Care in Haemodialysis: A Path to Independence**

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**Background:** Most dialysis patients spend many hours every week in hospital, which can leave patients feeling exhausted. Shared care haemodialysis programmes can improve patient satisfaction and may reduce costs. The Queens hospital dialysis unit is one of the satellite units of Royal London Hospital, United Kingdom. In order to promote more control of dialysis care to be delegated to patients we aimed to offer shared care programme to all suitable patients coming to the unit which enabled the patients to manage their care with nursing support. Shared haemodialysis care is when patients at dialysis units are supported to undertake tasks involved in their own treatment to the extent that they wish, which would range from performing selected tasks to complete independence in performing haemodialysis in the unit also named as self-care haemodialysis which is suitable for patients with housing issues.

**Methods:** All patients transferred to the unit were assessed for suitability for shared care. A dedicated link nurse for shared care offered these patients the list of performing 15 different dialysis related tasks. The performance data was collected from January 2018 to April 2019 and 3 months monthly was noted in patients’ capability to perform specific tasks related to haemodialysis care. All these patients were also offered to sign up to “Patient View” a web based system which enabled patients to review there blood results and physician’s letters.

**Results:** In January 2018, at the start of the programme 72 out of 100 (72%) patients were offered to perform the tasks. Only 19% were able to perform 5 or more tasks including 1 patient who could needle fistula independently. By April 2019, 97 out of 103 (92.4%) patients were offered to perform dialysis related tasks and 49.5% were performing 5 or more tasks with 2 patients needing their fistulas independently.

**Conclusions:** Shared care in haemodialysis is a good way of involving patients in the dialysis care which provides feeling of achievement and independence to patients. It provides dialysis space for patients who cannot perform home haemodialysis due to housing related issues. Achieving complete self care is a daunting task for both the patients as well as responsible health care providers as it was a slow progress to do more complicated tasks. Identifying barriers to achieve these tasks will help in implementation of shared care program.

**TH-PO276**

**Reasons for Referral to Kidney Supportive Care Clinic and Outcomes in Haemodialysis Population**

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**Background:** In Australia, 32-40% of deaths in the dialysis population are due to treatment withdrawal. Withdrawal from dialysis is usually triggered by failure to thrive on dialysis, high symptom burden, and its associated accelerated chronic comorbid illness. The role of a dedicated multidisciplinary kidney supportive care (KSC) clinic for those on dialysis is not only in managing these symptoms but also providing support surrounding dialysis cessation where appropriate. We aim to analyse the reasons for referral of chronic haemodialysis patients to a KSC clinic and assess decision-related outcomes following their visit.

**Methods:** Retrospective analysis of all persons on haemodialysis referred to KSC clinic in the 3 years from inception (February 2016). Reasons (for referral to clinic, documented advanced care planning, number of visits, potential change of pathway and timing of death were extracted from medical records and analysed descriptively.

**Results:** Of the total of 364 people referred to KSC clinic, 118/364 (32%) were receiving haemodialysis. Of these, 58% were male with a median age of 69 years (range 27-89 years). Reason for referral were: control of symptom burden (65%), resolve decision-making conflict (25%), advance care planning (50%), education surrounding cessation of dialysis (30%) although some had more than one reason. Post KSC review, 72% had documented advance care plan. Number of visits ranged from 1-12 with a median of 2 clinic reviews. 59/118 (50%) had died at the time of analysis. 38/59 (64%) opted to change pathway from receiving haemodialysis to conservative management pathway before death due to deteriorating health.

**Conclusions:** Access to KSC is vital in the journey of a patient with chronic kidney disease. A key role of KSC is the discussions on future planning which is usually started by the treating nephrologist and then further elaborated in KSC leading to advanced care planning. This offers tailored, patient-centred care that aligns their beliefs and preferences with their goals, aiming to not only improve quality of life, but quality of death.

**TH-PO277**

**Numeracy Relates to Communication and Clinical Outcomes in ESKD**

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**Background:** Numeracy is assessed subjectively via confidence in numerical tasks or objectively via computation. Low numeracy is associated with poor communication with providers and disease control in chronic illness. Understanding kidney function requires interpretation of numerical values, yet numeracy is unexplored in end-stage kidney disease (ESKD). We tested whether numeracy associates with increased confidence in communicating with nephrologists and phosphorus control.

**Methods:** In a cross-sectional study, we recruited demographics, clinical data, and validated surveys. Subjective and objective numeracy were measured via the Subjective Numeracy Scale (SNS) and Wide Range Achievement Test (WRAT), and communication via Patient Perceived Efficacy in Patient Physician Interactions. Pearson’s correlations tested associations, and regression models tested associations adjusting for age, sex, race, income, education, cognitive, dialysis vintage.

**Results:** In 150 patients on hemodialysis, subjective and objective numeracy associated with higher income, education, and white race (p<.01) (Table). Subjective numeracy associated with confidence in communication (r=.25,p<.01) even after covariate adjustment (β=−.25,p<.05), but not with phosphorus (p=.58). Objective numeracy did not associate with confidence in communication (p=.27) and associated with phosphorus (β=.18,p=.05) but not in adjusted models.

**Conclusions:** Poor numeracy is common in vulnerable ESKD patients. Supporting efficacy in numeracy may improve communication with nephrologists, but medication and diet control may be more influenced by computation. Numeracy in ESKD education and counseling may enhance patient engagement.

**Funding:** NIDDK Support

**Numeracy, Demographics, Outcomes with Median, IQR**

**TH-PO278**

**Concerns About and Impacts of Treatment for Kidney Failure from the Perspectives of African American Family Members**

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**Background:** Understanding African American families’ experiences with treatment for kidney failure is necessary for informing the delivery of family-centered care and the design of appropriate interventions. This qualitative study explored treatment-related questions, concerns, and positive and negative family impacts from the perspectives of African American family members of pre-kidney failure and kidney failure patients.

**Methods:** Thirty-five African American family members of kidney disease patients receiving medical care in Baltimore, Maryland participated in five focus groups stratified by patients’ treatment status in the past year (progressive kidney disease, hemodialysis, peritoneal dialysis, involved in living-donor kidney transplantation, or underwent living-donor kidney transplantation). Discussions were analyzed thematically. Themes present in discussions from multiple groups were highlighted to provide insight into common experiences. Exemplar quotes are provided.

**Results:** Family members raised questions and concerns about patients’ “high risk of infections,” “mental breakdowns,” “confined freedom of choice (“Dialysis would just bust her goals”), “the financial aspect” of treatment, and treatment delivery and logistics, specifically inconveniences (“The tube bothers her”), patients’ treatment adherence (“Sneaking around and getting the chocolate”), and care quality (“They should have better training”). Positive family impacts included improvements in patients’ well-being (“He’s a lot more compassionate”), “good” patient and family quality of life, strengthened family relationships (“rallying” around the patient), greater freedom of choice (“Going to work again”), and family members’ “chance to give life” to patients via transplantation. They identified decrements in patients’ well-being (“Her being down on herself”), family members’ adverse psychological treatment reactions (“I’m scared”), strained family relationships (“My son and I are not speaking”), and caregiving difficulties (“You as a family member need support too”) as negative family impacts.

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### TH-PO279

**Challenges to Hemodialysis Care and Solutions: Qualitative Analysis of the Can-SOLVE CKD Triple I Study**

**Clara Bohm,1,2 Krista F. Rossum,1 Juli Finlay,2 Arlene D. Desjarlais,3 Michael D. McCormick,4 Neesh I. Pannu,5 Matthew T. James,2 Karthik K. Tennankore,4 Manish M. Sood,3 Stephanie E. Thompson,7 Marcello Tonelli,1,2 University of Manitoba, Winnipeg, MB, Canada; 1University of Calgary, Calgary, AB, Canada; 2CanSolve CKD, Toronto, ON, Canada; 3Dalhousie University/NS Health Authority; Halifax, NS, Canada; 4Chronic Disease Innovation Centre, Winnipeg, MB, Canada; 4Ottawa Hospital Research Institute, Ottawa, ON, Canada; 5University of Alberta, Edmonton, AB, Canada; 6Can-solve CKD, Winnipeg, MB, Canada.

**Background:** Part of the Can-SOLVE CKD program, ‘Triple-I’ is a pan-Canadian study that aims to identify top priorities and solutions for improving patients’ hemodialysis (HD) experience in three areas: a) **Information** patients receive b) **Interactions** between provider and patient c) **Individualization** of care. Triple-I follows Can-SOLVE’s guiding principles to involve patients in all phases of research as co-creators of knowledge and solutions. In Phase 1, using focus groups and interviews, we identified challenges in HD care and potential solutions in the areas of information, interaction and individualization.

**Methods:** From July 1, 2017 to July 31, 2018, we performed focus groups and interviews with HD patients, their caregivers and healthcare providers in 5 academic centres (Edmonton, Calgary, Winnipeg, Ottawa and Halifax). Subsequently, 3 members of the research team conducted a pragmatic categorical analysis to code the data from identified transcripts of these sessions. Data were classified by respondent type (patients, caregivers or health care providers).

**Results:** A total 113 people (64 HD patients, 18 caregivers, 31 health care providers) participated in 8 focus groups or individual interviews, of which 41% were women. Mean age of patients and caregivers was 61 years and mean time on HD was 4.6 years. After accounting for redundancy, a total of 45 recurring challenges in HD care were identified (information n=18; interaction n=16; and individualization n=11). Highly prevalent challenges included information on modality/access, transplant and first day of care. Challenges with nephrologists, nurses and inconsistency of care with different healthcare providers; and, insufficient individualization of session set-up, transportation arrangements and ways to address socio-economic and emotional well-being. Although there were some differences in responses between patients/caregivers and health care providers, many of the challenges coded were identified by both groups.

**Conclusions:** Although a deeper qualitative analysis of this data is ongoing, the codes/challenges identified in this phase of the study will be used to prioritize challenges and identify and test potential solutions to these challenges in further phases of the study.

**Funding:** Government Support - Non-U.S.

### TH-PO280

**A Cross-Sectional Study of Insomnia in Chronic Hemodialysis Patients**

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**Background:** The most frequent complaint in chronic hemodialysis(CHD) patients(pts) is insomnia yet little research has identified all of the causes of this disorder in CHD pts.(Flythe, CJASN,14:150, 2018)

**Methods:** We conducted a review of sleep patterns in 103 CHD pts on the first & second shifts in our 2 largest dialysis units using these tools: the National Sleep Foundation Survey, the Sleep Diary, Insomnia Severity Index (>8 abnl), Stop-Bang-8 for sleep apnea SA, 5-7 high risk, Epworth Sleepiness Scale, Restless Leg(RL) Survey & the International RL Severity Score (>8 abnl).

**Results:** 25 CHD pts (24%) including 4 with SA had normal sleep patterns averaging 8.1 hours of sleep/nite & <1 awakening from the Sleep Diary & scores of < 7 on the Insomnia Severity Index. 63 on Epworth & 3 or < on Stop Bang-8. Insomnia occurred in 78 CHD pts (76%). Mean duration of sleep ws 3.9 hrs with 2.5 awakenings from the Sleep Diary, p<0.001 vs normal CHD pts. The National Sleep Foundation Survey & Epworth Scale were inconsistent in identifying these pts. There were no differences in age, duration of dialysis, sex, or causes for ESRD between groups. 24 CHD pts had known SA & in all 24 the STOP Bang-8 was 4 or >, mean 6.2 which is a high risk score for SA. 13 other CHD pts had a Stop Bang-8 of 4 or > & have been sent to sleep medicine. RL occurred in 19 CHD pts with a mean severity score of 25.14/19 CHD pts had iron deficiency vs 22/78(28%) of all other CHD pts with insomnia(p<0.01) The levels of serum iron & saturation did not correlate with the RL Severity Score. They are receiving iv iron therapy & will be re-scored. 5 CHD pts had both SA and RL. 13 CHD pts had newly reported causes for insomnia: painful neuropathy 9, cramps 2, puritus 1, & arthritis 1. Only 13 CHD pts had primary insomnia. Cognitive-behavioral therapy(CBT) has started for these pts.

**Conclusions:** Insomnia occurs in up to 75% of CHD pts from diverse causes. The most useful tools to identify insomnia are the Sleep Diary, Insomnia Severity Index & the Stop Bang-8 which correctly identified all 24 SA CHD pts. RL in CHD pts was associated with iron deficiency. We found 4 new insomnia causes in CHD pts including painful neuropathy, cramps, pruritis & arthritis. Algorithms to treat each cause of insomnia have been developed especially for safe sedatives for primary insomnia if CBT fails.

**Funding:** Clinical Revenue Support

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**TH-PO282**

**The Effect of Extracorporeal Shock Wave Therapy in Hemodialysis Patients: A Randomized Controlled Trial**

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**Background:** Muscle wasting is a common feature in the hemodialysis (HD) patients and associated with comorbid complications, poor quality of life, frailty and premature death. Extracorporeal Shock-Wave Therapy (ESWT) is able to relief pain, as well to positively regulate inflammation (probably as immunomodulator), to induce neangiogenesis and stem cells activities, thus improving tissue regeneration and healing, and has the advantages of easy application, and minimal risks for these patients. This study aimed to evaluate the effects of intradialytic ESWT.

**Methods:** This was a single center, prospective, randomized controlled trial. Seventeen HD patients were randomly assigned to either the ESWT group or the control group. The ESWT group received intradialytic ESWT over a 12-week period. Measurement of body composition using a dual energy X-ray absorptiometry, the handgrip strength test, gait speed test, five time sit to stand test, and the timed up and go test for physical function assessment, and blood tests were performed before and after the intervention period.

**Results:** The ESWT group demonstrated significant improvement compared with the control group in main functional parameters: decreased time in gait speed test (5.5 ± 13.3 vs. -0.5 ± 1.3 sec), five time sit to stand test (3.9 ± 10.7 vs. -1.4 ± 2.8 sec), and the timed up and go test (6.9 ± 17.8 vs. -3.1 ± 4.2 sec). After treatment, lipopolysaccharide concentrations were reduced, and glutathione peroxidase concentrations were increased significantly in ESWT group. However, there was no significant difference in muscle mass and other blood tests.

**Conclusions:** The ESWT group showed improvement after intervention in physical function test, and oxidative stress parameters. ESWT could be an effective treatment tool for HD patients with either muscle wasting, weakness, or sarcopenia.

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**TH-PO283**

**Physical Activity Levels In Hemodialysis Patients: The Fitbit Prospective Study**

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**Background:** Physical decline in end stage kidney disease is associated with morbidity and mortality. The aim of this study was to quantify physical activity (PA) in hemodialysis (HD) patients using the Fitbit. We hypothesis that PA measured as by the number of daily steps will be lower in older patients, and those from a rural HD unit.

**Methods:** In this prospective study, 52 chronic HD patients were recruited from outpatient HD units in urban San Diego and rural Imperial County, CA between March 2018 and April 2019. Key inclusion criteria included: 1) Receiving HD for ≥3 months 2) age ≥18 years and 3) able to walk without assistance or assistive devices. All HD patients wore Fitbit Charge 2 (Fitbit, San Francisco, CA) for 4 weeks. The display of the Fitbit was covered to minimize participation bias. The primary outcome was number of steps per day.

**Results:** Of 52 enrolled patients, 7 HD patients dropped out before completing 4 weeks study duration. The remaining 45 HD participants (urban=25; rural= 20) were included in the analysis. The mean age was 61 years, 42% were women and 64% were hispanic. The mean dialysis vintage was 4.4 years. On average, HD subjects walked 3687 steps per day. Elderly walked fewer steps compared to younger (age < 65 yrs) HD patients (1359 vs. 4387 steps, p=0.02). Although, not statistically significant average daily steps for participants from rural HD clinic (3141 vs. 4123 steps, respectively) and on dialysis days (3272 vs. 4070 steps, respectively) were less compared to participants from urban HD clinic and non-dialysis days. We found no difference in physical activity levels by gender and dialysis shift (Figure 1). Only about 10 percent of HD patients found activity tracker not comfortable to wear.

**Conclusions:** Participants on HD were found to be less PA on dialysis days and from rural dialysis clinic. Difference was more pronounced between younger and elderly individuals. Future studies should focus on patient-centered adaptive interventions to sustain and improve PA among HD patients.

**Funding:** Private Foundation Support

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NW, non-withdrawer; W, withdrawer.
TH-PO284

Framingham’s Cardiovascular Disease (CVD) Risk Score (FRS) and Its Components as Predictors of Mortality in Peritoneal Dialysis (PD) Patients

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Background: Non-traditional risk factors (e.g., inflammation and oxidative stress) contribute to the high mortality risk due to CVD in patients (pts) with chronic kidney disease (CKD). However, the impact of traditional risk factors represented by FRS, and its components, age, sex, hypertension, diabetes mellitus (DM), smoking, and hyperlipidemia, is less well documented. We analyzed the association of FRS with mortality in PD pts.

Methods: In 1276 incident PD pts (median age 50 years, 56% males), FRS and metabolomic biomarkers linked to CVD were analyzed by adjustment for baseline associations. FRS and its components with all-cause and CVD-related mortality during follow up of up to 60 months (median 44 months) was assessed using regression models with transplantation as competing risk.

Results: Pts in the highest tertile of FRS were predominately older men with DM, CVD and high BMI, and low serum creatinine, albumin, and parathyroid hormone (iPTH). In linear regression model, FRS associated with CVD, BMI, Hb, iPTH, alkaline phosphatase (ALP), calcium and albumin after adjustments for confounders. All-cause mortality risk (expressed as crude sHR) associated with 1 SD higher FRS (sHR 1.50), and its components, higher age (sHR 2.63), female gender (sHR 0.67), and DM (sHR 2.40), and crude CVD-mortality risk with 1 SD higher FRS (sHR 1.64), and age (sHR 2.90), DM (sHR 3.41) and cholesterol (sHR 1.08). In competing-risks regression analysis, elevated vs low tertile of FRS, independently associated with all-cause, sHR 3.65 (95% CI 2.07 - 6.44) and CVD, sHR 3.28 (95% CI 1.45 - 7.11) mortality risk after adjusting for CVD, year of recruitment, and 1-SD higher BMI, creatinine, uric acid, phosphate, ALP, iPTH, triglycerides, glucose, Hb, ASAT and ALAT.

Conclusions: FRS is independently associated with mortality risk in PD pts, underlining the importance of traditional risk factors in CKD. FRS is a useful risk assessment tool for predicting clinical outcomes in PD pts.

TH-PO285

Relationship of Short-Term and Long-Term Blood Pressure Variability with Death and Cardiovascular Events in Peritoneal Dialysis Patients

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Background: Blood pressure (BP) variability is associated with increased cardiovascular risk, not only in hypertensive patients but also in patients with chronic kidney disease. However, little is known about this association in peritoneal dialysis (PD) patients. This study aims to investigate the relationship of short-term (within 24-hour) and long-term (visit to visit) BP variability with death and cardiovascular events in patients on PD.

Methods: A total of fifty-two prevalent PD patients were enrolled and underwent 24-hour ambulatory BP monitoring. Short-term BP variability was assessed with the weighted standard deviation (w-SD) of 24-hour ambulatory systolic BP monitoring and long-term BP variability was assessed with the SD of systolic BP across clinic visits. We assessed the associations of short-term systolic BP variability and long-term systolic BP variability with a composite outcome of death and cardiovascular events.

Results: The average short-term systolic BP variability was 13±2.9 mmHg, and average long-term systolic BP variability was 20±5.9 mmHg. In unadjusted Cox regression analyses, higher short-term systolic BP variability was significantly associated with increased risk of death and cardiovascular events (HR, 1.437; 95% CI, 1.146-1.801; P=0.002). The significant association of short-term systolic BP variability with the composite outcome was also maintained, in adjusted multiple Cox regression model (HR, 1.342; 95% CI, 1.025-1.756; P=0.033). However, long-term systolic BP variability was not related to the composite outcome in both the unadjusted (HR, 1.067; 95% CI, 0.958-1.188; P=0.239) and adjusted (HR, 1.083; 95% CI, 0.955-1.229; P=0.214) models.

Conclusions: In patients on PD, increased short-term systolic BP variability is related to higher risk of death and cardiovascular events, whereas long-term systolic BP variability is not.

TH-PO286

The Beneficial Role of Peritoneal Dialysis on Cardiac Functional Parameters in Patients with Congestive Heart Failure: A 3.5-Year Follow-Up

Panagiotis Pandiag,1 Andreas Bozikas,1 Fotini Lazaridou,2 Styliani Vakian,1 Elefri Kitouskidi,1 Kalliopi Pozoukoudi,1 Evlabria Stamatopoulou,1 Ioanna Sofroniou,1 Sophia Spata,1 Nephrology, General Hospital of Thessaloniki “Agios Pavlos”, Thessaloniki, Greece; 2Cardiology, General Hospital of Thessaloniki “Agios Pavlos”, Thessaloniki, Greece.

Background: Peritoneal Dialysis (PD) applied in patients (pts) with congestive heart failure (CHF), resistant to diuretic therapy, results in significant improvement of their condition. We examined the effect of PD on extended time period, as a continuous ultrafiltration treatment to pts with CHF (NYHA class IV) and renal disease stage ≥ IIb on cardiac functional parameters. We performed a detailed Cardiac Ultrasound (CU) in an effort to identify markers to distinguish population that might benefit of early PD application.

Methods: We enrolled 28 pts (mean age 78.3 years) in PD over 42 months (mo). Inclusion criteria were CHF (NYHA class IV) symptoms, resistant to diuretics, and deterioration of renal function. Assessment of cardiac function by CU on the initiation of PD, 6 and 12 mo later. We recorded and evaluated the Ejection Fraction (LVEF), Relative Wall Thickness (RWT), Left Ventricular Mass Index (LV), LVEF, Left Atrium Volume Index (LA), Pulmonary Artery Systolic Pressure (PASP), Tricuspid Anular Plame Systolic Excursion (TAPSE).

Results: Mean time on the method was 21 ± 10.16 (-42) mo. Remarkably, significant reduction of all RU parameters, was noted, during period 0 – 6 mo and 6 – 12 mo for every patient. In contrast, no important changes were observed in period 6 – 12 mo. Also, there was substantial decrease of diuretics, as well as elimination of hospitalizations due to CHF decompensation and noteworthy improvement of NYHA class. As it was expected we observed significant body weight decrease in period 0 – 6 mo as well as in 0 – 12 months. But, no important changes were noted in period 6 – 12 mo.

Conclusions: The gradual and continuous removal of excess fluid resulted in clinical improvement of the living status of all our pts. Furthermore, there was a long term improvement of the left and right cardiac functional parameters in CU. Thus, dramatically diminishing hospitalizations, due to decompensation of CHF, and restoring pts autonomy. The application of PD can be an important choice in the management of CHF NYHA class IV. The outcome of this prospective study supports the use of PD in selected pts of this cohort.

TH-PO287

Cardiovascular Effects of Peritoneal Dialysis in a Uremic Rat Model

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Background: In the US more than 700,000 people suffer from end stage renal disease (ESRD) of which 97.5% are reliant on dialysis. Among dialysis patients, cardiovascular (CV) related events are the leading cause of death. Despite therapeutic advancements the continued CVD following the onset of dialysis poses an interesting clinical challenge that necessitates further studies into the effects and effectiveness of dialysis. Based on clinical outcomes, we hypothesized that peritoneal dialysis (PD) would have no effect on CV outcomes in the 5/6 nephrectomy (5/6Nx) rat model.

Methods: We performed 5/6Nx (n=13), or sham surgery (n=10), on 10 week old male Sprague-Dawley rats. Peritoneal catheters were implanted 6 weeks post-surgery. PD was initiated 2 days later in some of the 5/6Nx (n=6) and sham (n=5) animals (15 ml [Baxter PD-2 2.5%] 1-hour dwell 3x/day x 7days). Echocardiography was performed at baseline, week 6, and 7 weeks post-surgery. We examined the effect of PD on extended time period, as a continuous ultrafiltration treatment to pts with CHF (NYHA class IV). The outcome of this prospective study supports the use of PD in selected pts of this cohort.

Results: Blood urea nitrogen (BUN) was increased by 5/6Nx (5/6Nx 41.57 ± 2.78 vs. 5/6Nx-PD 31.5 ± 1.48, p<0.05). PD had no effect on BUN in sham animals, but decreased BUN in 5/6Nx (5/6Nx 41.57 ± 2.78 vs. 5/6Nx-PD 31.5 ± 1.48, p<0.05). PD had no effect on serum sodium, potassium, or bicarbonate levels, nor did it effect serum cholesterol. PD had no effect on albumin excretion in both 5/6Nx and 5/6Nx animals. PD did not alter kidney weight in sham animals, but reduced remnant kidney weight in 5/6Nx (5/6Nx 0.40 ± 0.03 vs. 5/6Nx-PD 0.39 ± 0.01, p=0.05). 5/6Nx increased heart weight (5/6Nx 0.42 ± 0.02 vs. 0.35 ± 0.01, p<0.05). PD had no effect on heart weight in sham animals, but attenuated the increase in 5/6Nx (5/6Nx 0.42 ± 0.02 vs. 0.39 ± 0.02, p=0.08). PD had no effect on CV functional parameters in sham animals and in 5/6Nx neither improved nor worsened CV outcomes.

Conclusions: These data combined suggests that PD may reduce renal pathology by reducing stress on remaining functional nephrons. Importantly, we did not observe an improvement in CV parameters with PD, which is consistent with persistent CV risk in the PD population. These findings indicate this is an appropriate model for future studies focusing on improving dialysis outcomes for ESRD patients.

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Prognostic Value of Soluble ST2 and Soluble LR11 on Mortality and Cardiovascular Events in Peritoneal Dialysis Patients
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Background: Because end-stage renal disease (ESRD) patients are at high risk of cardiovascular (CV) disease, developing a biomarker for CV risk stratification has clinical importance. Soluble form of suppression of tumorigenicity 2 (sST2) and soluble low-density lipoprotein receptor relative with 11 ligand-binding repeats (sLR11) are emerging as biomarkers that are associated with all-cause mortality and major adverse cardiac and cerebrovascular events (MACCE) in ESRD patients. However, the role of sST2 and sLR11 in peritoneal dialysis (PD) patients remains to be clarified.

Methods: We determined serum sST2 and sLR11 concentrations using enzyme-linked immunosorbent assay, and evaluated the association of those biomarkers with all-cause mortality and major adverse cardiovascular outcomes in PD patients.

Results: The median (interquartile range) concentrations of sST2 and sLR11 were 70.9 (57.8-89.8) ng/mL and 15.2 (12.3-19.6) ng/mL, respectively. During a median follow-up of 38.5 months, 15 (17.6%) patients died and MACCE was observed in 23 (31.3%) patients. When patients were dichotomized by median value of sST2 and sLR11, Kaplan-Meier analyses showed that higher sST2 group was significantly associated with lower event-free survival rates (log-rank test: P=0.002 for all-cause death; P=0.01 for MACCE). In multivariable Cox analyses, higher sST2 was independent risk factor for all-cause mortality (per 1 standard deviation [SD] increase: hazard ratio [HR]=1.947; 95% confidence interval [CI]=1.124-3.371) and MACCE (per 1 SD increase: HR=1.647; 95% CI=1.079-2.516). In contrast, sLR11 did not have a significant association with all-cause mortality or MACCE. Furthermore, only sST2 provided a significant predictive value for all-cause mortality (C-index 0.681; P=0.03).

Conclusions: sST2, not sLR11, was independently associated with greater risk of all-cause mortality and CV outcome in prevalent PD patients. Additional studies are needed to confirm these findings and examine underlying mechanism between new biomarkers and CV disease in ESRD populations.

Incremental Peritoneal Dialysis and Clinical Outcomes: A Propensity Score Matching Study
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Background: Incremental peritoneal dialysis (iPD) can be useful in selected patients with higher residual renal function, needing lower financial cost, or wanting less time burden of PD treatment. In addition, patients on iPD would have a reduced risk of peritonitis or peritoneal glucose exposure. However, the long-term effects of iPD on patient survival and PD survival are not clear compared to conventional PD (cPD). The aim of the study was to evaluate the differences in survival rates between iPD and cPD in PD patients.

Methods: Clinical data was retrospectively collected from a single center between January 2007 and December 2018. We included 303 patients percutaneously inserted PD catheter by surgical methods. An analysis performed using propensity score matching for age, gender, and the type of DM. Finally, 46 PD patients and 48 iPD patients were included. iPD was defined as starting PD with 3 or fewer peritoneal exchanges per day.

Results: Median duration of iPD was 31.2±22.5 months and mean PD duration of iPD was longer than that of cPD. Initial blood uric acid and serum creatinine levels (7.3±2.7 vs. 9.7±3.7 mg/dL, p<0.001) were significantly lower in iPD patients than cPD patients. Mortality as well as rates of peritonitis and hospitalization was significantly lower in patients with iPD than those with cPD (log-rank, p=0.034, p=0.001 and p=0.023). Mortality and hospitalization rate were prominent in cPD patients with diabetes. However, there was no significant difference in PD survival between iPD and cPD.

Conclusions: Incremental PD may be not only safe PD modality but also has better clinical outcome in less uremic patients to initiate and maintain PD. Further prospective study will be necessary to confirm the benefits of incremental peritoneal dialysis (iPD).

Safety and Efficacy of a Zero Sodium Peritoneal Solution
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Background: Sodium (Na) removal with conventional peritoneal dialysis solutions, which have a Na concentration similar to serum, primarily occurs by means of convective clearance. Zero Na peritoneal solution with a Na concentration much lower than serum Na removal given the large pore size of peritoneum and the high Na concentration gradient to serum. This solution could have clinical application as an intermittent therapy for venous congestion.

Methods: This was a randomized open label crossover study in 10 established peritoneal dialysis patients comparing zero Na dialysis solution (10% dextrose, ~505mOsm/L) to standard 4.25% dextrose solution (485mOsm/L). Patients underwent a 1liter dwell for 120 minutes with both solutions at two separate study visits. Serum and dialysate sodium were monitored every 15 minutes, and intraperitoneal volume was determined using indicator dilution technique with I-131 albumin. (NCT03801226; NIDDK103)

Results: Total Na removal and ultrafiltration were significantly greater with the zero Na solution, and Na removal rate was highest in the first 30 minutes (figure 1). There was a small decrease in serum Na of 1mg/L after 120 minutes with the zero Na solution. There were no significant differences between the two solutions in non-Na plasma electrolytes at 120 minutes. While serum glucose increased with both solutions, this increase was not significantly different between the two solutions at 120 minutes. There were no significant differences in blood pressure trends.

Conclusions: Despite similar osmolarities, zero Na peritoneal solution results in more effective Na clearance and higher UF volume. The solution was well tolerated without significant adverse changes in blood pressure or off target electrolytes.

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Peritoneal Sodium Removal Technique with Salt-Free Solution in Pigs
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Background: Over time, interest in the concept of sodium and fluid removal via non-renal routes in heart failure (HF) has grown significantly. One approach to removing serum sodium and fluid without diuretics is peritoneal dialysis (PD). Traditional PD, however, is inefficient in that it requires large intraperitoneal volumes with long dwell times while only offering limited sodium and fluid removal. Utilization of salt-free peritoneal solution will result in removal of a clinically significant amount of sodium and fluid.

Methods: Eighty kg anesthetized pigs (N=15) underwent surgical implantation of PD catheters. In 5 pigs, we allowed a 6 hour dwell and the intraperitoneal volume was determined serially using indicator dilution technique with I-131 radiolabeled albumen. 10 pigs underwent a 2 hour dwell with fluid volume measured by manual removal. To understand the effects of higher peritoneal solution volumes, 4 of these pigs then underwent 4 cycles of 2.5 L of 10% dextrose with 90 minute dwell times, for a total of 11 L cycled. These 4 animals had plasma volume measured with I-131 radiolabeled albumen prior to and after cycling was complete. Serial plasma and peritoneal fluid samples were obtained and glucose and electrolyte concentrations were determined.

Results: In the 5 animals with a 6 hour dwell, ultrafiltration approached 1.5 L and 5.1±0.4 grams of sodium was removed. In the 10 pigs that underwent a 2 hour dwell, an average of 0.9±0.2 L of ultrafiltration occurred with a corresponding 3.9±0.5 g of sodium removed. Despite a much higher glucose concentration in the dialysate, the 2-hour dwell was only 2.2±0.3 mmol/L (P=0.0001). In the pigs that underwent ultrafiltration, an average of 22.5±3.5 g of sodium was removed and plasma volume decreased dramatically in these animals.

Conclusions: These findings suggest that high salt intake under uremic condition could increase peritoneal local IL-6 production leading to higher peritoneal solute transport rate.
Peritoneal Dialysis: CVD, Fluid, Nutrition

TH-PO293
Is There a Place for Peritoneal Dialysis in Treatment of Refractory Heart Failure?
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Background: Ultrafiltration techniques have shown promise in the treatment of diuretic-resistant heart failure (HF). The aim of this study was to describe a single-center experience in the treatment of refractory HF patients with PD.

Methods: Retrospective study of 14 patients presenting symptoms and signs of severe refractory congestive HF despite optimal pharmaceutical therapy. Baseline characteristics and laboratory data were recorded. Charlson score and Doppler-echocardiogram results were collected at the beginning and end of follow-up period. PD adequacy was evaluated through peritoneal equilibration test (PET) results.

Results: We followed a cohort of 14 patients with HF, all excluded as candidates for heart transplantation. 12 were males (85.7%) and 2 females (14.3%), with a median age of 72.13 (IQR 42.5 - 75.38) years. The mean following time was 52.5 ± 23.5 (range 18 – 95) months. Seven patients (50%) had hypertension, 7 (50%) were diabetic and 2 (14.3%) had hepatitis C infection. The etiology of HF was arterial hypertension in 7 patients (50%), ischemic cardiopathy in 3 (21.4%), valvular cardiopathy in 3 (21.4%) and in 1 patient (7.1%) congenital cardiopathy. Three patients (21.4%) had been previously treated with intermittent hemodialfiltration, which was suspended due to hemodynamic instability; the other 11 patients started PD ab initium. Symptoms of HF improved in 35.7% (N=5) of patients, with an upgrade of New York Heart Association (NYHA) Functional Classification and improvement in ejection fraction (EF). At the beginning of PD treatment the mean Charlson score value was 5.7 ± 2.3, which reduced to 5.3 ± 2.6 by the end of observation time. There was a positive correlation between the first and the last Charlson score accessed (r=0.984; n=12; p<0.001). Six patients presented 1 episode of decompensated heart failure needing hospitalization, with a median length of stay of 2 (IQR 0 - 6.75) days. During the observation period seven patients were transferred to HD. In 3 cases this was lead by peritonitis episodes and in 4 by ultrafiltration failure. Two patients died, one from an acute hemorrhagic stroke and the other with a septic shock.

Conclusions: PD treatment in refractory HF, in addition to optimal pharmacological therapy, seems to be effective, it improves its quality of life and functional class.

TH-PO294
Follow -Up and Survival in Refractory Congestive Heart Failure Patients Treated with Peritoneal Dialysis

Background: Data on survival rates of patients (pts) suffering from Refractory Congestive Heart Failure (RCHF) treated with Peritoneal Dialysis (PD) are limited. We have previously reported the beneficial effect of PD application for RCHF for a period of 12 months. According to our results body weight, use of diuretics and hospitalisations were decreased, while clinical status and their New York Heart Association (NYHA) class were improved along with cardiac function parameters on Cardiac Echo. We followed this cohort and evaluated the mortality over a 48 months observational period.

Methods: We had enrolled 18 pts (mean age 82.6 years). Inclusion criteria were NYHA IV symptoms for a 6 months interval with deterioration of renal function. Mean time on PD was 26.7 (6 - 48) months.

Results: Overall, while on PD, 10 pts died (55.5%) during the 4 year period. Cardiac arrest was the main cause of death (6/10), infections being the second (4/10). Two pts died of complicated urinary tract infection and one of respiratory infection. One patient developed fungal peritonitis, had the PD catheter removed, was transferred to hemodialysis and later died. One patient suffered from Encapsulating Peritoneal Sclerosis and had the PD catheter removed, transferred to hemodialysis and doing well. 7 pts still remain in PD, on good clinical condition and stable body weight. During this period, no hospitalisation was recorded due to RCHF decompensation, in any of the pts. Mean survival time in PD was 32 months ± 6 SE 4 months.

Conclusions: Cardiac arrest is still the major cause of death in this cohort, however, 40 % of pts died of non-cardiovascular causes. According to literature ≤ 50 % pts with NYHA class IV RCHF, survive 6 months. Impressively in this cohort mean survival time was 5 times longer indicating that PD not only contributes to life elongation, but also offers better quality.

TH-PO295
Peritoneal Dialysis for Refractory Heart Failure: Decongestion, Cardiac Function, and Functional Status: A Reappraisal

Background: Congestion is an integral component of heart failure (HF) syndrome. Growing evidence points to peritoneal dialysis (PD) as an efficient therapeutic modality for management of fluid overload in refractory HF. Improvement in left ventricular ejection fraction (LVEF) is a frequently reported benefit of PD in this setting. We sought to explore whether the observed salutary impact of PD on cardiac function and functional status is due to efficient decongestion (i.e. Frank-Starling law).

Methods: Available data from contemporary clinical trials of PD in HF (performed between January 2010 and May 2019) that included more than 20 patients were selected and reviewed. Those studies evaluating the impact of PD on LVEF and volume status (assessed through changes in weight) in patients without end-stage kidney disease were included. Pertinent data were extracted and using Pearson product-moment correlation, the degree of linear dependence and correlation between these two variables was determined.

Results: Out of 11 clinical studies meeting the criteria, 1 was a duplicate and 3 did not have the needed data; 7 studies (4 retrospective and 3 prospective) with a total of 399 participants were included. The mean age was 71 years, and the mean baseline LVEF and weight were 35.1% and 76 Kg respectively. The median follow up was 14 months. There was substantial variation in the reporting of time point for cardiac function, functional status, and weight. LVEF changes ranged from -1.4 to +6.0 % (mean 1.51 ± 2.71) and weight changes ranged from -8.3 to +3.3 Kg (mean 2.09 ± 3.95). No correlation was observed between changes in LVEF and weight (r = 0.39, p = 0.37). All studies that evaluated functional status reported on its improvement after PD therapy.

Conclusions: While PD therapy for management of refractory HF is associated with improvement in cardiac function and functional status, data from contemporary trials suggest that changes in LVEF and weight do not have a strong correlation. Therefore, it is unlikely that efficient decongestion could fully explain the beneficial impact of PD on cardiac function. Since these studies did not included nutritional indices, an alternative explanation is that the relationship between weight and volume status in HF may be confounded by changes in muscle mass after initiation of PD therapy.

TH-PO296
The Effect of Dialysis Modality Choice on Cognitive Functions in Patients with ESRD: A Meta-Analysis
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Background: Cognitive dysfunction is a major debilitating co-morbidity of end-stage renal disease, affecting up to 80% of the dialysis population. However, differential effect of hemodialysis (HD) versus peritoneal dialysis (PD) on cognitive dysfunction remains debated.

Methods: We performed a systematic review in different databases including Pubmed, Medline, Embase and Cochrane to identify studies that assessed effect of different dialysis modalities on cognitive functions. Inclusion criteria for our meta-analysis were all studies that compared effect of PD to intermittent HD on cognitive function. Studies were included with reviewing the journal title, year of publication, name of the first author, country of study and the number of enrolees in the PD and HD arms and the methods of assessment of cognitive functions were reported. A fixed effects model was used for the meta-analysis. Publication bias was assessed using a Funnel plot and Galbraith plot analysis.

Results: Out of 200 abstracts reviewed, 11 papers as well as registry studies were identified for this meta-analysis with a total of 219,320 subjects included (Figure 1). Forest plot analysis for the rate of cognitive impairment in different dialysis modalities showed less cognitive impairment in PD population compared to HD patients (Relative Risk = 0.49, 95% Confidence Intervals: 0.46 - 0.52). There was no evidence of heterogeneity in the forest plot analysis (I2 = 0.00%, P = 0.58, Figure 2). Moreover, there was no evidence of publication bias among the studies included (Figure 3 and 4).

Conclusions: Patients on PD show less cognitive dysfunction compared to those on HD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**TH-PO297**

The Predictive Value of Neutrophil-to-Lymphocyte Ratio in Peritoneal Dialysis


**Background:** Neutrophil-to-lymphocyte ratio (NLR) may reflect a shift in immune response towards a pro-inflammatory pattern (i.e. high value of neutrophils) balanced with a depression of cell-mediated immunity (i.e. low values of lymphocytes). It has been used as a prognostic factor in cardiovascular and oncologic diseases. In dialysis studies are scarce. The aim of this study was to evaluate NLR as a predictor of mortality in peritoneal dialysis (PD) patients.

**Methods:** In this longitudinal study, incident PD patients with a peritoneal equilibration test (PET) between 2004 and 2018 were included. Demographic, clinical and laboratory data were collected. Univariate and multivariate Cox regression analysis were performed to determine the association of NLR with survival.

**Results:** We included 122 PD patients (55.0 ± 17.5 years, 31.1% diabetic, Charlson Comorbidity Index (CCI): 5.0±2.5) with a mean follow-up of 30.2±24.0 months. Our population was dialysed with a mean Kt/V 2.75±0.94, and the mean evaluated parameters were: nGFR 6.7±4.7 ml/min/1.73m2, prealbumin 39.3±11.3 mg/dL, neutrophils 5.6±2.5×10⁹/L, lymphocytes 1.8±2.3×10⁹/L, NLR 3.99±2.6. Using the Cox model we found that higher CCI (HR=1.650, 95% CI 1.174-2.320), higher NLR (HR=1.662, 95% CI 1.117-2.472) and lower nGFR (HR: 0.706, 95% CI 0.554-0.900) were associated with higher mortality, when adjusted for nutritional status (n.s.).

**Conclusions:** In dialysis inflamation is associated with global cause mortality. The neutrophil-to-lymphocyte ratio is a simple calculation and it predicted survival in our PD patients.

**TH-PO298**

Continuous Measurement of Intraperitoneal Volume Using Bioimpedance: Importance of Electrode Placement Sites

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**Background:** Continuous monitoring of intraperitoneal volume (IPV) may benefit peritoneal dialysis (PD) patients, e.g. by determining the peak ultrafiltration volume (UFV). The aim of this study was to optimize the placement sites of bioimpedance electrodes.

**Methods:** Six PD patients (age 61.3±7.6 years, 5 males, weight 87.3±25 kg) were studied with 2 different electrode placement sites. In group A, we used 4 and in group B 8 standard ECG electrodes (3M Red Dot Electrode; locations shown in Fig. 1A and B). Measurements were done with the patients in a sitting position and their legs placed horizontally. We used the Hydra 4200 bioimpedance device (Xitron Technologies) for continuous measurement during the PD session. The PD sessions comprised three phases: filling (diaysate volume 2 L), diaysate dwell time (4 hours), and draining. The drain volume was weighted; we assumed that 1 kg equals 1 L.

**Results:** The average drain volume was 2.3±0.3 L. 5 kHz resistance data were extracted to assess intraperitoneal fluid changes. While in group A the 3 treatment phassses were not obvious (Fig. 2A), they can be clearly discerned in group B (Fig. 2B).

**Conclusions:** These results show that electrode placement is key to successful continuous IPV measurements. In setup A (Fig. 1A), 2 resistors are in parallel and the interstitial resistance (R₂) is smaller than the peritoneal resistance (Rₚ); hence the measurement provides information only about the interstitial space. In setup B (Fig. 1B), the current travels through the peritoneal cavity so that IPV changes translate into resistance changes. If corroborated in larger studies, setup B has the potential to evolve into a future standard.

**TH-PO299**

Dietary Potassium Intake and Hypokalemia in Peritoneal Dialysis

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**Background:** Poor dietary intake might account for the high prevalence of hypokalemia in peritoneal dialysis (PD) patients in Thailand but the clinical evidence is still lacking.

**Methods:** A cross-sectional study was performed in stable prevalent PD patients at 4 PD centers in Thailand. Hypokalemia was defined as the average serum potassium level during the last 3 consecutive visits was <3.5 mEq/L, while the patients were considered normokalemic if the average serum potassium was 3.5 to 5.5 mEq/L. Patients were asked to perform 3-day dietary food record and take pre- and post-meal pictures of all foods they had taken following the provided instruction. Daily dietary nutrients including dietary potassium of all eligible patients were then estimated by a dietitian using INMUCAL-N software. Total potassium excretion was determined by 24-hour PD effluents and urine collection. Intra- and extra-cellular water status were also assessed by electrical bioimpedance assay to explore the role of intracellular potassium shift and serum potassium status.

**Results:** Among 60 consecutive eligible PD patients, 19 (31.0%) had hypokalemia. Mean dietary potassium and total calories intake were 28.6±10.3 mEq/day and 1,085.0±335.4 Kcal/day, respectively. Dietary potassium intake was significantly lower in hypokalemic patients compared to normokalemic patients (24.4±11.1 vs. 30.5±9.4 mEq/day, p=0.031). Surprisingly, total potassium excretion was significantly lower in patients with hypokalemia (28.5±8.4 vs. 36.7±11.2 mEq/day, p=0.006). There was no significant correlation between serum potassium and daily PD exchange volume, total K/Vurea, urine volume, residual glomerular filtration rate, concurrent medications (insulin, ACEI/ARB, beta blocker, and spironolactone) or intracellular water (ICW). Low dietary potassium was an independent risk factor for hypokalemia after adjustment for insulin therapy, diuretic use, and peritoneal membrane transport. The risk of hypokalemia decreased by 15% for every 10 mEq increase in daily potassium intake.

**Conclusions:** Low dietary potassium intake, rather than increased potassium excretion or intracellular shift, is the major contributing factor to hypokalemia in Thai PD patients. Dietary intervention or potassium supplement protocol should be implemented.

**Funding:** Private Foundation Support

**TH-PO300**

Dental Care Decreased the Risk of Not Only Cardiovascular Events but Peritonitis for the Patients on Peritoneal Dialysis

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**Background:** Oral disease may be increased in people with end stage renal disease (ESRD) and associated with inflammation, cardiovascular disease and mortality. We had the patients had severe gingivitis and suffered from sepsis due to oral Streptococcus Salivarius, and followed splenic abscess and peritonitis on January 2010. Hence we noticed the importance of dental care, and after Jan. 2010, we have been recommended to patients on peritoneal dialysis to have dental care, including 3 and more times tooth brushing, oral hygiene, more frequent dental visit and prophylactic antibiotics treatment before scaling or caries treatment.

**Methods:** We evaluated the difference of the incidence between two groups; peritoneal dialysis (PD) treatment from January 2000 to December 2009 (Group A), and January 2010 to May 2019 (Group B). We compared the admission rate of peritonitis, especially Streptococcus peritonitis, congestive heart failure (HF), acute coronary syndrome (ACS), cerebrovascular disease (CVD), and pneumonia. And the causes of death were also evaluated.

**Results:** The cumulative annual peritoneal dialysis patients in group A and B were 342 and 65 (mean age; 61.8 vs 65.9 years ; p < 0.01) respectively, and PD treatment were 3404 vs 6219month persony (p < 0.01). According to the cause of disease, diabetes was same, but golomerulonephritis was decreased, and nephroclerosis was increased after 2010.
The incidence of peritonitis (0.275 vs 0.179/person·year; p < 0.001), Streptococcal peritonitis (0.081 vs 0.046/person·year; p < 0.05), HF (0.159 vs 0.089/person·year; p < 0.005), ACS (0.109 vs 0.025/person·year; p < 0.001), CVD (0.060 vs 0.029/person·year; p < 0.05), Pneumonia (0.078 vs 0.041/person·year; p < 0.05) were lower in group B than in group A. Moreover, according to the cause of death, the data were the same fashion as above.

Conclusions: Dental care was beneficial for not only CVD, but also peritonitis, especially Staphylococcal peritonitis. Considering, peritonitis and CVD may provide poor QOL and mortality, dental care (3 and more times tooth brushing, oral hygiene, more frequent dental visit and prophylactic antibiotics treatment before scaling or caries treatment) is important for better QOL and treatment survival and mortality.

TH-PO301

The Value of Geriatric Nutritional Risk Index in the Prognosis of Patients with Maintenance Peritoneal Dialysis (MPD)

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Background: Geriatric Nutritional Risk Index (GNRI) has been reported related to the prognosis and medical expenses of dialysis patients, but there are few related studies about Chinese patients, especially in terms of peritoneal dialysis (PD). The aim of this study was to explore the value of the GNRI in patients with end-stage renal disease at the beginning of PD treatment.

Methods: Retrospectively analyze the medical records of patients undergoing peritoneal dialysis catheterization and starting peritoneal dialysis in the First Affiliated Hospital of Zhengzhou University from January 1, 2013 to December 30, 2018. Collect basic data and biochemical indicators of these patients in the first hospitalization for peritoneal dialysis catheterization. Follow-up these patients until March 1, 2019, and using death or turning to hemodialysis as endpoints, divide the patients into two groups according to the GNRI cutoff based on the ROC curve. Compare the clinical data and laboratory test results between the two groups, Kaplan-Meier analysis was used to observe the difference during follow-up, and the relevant factors affecting effect of peritoneal dialysis were estimated by binary logistic regression.

Results: The GNRI cut-off value was determined to be 90.5 according to the ROC curve, and the drop-out rate of GNRI≥90.5 group was significantly higher than the GNRI<90.5 group (53.9% vs 21.6%, P = 0.0031), and Kaplan-Meier survival curves showed a higher rate of peritoneal dialysis in the higher GNRI group during follow-up (P = 0.021). Logistic univariate regression showed that male, GNRI and Alb were protective factors for PD patients, and after multi-factor correction, male and GNRI were also shown to be protective factors for PD patients.

Conclusions: The baseline GNRI can be used as a prognostic indicator for peritoneal dialysis patients.

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TH-PO302

Elderly Patients in Peritoneal Dialysis: Concerns Regarding Albumin Loss

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Background: Albumin loss in peritoneal dialysis is associated with morbidity and mortality among patients on peritoneal dialysis (PD). Since elderly patients had a higher risk of protein-energy wasting, there has been a concern of further impairment of nutritional status in this population.

Methods: This is an observational prospective study that included patients >65 years (elderly group, N=18) compared to patients <65 years (younger group, N=73). Patients were followed for a median period of 21.8 months after PD initiation in a single center.

Results: Patients >65years (50% diabetic, 78% men) started PD with a residual diuresis of 1.4±0.5L, which did not differ from the young group (1.5±0.7L; p=0.778). Elderly patients had lower serum creatinine (p=0.0001), serum phosphate (p=0.010), total protein (p=0.010), and higher bicarbonate (p=0.003), denoting impaired nutritional status. Serum 25(OH)-vitamin D at PD initiation was similar between groups (p=0.705). During follow-up, there was a slightly reduction of serum albumin in young patients (from 3.76±0.5 to 3.62±0.4mg/dl, p=0.0001), which did not reach statistical significance in the elderly population (from 3.67±0.4 to 3.57±0.4mg/dl, p=0.335), with a median change overtime of 0.14 and 0.10mg/dl in young and elderly patients, respectively (p=0.834). As expected, there was a weight increase over time, although not different comparing young and elderly patients (p=0.579). In addition, loss of residual renal function, and changes in hemoglobin, serum ferritin, iron saturation, β2-microglobulin, and parathormone were similar between groups (all p>0.05).

Conclusions: Our findings suggest that there is no medical concern to avoid PD therapy in elderly patients with end-stage renal disease, at least in those who start therapy with no critical nutritional condition.

TH-PO303

Effects of Initial Hypoalbuminemia on the Longitudinal Changes of Residual Renal Function and Peritoneal Membrane in Incident Peritoneal Dialysis Patients: A Single-Center, Long-Term Follow-Up Study

Harin Rhee,1 Hyeyun Jeong,2 Miyuceu Han,1 Il Young Kim,2 Sang Heon Song,1 Eun Young Seong,1 Dong Won Lee,1 Soo Bong Lee,1 1Pusan National University Hospital, Busan, Republic of Korea; 2Pusan National University Yangsan Hospital, Yangsan, Republic of Korea.

Background: Hypoalbuminemia was reported closely associated with increased patients’ mortality and technical failure rate in PD patients. However, there were little studies that compared longitudinal changes of residual renal function or peritoneal membrane function according to the serum albumin level.

Methods: We retrospectively included patients who started PD between January 2010 and December 2015. We divided patients into two groups according to the initial serum albumin level. Hypoalbuminemia was defined as the serum albumin level lower than 3.5 g/dl. To compare longitudinal changes of residual renal function and peritoneal membrane status between two groups, we repeatedly collected data for urine output, uKt/V, peritoneal ultrafiltration, pKt/V, 4hr DPcr ratio per 1 year. We also checked technical failure rate and all-cause mortality rate of them.

Results: A total of 153 patients were included and 36.6% of them had hypoalbuminemia. During the median follow up period of 42.5 months, 9.8% of the patients were dead, 30.3% of the patients received kidney transplantation and the other 30.3% of the patients changed modality to hemodialysis. All-cause mortality rate was significantly higher in the hypoalbuminemia group (log rank 0.001). In both groups, residual renal function showed decreasing trend, peritoneal UF and pKt/V showed increasing trend and their changing rates were more rapid in hypoalbuminemia group (Figure 1).

Conclusions: Initial hypoalbuminemia was associated with rapid decline of residual renal function and increased all-cause mortality rate in incident PD patients. Thus, patients with hypoalbuminemia needed to be closely monitored.

TH-PO304

The Associations of Serum Uric Acid and All-Cause Mortality in Peritoneal Dialysis Patients

Shanfang Ou. The first affiliated hospital of xiamen university, Xiamen, China.

Background: The relationship between serum uric acid and prognosis in diabetic peritoneal dialysis (PD) patients is unclear. This study was investigate whether baseline uric acid (UA) is an independent predictor of all-cause mortality in chronic renal failure patients (CRF) with peritoneal dialysis (PD).

Methods: A retrospective cohort study was designed. A total of 140 patients unstable continuous ambulatory peritoneal dialysis (CAPD) treatment for more than 3 months
were collected and follow up at First affiliated hospital of Xi'an University Peritoneal Dialysis Center from January 1, 2001 to the December 31st, 2017. All demographic and laboratory data were recorded at baseline. The subjects were divided into three groups based on the tertile of UA val(UA1:UA<387umol/L,UA2:UA387~519umol/L,UA3:UA>519umol/L).Multivariate Cox regression and Kaplan-Meier method was used to calculate the hazard ratio (HR) of all-cause mortality.

Results: A total of 140 CAPD patients were enrolled in this study, including 63 cases of male (45%),77 cases of female (55%). The average age was 57 (range: 46-65) years. The median follow-up time was 31.9 (IQR:19.6,66.6) months. The average UA of all participants was 450.1±14.1 umol/L. No significant differences of baseline parameters between patients with age, sex ratio, body mass index, duration of dialysis, proportion of patients with hypertension, diabetes mellitus and cardiovascular diseases. Compared to M1 group, the levels of serum creatinine, urea nitrogen, blood phosphorus and blood potassium were higher (P < 0.05). The Cox regression analysis suggested a positive correlation between all-cause mortality and baseline uric acid (UA HR=1.04,95%CI:1.00-1.09, P=0.048).Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048). Multivariate Cox regression analysis showed that increased baseline UA was an independent risk factor for all-cause mortality in PD patients (HR=1.04, 95%CI: 1.00-1.08, P=0.048).

Conclusions: UA was positively correlated with all-cause mortality in patients undergoing maintenance peritoneal dialysis. The increase of baseline UA level is an independent risk factor for all-cause mortality in those patients. The control of UA level may be helpful to prolong the survival time of patients with Peritoneal Dialysis.

Funding: Clinical Revenue Support

**TH-PO305**

**Prognostic Role of Platelet-to-Lymphocyte Ratio in Peritoneal Dialysis**


**Background:** Platelet-to-lymphocyte ratio (PLR) has been introduced as useful inflammatory marker to predict the outcome for a wide spectrum of diseases such as malignancies and cardiovascular pathologies. Since platelets are active players in inflammatory response, both thrombocytosis and high PLR are probably part of the same pathophysiological process. In dialysis studies are scarce. The aim of this study was to evaluate PLR as a predictor of mortality in peritoneal dialysis (PD) patients.

**Methods:** In this longitudinal study, incident PD patients with a peritoneal equilibration test (PET) between 2004 and 2018 were included. Demographic, clinical and laboratory data were collected. Univariate and multivariate Cox regression analysis were performed to determine the association of PLR with survival.

**Results:** We included 122 PD patients (55.0 ± 17.5 years, 31.1% diabetic, Charlson Comorbidity Index (CCI): 5.0±2.5) with a mean follow-up of 30.2±24.0 months. Our population was dialysed with a mean Kt/V 6.7±4.7 mJ/m²min, 1.7±2mLHCO3 in 39.3±11.3 mg/dL, platelet 269±686±3.10^9/L, lymphocytes 1.8±2±10^9/L, higher PLR (HR=1.010, 95%CI 1.004±1.015) and lower nGFR (HR=0.675, 95%CI 0.513-0.883) were associated with higher mortality, when adjusted for nutritional status (n.s.).

**Conclusions:** Inflammation is a known risk factor for global cause mortality in dialysis. In this study platelet-to-lymphocyte ratio, which is quite simple and cheap method, was validated as an inflammatory marker in PD patients.

**TH-PO306**

**Impact of Residual Renal Function (RRF) on Phosphate Clearance (PhCl) in Peritoneal Dialysis (PD)**

Smith J, Anam,1 Enrica Fung,1 Seyed-ali Sadjadi,1 Nephrology, Jerry L Pettis VA Medical Center, Loma Linda, CA; 2Nephrology, Loma Linda University Medical Center, Loma Linda, CA.

**Background:** Hyperphosphatemia is common in ESRD & is independently associated with increased risk of death among dialysis patients. In PD, the relationship between PhCl & D/P PO4 is stronger than with D/P Cr (R=0.53 vs 0.36), although in multivariate analysis the relationship between PhCl & D/P PO4 was adequate for PD treatment (Table 1). There was stronger correlation between PhCl & D/P PO4 than with D/P Cr (R=0.53 vs 0.36), although in multivariate analysis the relationship between PhCl & D/P PO4 was not statistically significant (P < 0.05).

**Methods:** A total of 140 CAPD patients were enrolled in this study, including 63 cases of male (45%),77 cases of female (55%). The average age was 57 (range: 44-65) years. Our population was dialysed with a mean Kt/V 2.75±0.94, and the mean evaluated nGFR 6.7±2.5) with a mean follow-up of 30.2±24.0 months.

**Results:** Overall prevalence of hyperphosphatemia (PO4 > 5.5mg/dl) between D/P PO4 and PhCl was not statistically significant (P=0.6). There was stronger correlation between PhCl & D/P PO4 than with D/P Cr (R=0.53 vs 0.36), although in multivariate analysis the relationship between PhCl & D/P PO4 was not statistically significant (P=0.6).

**Conclusions:** There was stronger correlation between PhCl & D/P PO4 than with D/P Cr (R=0.53 vs 0.36), although in multivariate analysis the relationship between PhCl & D/P PO4 was not statistically significant (P=0.6).

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underlines represents presenting author.**
Impact of Peritonitis on Patients’ Quality of Life and Symptom Burden

Erwin Yap,1 Shuchita Sharma,2 Osama El Shamy,3 Alan D. Weinberg,2 Jaime Ubirbari,2 Subodh J. Saggi.1 SUNY Downstate Medical Center, New York, NY; 2Icahn School of Medicine at Mount Sinai, New York, NY

Background: Peritonitis is a frequent complication in the management of peritoneal dialysis (PD) patients and is associated with increased hospitalization, mortality, and the cost of care. It is also a significant cause of PD discontinuation. We conducted this study to determine the impact of peritonitis on the QoL and symptomatic burden of PD patients.

Methods: This was a cross-sectional study that enrolled adult PD patients who experienced at least one episode of peritonitis in the prior 12 months. The validated PDQ-36 and the PHQ-9 were administered by telephone interview to patients. Results were compared with normative data. The study was approved by the Institutional Review Board.

Results: The study included 1801 PD patients. The mean age of the study population was 60 ± 14 years, 55% were male, 45% were black, and 43% were Hispanic. The median peritonitis rate for 2015 was 0.8 per patient-year, and 0.20 per patient-year in 2016. The mean technique survival for the overall study period was 331 days in period 1 vs 399 days in period 2 (p < 0.0001).

Conclusions: The use of CQI has proven to be an effective tool to reduce peritonitis in Dominican Republic PD program and improve technical and patient survival.

Funding: Commercial Support - Macrotech, Baxter

TH-PO313
Regionalization of Peritoneal Dialysis Services in an Era of Health Reform, 2006-2013
Abby Hoffman,3 Caroline E. Sloan,2 Matthew L. Maciejewski,2 Cynthia Coffman,2 Linda L. Sanders,3 Richard A. Hirth,2 Shou-Yih D. Lee,3 Virginia Wang,2 1Department of Population Health Sci, Duke University, Durham, NC; 2HSRD, Durham VAHCS, Durham, NC; 3University of Michigan Ann Arbor, MT; 4Duke University Medical Center, Durham, NC; 5Div of General Internal Med, Duke University, Durham, NC

Background: Over the last 15 years, Medicare has adjusted payment policy to promote peritoneal dialysis (PD) programs and use. Nationally, PD provision has grown modestly despite notable growth in patient PD use. A potential explanation underlying this trend is possible regionalization of PD services among dialysis chains. Regionalization may improve facility finances while maintaining patient access because: (1) consolidation increases economies of scale and (2) PD requires minimal travel and impacts from regionalization of services. This study is the first to empirically assess the extent of PD program regionalization among dialysis chains.

Methods: We conducted a retrospective cohort study of non-federal US outpatient dialysis chains 2005-2013 with data from the US Renal Data System and Medicare Provider of Service files. Two outcomes were observed at the chain-hospital referral region level in 3-year time periods 2005-2013: (1) PD regionalization – decrease in PD facilities without decreasing PD patients; (2) expansion – increase in PD facilities without increasing PD patients. Generalized estimating equations with a logit link identified correlates of PD regionalization and expansion adjusting for chain and market characteristics.

Results: During the study, there were 2,799 market-chains; 49% large dialysis organizations ([LDOs] DaVita or Fresenius). We observed PD regionalization 103 market-chains (19.8%) and expansion in 728. Regionalization increased from 29 market-chains in 2005-2007 to 44 in 2011-2013. Expansion also increased from 175 market-chains to 293. In adjusted expansion increased over time (odds ratio [OR] 1.33; 95% confidence interval [CI] 1.18-1.49). Overall, LDOs had higher odds of regionalization (OR 3.92; CI 3.59-6.42) and expansion (OR 1.79; CI 1.48-2.17).

Conclusions: We provide preliminary evidence that early chains are expanding PD services and that LDOs are more likely to regionalize PD services. Dialysis chains have not regionalized PD services in response to reforms 2005-2013; but continued monitoring of PD care patterns will inform long-term effects of dialysis payment reform on dialysis industry service strategies and identify important implications for patients.

Funding: NIDDK Support

TH-PO314
The Feasibility of Using Computerized Adaptive Testing (CAT) to Assess PD Patients’ Quality of Life and Symptom Burden
Frederic O. Finkelstein, Yale University, New Haven, CT

Background: Dialysis pts complain of myriad symptoms that negatively impact on their HRQOL and are often not appreciated by health care providers (HCP). How best to document these symptoms and their impact on pts and then incorporate the information into rx plans is challenging. Recent work has suggested that using CAT could provide a useful way for HCP to better understand difficulties experienced by pts.

Methods: This study was undertaken as a feasibility study. 20 questions, incorporating common symptoms reported by ESRD pts, were incorporated into a CAT program developed by the authors and Owl Insights. Questions dealing with pain, depression, and anxiety were expanded to the PHQ2 if PHQ2 scores were ≥3 if pts reported problems with these domains. The CAT program with domains expanded to the PHQ9 if PHQ2 scores were ≥3. If pts reported problems with anxiety, then the Generalized Anxiety Disorder (GAD7) questionnaire was administered. PHQ2 which expanded to the PHQ9 if PHQ2 scores were ≥3. If pts reported problems with anxiety, then the Generalized Anxiety Disorder (GAD7) questionnaire was administered. PHQ2 which expanded to the PHQ9 if PHQ2 scores were ≥3. If pts reported problems with anxiety, then the Generalized Anxiety Disorder (GAD7) questionnaire was administered.

Results: Among All 48 English-speaking pts in our inner-city PD program were asked to complete the questionnaires 7 months. The mean ±SD age was 60 ±14. 55% were male, 43% AA, 33% white, 20% Hispanic, 5% Asian. 92% completed the initial questionnaire; 86% completing this questionnaire completed the 2nd. The mean time to complete the questionnaire was 11 ±2 mins. Pts were asked for assistance with scale and (2) 23 pts (58%) had no difficulty with the PHQ2, 17 scored ≥3. Pts with PHQ2 scores ≥3 completed the PHQ9. 50% reported significant sleep problems and completed the sleep questionnaire. 30% were troubled by anxiety and completed the GAD7. Other problems frequently reported included fatigue, loss of energy, pain, and pruritus. HCPs (4 nurses, 2 dieticians, 7 MDs, 1, 2, 3 MDs uniformly

Conclusions: We provide preliminary evidence that early chains are expanding PD services and that LDOs are more likely to regionalize PD services. Dialysis chains have not regionalized PD services in response to reforms 2005-2013; but continued monitoring of PD care patterns will inform long-term effects of dialysis payment reform on dialysis industry service strategies and identify important implications for patients.

Funding: NIDDK Support
Peritoneal Dialysis: CVD, Fluid, Nutrition  Poster/Thursday

TH-PO314
Implementing the PD Easy Application in Mobile Phones, Enhancing Self-Management and Communications: Pilot Study
Piyattida Chaopreesaman, Medicine, Banphacho-Charoenkrung PD Center, Bangkok, Thailand.

Background: Since implementing Thai PD First Policy, we now take care 880 patients, biggest center in Thailand. Our center developed many retraining styles to capture our patient’s diversity. Now, we develop our own mobile phone application, called PDeasy. The objective is to monitor, communicate, self-educate and promote self-management. We try with first 52 volunteer patients, exploring the barriers to implement the application.

Methods: The education level and the past experiences using any other IT device, were collected. The duration before using this fluently, problems and usefulness of this application were asked. We also compared baseline and 6-month self-management score by Wilcoxon signed rank test.

Results: There were 41 patients who completed the questionnaire. The average age is 54 (min 23, max 74). The percentage of patients who use the application by themselves is 61% and 39% by their caregivers. Education level, less than 6 years, is 47%. Past experiences of using IT device is 88%. The duration to learn to use this application fluently, less than 3 days, is 83% and most can use it immediately. The self-management score comparing baseline and 6-month, is not different, as shown. 92% of the users give good satisfaction and the most useful part are the self-education and the warning system.

Conclusions: Our mobile phone PDeasy application, is user-friendly and helpful in terms of promoting self-care.

Self-Management score

<table>
<thead>
<tr>
<th>Score</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exchange frequency</td>
<td>0.06, 0.14, 0.96, 0.12</td>
</tr>
<tr>
<td>Salt and water balance</td>
<td>0.12, 0.13, 0.01, 0.11</td>
</tr>
<tr>
<td>Patient adherence</td>
<td>0.16, 0.10</td>
</tr>
<tr>
<td>Self-assessment</td>
<td>0.13, 0.12, 0.09</td>
</tr>
<tr>
<td>Management of complication</td>
<td>0.10, 0.08</td>
</tr>
<tr>
<td>Total</td>
<td>0.09, 0.08</td>
</tr>
</tbody>
</table>

TH-PO315
Mario Rojas-Diaz.1,2 Victor A. Mercado,1 Abril E. Cisneros,1 Alfonso Ramos,2 Sergio O. Hernandez-Ordonez.2 SEDESA, Mexico, City, Mexico; Baxter Mexico, San Andres Occatan, Mexico; Hospital Dr Belisario Dominguez SEDESA, Mexico, Mexico.

Background: The recent introduction of a two-way Remote Patient Monitoring (RPM) for the management of Automated Peritoneal Dialysis (APD) patient has made it possible to assess patient’s adherence to the therapy, as well as dialysis treatment-related complications. This system was introduced in this hospital 2 years ago. The purpose of the study is to assess the impact on the adherence and lost treatment times after the implementation of protocols using the signals provided by the RPM system.

Methods: This is a retrospective study in a cohort of patients receiving APD. 183 patients in the APD program of the Hospital Belisario Dominguez under remote monitoring were included. On the basis of the messages provided by the system, a program was developed in order to prioritize patient care and interventions according to the type and number of flags shown; then, signals were categorized into treatment-related signals and system-related signals. Based on this, protocols of care and management strategies were established, and change in the number medium priority signals (MPS) and High priority signals (HPS), impact on lost treatment times and adherence to treatment were assessed.

Results: Signals from 203 patients provided by the RPM program throughout one week were assessed and dedicated protocols were implemented afterwards. Patients were reassessed 6 months after the implementation of the protocols. Patients without MPS improve 20% (p=0.001) and patients with more than 6 MPS reduce 67% (0.0001). Patient without HPS signals improve 36% (p=0.0001) and patients with more than 6HPS decrease 73% (p<0.0001). Patients with not loss of treatment time increase 6% and patients with more than 300 minutes lost reduce 20% (p=0.0004), adherence improve 29% (0.001)

Conclusions: Remote monitoring makes it possible to differentiate treatment-related complications and to establish specific processes of care, allowing for more effective treatment times and enhanced patient’s adherence to his/her treatment.

TH-PO316
Factors Associated with Discordance in Initial ESKD Treatment Decision and Eventual Dialysis Modality
Adrian Liew, Tan Tock Seng Hospital, Singapore, Singapore.

Background: Pre-Dialysis counselling (DC) prepares patients with ESKD for renal replacement therapy (RRT). However, the eventual RRT modality may differ from the initial decision made at DC, making a prepared start on dialysis challenging. We study the distribution of treatment decisions made after DC and factors associated with a change in the eventual RRT modality at initiation.

Methods: This prospective cohort study included patients who underwent DC from APR 2010 to DEC 2015, and followed till 30 APR 2019 for their eventual RRT modality. All data were collected prospectively, with the study population grouped according to the initial treatment decision and stratified by eventual RRT modality (Table 1). Multivariate logistic regression was performed, examining factors that influence discordance in treatment decision and eventual modality. Variables were included in the model if univariate analysis has p-value<0.20.

Results: 1644 patients (63.3±31.1 years, 57% males, 77% DM) were included in the study, after excluding 47 without any decision and 42 who had not initiated RRT. HD (65.6%) was the most common choice of RRT after DC, while patients who chose PD were less likely to be actualized on their chosen therapy (PD 50.4%, HD 96.9%; p<0.001).

Patients who chose PD were also more likely to die before needing RRT (PD 12.3%, HD 3.0%; p<0.001). Multivariate analysis showed that failure to actualize the decision for PD was associated with factors that suggested greater frailty or potential challenges to PD (Table 2).

Conclusions: Patients who chose PD were less likely to receive this RRT modality. These patients were older and frail, with a high proportion who died before requiring RRT. Difficulties with PD such as obesity, poor diabetic control and lack of home storage space for PD solutions may also influence a subsequent switch to HD.

Table 1: Distribution of Initial Treatment Decision and Eventual RRT Modality

<table>
<thead>
<tr>
<th>Initial RRT Decision</th>
<th>Death</th>
<th>WO DF</th>
<th>PD</th>
<th>PA</th>
<th>Transparent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO DF</td>
<td>32</td>
<td>0.045</td>
<td>0.054</td>
<td>0</td>
<td>0.012</td>
<td>0.012</td>
</tr>
<tr>
<td>PD</td>
<td>196</td>
<td>0.645</td>
<td>0.235</td>
<td>0.021</td>
<td>0.005</td>
<td>0.309</td>
</tr>
</tbody>
</table>

Table 2: Adjusted Factors Associated with Non-Actualization of PD when made as Initial Treatment Decision

<table>
<thead>
<tr>
<th>Associated with PD</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.004</td>
<td>1.001</td>
<td>0.001</td>
</tr>
<tr>
<td>AD, Assistance</td>
<td>0.586</td>
<td>0.494</td>
<td>0.702</td>
</tr>
<tr>
<td>Charlson Score</td>
<td>1.034</td>
<td>0.994</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.010</td>
<td>0.986</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>1.001</td>
<td>0.971</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.004</td>
<td>0.980</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.004</td>
<td>0.984</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
TH-PO318

Standardized Outcomes in Nephrology-Peritoneal Dialysis (SONG-PD) Consensus Workshop with Patients, Caregivers, and Health Professionals to Establish a Core Outcome Set for Trials in PD

Karina E. Manera,1,2 Allison Tong,1,2 Jonathan C. Craig,1 Jenny I. Shen,4 Yeong Jee Cho,5,6 David W. Johnson.1,3 The University of Sydney, Westmead, NSW, Australia; 2Centre for Kidney Research, The Children’s Hospital at Westmead, NSW, Australia; 3Flinders University, Adelaide, SA, Australia; 4LaBiomed at Harbor-UCLA, Torrance, CA; 5Princess Alexandra Institute, Bucharest, Romania; 6Nephrology Department, Fundeni Clinical Hospital, Bucharest, Romania; 7University of Queensland, Brisbane, QLD, Australia.

Background: Outcomes reported in peritoneal dialysis (PD) trials are very diverse, measured inconsistently and may not be important to patients, families and clinicians. We aimed to establish a core outcome set based on the shared priorities of all stakeholders to improve the consistency and relevance of outcomes to patients and healthcare providers to inform decision-making.

Methods: We convened an international Standardized Outcomes in Nephrology-Peritoneal Dialysis stakeholder consensus workshop in May 2018 in Vancouver, Canada. In facilitated breakout groups, participants discussed the development and implementation of core outcomes for trials in PD.

Results: Nineteen patients/caregivers and 51 health professionals attended the workshop. Participants confirmed that "life participation" was a main goal of PD, which reflected the need for flexibility and freedom. Participants regarded life participation to be as important as key clinical outcomes (such as cardiovascular disease, infection or mortality) for indicating treatment success. Severity and immediacy of symptoms encompassed the debilitating impact of symptoms such as fatigue, which was identified as a key contributing factor to reduced life participation. Empowered for preparation and planning was a crucial area of interest for patients who preferred the freedom of PD, enabling them to be mentally and physically equipped to deal with potential PD failure. Demarcating distinct outcomes for clarity was suggested as participants recognized the conceptual overlap among outcomes, such as membrane function and PD failure. Participants also discussed the importance of ensuring that the core outcome set be measurable and feasible for implementation, including the need for simplified, standardized and validated measures, particularly for life participation.

Conclusions: Patients, caregivers and health professionals supported the inclusion of life participation, mortality, cardiovascular disease, PD-failure and the patient-reported outcome of life participation as core outcome domains for PD. Recommendations from this workshop will be integrated into the establishment of a core outcome set for use in trials and other research to ensure that research evidence can better inform decision-making.

TH-PO319

Can Cardiovascular Risk Score Calculators Be Used for Nondiabetic Peritoneal Dialysis Patients?

Arundeep G. Prapatap,1,3 Bogdan Obricsca,1 Bogdan M. Sorohan,1,3 Gabriela Lupusor,1 Danut Andronesci,1 Mirea Lupusor,1 Genar Inmaili,1 1"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; 2General Surgery and Liver Transplantation Department, Fundeni Clinical Institute, Bucharest, Romania; 3Nephrology Department, Fundeni Clinical Institute, Bucharest, Romania.

Background: Cardiovascular diseases carries a significant burden upon peritoneal dialysis (PD) patients. Despite overwhelming data regarding the usefulness of cardiovascular risk score calculators in the general population, only very few studies addressed this issue for PD.

Methods: We performed a prospective study. Three risk score calculators were evaluated at inclusion in the study: SCORE chart, Framingham and simplified Framingham risk score calculators. We excluded diabetic patients since they are already at increased cardiovascular risk. Finally, cardiac history, PD-failure and the patient-reported outcome of life participation as core outcome domains for PD. Recommendations from this workshop will be integrated into the establishment of a core outcome set for use in trials and other research to ensure that research evidence can better inform decision-making.

Results: We included 246 non-diabetic patients (118F, mean age 56.3 ± 15.7 years in stable PD for at least 6 months. Mean follow up time was 6.2 years. All the three risk scores were significantly higher in patients with renal hypertensive disease, compared to patients with glomerulonephritis, tubular interstitial diseases and other end stage renal disease etiologies (Table 1). The two Framingham risk scores were also significantly higher in patients with subclinical atherosclerosis as appreciated by an intima-media thickness (IMT) >0.9 mm at carotid ultrasound and the best predictive value for an IMT >0.9 mm was obtained by Framingham risk score (Tables 2 and 3). The best predictive value for developing acute coronary syndrome (ACS), heart failure (HF) and cardiovascular death (CvD) during the follow up period was obtained by Framingham risk score (AUC 0.887 for ACS, 0.731 for HF, and 0.809 for CvD), and by simplified Framingham risk score for ischemic stroke (AUC 0.883).

Conclusions: Risk score calculators, especially the Framingham one, may be useful for non-diabetic PD patients to both predict subclinical atherosclerosis and established cardiovascular disease and thus improve patients' management. Our results need to be validated in larger multi-center studies.

TH-PO320

Mouse Model of Venous Stenosis

Salvatore DiBartolo, Mehmet M. Altintas, Beata Samelko, Monnie Wasse. Rush University Medical Center, Chicago, IL.

Background: A response of the vein wall to balloon angioplasty results in post-angioplasty restenosis (PARS). PARS impedes normal blood flow leading to a spectrum of complications and morbidity that exacerbates the outcome of peritoneal dialysis patients, and remains a limiting factor for successful vascular intervention. Previous studies have indicated that mice of different inbred backgrounds have differences in arterial remodeling response, however, we have not assessed the venous remodelling response.

Methods: To objectively evaluate the influence of uremia on venous remodeling, we utilized a CKD mouse model and developed a surgical technique that mimics the vascular damage of angioplasty. We recapitulated renal failure by inducing chronic renal function insufficiency via partial nephrectomy (2/3-nephrectomy) model with a high protein diet, and measured restenosis via histology of the extrarenal jugular vein. To provide the basis for a genetic analysis of venous remodelling, we subjected 3 different inbred strains of mice; chosen based on their remodeling response to arterial injury (C57BL6, FVB, and SJL/J), to EJV wire injury to evaluate the cellular response involved in venous remodeling influenced by uremia.

Results: We developed a model that mimics venous stenosis in mice. Our model was validated via assessing vascular composition by immunological and histological staining and geometrical analysis (i.e., the evaluation of the lumen, intimal and medial area) by microscopy of the injured vein.

Conclusions: Our model helps us elucidate and further understand the pathophysiology of venous remodeling that occurs in hemodialysis vascular access dysfunction.

Funding: NIDDK Support

TH-PO321

Uremia Induces Functional and Histological Changes in a Mouse Model of Arteriovenous Fistula (AVF) Stenosis

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Background: Arteriovenous Fistula (AVF) stenosis is responsible for a very significant morbidity, mortality and economic cost. Despite the magnitude of the clinical problem there are currently no effective therapies for AVF stenosis. The focus of this project was therefore to identify uremia specific functional and histological differences in AVF stenosis in a mouse model.

Methods: Mice were made uremic through the removal of the upper and lower poles of one kidney followed by a nephrectomy of the contralateral kidney. AVFs were created through an end (vein) to side (artery) anastomosis using standard technical techniques. Functional parameters included flow mediated dilation (FMD) and the area enclosed within the normal arterial remodelling response, however have not assessed the venous remodeling response.
Effect of Endothelial Nitric Oxide Synthase on Geometrical Parameters of Murine Arteriovenous Fistulas

Isabelle D. Falzon,1 Yan-Ting Shiu,1 Daniel Pike,1 Hannah M. Northrup,1 Maheshika S. Somarathna,2 Lingling Guo,2 Timmy C. Lee,3 University of Utah, Salt Lake City, UT; 4VASLCHCS, Salt Lake City, UT; 5University of Alabama at Birmingham, Birmingham, AL; 6Veterans Affairs Medical Center, Birmingham, AL.

Background: Arteriovenous fistula (AVF) maturation failure is a significant clinical issue. Endothelial nitric oxide synthase (NOS3) leads to the production of nitric oxide, a vasodilator, which contributes to successful AVF maturation in mice. Previous small clinical studies have reported the association between the AVF geometrical parameters and AVF maturation. Here we investigated the effect of NOS3 on AVF geometry in mice.

Methods: Carotid-jugular AVFs were created in NOS3 over expression (OE) and NOS3 knock out (KO) mice on C57BL/6 background, with C57BL/6 mice as wild type (WT) control (n=1 per strain). Black-blood MR images were taken at Day 7 and Day 21 post AVF creation and used to reconstruct AVF lumen geometries. Geometrical analysis (Fig. 1A) quantified the anastomosis angle (AA), nonplanarity angle magnitude (NA) and tortuosity of the AVF vein.

Results: The AVF lumen area was bigger in the NOS3 OE mice than in NOS3 KO and WT mice. Lumen reconstructions are shown in Fig. 1B. Overexpression of NOS3 led to a reduced AA and NA by 16° and 10°, respectively, from Day 7 to Day 21, indicating that the AVF vein remodeled to align more parallel with and on the same plain of the feeding artery. In contrast, NOS3 KO increased AA by 14° and decreased NA by 0.3° from Day 7 to Day 21. WT increased AA and NA by 17° and 5°, respectively, from Day 7 to Day 21. While OE and KO decreased in tortuosity by 0.15 and 0.14, respectively, WT increased tortuosity by 0.08 from Day 7 to Day 21.

Conclusions: Geometrical parameters differ with varying NOS3 expression and over time. More research is needed to understand how these geometrical parameters affect AVF maturation and the mechanisms leading to geometrical changes.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

Activation of Formyl Peptide Receptor 1 Causes Arteriovenous Fistula Failure in Rats

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Background: Formyl peptide receptor 1 (FPR1) is a recognition receptor for damage-associated molecular patterns. It is best known for mediating myeloid cell chemotaxis and activation of neutrophils containing formylated peptides. However, it can also recognize mitochondria-derived proteins from apoptotic/necrotic cells due to the evolutionary origins of mitochondria. In a recent transcriptomics analysis of human arteriovenous fistulas (AVFs) that matured or failed after creation, higher expression of FPR1 in the native vein was associated with non-maturation. Immunohistochemistry analyses demonstrated that FPR1 was expressed in smooth muscle cells (SMCs) in the media, where it possibly sensed apoptotic/necrotic cells as a result of vascular trauma after AVF creation. In this study, we tested the effects of FPR1 activation in the maturation of experimental fistulas. We hypothesized that activation of FPR1 at the time of AVF creation would increase the frequency of fistula failure.

Methods: AVFs were created in Sprague Dawley rats (n=16) by anastomosing the superficial epigastric vein to the common femoral artery. Twenty nanograms

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
(20 ng) of the FPR1 agonist imlrefl were applied perivascularly to eight AVFs in 200 μL of Matrigel plus vehicle (control group). AVFs were harvested at 21 days after creation.

Results: Five out of eight AVFs (62.5%) failed to mature in the IMLE-treated subgroup, compared to one out of eight (12.5%) in control animals. Blood flow decreased from 14.26 ± 5.40 mL/min in control AVFs to 0.0 [0.0-6.6] mL/min in IMLE-treated fistulas (P=0.018). Venous distensibility was also significantly lower in the latter than in control AVFs, both in the juxta-anastomotic area and in the distal fistula (P=0.05).

Conclusions: Together with the human transcriptomics data, these results suggest that FPR1 activation is implicated in AVF maturation failure.

TH-PO325
Decreased Jagged1 Expression in Vascular Smooth Muscle Cells Delays Maturation of Arteriovenous Graft

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Background: It is well-known that endothelial dysfunction promotes activation of vascular smooth muscle cell (VSMC). Whether decreased accumulation of VSMCs affects endothelial regeneration and functions in arteriovenous graft (AVG) remodeling has not been studied. We plan to identify mechanisms by which the Notch ligand, Jagged1, in VSMCs regulates EC functions in AVGs.

Methods: AVGs were created in transgenic mice bearing VSMC-specific knockout (KO) or overexpression of Jagged1. VSMC migration, EC regeneration and its barrier functions as well as AVG remodeling were evaluated.

Results: Jagged1 expression was induced in VSMCs of neointima in the AVGs. Jagged1 KO in VSMCs inhibited the accumulation of extracellular matrix as well as VSMC migration. Fewer α-SMA-positive VSMCs were found in AVGs created in Jagged1 KO mice vs. results in WT mice. Decreased VSMCs in AVGs were associated with deteriorated the EC functions. In AVGs created in transgenic mice bearing Jagged1 KO in VSMCs exhibited delayed EC regeneration and impaired EC barrier function. Jagged1 KO deficiency in VSMCs increased the inflammatory cell infiltration and dysregulation of AVG arterialization. In contrast, AVGs created in mice with overexpression of Jagged1 in VSMCs exhibited improved EC regeneration plus decreased macrophage infiltration. This led to AVG remodeling and arterialization. In co-cultures of ECs and VSMCs, Jagged1 deficiency in VSMCs suppressed N-cadherin and integrin β3 expression in ECs. Inhibition of integrin β3 activation delayed EC spreading and migration. Notably, Jagged1 overexpression in VSMCs stimulated the expression of N-cadherin and integrin β3 in ECs. Jagged1-induced responses were blocked by inhibition of Notch signaling.

Conclusions: Our results demonstrate that Jagged1 expression in VSMCs maintains EC barrier functions and blocks infiltration of macrophages. These responses promote remodeling and arterialization of AVGs.

Funding: NIDDK Support

TH-PO326
p-Cresyl Sulfate Induced Oxidative Stress and Inflammation on Endothelial and Vascular Smooth Muscle Cells

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Background: Vascular access dysfunction affects negatively patient morbidity and mortality. The most common problem in AVF and AVG is venous stenosis, resulting from a neointimal hyperplasia development. Recent study reported that p-Cresyl sulfate (p-CS), poorly removed by conventional dialysis, has been known to exhibit pro-oxidant property in human vascular toxicity induced by p-CS was poorly understood. The aim of the study was to determine whether p-CS enhances the production of ROS in vascular endothelial cell and proliferation of smooth muscle cell resulting in neointimal hyperplasia. Additionally, we aimed to determine whether p-CS induces the expression of ICAM-1 and MCP-1 by ROS induced activation of NF-κB in endothelial cell.

Methods: Aortic smooth muscle cells (SMCs) were treated with p-CS (10-1000 μmol/L), and aortic SMC proliferation was measured Bromodeoxyuridine cell proliferation assay. Western blot analysis was done for ERK/1,2 and p38 MAPK. Human umbilical vein endothelial cells (HUVEC) were also treated with p-CS (1000 μmol/L). The productions of NF-κB, ICAM-1, MCP-1 and eNOS in HUVEC were assessed using RT-PCR and ELISA.

Results: p-CS stimulated the proliferation of aortic SMCs in a dose dependent manner, and promoted the phosphorylation of ERK/1,2 and p38 MAPK. In HUVEC, p-CS, p-cresyl sulfate induces ROS production by enhancing NAD(P)H oxidase and upregulates the expression of ICAM-1 and MCP-1 by ROS-induced activation of NF-κB. However, NO synthase seemed not to be involved in p-cresyl sulfate induced oxidative stress in HUVEC.

Conclusions: Our data confirmed that p-CS was attributed to vascular SMC proliferation and inflammation and oxidative stress in HUVECs in vitro. Further evaluation will be needed to clarify the role of p-CS in vascular access stenosis and neointimal hyperplasia.

TH-PO327
Human Arteriovenous Fistula Wall Thickness in the First 6 Months After Creation

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Background: Previous studies of the arteriovenous fistula (AVF) maturation process have focused almost exclusively on enlargement of the AVF lumen to allow increases in AVF blood flow. There is a lack of information regarding AVF wall thickness. Here we assess the change in AVF wall thickness, in conjunction with AVF lumen area, during the first 6 months after creation. We hypothesize that during AVF development, the wall thickens in response to lumen enlargement to maintain the structural strength and integrity of the wall.

Methods: Non-contact black-magnetic resonance imaging (MRI) scans were performed on newly-created AVFs at 3 post-operative time points (1-3 days, 6 weeks and 6 months) in 10 ESRD patients at the University of Utah Hospital. MRI images were used to reconstruct 3D geometries of the AVF veins, from which the lumen area and wall thickness were calculated for the cross sections perpendicular to the lumen centerline at 1 mm intervals for 20 mm along the AVF length starting from the anastomosis.

Results: Fig. 1A-B shows the lumen area and wall thickness of each AVF at 3 sequential MRI scans. The lumen area increased from 14.26 ± 5.40 mm² at 1-3 days to 21.9 ± 8.79 mm² at 6 weeks to 30.62 ± 12.78 mm² at 6 months (P=0.0005 by ANOVA for 3 time points), while the wall thickness increased from 0.76 ± 0.09 mm at 1-3 days to 1.05 ± 0.23 mm at 6 weeks to 1.21 ± 0.18 mm at 6 months (P=0.0001 by ANOVA for 3 time points). During this 6-month period, the lumen area change was positively associated with the wall thickness change (P=0.0369) (Fig. 1C).

Conclusions: In ESRD patients, AVF wall thickened as their AVF lumen area enlarged. More rigorous validation of this observation using a larger cohort is necessary.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO328
Secondary Hyperparathyroidism Stimulates Neointimal Hyperplasia of Arteriovenous Fistula in Mice

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Background: Arteriovenous fistula (AVF) is the preferred vascular access due to superior patency and lower infection rates. Nonetheless, its suboptimal maturation rate remains to be resolved. Previous clinical studies had shown that elevated parathyroid hormone (PTH) associated with AVF maturation failure. In this study, we try to repeat this finding in a mice model of secondary hyperparathyroidism and AVF.

Methods: Chronic kidney disease (CKD) and secondary hyperparathyroidism were induced by feeding diet containing 0.2% adenine (adenine group) or 0.2% adenine and additional 2% phosphorus (high P group) in C57BL/6 mice. After 8 weeks of induction, AVF was created by aorto-caval puncture. AVF was resected 6 weeks later. AVF was stained for α-SMA-positive VSMCs to show neointimal hyperplasia. The severity of neointimal hyperplasia was expressed by ratio of area of α-SMA/entire AVF.

Results: At the 4th week, renal function CKD was induced in adenine group and high P group (Figure 1A-B). Serum phosphorus level was insignificantly higher in high P group (Figure 1C). Compared with control group, serum PTH level was insignificantly higher in adenine group, while it was significantly higher in high P group (Figure 1D), indicating successful induction of secondary hyperparathyroidism in high P group. The severity of AVF neointimal hyperplasia was similar between control group and adenine group, while it was significantly more severe in high P group (Figure 1E-H). The above findings showed that secondary hyperparathyroidism may stimulate neointimal hyperplasia in AVF and play a role in AVF maturation failure.

Conclusions: The deleterious effect of PTH on AVF maturation should be confirmed by pharmacological suppression of PTH to reverse neointimal hyperplasia.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Background: Far-infrared Ray (FIR), wavelength between 3-1000 µm, bears multiple effects on cardiovascular system and thrombogenesis. The von Willebrand factor (vWF), a large multimeric plasma glycoprotein as crucial player in arterial thrombus formation, can be cleaved by metalloprotease ADAMTS13 at its A2 domain cryptic in normal circulating vWF. We hypothesized FIR may induce ADAMTS13 release and decrease platelet adhesion to endothelial cells via induction of ADAMTS13 which cleaves vWF on cell surface and resulted in decreased higher molecular weight forms of multimers of vWF.

Methods: Cultured HUVECs treated with FIR irradiation for 30 minutes. Extracted mRNA and protein were measured by real time PCR, western blot, or ELISA. Supernatants were subjected to nonreducing gel electrophoresis to assess vWF multimer pattern. ADAMTS13 and reduced higher molecular weight forms of multimers of vWF were measured by immunoassay and multimeric vWF pattern by SDS-agarose gel western blot. The mRNA level of ADAMTS13 after FIR irradiation showed a time-duration effect. FIR also stimulated ADAMTS13 but not vWF protein expressions in HUVECs. The levels of ADAMTS13 and vWF D4-CR domain in culture media measured showed increased after FIR irradiation. These findings reflected the possibility of vWF been cleaved from cell surface into medium, and it was demonstrated by the significantly reduced vWF D4-CR terminal expression on the surface of endothelial cells after FIR irradiation. The vWF multimer patterns in supernatants showed less presence of higher molecular weight forms, and binding of platelets to HUVEC cells was significantly reduced in FIR-treated cells. In healthy subjects, FIR irradiation increased blood levels of ADAMTS13 and reduced higher molecular weight forms of multimers of vWF.

Conclusions: We concluded FIR irradiation may inhibit platelet adhesion to endothelial cells via induction of ADAMTS13 which cleaves vWF on cell surface and results in decrease of platelet adhesion to endothelial cells. Our results provide information for further exploring the mechanisms of FIR in prevention of thrombus formation.

Funding: Private Foundation Support, Government Support - Non-U.S.

**TH-PO330**

Perivascular Administration of Sirolimus During Arteriovenous Access Surgery: Delivering Therapeutic Outcomes Minimizing Risk of Systemic Side Effects

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Background: Unmitigated cell proliferation at and around the vascular anastomosis resulting in flow limiting stenosis is an important cause of access dysfunction. mTOR (mammalian target of rapamycin), controls cell growth, proliferation and survival. Oral sirolimus is an immunosuppressant. Sirolimus (cytostatic) delivered locally to site(s) of vascular injury downregulates mTOR and inhibits cell proliferation by causing cell cycle arrest between G1 & S phases. Perivascular delivery of sirolimus is a novel method of harnessing its anti-proliferative effect with the intent of improving access outcomes. A prior Paclitaxel (cytotoxic; anti-mitotic) perivascular AVG study was prematurely terminated because of excessive infections.

Methods: Data from 56 AVG pts (includes open label subset of a US Phase 3 randomized, data safety monitored study; 55 ESRD and 12 AVG pts (Paulson NDT 2012) treated with perivascular sirolimus at & around the anastomosis (AVF) & venous anastomosis (AVG) delivered from a collagen matrix (Stirotom®) perivascular Therapies, Cresskill NJ) were analyzed. Access functional outcomes were evaluated using 2 needle cannulation for dialysis. Blood drawn at protocol specified time points yielded pharmacokinetic (PK) data.

Results: One AVF wound dehiscence required secondary suturing & local treatment with subsequent healing & preserved 12 mo. fistula primary functional patency; no cases of local infection. PK: Sirolimus levels peak ~6 hrs. after start of drug delivery (4-5ng/ml), declines to <1ng/ml by 96 hrs. PK profile for AVF and AVG are similar. Key efficacy metrics are tabulated.

Conclusions: 1. Perivascular sirolimus delivery with targeted high local concentrations of sirolimus achieves therapeutic effectiveness without increasing risk of problems with wound healing and infection. 2. Systemic release of sirolimus is negligible and levels are sub-therapeutic for systemic immunosuppression. 3. The US Phase 3 study is nearing enrollment completion.

Funding: Commercial Support - Vascular Therapies, Inc.
Effectiveness of Flow Volume Measurement Training Using Custom-Made Doppler Flow Simulator
Cheolju Kim, Sung gyun Kim, Hyungseok Lee, Narae Joo. Department of Nephrology, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea; Department of Nephrology, Hallym University, Anyang, Republic of Korea.

Background: The purpose of this paper was to present the effectiveness of custom-made Doppler ultrasound (DU) flow simulator, vascular phantom, and Doppler test fluid in training dialysis staffs on the flow volume (FV) measurement for arteriovenous (AV) access of hemodialysis (HD) patients.

Methods: A DU flow simulator was constructed using a continuous renal replacement therapy machine. Vascular phantoms were made with a rubber enema tube and keyboard cleaning gel. Doppler test fluid consisted of freeze-dried instant coffee granules and 0.9% saline. This easy and affordable simulator was applied to the training DU flow volume measurement on 12 dialysis staffs who had never experienced DU examination. After 3 days of theoretical education, dialysis staffs performed DU on AV access of HD patients. Thereafter, they underwent a 3-day training course using the simulator and then measured FV of AV access again. Each dialysis staff assessed FV 3 times, and the mean values of measurements between pre and post-training were analyzed by paired t-test.

Results: The difference in mean value of FV measurements from the reference value decreased from 131.6 ml/min to 62.5 ml/min (95% CI 30.0-108.0, P = 0.002), and the standard deviation of FV measurements were decreased from 96.9 ml/min to 47.0 ml/min (95% CI 7.9-91.8, P = 0.023) after DU training with the simulator.

Conclusions: The accuracy and reproducibility of FV measurement by dialysis staffs were markedly improved after training using the current simulator, and it may be helpful for defining fistula maturation. Using data from the multicenter, prospective NIDDK for improving fistula outcomes is the lack of standardized and readily ascertainable criteria for ascertainment had low sensitivity (36-67%).

Proving the Value of the Bluedop™ Device in the Renal Unit
David H. King, Abdelgalil A. Ali, Mid Essex Hospitals, Chelmsford, United Kingdom; Broomfield Hospital, Chelmsford, United Kingdom.

Background: Static Pressure Ratio SPR, showed early promise as a monitoring device in prediction of Arteriovenous Fistula Failure. 'Arterial' needle pressure is monitored with dialysis pump switched off. Blood pressure on the venous outflow will rise towards central arterial level in the presence of a 'blood flow limiting' venous stenosis. The method is not widely used, possibly due to difficulties in compensating for hydrostatic height difference between needle and mean blood pressure MAP measured on the contralateral arm. We suggest a simpler alternative using identical principles solves many of the practical problems associated with the technique.

Methods: The Bluedop™ device is intended to measure mean blood pressure non-invasively, without the use of needles, is unaffected by pump speed and can be applied at any suitable point of the AVF without any requirement for hydrostatic height correction. We studied the accuracy of our parameter 'Non Invasive Static Pressure Ratio' SPRn. A Doppler ultrasound probe is used to sample blood flow waveforms from the distal brachial arterial level in the presence of a 'blood flow limiting' venous stenosis. The method is not widely used, possibly due to difficulties in compensating for hydrostatic height difference between needle and mean blood pressure MAP measured on the contralateral arm. A patented function based on blood velocity waveform shape calculates non-invasive intra AVF mean perfusion pressure MPP®. This is comparable to the needle pressure measured invasively, without the use of needles, is unaffected by pump speed and can be applied at any suitable point of the AVF without any requirement for hydrostatic height correction. SPRn is calculated as SPRn = MPP® / MAP. The complete measurement takes approximately 5 minutes, and can be carried out by regular Renal Unit Staff without significantly interferring with their normal duties.

Results: The range of SPRn values in normally functioning AVF was established in 24 patients in 24 patients. Following this 340 prospective measurements were made on 73 patients over a 10 week period. SPRn in 27 AVF rose above the 2SD normal limit. Of these 23 had 60% or greater focal stenosis shown on Duplex scanning, 2 were maturing AVF and 2 had no significant stenosis. A review of clinically identified 'failing' AVF in the same unit showed that 48% were found to be ‘false alarms’ in Duplex studies. Bluedop™ reduced the number of false alarms to 18%.

Conclusions: Bluedop™ offers a practical solution to the perennial problem of unheralded AVF failure. It also has the desirable property of indicating AVF status during the maturing phase References: 1 A Besarab et al, vol.47, no.5, pp 1364-1373, 1995 2 D H King et al, J Vasc Access, 2015, 16 (3):211-217, DOI: 10.5301/jva.5000324

Background: The arteriovenous vascular access is the Achilles’ heel of hemodialysis (HD). Access malfunction, often caused by stenosis or thrombosis, results in reduced access flow, increased access recirculation (AR), and lower Kt/V. Measurement of access recirculation is a common method to detect fistula problems; however, existing methods are either invasive, costly, or labor intensive. We propose a novel method to measure AR using the Crit-Line® Monitor (CLM), which is non-invasive and free for existing CLM users.

Methods: The proposed method is based on an abrupt increase in ultrafiltration rate (UFR) for a brief period, which will increase the hemoglobin (Hgb) concentration at the dialyzer outlet. When a fraction of this venous return recirculates in the access, we will observe the effect of UFR perturbation on CLM-reported Hgb. In the simulations, we start with a known AR and baseline Hgb concentration. We then simulate the recirculation of venous return (reduced UFR) and observe the effect on CLM-reported Hgb concentration. We use mathematical modeling to calculate AR from the CLM data.

Results: We conducted a retrospective study in 23 patients (M:F=13:10, median of age 71 (IQR 63–80) years, HD duration 80 (43–128) months, AVF:AVG=7:16, DM:non-DM=12:11) undergoing 29 times of intervention for VAD between Jan 2017 and Apr 2018. We gathered demographic data and available Kt/V in our subjects for 14 days just before the intervention. Our simulation results warrant validation in a clinical study.

Conclusions: Using the Crit-Line® Monitor in Hemodialysis Patients: An In Silico Analysis

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Background: Arteriovenous fistula (AVF) is the preferred access for hemodialysis. Percutaneous transluminal angioplasty (PTA) has become a choice for AVF stenosis and ultrasound has been used in PTA more and more frequently.

Methods: In 2016-192 patients underwent PTA in our hospital. Angioplasty was performed using a non-compliant high pressure balloon. The process was visualized by duplex scan. Our inclusion criteria were: 1) Stenoses or occlusions were located at juxta-anastomosis; 2) Stenosis was confirmed with conditions: a. flow rate is <500ml/min in brachial artery and <200ml/min in fistula during dialysis; b. diameter of stenosis is <1.7mm.

Results: 129 patients with 76 males were analyzed. 104 of them have AVFs on left arm, and there is one Ulnar-basilic AVF while others are Radial-cephalic AVF. The diameter of stenosis is <1.7mm.

Conclusions: For the juxta-anastomosis’s stenosis or occlusion, PTA can be used to obtain satisfactory results.

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<th>Variables comparison</th>
<th>Before the procedure</th>
<th>After the procedure</th>
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<td>Diameters of ulnar artery</td>
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<tr>
<td>Flow rate in radial artery</td>
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<td>Flow rate in ulnar artery</td>
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KM curve

TH-PO341
Comparison of Peripheral Cutting Balloon vs. Conventional Balloon Angioplasty for Hemodialysis Vascular Access Stenosis: Prospective Randomized Controlled Trial
Masaki Murakami,1,2 Kiyoshi Mori,1 Masashi Mukoyama,4 Nephrology, Shizuoka General Hospital, Shizuoka, Japan; 2nephrology, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; 1University of Shizuoka, School of Pharmaceut Sci, Shizuoka, Japan; 4Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan.

Background: Adequate vascular access is essential for undergoing hemodialysis treatment. Even though clinical success rate of PTA is high, the patency of conventional PTA is relatively low. The cutting balloon which has small blades to create sharp incisions into neointimal hyperplasia is designed to minimize vessel damage. Although few randomized trials have evaluated cutting balloon angioplasty for vascular access, larger study are needed.

Methods: This prospective, randomized single-center clinical trial included patients who had a hemodynamically significant vascular access stenosis within 6 months after the previous procedure. The study was designed to evaluate the efficacy and safety of cutting balloon angioplasty (cutting balloon group) as compared with conventional balloon angioplasty (conventional balloon group) for the short-time patency cases in the previous treatment. The Kaplan-Meier method was performed to assess the primary and secondary patency of treatment lesion and whole access circuit. A log-rank test was used to evaluate the differences of patency between each group.

Results: One hundred fifty-seven patients provided informed consent and were randomly assigned to undergo cutting balloon angioplasty or conventional balloon angioplasty from December 2012 to November 2017. The clinical success rate was 100% in both groups. The anatomical success rates were 64.0% in cutting balloon group and 57.5±28.5% (P=0.001) in conventional balloon group. The primary patency rates were significantly better in the cutting balloon group (28.3%) than in the conventional balloon group (14.1%) at 6 months (P=0.009). The mean pain scale measured using Visual Analogue Scale during the cutting balloon dilation (38.8±25.1) was much lower than the conventional balloon (57.5±28.5) (P<0.001). The average percent stenosis decreased significantly after PTA using the cutting balloon (Δ-49.1%) compared with the conventional balloon (Δ-40.9% (P=0.007). Access flow measured by the duplex doppler ultrasonography improved after PTA in both groups. Change in access flow in the cutting balloon group (Δ+308±221) was greater than conventional balloon group (Δ+240±152) (P=0.027).

Conclusions: Our data suggest that cutting balloon angioplasty is effective for patients whose vascular access were short-lived.

TH-PO342
Drug Eluting Balloon Angioplasty in Dialysis Access
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Background: Recurrent stenosis is responsible for less than 50 percent patency at 6 months. Neo-intimal hyperplasia (NIH) is driven by hemodynamic factors and barotrauma from angioplasty. Paclitaxel has been shown to reduce NIH. In a RCT, paclitaxel-coated
balloon (Lutonix®) angioplasty compared to conventional angioplasty in AVFs showed better target lesion primary patency (TLPP) at 24 months. We present our data using Lutonix® in the treatment of recurrent stenosis in dialysis accesses.

Methods: This is a retrospective review of all angioplasties from June 1, 2017 to December 31, 2018 done at our hospital. A total of ten patients who underwent Lutonix®/angioplasties after successful conventional balloon angioplasties (>30% residual stenosis) were included in the study. The target lesion angioplasty free periods before and following Lutonix® angioplasty were reviewed. Re-interventions requiring angioplasty were clinically driven.

Results: Technical success of target lesion angioplasty was 100% for all angioplasties. The Lutonix® application following conventional angioplasty had a twice longer angioplasty free period compared to conventional angioplasty alone (mean of 320 versus 166 days, respectively) which represents a difference of 154 days, p = 0.04, 95% CI (11, 297). The 6-month TLPP (the index lesion) following Lutonix® angioplasty was 80%. No complications were reported with its use.

Conclusions: Lutonix® application following successful conventional angioplasty appears effective in delaying dialysis access clinically-driven re-stenosis requiring angioplasty. Further longer term studies are required to confirm the effectiveness of the Lutonix® angioplasty and see it is a suitable alternative for stent placement.

TH-PO343
No Increase in All-Cause Mortality from Paclitaxel Coated Balloons (DCB) Used in an Arteriovenous Circuit in Dialysis Patients
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Background: Recent data have suggested an increased mortality in patients treated with paclitaxel balloons (DCB) in the femoropopliteal circulation. In order to assess this issue, in the setting of hemodialysis patients, a post-hoc analysis was performed to describe short (6 month), medium (12 month) and long term (24 month) mortality, in a randomized study on the use of DCB in failing arteriovenous fistulae (AVF).

Methods: 285 patients were enrolled at 23 centers. Patients in both arms received vessel pre-dilatation followed by treatment with either a DCB or a control balloon of similar design to the DCB but without drug (PTA group). Endpoints included 3, 6, 9, 12, 18 and 24 month target lesion primary patency (TLPP). number of interventions required to maintain target lesion patency, and safety endpoints. A special focus of this presentation is a comparison of survival at 6, 12 and 24 months in the two arms of this study.

Results: The DCB and Control (PTA) groups were evenly matched with regard to age, sex, comorbidities, dialysis vintage and primary indication for intervention. No significant differences in survival were observed in the short (6 months), medium (12 months) and long term (24 months) survival analysis. In terms of differences between A VF/A VG, 32% of patients, 26% of nurses and 10% of physicians estimated that there was no difference. Around 30% of the interviewed stated that bleeding may be related to the heparin administration. Use of an hemostatic device was registered by patients in 37%, nurses in 77% and physicians in 90%. Fifty percent of patients thought that bleeding may be related to high venous pressure, as opposed to 88% of the nurses and 100% of the physicians.

Conclusions: Bleeding from the puncture site concern patients, nurses and physicians. Differences of understanding and expectations were appreciated between these groups, showing how much more education must be provided in this field.

TH-PO346
An Endovascular Treatment System for Occluded Native Arteriovenous Fistula
Christopher C. Loo,1 Jan Swinnen.1 National University Hospital, Singapore, Singapore; 2Westmead Hospital, Sydney, NSW, Australia.

Background: Westmead Hospital looks after a high number of patients on haemodialysis and because of the superior outcomes achieved with our endovascular techniques in occluded fistulas, from 2005 onwards, all patients who presented with an occluded native arteriovenous fistula (nAVF) to the Western Renal Area institution, were referred to our unit. We have also developed minimally invasive techniques to mature and repair dysfunctional nAVF including techniques to reestablish the flow through a thrombosed nAVF. The aim of this study is to present the techniques and results of the Endovascular Treatment System that we have developed for managing the occluded nAVF.

Methods: The current study is a retrospective chart review on all patients who presented with an occluded nAVF and underwent attempted resuscitation between the 1st January 2005 to 31st of December 2014.

Results: 130 patients were included in the study. Post intervention primary access patency was 83.8% at 6 months, 78.7% at 12 months, 64.6% at 2 years and 59.6% at 3 years. Post intervention assisted access patency in fistulas-in-use was 86.5% at 6 months, 81% at 12 months, 66.8% at 2 years and 61.2% at 3 years. Post intervention secondary patency for all cases was 84.7% at 6 months, 80.2% at 12 months, 66.1% at 2 years and 62% at 3 years. Post intervention secondary patency in fistula-in-use was 91.1% at 6 months, 90% at 12 months, 85% at 2 years and 74.6% at 3 years. Neither access survival nor patency differed significantly when incisional thrombectomy was compared to angioplasty or without stenting with access survival of 91.2% and 92.5% at 12 months and access patency of 82.9% and 89.7% at 12 months (p = .384 and p = .898 respectively).

Conclusions: In autologous arteriovenous thrombosed fistulae the use of purely endovascular techniques to revive the access is a viable and safe technique to employ in most cases.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO347
Primary Patency of Single-Needle Puncture for Arteriovenous Fistula
Stenosis Resistant to High-Pressure Balloon
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Background: To evaluate primary patency, safety and Doppler ultrasound data of single-needle puncture (SNP) treatment for AVF stenosis resistant to high-pressure balloon (HPB).

Methods: A retrospective study was conducted from June 2017 to August 2018 that included 83 patients who received PTA for AVF stenosis. Patients were allocated to SNP if AVF stenosis was resistant to HPB. Data collection included AVF stenosis location, stenosis length, percent stenosis, resident inner diameter, balloon pressure, intima thickness, mean access blood flow before and after intervention, complication and primary patency determined by Kaplan-Meier analysis.

Results: 1 type AVF stenosis (55.4%) were the most in 83 enrolled patients. Sixty-eight patients (81.9) got technical success with HPB. The remaining 15 patients were allocated to SNP. Ten of 15 patients (88.0%) resistant to HPB got technical success with SNP. There were no significant difference in AVF stenosis location, stenosis length, residual inner diameter and percent stenosis between SNP and HPB. Balloon inflation pressure and inflation times during operation in SNP group (21.9±2.1 atm and 4.4±2.1 times) were higher compared with HPB (15.6±4.5 atm and 1.9±0.6 times). The mean increases in access blood flow after PTA were 578.9±150.8ml/min with SNP and 487.2±100.5ml/min with HPB (p=0.006). Primary patency were similar with SNP and HPB (63.6% v.s 66.5% in the 6th month and 14.5% v.s 7.7% in the 12th month, p=0.65). Intima were thicker in SNP group than HPB group before PTA (1.2±0.3 vs 1.0±0.3, p=0.029), but were similar 6 months after PTA (1.5±0.3 vs 1.3±0.4, p=0.24). No uncontrolled complication endangered AVF occurred.

Conclusions: SNP is a safe option for AVF stenosis resistant to HPB with satisfied primary patency and no more financial burden.

Funding: Government Support - Non-U.S.

TH-PO348
Risk Factor Profile for Thrombophilia in Patients with ESRD on Maintenance Hemodialysis with Recurrent Arteriovenous Fistula Clotting
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Background: Vascular access is critically important for hemodialysis patients, being both a lifeline and an Achilles heel. Failure of arteriovenous fistula (AVF) has a substantial impact on the patient in terms of economic burden, morbidity and all-cause mortality. Thrombosis is the leading cause of AVF failure accounting for 80-85% of AV access loss. Since limited number of well-established risk factors for access thrombosis are known, in the present study we evaluated the relation between hereditary and acquired thrombotic factors contributing to recurrent AVF thrombosis. We also studied the association between recurrent AVF thrombosis with thrombotic factors in comparison with well-functioning fistulas and its association with ABO blood group, age, gender and diabetes.

Methods: This is a cross-sectional observational study with a total of 109 hemodialysis patients. 50 patients with recurrent AVF failure secondary to access thrombosis served as controls and 50 cases with well working AVFs as controls. Parameters studied were hereditary thrombotic risk factors- Factor V Leiden (G1691A), Factor XIII (val34leu), Prothrombin (G20210A), MTHFR (C677T) by DNR isolation and PCR products and acquired thrombotic factors - Lipoprotein (a), Fibrinogen using immunoturbidimetry, Homocysteine by enzyme recyclic and Anticardiolipin antibody(IgG and IgM) by ELISA method.

Results: In our study hereditary factors were not significantly different between the two groups but acquired factors Lipoprotein (a), Fibrinogen, Homocysteine, Anticardiolipin Antibody IgG and IgM were found to be elevated in patient with recurrent AVF thrombosis when compared to controls (P=0.001). There was significant association between recurrent vascular access thrombosis and non O blood groups (P=0.047). Anemia (Hb < 10 gm/dl) was observed in patients with recurrent vascular access thrombosis when compared to well working fistulas. We did not find a significant association between age, gender and presence of diabetes contributing to recurrent vascular access thrombosis (P>0.826).

Conclusions: Acquired thrombotic factors contribute to recurrent AVF clotting in patients on maintenance hemodialysis. Recurrent AVF thrombosis is more common in non-O blood group and in patients with anemia.

TH-PO349
Coagulation Differences in Dialysis Vascular Access Failure
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Background: Vascular access failure in hemodialysis patients is often caused by access stenosis or thrombosis. Neointimal proliferation and abnormal coagulation play important pathogenetic roles. Currently, no biomarker is available for prediction of access failure leading to stenosis and thrombosis. Sonorheometry is a novel tool assessing blood clot elasticity. We hypothesize blood clot elasticity can be a valuable tool to diagnose vascular access complications in hemodialysis.

Methods: In a cross-sectional study, conventional markers of coagulation including Fibrinogen, platelet count, PT/INR, and aPTT were measured in 21 patients on chronic hemodialysis (for over 3 months). 6 patients had recurrent vascular access failure caused by concurrent thrombosis and stenosis, 9 patients had recurrent access stenosis without thrombosis and 6 patients had functioning access without complications. For each patient, QPlus Cartridge was run on Quantra analyzer to measure coagulation parameters, including Clot Stiffness (CS). Kruskal – Wallis Test was used for in group comparisons and Pearson / Spearman analysis for correlation of fibrinogen level, platelets count and CS.

Results: There was no statistical differences in stiffness parameters in the 3 subpopulations. However, the patients with recurrent vascular access complications caused by Thrombosis/Stenosis had high CS values (figure 1). Numerically higher fibrinogen values were found in patients with vascular access complications.

Conclusions: Hemodialysis patients with recurrent vascular access complications due to thrombosis/stenosis might have higher clot stiffness and signs for a hypercoagulable state explained by the renal failure. A larger cohort needs to be examined to confirm findings and demonstrate that clot stiffness can be utilized to monitor dialysis patients for vascular access complications.

TH-PO350
Antiphospholipid Antibodies Significance in Hemodialysis Patients: A Single-Center Cohort Study
Fatim Camara, Maxime Taghavi, Agnieszka Pozdzik. Centre Hospitalier Universitaire Brugmann, Brussels, Belgium.

Background: Antiphospholipid syndrome (APS) is an autoimmune disease characterized by arterio-venous thrombotic manifestations and persistently positive antiphospholipid antibodies (APAb) as reported in the revised Sapporo classification criteria. The prevalence of APAb in haemodialysed patients is higher compared to the general population. Their role in the occurrence of vascular access thrombosis remains controversial. This study aims to determine the prevalence of APAb in patients and to evaluate their association with vascular access thrombosis and quality of extrarenal purification in haemodialysis patients.

Methods: This is a single-center cross sectional study including 149 haemodialysis patients with available demographic, clinical, biological and immunological parameters (APAb) as well as haemodialysis characteristics. Antiphospholipid biology was defined as persistently positive antibodies (at least 12 weeks apart) without history of clinical manifestation.

Results: The prevalence of antiphospholipid biology (ABP) and APS were respectively 17.7% (12/ 117) and 10.3% (6/117). Those patients were younger. Antiphospholipid biology is significantly associated with arterial hypertension and diabetes while the antiphospholipid syndrome with dyslipidaemia. Antiphospholipid biology is a significant risk factor for lower Kt/V independently of type of membrane or haemodialysis modality (conventional haemodialysis versus hemodiafiltration). The APS is associated with vascular access thrombosis. Interestingly, patients with one positive APAb at the screening that were controlled negative during the follow-up were still expose to an increased risk of arterial thrombosis (however this did not reach statistical significance, p = 0.054). These patients were not at risk for vascular access thrombosis.

Conclusions: Despite a small sample size, we report that antiphospholipid syndrome increases the risk of vascular access thrombosis and is an independent risk factor of a lower Kt/V. Our observation underlines the importance of antiphospholipid antibodies screening in hemodialysis patients and needsmers to be validated by prospective studies.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Quantified Vascular Calcification of Vascular Access: Correlation with Coronary Artery Calcium Score and Survival Analysis of Access and Cardiovascular Outcome

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Background: Vascular calcification (VC) is the major contributor to mortality and morbidity in end-stage renal disease (ESRD) patients. We investigated whether there is a correlation between Coronary artery calcium score (CACS) and quantified vascular calcification score (VCS) of the arm including vascular access and whether VC increases the incidence of intervention and major adverse cardiac and cerebrovascular events.

Methods: EGAT gate, non-contrast arm CT scan including vascular access and the coronary vessel was taken. Later, CACS and VCS were measured by using Aquarius Ver. 4.4.12 simulating the Agatston Method. We examined if the subjects with CACS=400 was higher in the group of VC=500, a cutoff of the highest 40% of VC. Survival analysis according to VCS groups was also performed.

Results: In the total 77 patients, there were 44 males (57.1%), and the mean age was 63.9 years. The median vintage of hemodialysis was 49.4 [31.5, 99.2] months. When dividing the patients into two groups based on VCS 500 (lower VCS vs. higher VCS), there were no differences between the 2 groups in sex, age, ESRD etiology, and type of vascular access. However, the HD vintage was significantly older in higher VCS group. Median VC and CACS were higher in the higher VC group (VC; 144[75,264] vs. 1058 [713, 3353]; CACS; 21 [0, 171] vs. 552 [93, 2430]) and the ratio of the subjects with CACS=400 was higher (17.4% vs. 61.3% p<0.001). Since interventions can occur multiple times in one patient and each intervention is not independent, the Prentice, Williams and Peterson Total Time survival analysis model was used. Intervention Hazard ratio (HR) of the higher VCS group increased by 3.2 times. Additionally, longer duration of hemodialysis and higher magnesium (>2.5 mg/dL) had the lower HR of intervention. Moreover, in the higher VCS group, the HR of MACCE increased 2.3 times.

Conclusions: We quantified the VC and found for the first time that it is associated with CACS. Considering that CACS is closely related to the cardiovascular outcome, VC may also be suggested as a new biomarker to predict the outcome of ESRD patients. Higher vascular calcification increased the risk of access intervention and MACCE.

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An Online Ultrafiltration Rate Calculator to Empower Home HD Patients

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Background: Despite a 3-decade solute clearance focus, hemodialysis (HD) outcomes correlate more closely with volume factors, especially the rate of change of blood volume. A high ultrafiltration rate (UFR) induces hypotension, hypoperfusion, and functional organ stunning. Thus, a low sdalional UFR is critical for circulatory stability. As salt and fluid restriction often manifestly fail to limit interdialytic weight gain, HD sessional duration becomes the governing variable to assure a low, safe UFR. While the ideal safe mean maximum per treatment UFR remains in debate, clinical risk increases as the UFR exceeds 6-8 ml/kg/hr. Although US guidelines currently recommend a UFR <13ml/kg/hr. Since home HD (HHD) patients can self-adjust their treatment time to ensure a low UFR, we devised an on-line UFR calculator to display the impact of UFR and encourage patients to safely use this flexibility.

Methods: Using the interdialytic weight gain (IDWG), pre-dialysis weight (pre-DW), and intended upcoming treatment time (t), the mean treatment UFR (ml/kg/hr) can be calculated by UFR = (IDWG + pre-DW - t) ÷ pre-DW. We have interrogated the site analytics for patterns of use. Results: Key data (25/2/2016 - 5/5/2019) are shown (attached diagram: Analytics Overview). Rising through 2017-2018, regular use has stabilised in 2019 at 2000-2250 pageviews/week and 0.36 minutes/view. User feedback is uniformly positive. Many HHD patients now routinely use the calculator to adjust their upcoming sessional duration.

Conclusions: HHD patients and professionals can now be empowered to regulate the UFR by directional adjustments based on the UFR calculator. The calculator encourages and empowers flexibility in treatment time and a safe, gentler rate of volume change.

Vancomycin and Teicoplanin Clearance During an In Vitro Model of Continuous Venovenous Hemofiltration Using Different Membranes
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Background: Continuous renal replacement therapies (CRRT) can affect pharmacokinetic behavior of antibiotics. The factors that need to be considered are related to the drug characteristics, CRRT features and patient status. Particularly, the type of membrane can play a major role in drug removal. The aim of this study was to evaluate in an in vitro system the convective and adsorptive drug clearance of vancomycin (VAN) and teicoplanin (TEC) during continuous venovenous hemofiltration (CVVH) with polysulfone (PS), polymethylmethacrylate (PMMA) and polyacrylonitrile (PAN) filters.

Methods: VAN and TEC clearance was assessed in vitro in blood from healthy donors. Closed circuit simulation CVVH was performed using PS, PMMA and PAN mini-filters at 10ml/min ultrafiltrate and 50 ml/min blood flow rates. The duration of the experiment was of 360 min. Samples were collected in 5, 10, 30, 60, 120, 240 and 360 minutes from in-flow, out-flow and ultrafiltrate line; antibiotic concentrations were measured by biochemistry analyzer. Convective evaluation was conducted in terms of sieving coefficient (SC), and adsorptive clearance was calculated using mass balance analysis.

Results: VAN and TEC blood SC are shown in Fig 1, as well as the reduction ratio of plasmatic concentrations for each membrane. During CVVH using PS, PMMA and PAN membranes, the estimated total adsorbed mass per surface area for VAN was 36.52mg/m2, 11.33mg/m2 and 6.97mg/m2, and for TEC was 98.17mg/m2, 51.33mg/m2 and 9.77mg/m2, respectively.

Conclusions: Our findings show that during CRRT both convective and adsorptive mechanisms have a role in antibiotics clearance. When dosing patients on CRRT, physicians should take into account not only CVRT flow rate settings and modality but also drug–membrane interaction.

Analytcs Overview

TH-PO355

Application of Individualized Physiologically Based Pharmacokinetic Modeling of Rate Data (iPBPK-R) to Estimate the Effect of Hemodialysis on Nonrenal Clearance Pathways

We previously developed an individualized physiologically-based pharmacokinetic modeling approach using rate data (iPBPK-R) to differentiate contributions of nonrenal metabolic and transport pathways to the disposition of the non-specific probe drug erythromycin. The objectives of the current work were (1) to differentially estimate contributions of nonrenal clearance pathways to erythromycin in patients with ESRD, (2) to investigate the effect of hemodialysis (HD) on these pathways, and (3) to explore the relationship between parameter estimates and uremic toxin concentrations.

Methods: Twelve patients with ESRD received erythromycin (0.074 mmol IV) pre- and again post-HD and 11 breath samples were collected over 2 hours after each dose. iPBPK-R was applied to measured 14CO2 production rates. Eight PBPK parameters were co-optimized between pre- and post-HD periods within patients while activity of CYP3A4 clearance was independently estimated. Inhibitory coefficients of uptake transporters (i.e., OATP) were also estimated. Nonrenal clearance parameter estimates were compared pre- vs post-HD and by gender. As exploratory analysis, the parameter estimates were correlated with uremic solutes and used in hierarchical cluster analysis (HCA). Optimization were run on the Bridges supercomputer (PSC via NSF XSEDE).

Results: Seven compartments with OATP uptake and CYP3A4 clearance were modeled. Mean relative increase in CYP3A4 clearance pre- vs post-HD within individual patients was 12% which was not statistically significant (p=0.06). However, males had 16% and 19.3% lower median CYP3A4 activity than females pre- (p=0.001) and post-HD (p=0.001), respectively. The estimated inhibition coefficient of uptake transport did not differ between pre- and post-HD (p=0.12). A sub-cluster of two patients with more improved CYP3A4 activity at post-HD (9.4% increase) was identified compared to the other patients (0.5% increase). β2-microglobulin was inversely correlated with CYP3A4 activity in males pre- (Spearman r=−0.79, p<0.04) but not post-HD.

Conclusions: iPBPK-R is a novel tool to estimate nonrenal clearance parameters within individuals and to explore the effect of HD and uremic toxins on drug disposition in patients with ESRD. Further work is required to validate the iPBPK-R based results.

Funding: Other NIH Support - National Institute of General Medical Sciences, Other U.S. Government Support, Government Support - Non-U.S.

TH-PO357

Characterization of Metabolite and Metabolite Concentrations Pre and Post Hemodialysis: Potential Implications for Intradialytic Hypotension and Post-Dialysis Fatigue

Background: Previous pharmacokinetic (PK) studies of metabolite succinate (MPL) were conducted before high-flux HD and did not evaluate post-HD rebound or parent/metabolite (P:M) ratios. Intercompartamental redistribution of antihypertensives may contribute to intradialytic hypotension and post-dialysis fatigue. The aim of this study was to characterize the PK of MPL and α-hydroxymetoprolol during and post-HD.

Methods: Eligible patients were ≥18 years, on HD 3 days a week for 3.5-5 hours (h), daily dose of MPL 25-200mg, and hemoglobin >9.5 g/dl. Artery-venous (AV) paired samples were collected prior to HD initiation, 0.5h, 2h, and end of treatment. Post-HD sampling occurred at 0.5, 2, and 4h. Serum samples were assayed by liquid chromatography-tandem mass spectrometry and a non-parametric population PK model was used (PMEMetrics<sup>TM</sup> LAPK). T0 samples were analyzed for CYP2D6<sup>∗</sup>4.

Results: Eight patients (5 male, 3 female; Age 59±17 years) were enrolled. The MPL PK data were best fit with a linear, 2-compartment model. Absolute MPL and fraction absorbed fixed to known values from literature. The model predicted MPL clearance (CL) was relatively unchanged on- and post-HD with a mean (CV) of 46.5 (17.4%) and 41.9 (54.4%) L/h, respectively. AV-dialytic CL was minimal (13.1±8.8% of total CL). The mean volume of distribution (Vd) in central compartment (Vc) decreased: 119.7 (103.2%) L on-HD to 18.4 (128.7%) L post-HD. Mean peripheral compartment Vd (Vp) increased: 17.7 (252.2%) L on-HD to 160.0 (0.0%) L post-HD. Vd changes resulted in significant MPL flux from Vp to Vc on-HD driven by redistribution and from Vc to Vp post-HD due to hemoconcentration. Higher MPL concentrations were seen at 2h on-HD and 4h post-HD. The P:M ratios were variable suggesting phenotypic differences in CYP2D6 activity. Three CYP2D6<sup>∗</sup>4 heterozygotes were identified, but only one showed decreased metabolism based on P:M ratio.

Conclusions: Large changes in Vd due to ultrafiltration drive fluctuating MPL concentrations during and after HD, resulting in highly variable MPL serum concentrations. This may contribute to intradialytic hypotension and/or post-dialysis fatigue. Dialytic CL does not appear to contribute significantly to varying MPL concentration profiles.

TH-PO358

Effect of CKD on the Ex Vivo Metabolism of 9-THC into 11-OH-9-THC into 11-OH-9-THC
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Background: Over 40% of chronic kidney disease (CKD) patients experience adverse drug reactions. Cytochrome P450s (CYPs) are major contributors to drug disposition, as they mediate drug metabolism to help facilitate clearance. Rodent models of CKD have shown reduced CYP expression and drug metabolic activity. The use of cannabis for both medicinal and recreational purposes has increased recently and cannabis has been legal for several regions of the world. While CKD is known to impact the disposition of many drugs, there have been no studies investigating the impact of CKD on the hepatic metabolism of cannabis. This study utilized a rat model of CKD to investigate the impact of CKD on the metabolism of the psychoactive component of cannabis (9-THC) to its active metabolite 11-OH-9-THC. It was hypothesized that CKD would decrease 9-THC metabolism.

Methods: CKD was induced in male Wistar rats (n=13) by feeding chow supplemented with 0.5% adenine (n=7) for a total of 42 days while controls (n=6) received standard chow. Blood, organs and chow were collected, and plasma creatinine concentrations were measured utilizing ultra performance liquid chromatography coupled to mass spectrometry (UPLC-MS). Hepatic microsomal fractions, isolated by differential centrifugation, were incubated with THC (10mM and 20 mM) for 4 minutes, and 11-OH-9-THC concentrations were measured by UPLC-MS, and the metabolite formation rate (pmol/min/mg protein) was calculated.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
mortality among patient groups, as well as the values of C3, C4 and anti-dsDNA.

MMF (30). There were no statistically significant differences in clinical response and (p <0.05) difference was found. Regarding the response to induction therapy, 225 (49%) significant proteinuria in 24 hours and creatinine in both treatment groups (MMF vs CFM) was predominant proliferative class IV (66%), followed by Class III (23%). Statistically common clinical presentation was nephrotic syndrome (70%). Histological class was chosen according to clinical and histological criteria. The objective was to assessing the potential clinical value of the CYP3A5 genotype to personalize therapy in Chile, to facilitate post-RTx monitoring, as well as improve credibility of patients TAC adherence. Grants FONDECYT 111-40242, FONDECYT 116-0465.

Background: Lupus nephritis (LN) is the most severe complication of systemic lupus erythematosus and induction therapy defines the prognosis of the disease. The type of immunosuppressive therapy (Myophenolate Mofetil; MMF and Cyclophosphamide; CP) is chosen according to clinical and histological criteria. The objective was to assessing response to induction therapy with MMF vs CFM and mortality in a number of cases from the Colombian Caribbean region with LN.

Methods: A retrospective study was performed in 57 RTx adults of a single center using immunosuppressive therapy for more than 5 months. The SNP rs776746 was analyzed by PCR Taqman/sequencing. AUC was determined in 16 patients with the three genotypes (GG/AA/AG) analyzed with the DNA repository in ChileGenomic.

Results: A total of 43 yrs [17-71 yrs], 51% female, 81% RTx with cadaveric donor, median time of RTx was 2.7 yrs. At the time of recruitment, 60% presented C0 between 5-10 mg/mL. We identified 58%, 26% and 16% of subjects with the GG, AG or AA genotype, respectively. The dose/dosing strategy was determined and the mean AUC=0.15±0.05 (mg/kg) that were statistically different between GG/AA and AG=GG (p<0.001). The highest correlation between Cx and AUC was C12 (r=0.97) and C0 (r=0.96), independently of the genotype. The Mapuche ancestry was associated with higher TAC doses, because of higher A allele frequency. Co turns to be an important 500 weeks (9 years) by Kaplan-Meier estimator was calculated. (CR), partial remission (PR) and no remission (NR). Furthermore, the mortality associated with MMF vs CFM to 500 weeks (9 years) by Kaplan-Meier estimator was calculated.

MMF was superior in terms of averages, in response and decreased mortality, but this does not reach a statistical difference.

TH-P0361
Fosfomycin Treatment Administration Enhances Cyclosporine Nephrotoxicity
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Background: Urinary tract infection (UTI) is very frequent in renal transplant immunosuppressed patients and the clinicians face the growing increase in antibiotic resistance. Fosfomycin trometamol (Fos) has emerged as a potential UTI treatment, however its influence on calcineurin inhibitors nephrotoxicity (CIN) has not been explored. This study was designed to evaluate the effect of Fos in combination with cyclosporine (CsA) on CIN in the rat.

Methods: Twenty-four male Wistar rats were included and divided into four groups: 1) Control, 2) CsA 15 mg/kg s.c., 3) CsA+Fos 62.5 mg/kg and 4) CsA+Fos 500 mg/kg. Cyclosporin was daily administered for 14 days, whereas, fosfomycin was started on day 9 with three doses every 48 h. At the end of the study, functional studies were performed, and tissue samples were obtained.

Results: Table 1 shows CsA nephrotoxicity was characterized by a significant decrease in RBF and GFR, as well as with a reduction in eNOS, AGT, and AT1R mRNA levels. In CsA+Fos group, greater hyperperfusion, oxidative stress, and increased mRNA levels of pro-inflammatory cytokines were observed. This study shows that Fos increases CsA nephrotoxicity through increasing renal inflammation and alerts us to the combined use of these drugs in the clinical scenario.

TH-P0362
Improved Early Treatment Response of Eculizumab with a Patient-Friendly Dosing Scheme in Adult Patients with Atypical Hemolytic Uremic Syndrome
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Pharmacy, Radboud university medical center, Nijmegen, Netherlands; 2Radboud university medical center, Nijmegen, Netherlands; 3Leiden University Medical Center, Leiden, Netherlands; 4Radboud Institute for Health Sciences, Nijmegen, Netherlands.

Background: With the currently approved dosing schedule of eculizumab in adult aHUS patients (900mg weekly, followed by 1200mg in the fifth week and every 14 days thereafter), exposure is often sub-therapeutic after the first dose, while being supra-therapeutic when starting the maintenance phase. We aimed to develop a dosing strategy to improve early treatment response.

Methods: Pharmacokinetic (PK) and pharmacodynamic (PD) data from 30 aHUS patients data were available, consisting of 647 eculizumab time-concentration data and 504 classical PK description was released with an inhibitory Enzyme model, with an IC50 of 21.3 mg/L (RSE 17.1%). A weight-based loading dose of eculizumab (<60kg: 1500mg, 60–<90kg: 1800mg, 90–<120kg: 2100mg and ≥120kg: 2400mg) on day 1, followed by 1200mg on day 14 and 28 was found to improve treatment. In total, 96.6% of the patients reached the CP target on day 7, compared to 81.3% with standard dosing (Figure 1). This also resulted in a dose reduction of 12.5% compared to the first 28 days of the approved dosing regimen.
Conclusions: A patient-friendly weight-based dosing strategy of eculizumab results in better treatment response during the initial phase at lower costs.

Funding: Government Support - Non-U.S.

TH-PO363
Darunavir Localizes to Cytoplasmic Stress Granules in Human Proximal Tubular Cells
Alfred A. Essig,1,2 Buadi K. Tandoh,3 Xiaobo Gao,3 Heidi Karttunen,2 Michael J. Ross.1,2 Albert Einstein College of Medicine/ Montefiore Medical Center, Bronx, NY;1 Albert Einstein College of Medicine, Bronx, NY.

Background: HIV protease inhibitors (PI) have off-target effects on many cellular pathways data from our laboratory demonstrated that darunavir (DRV), the most commonly used PI, protects renal epithelial cells from HIV-induced injury and inflammatory responses via mechanisms independent of HIV protease. Since the mechanism by which DRV protects kidneys from injury is poorly understood, we performed studies to identify cellular protein targets of DRV in human renal epithelial cells.

Methods: We used the Direct Magnetic IP/Co-IP Kit to covalently link DRV to NHS-activated magnetic beads. DRV bound- and unbound- beads were incubated with HPTib whole cell lysate from immortalized human proximal tubular cells (HPTib). Bound and unbound proteomes were resolved by mass spectrometry. DRV was also covalently linked to NIH-AlexFluor 488 and cellular localization of DRV-488 and stress granule protein G3BP1 were analyzed by fluorescence microscopy.

Results: 52 proteins were identified in all 3 samples from DRV-bound beads at 100-fold or greater abundance than control samples. 23 of the 52 proteins are RNA-binding proteins, most of which are components of cytoplasmic stress granules (SG), including canonical SG proteins G3BP1, G3BP2, and Caprin1. DRV-G3BP1 interaction was confirmed by western blotting of protein eluted from DRV- and control-conjugated beads. To determine if DRV colocalizes with G3BP1 in SG, SG formation was induced in HPTib cells by incubation with NaAsO2. Fluorescence microscopy localized G3BP1 and DRV-488 in the cytoplasm and in cytoplasmic punctae, consistent with SG localization. HIV transduction of HPTib cells increased G3BP1 punctate staining, demonstrating that HIV induced SG formation. We examined phosphorylation of G3BP1, which promotes SG disassembly. A reduction in p-G3BP1 (Ser149) was observed in HIV transduced HPTib cells treated with DRV, suggesting that DRV prevents SG disassembly.

Conclusions: These data demonstrate that DRV localizes preferentially to SG in renal proximal tubular cells. SGs in intracellular compartments that regulate response to stress. DRV may attenuate renal epithelial injury via novel effects upon SG dynamics. Additional studies are needed to determine the role of SG proteins in mediating the protective effects of DRV against kidney injury.

Funding: NIDDK Support

TH-PO364
Tenofevir Alafenamide Fumarate (TAF) and Tenofevir (TFV) Have a Different Impact on the Proteome of Proximal Tubular Cells (PTCs)
Hassan Aouna,1 Bastien Barutac,2 Francois-Ludovic Sauvage,1 Marie Essig,3,1 INSERM, UMR 1248 IPPRITT, University of Limoges, Limoges, France,1 AHPH, Poulevard Billancourt, France.

Background: TAF, a new produg of TFV was developed to be less nephrotoxic than TFV and TFV and ABC (as control macrolide inhibitor) on PTC.

Methods: iTRAQ differential proteomic strategy was used to analyse the effects of TFV, TAF and ABC (as control macrolide inhibitor) on PTC.

Results: 52 proteins were identified in all 3 samples from DRV-bound beads at 100-fold or greater abundance than control samples. 23 of the 52 proteins are RNA-binding proteins, most of which are components of cytoplasmic stress granules (SG), including canonical SG proteins G3BP1, G3BP2, and Caprin1. DRV-G3BP1 interaction was confirmed by western blotting of protein eluted from DRV- and control-conjugated beads. To determine if DRV colocalizes with G3BP1 in SG, SG formation was induced in HPTib cells by incubation with NaAsO2. Fluorescence microscopy localized G3BP1 and DRV-488 in the cytoplasm and in cytoplasmic punctae, consistent with SG localization. HIV transduction of HPTib cells increased G3BP1 punctate staining, demonstrating that HIV induced SG formation. We examined phosphorylation of G3BP1, which promotes SG disassembly. A reduction in p-G3BP1 (Ser149) was observed in HIV transduced HPTib cells treated with DRV, suggesting that DRV prevents SG disassembly.

Conclusions: These data demonstrate that DRV localizes preferentially to SG in renal proximal tubular cells. SGs in intracellular compartments that regulate response to stress. DRV may attenuate renal epithelial injury via novel effects upon SG dynamics. Additional studies are needed to determine the role of SG proteins in mediating the protective effects of DRV against kidney injury.

Funding: NIDDK Support

TH-PO365
Metabolomics Analytic Approach Reveals Global Metabolic Influences by Xanthine Oxidase Inhibitors in a Rat Model of Unilateral Renal Ischemia-Reperfusion Injury
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Background: Xanthine oxidase (XOR) inhibitors are clinically applied as anti-gout drugs to inhibit the conversion of xanthine to uric acid by XOR. They reportedly exert an organ-protective, especially the potent and selective XOR inhibitors, febuxostat and topiroxostat. We aimed to verify the hypothesis that preservation of tissue high-energy phosphate concentrations contributes to these positive effects in a rat model of unilateral renal ischemia-reperfusion (I/R) injury through global metabolic pathway analysis.

Methods: Six-week-old male Sprague-Dawley rats were orally administered either 10 mg/kg topiroxostat, 50 mg/kg of allopurinol, or vehicle (water) 60 min before they were subjected to 30 min of unilateral I/R injury. Kidney samples were collected at three time points; before I/R injury (stationary group), 30 min left renal ischemia (ischemic group), 30 min after I/R injury (reperfusion group). Metabolites in kidney lysates were analyzed by HPLC and CE-TOFMS metabolomics.

Results: Metabolomics analysis revealed global impact of I/R injury on metabolic pathways. In XOR-selective-inhibitor-treated groups, tissue concentrations of high-energy phosphates were higher before and after I/R injury, and renal adenine compounds were better preserved throughout I/R injury than in vehicle and allopurinol groups. The XOR-selective inhibitors were also able to restore markers of cellular injury, including an increase in uric acid and decreases in N-acetyl-glucosamine and cytokines.

Conclusions: These findings were well in accordance with the proposed hypothesis that the re-expression of high-energy phosphates, such as ATP and ADP, is promoted by the XOR-selective inhibitors via the salvage pathway through blockade of hypoxanthine catabolism, whereas non-specific inhibitory effects of allopurinol on purine/pyrimidine enzymes impede this re-synthesis process. The unique global metabolic alterations by the XOR-selective inhibitors, presumably by a change in the ATP/AMP ratio, acting as an allosteric effector, remained further to be investigated. This study revealed novel findings of the XOR inhibitors’ influences on global metabolic pathway, and sheds light on the undetermined physiology of the organ-protective effects of XOR inhibitors.

TH-PO366
Renoprotective Effects of Phosphodiesterase 5 Inhibitor in Models of CKD with Hypertension and Nephrotic Syndrome
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Background: Phosphodiesterase (PDE) 5 inhibitor has a renoprotective effect. PDE5 expression in glomeruli is confirmed, but its role has been unclear. In this study, we assessed the effects of tadalafil (Tad), a PDE5 inhibitor, using two renal dysfunction models that mimic chronic kidney disease (CKD) with hypertension and nephrotic syndrome. CKD was induced by feeding Dahl salt-sensitive rats with hypertension and CKD induced by a high-salt diet. The rats were divided into normal salt, high salt, and Tad 1- and 10-mg/kg treatment groups. After 8 weeks of treatment, we analyzed kidney function, blood pressure, and histopathological changes. 2) Nephrotic syndrome model. A nephrotic syndrome model was created with Wistar-ST rats by adriamycin (ADR) injection. The rats were divided into control, ADR, and ADR+Tad 10 mg/kg groups. After 2 or 4 weeks of treatment, urinary protein and serum albumin levels were evaluated.

Results: 1) CKD model. High-salt diet induced kidney dysfunction and severe hyperfiltration. Tad 10 mg/kg treatment prevented increases in serum creatinine (SCr) and urinary protein levels and hypertension (Fig. 1). Tad 1 mg/kg treatment significantly prevented the increase in SCr and urinary protein levels, but not hypertension. Histopathological analysis revealed that Tad treatment attenuated glomerular injury. 2) Nephrotic syndrome model. Tad 1 mg/kg concentration induced high urinary protein level and low serum albumin level. Tad treatment attenuated proteinuria at 2 and 4 weeks and reduction of serum albumin level at 4 weeks.

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Poster/Thursday
SNF472 Is More Efficacious In Vivo Than Its 4,6-bisPEGylated Derivative in Inhibiting Vascular Calcification in Rats
Miquel D. Ferrer,1,2 María del mar Perez,1 Firas Bassissi,1 Joan Perelló,1,2 Carolina Salcedo,1 Sanifit Therapeutics, Palma, Spain; 2Universitat de les Illes Balears, Palma, Spain.

Background: Vascular calcification (VC) is a major contributor to increased morbidity and mortality in Chronic Kidney Disease patients undergoing dialysis. Although VC is a multifactorial process, the final common pathway is deposition of solid hydroxyapatite (HAP) within the arteries. SNF472, salt of InsP6, is a selective calcification inhibitor that interferes in the formation and growth of ectopic HAP. SNF472 is currently being developed for the treatment of calciphylaxis in patients on dialysis. Insitol-1,2,3,5,6-pentakisphosphate-6-[bis(PEG100)] (InsP4bisPEG) is an inositol phosphate derivative resulting from the PEGylation of InsP6. This study aimed to compare the relative bioavailability and in vivo efficacy in the inhibition of calcification of subcutaneous (s.c.) InsP4bisPEG and SNF472 at equimolar doses in rats.

Methods: S.c. pharmacokinetics (PK) of InsP4bisPEG and SNF472 were assessed in male Sprague Dawley rats in single administration. Plasma samples were obtained and analyzed. The in vivo efficacy was evaluated in 24 male Sprague Dawley rats, divided into three groups of eight rats receiving placebo (NaCl 0.9%) or equimolar doses (36 µmol/kg) of SNF472 or InsP4bisPEG. Vascular calcification was induced by 3 consecutive daily s.c. administrations of 150 µg/kg vitamin D3, starting on day 1. Rats were sacrificed 5 days after induction of calcification, and aorta was collected for calcium analysis.

Results: The plasma Cmax of InsP4bisPEG was 9.8 µM, at a tmax of approximately 30 minutes. AUC(0-∞) was 13.1 µM*h/mL and the terminal half-life (τ1/2) was 46 min. SNF472 showed a plasma Cmax of 7.4 µM at around 15 min, with an AUC(0-∞) of 2.5 µM*h/mL and a terminal T1/2 of 17 min. SNF472 treated animals presented significantly lower calcium levels in aorta, which were 38% and 55% lower than placebo and InsP4bisPEG treated animals, respectively.

Conclusions: InsP4bisPEG is more bioavailable than SNF472 and presents a longer plasma half-life. However, SNF472 is more efficacious inhibiting aorta calcification than this InsP6 PEGylated derivative in an in vivo model of vascular calcification. AUC(0-∞) and half-life (t1/2) are recommended to be assessed throughout the study.

Results: All 16 enrolled participants completed the study (hepatic impairment, n=8; normal, n=8). Demographics were similar between groups (overall: 100% white, 62.5% female, mean age 59.2 y). Vasadustat plasma exposure (AUC) was substantially higher in the hepatic impairment group, whereas Cmax was generally similar between groups (Table). Point estimates of the hepatic impairment: normal geometric mean ratios (90% CI) for AUC(0-∞) and Cmax were 1.05 (0.82-1.35), 1.06 (0.82-1.36), and 1.02 (0.79-1.32), respectively. Mean elimination half-life was 5.8 h in the normal group and 7.8 h in the hepatic impairment group. Treatment-emergent adverse events (TEAEs) were reported by 1 participant in the hepatic impairment group and 2 in the normal group. Most TEAEs (60%) were mild in severity; none were severe.

Conclusions: In this study, moderate hepatic impairment did not significantly impact vasodustat systemic exposure. A single dose of 450 mg vasadustat was generally well tolerated by participants with both normal and moderately impaired hepatic function.

Funding: Commercial Support - Eloxx Pharmaceuticals, Inc.

TH-PO369
Effect of Moderate Hepatic Impairment on Pharmacokinetics of Vadadustat, an Oral HIF-Inducible Factor Prolyl Hydroxylase Inhibitor (HIF-PHI)

Background: Vadadustat is an oral HIF-PHI in development for the treatment of anemia due to chronic kidney disease. Vadadustat is primarily metabolized to O-glucuronide by UDP-glucuronosyltransferases (UGT). The predominant UGT involved in the metabolism of vadadustat is UGT1A9, which is expressed in the liver and kidney. Therefore, the role of hepatic impairment in vadadustat clearance was evaluated.

Methods: This phase 1, open-label, parallel-group, single-dose study evaluated pharmacokinetics (PK) of 450 mg vadadustat in adults (18-70 y) with moderate hepatic impairment (Child-Pugh Class B) and those with normal hepatic function. Blood samples were collected pre-dose and up to 72 h post-dose. Primary endpoints were area under the curve from dosing to last concentrations (AUC(last)) and to infinity (AUC(∞)) as well as maximum concentration (Cmax); additional PK parameters included time to Cmax (Tmax) and half-life (T1/2). Safety and tolerability were assessed throughout the study.

Results: All 16 enrolled participants completed the study (hepatic impairment, n=8; normal, n=8). Demographics were similar between groups (overall: 100% white, 62.5% female, mean age 59.2 y). Vadadustat plasma exposure (AUC) was substantially higher in the hepatic impairment group, whereas Cmax was generally similar between groups (Table). Point estimates of the hepatic impairment: normal geometric mean ratios (90% CI) for AUC(0-∞) and Cmax were 1.05 (0.82-1.35), 1.06 (0.82-1.36), and 1.02 (0.79-1.32), respectively. Mean elimination half-life was 5.8 h in the normal group and 7.8 h in the hepatic impairment group. Treatment-emergent adverse events (TEAEs) were reported by 1 participant in the hepatic impairment group and 2 in the normal group. Most TEAEs (60%) were mild in severity; none were severe.

Conclusions: In this study, moderate hepatic impairment did not significantly impact vadadustat systemic exposure. A single dose of 450 mg vadadustat was generally well tolerated by participants with both normal and moderately impaired hepatic function.

Funding: Commercial Support - Akebia Therapeutics Inc.

TH-PO370
A Systematic Meta-Analysis on Interspecies Differences in Renal Drug Clearance
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Background: Various animal models are used to study drug efficacy and safety prior to approval for human use. Renal clearance (CLR) is a standard pharmacokinetic measure, for which animal data is extrapolated to humans by allometric scaling, using exponents of 0.55-0.75. It is worth noting that the physiological system of waste removal is designed to respond to the demand set by metabolic rate, which in turn scales with body weight to the power of 0.75 (Kleiber’s law). Thus, human CLR should be predictable based on body weight by scaling with 0.75. The exponents used in literature aim for best fit, thus deviations from 0.75 might result from biological interspecies differences. Using the allometric exponent of 0.75, our study aimed at quantifying interspecies differences in renal drug clearance. To find possible mechanistic explanations for these differences, we related them to the physicochemical properties of drugs.

Methods: Using PubMed and EMBASE, we systematically reviewed literature on human and animal CLR measures for 20 renally excreted drugs. Based on the human data and simple allometric principles, we calculated the CLR value expected for the respective animal body weight. Subsequently, average fold errors (AFE) were calculated as the ratio between the literature-derived CLR values and the expected CLR values. Finally, we quantified mean differences between animal and human CLR measures.

Results: Based on 264 included studies, we calculated AFES ranging from 0.45-3.05 for mice, 0.77-3.34 for rats, 0.28-1.61 for rabbits, 0.27-3.4 for dogs, 0.57-1.78 for monkeys and 1.01-3.11 for humans. Comparing animal to human AFES, we determined for all drugs an average MD [95% CI] of 0.01 [0.23, 0.26] for mice, 0.47 [0.17, 0.77] for

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Drugs Applied to Kidney Patients May Interact with Uremic Toxins for Renal Excretion

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Background: Organic anion transporters (OATs) are involved in the tubular secretion of protein-bound uremic toxins (PBUTs). In CKD, excretion of PBUTs is compromised leading to their accumulation, exacerbating CKD and contributing to uremic complications. Recently, we showed that conditionally immortalized proximal tubule epithelial cells (cPTECs) expressing OAT and cultured on biofunctionalized membranes, actively secrete PBUTs [1,2]. However, OAT1 also handles a wide range of drugs. Here, we investigated the interaction between drugs commonly prescribed to CKD patients and PBUTs for OAT1-mediated transport, using indoxyl sulfate (IS) as prototype PBUT.

Methods: A panel of 9 drugs was screened for interactions in cPTECs/OAT1 monolayers in the presence (+) and absence (-) of IS, at a uremic concentration (110 µM). To evaluate OAT1 function, fluorescein was used as substrate and its uptake was measured using a multi-plate reader.

Results: Our results show that ACE-inhibitors and cimetidine have either no or a slight effect at non-therapeutic concentrations on OAT1-mediated fluorescein uptake. On the contrary, ATII and low- and low-sodium drugs significantly reduce fluorescein uptake, with the highest potency for ATII-inhibitors. This trend was maintained in presence of IS, suggesting that these drugs could negatively influence secretion of PBUTs by cPTECs (Table 1).


Funding: Government Support - Non-U.S.

Table 1. OAT1-mediated fluorescein uptake: IC50 (µM) in the absence (-) and presence (+) of IS

<table>
<thead>
<tr>
<th>Drug</th>
<th>OAT1 (+)</th>
<th>OAT1 (-)</th>
<th>Drug</th>
<th>OAT1 (+)</th>
<th>OAT1 (-)</th>
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<tr>
<td>ACE-inhibitors</td>
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<td>NT</td>
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<tr>
<td>ATII</td>
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<td>Fluorescein</td>
<td>NT</td>
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</tr>
</tbody>
</table>

* Values are given as mean of two independent observations. NT=non-therapeutic concentration.

Kidney-Targeted Drug Delivery via Chitosan-Modified Liposome

Peng Xia,1,2 Wei Li,1,3 Yao Zhou,1 Wei Sun,1 Kun Gao,1,4,5 1Nephrology Division, 2Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China; 3Nanjing University of Chinese Medicine, Nanjing, China; 4Xazhou Medical University, Xuzhou, China.

Background: Regarding kidney disease therapy, extra-renal effects, the inactivation of drug before reaching kidney or altered distribution due to the pathophysiology of diseases limit some medication widely use. The specific delivery or selective activation in kidney maximizes therapeutic effectiveness and minimizes toxic side effects. The improvement of the pharmaceutical profile should be accomplished by drug targeting strategies. Liposome is single-layer or multi-layered vesicles composed of ordered lipid bilayers with an aqueous phase inside. Selective delivery of drugs in liposomes has been used clinically to treat some diseases because of their excellent biocompatibility, wide range of drug loading and low toxicity. They can increase the stability and solubility of the drug, give drug delivery and sustained release drug characteristics, and effectively improve the drug bioavailability. In this study, we evaluated the safety and effectiveness of chitosan-modified liposome as a kidney-targeted delivery system.

Methods: To establish chitosan-modified liposome delivery system, liposomes were prepared by thin-film methods and post-insertion technology was performed to achieve chitosan modification. The morphology was confirmed by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). To study the safety of the system, the cellular viability of human renal tubular epithelial cells, HK-2, was evaluated by cell proliferation kit. Drug release from the nanoparticle was analyzed at pH 7.4, 6.8 and 5.0 using the dialysis method. To investigate the specific kidney-targeted delivery, the vector

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Additive Renoprotective Effects of Angiotensin Converting Enzyme Inhibition and Nitro Fatty Acid (CXA-10) Combination

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Background: Underlying pathogenic mechanisms in chronic kidney disease (CKD) include chronic inflammation, oxidant stress, and matrix remodeling associated with dysregulated NF-κB, NRF2 and SMAD signaling pathways, respectively. During CKD progression these pathogenic mechanisms overwhelm endogenous cytoprotective mechanisms mediated by nitro fatty acids (NO₂-PA) that act through posttranslational drug modification to limit inflammation and oxidant stress.

Methods: To restore cytoprotective balance, we evaluated the effects of chronic treatment with CXA-10 (10-nitro-9E-oc-tadec-9-enonic acid), a nitro fatty acid, in a reduced renal mass (RRM) – high salt rat model of progressive CKD. Five treatment groups were examined (Control, CXA-10 (1.25 and 3.75 mg/kg, p.o.), enalapril and enalapril + CXA-10), for a 3-week dosing period that commenced 4 weeks following RRM.

Results: Enalapril significantly attenuated the increase in mean arterial pressure (MAP) and mildly blunted proteinuria, non-significantly. Similarly, the low dose of...
Rhein Reverses miR-34a-Mediated Autophagy in D-Galactose-Induced Renal Aging Rats via the Regulation of Gut Microbiome

Background: The alterations of gut microbiota in composition, diversity and functional features have a close relationship with aging-associated pathologies, including renal aging. microRNAs (miRNAs)-mediated autophagy also has an important role in aging. Recently, traditional Chinese herbal medications have been reported to possess potent anti-aging activities. Rhein is a bioactive constituent of rhubarb, derived from the root of Rheum palmatum with the anti-aging pharmacological effect. But the characteristics of gut microbiome and its relationship with miRNAs-mediated autophagy of rhein in anti-renal aging are unknown.

Methods: Forty rats were divided into Normal (N), Model (M), Rhein (R) and Vitamin E (E) groups. A modification of TFEB (165 pg/mL) was used to induce renal aging. The appropriate addition of rhein, VE and distilled water were administered with oral, respectively. All rats were sacrificed after 8 weeks treatments. Blood serum, fecal samples and kidneys were collected for the detection of various indicators. The characteristics of gut microbiome were determined through high-throughput sequencing. Serum concentrations of urea, creatinine, and cystatin C (Ct-C) were detected by ELISA. miR-34a expression level was detected by RT-PCR. The senescence-associated-β-galactosidase (SA-β-gal) staining was observed. The aging-related protein expressions of Klotho, p38, p-JNK, and p-Akt were detected by Western blot.

Results: Results showed that the structure and diversity of gut microbiota in 4 groups were different. Rhein and VE could reverse the abundance of some genus changed significantly in M group and compared with N group. NPG and VE could significantly decrease the increased IS, p38, p-JNK and p-Akt compared with N, E and R groups. Rhein and VE markedly alleviated the up-regulation of miR-34a in M group. In addition, Chlamydia and Veillonella could attenuate strong staining for SA-β-gal, and reverse the significantly changed aging-related protein expressions and autophagy markers in M group.

Conclusions: This study proved that rhein, similar to VE, could alleviate renal aging via regulating gut microbiome and miR-34a-mediated autophagy. Thus, targeting gut-kidney axis and miR-34a-mediated autophagy may provide new strategies in age-associated renal damage of the elderly patients.

Funding: Government Support - Non-U.S.

Hyposerial Ameliorates Renal Tubular Epithelial Cells Aging Induced by D-Galactose via Regulating mRNA Modification of TFEB mRNA

Background: The kidney is a typical organ that undergoes age-related tissue injury, however, there is little information on therapeutic effects underlying age-associated renal damage. Hyposerial (HYP), a component of Abelmoschus manihot, is reported to be useful for the treatment of age-related renal damage. We aimed to induce renal aging. The appropriate addition of HYP, and the VE could reduce the increased IS, p38 and p-Akt compare with N, E and R groups. HYP and VE could significantly decrease the increased IS, p38 and p-Akt compared with N, E and R groups. HYP and VE markedly alleviated the up-regulation of miR-34a and miR-196a in M group. In addition, HYP and VE could attenuate strong staining for SA-β-gal, and reverse the significantly changed aging-related protein expressions and autophagy markers in M group.

Conclusions: This study proved that HYP, similar to VE, could alleviate renal aging via regulating gut microbiome and miR-34a-mediated autophagy. Thus, targeting gut-kidney axis and miR-34a-mediated autophagy may provide new strategies in age-associated renal damage of the elderly patients.

Funding: Government Support - Non-U.S.
TH-P0379
PEGylation of Inositol Hexaphosphate (InsP6) Decreases Its Binding Affinity for Hydroxyapatite and Its Capacity to Inhibit Plasma Calcification In Vitro
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Background: Vascular calcification (VC) is a major contributor to increased morbidity and mortality in Chronic Kidney Disease patients undergoing dialysis. Although VC is a multifactorial process, the final common pathway is deposition of solid hydroxyapatite (HAP) within the arteries. SNF472, a salt of InsP6, is a selective calcification inhibitor that interferes in the formation and growth of ectopic HAP. SNF472 is currently being developed for the treatment of calciphylaxis in patients on dialysis. Insitol-1,2,3,5-tetraphosphate-4,6-bisPEG100 (InsP4bisPEG100) is an inositol phosphate derivative resulting from the PEGylation of inositol tetraphosphate (InsP4) with polyethylene glycol (PEG) 100. Our aim was to study the binding affinities of SNF472, InsP4bisPEG and InsP4 for the HAP surface, and its relationship with their in vitro efficacy by inhibiting calcium phosphate crystalization.

Methods: To evaluate the adsorption binding affinity (E_ads) of SNF472, InsP4bisPEG and InsP4 to the HAP crystal surface, computational studies were performed using Density Functional Theory calculations with DMOL3 (2016). The in vitro efficacy of InsP4bisPEG and InsP4 was evaluated using a pharmacodynamic assay to measure the plasma calcification potential using a previously validated spectrophotometric method, and compared to SNF472 in the 0-100 µM range.

Results: Molecular modelling revealed that SNF472 binds to the HAP surface with higher affinity than InsP4bisPEG, as revealed by their relative energies of absorption taking InsP4 as reference (AE = -110 kcal/mol for SNF472 and AE = -41.1 kcal/mol for InsP4bisPEG). These results are correlated with the inhibition potencies observed in the human plasma HAP crystalization assay. E_ads was 2.2 µM, 3.8 µM and 8.5 µM, for SNF472, InsP4bisPEG and InsP4, respectively.

Conclusions: SNF472 shows the highest binding affinity and the highest in vitro potency in the inhibition of HAP crystalization in human plasma, which is concordant with the larger electrostatic interactions between SNF472 and HAP, since it is a more charged molecule.

Funding: Commercial Support - Sanfiti Therapeutics

TH-P0380
Antisense Oligonucleotides Target Proximal Tubular Epithelial Cells in Kidney
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Background: Developing, refining and deploying new drugs to target specific molecules in cell types and tissues of interest is crucial for advancing towards precision medicine. Antisense oligonucleotides (ASO) are chemically synthesized, short DNA oligomers that can be applied to target specific mRNAs via hybridization and degradation, thus resulting in a reduced synthesis of related proteins. Recent data suggest that newer, more stable and effective generations of ASO may be of therapeutic value, including in kidney cell types and tissues of interest is crucial for advancing towards precision medicine. To develop and validate a predictive model to identify patients (pts) with chronic kidney disease (CKD) Stage 3 or 4 at high risk for progression to kidney failure (KF) over a 24-mo period.

Methods: A predictive model was developed and validated utilizing a retrospective claims database of CKD Stage 3 or 4 pts from a large US payer. The study covered 36 mo with a 12-mo (2015) baseline period and 24-mo (2016–2017) prediction period. All pts were ≥18 yrs of age without dialysis or kidney transplant and had ≥36 months of enrollment. KF was defined as: eGFR <15 ml/min/1.73 m²; or dialysis; or kidney transplant; or one diagnosis (ICD-10-CM: N18.5, N18.6) in prediction period. Multivariate logistic regression analysis was used to develop a model estimating the 2-yr probability of KF as a function of baseline covariates. Area under receiver operating characteristic (ROC) curve (AUC), calibration, gain and lift charts of the validation sample were used to assess the predictive model performance.

Results: Of the 74,114 pts studied, 2476 (3.34%) had incident KF in the prediction period. The predictive model for KF in the CKD stage 3 or 4 analyzed the following variables: High risk for progression to ESRD (PHS), anemia, hyperkalemia (HK), and poor RAAS inhibitors adherence. The strongest predictors were KDF Stage 4 (4 vs 3), HTN, BM and HK. The ROC curve and calibration analyses in the validation sample showed good predictive accuracy (AUC=0.834) and good calibration.

Funding: Government Support - Non-U.S., NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Conclusions: This predictive model provides a good level of accuracy in identifying CKD pts at high risk of progressing to CKF up to 2 yrs in advance in a national health plan with over 10 million lives. Early identification using this model could potentially lead to improved health outcomes and reduce health care expenditure.

Funding: Commercial Support - Funded by Relypsy, Inc., a Vifor Pharma Group Company

TH-PO383
Prognostic Score for Chronic Renal Disease in Patients with Lupus Nephritis
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Background: There is currently a prognostic score of progression to chronic kidney disease (CKD) in patients with lupus nephritis (LN), this tool evaluates: cellular and fibrous crescents; activity and chronicity index; glomerular sclerosis; interstitial fibrosis; nephrotic syndrome and glomerular filtration rate. The resulting data divides the population at low risk; moderate; and severe risk. The objective of this study was to apply this score to Mexican patients with LN and to predict their progression to CKD.

Methods: Study of ambilieective cohort of patients with NL of the HGM from August 2012 to August 2017, in which the prognostic score was applied. Descriptive statistics and survival analysis were performed with Cox regression, with 95% CI, considered a value of \( p < 0.05 \) as statistically significative.

Results: 141 patients were analyzed; we found a mean age of 32.01±10.95 years, 73% (103) women. According to the ISN/RPS class IV (38%) and class IV-V (34%) were identified and classes II, III, III+IV and V were present with frequency of 11% or less. The score stratified 54% (76) patients in the low risk; 43% (60) moderate; and 3% (4) severe. During the follow-up at 6 months, 29 patients (26%) presented total remission (RT); 42% (48) partial remission (PR); and 32% (36) without remission (SR). Progression to CKD: Risk Scores and Translational Epidemiology

TH-PO384
Prediction Model from Big Data for Rapid GFR Decline in CKD Patients with Machine Learning Technique
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Background: Recent studies have focused on kidney function trajectory because it might be related to the incidence of cardiovascular (CV) disease and all-cause mortality. We aimed to investegate risk factors for rapid GFR decline and create a machine learning-based predictive model by using one big hospital database.

Methods: We used a database derived from the Fujita Health University Hospital. Medical data were available for 120,689 eGFR-recorded patients in this study. Among them, 21,198 patients met the CKD criteria. Rapid GFR decline in patients with CKD was defined as eGFR decline of ≥30% per 2 years; we used average eGFR of past 90 days to avoid temporal spikes of measurements. We then selected unique 5,818 CKD patients with rapid GFR decline, from which 10,093 samples of rapid GFR decline were obtained. We built a prediction model to classify rapid GFR decline using machine learning algorithms including logistic regression, decision tree, and random forest. We used explanatory variables including 90-day past data of eGFR, proteinuria, serum creatinine (Cr), blood pressure, body mass index, sex, and age. Among those longitudinal data, we used average, standard deviation (SD), and exponentially smoothed average (ESA) to form exploratory variables for the prediction model. Contribution to rapid GFR decline was examined by weight of each variable.

Results: We used serial 10,093 data each from 5,818 CKD patients with rapid GFR decline and without rapid GFR decline for the prediction model. There were no significant differences in age and sex between the two groups. Mean proteinuria, ESA of proteinuria, SD of serum Cr, ESA of serum Cr, and SD of Hematocrit were associated with rapid GFR decline in the random forest model. Moreover, the random forest model predicted rapid GFR decline with an accuracy of 0.75 (area under the curve). Meanwhile, area under the curves for predicting rapid GFR decline were 0.69 and 0.69 in the logistic regression and decision tree models, respectively. By the decision tree analysis, the incidence of rapid GFR decline was 90% if the following criteria were fulfilled: 4+ or more of mean urine protein; ≤0.33 ESA of serum Cr; ≤0.33 SD of hemoglobin.

Conclusions: The random forest model by machine learning could be useful to identify patients with rapid GFR decline in real world clinical setting.

TH-PO385
Discovery of CKD Patient Subgroups by Consensus Clustering: The CRIC Study
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Background: CKD is a heterogeneous condition with multiple underlying causes, risk factors, and outcomes. Consensus clustering may reveal CKD subgroups with different risk profiles of adverse outcomes.

Methods: Among 2,060 participants in the prospective CRIC Study, we performed unsupervised consensus clustering with K-means, without using outcome information, on 72 baseline characteristics of traditional and novel factors to discover patient subgroups. We calculated the standardized difference of all predictors across subgroups, and used the cut-off of ±0.3 to show key features. We examined the associations of each subgroup with ESRD, cardiovascular diseases (composite of heart failure, MI, stroke, and PAD), and death.

Results: Three unique CKD subgroups, identified using only baseline factors, were associated with low (Cluster 1, N=1,203), medium (Cluster 2, N=1,098), and high (Cluster 3, N=95) risks of the outcomes (Fig 1). Patients in cluster 1 (lowest risk) had lower bone & mineral, diabetes, cardiac, and obesity markers, greater eGFR, and used fewer medications. Patients in cluster 2 had higher diabetes and obesity markers, and used more medications. Patients in cluster 3 (highest risk) had higher bone & mineral (except for lower serum calcium), cardiac (except for lower serum CO2), inflammation (except for lower serum albumin), and kidney markers (except for lower eGFR) (Fig 2).

Conclusions: Consensus clustering discovered distinct subgroups of CKD patients with distinguishing patterns of baseline clinical and laboratory factors yielding markedly different risks of important clinical outcomes. Specific biomarkers featuring high-risk CKD subgroup could provide potential treatment targets.

Funding: NIDDK Support
**TH-PO386**

Optimizing Machine Learning Methods for Clinical Outcome Prediction

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**Background:** Machine learning (ML) is useful to identify novel biomarkers and predict clinical outcomes, especially when predictors outnumber patients, but model building procedures are underutilized. We compared two ML methods and the impact of pre-specifying covariate functional forms on predictive accuracy and variable importance using data from NEPTUNE, a prospective cohort study of glomerular disease patient.

**Methods:** The sample was split into training (70%) and validation (30%) sets. Ridge regression and random forest models were developed in the training set to predict to time to two clinical outcomes: disease progression (ESRD or ≥40% eGFR decline with last eGFR <60) and complete remission of proteinuria (UPCR <0.3), with and without categorizing continuous covariates to accommodate non-linear associations with outcomes. Predictors included 56 demographic/clinical characteristics, which were ranked by variable importance. Discrimination was estimated in the validation set using integrated area under the curve (iAUC).

**Results:** Using pre-specified covariate functional forms in ridge regression increased iAUC from 0.68 to 0.74 for the progression outcome, but had little impact for remission (0.79 vs. 0.78; Fig) or the random forest method for both outcomes. iAUCs from random forest were higher than those from ridge for progression but not remission. After pre-specified functional forms in ridge regression, variable importance ranks increased for some known risk factors: rank of UPCR for predicting remission rose from 48 to 5 and rank of eGFR for predicting progression rose from 52 to 1. Other important predictors were disease diagnosis, age, and immunosuppression use for remission and disease diagnosis, race, and hypertension for progression.

**Conclusions:** For ML methods assuming linear associations, like ridge regression, pre-specifying covariate functional forms is important for predictive accuracy and detecting important predictors. Different ML methods may improve prediction for different outcomes. Higher ranking of known risk factors improves face validity in prediction models and may have positive implications for external validation performance.

**Funding:** Other NIH Support - National Center for Advancing Translational Sciences

**TH-PO387**

Study on Glomerular Filtration Rate Equation Using Ensemble Learning and Linear Regression

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**Background:** Accurate estimating glomerular filtration rate (GFR) is crucial both in clinical practice and epidemiological survey. We incorporated semi-supervised learning technology to improve GFR estimation performance.

**Methods:** Databases of AASK, CRIC and DCCT studies were pooled together for model development, whereas MDRD and CRISP studies for model external validation. The pooled development data set contained 2,719 participants, whereas the pooled external validation data set contained 1,952 participants. 4,829 participants only without GFR records but all other information available were pooled into an unlabeled data set for semi-supervised learning. New Predictors & Established Predictors : Serum creatinine, Age, Sex, Black race, Diabetes status, Hypertension and Body Mass Index. GFR measured from DTPA) renogram to obtain the standard value of GFR. We measured serum creatinine and CKD-EPI. Furthermore, we developed a DNN model with three hidden layers. The proposed semi-supervised model was essentially an artificial neural network developed by Ladder Network algorithm. Head-to-head performance comparisons were conducted between revised equations and semi-supervised models from 4-variable to 7-variable.

**Results:** In each independent variable combination, the semi-supervised models consistently achieved superior results in all 7 performance indicators compared with corresponding revised CKD-EPI equations in the external validation data set. When selecting one representative revised equation and semi-supervised model for further comparison, compared with revised 4-variable CKD-EPI equation, the 7-variable semi-supervised model performed best (iAUC 75.55 [73.75, 77.35], P < 0.001), more precise (interquartile range of difference: 0.14 [0.01, 0.28], P < 0.001) than the revised 4-variable equation in the external validation performance comparison. The proposed semi-supervised model still requires extra care, validation, and further improvement is expected by integrating more cohort data.

**Funding:** Government Support - Non-U.S.

**TH-PO389**

Development of the Deep Neural Network for Estimating Glomerular Filtration Rate

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**Background:** A variety of calculation formulas to estimate glomerular filtration rate (GFR) have been developed for decades. Recently, modern clinical medicine has been trying to use a deep neural network (DNN) in various clinical fields. Thus, we aimed to use the DNN model for estimation of GFR in the study.

**Methods:** A total of 241 patients with chronic kidney disease were enrolled in the study. All participants had technetium-99m diethylenetriaminepentaacetic acid (99mTc-DTPA) renogram to obtain the standard value of GFR. We measured serum creatinine levels from all participants and calculated GFRs using various formulas such as MDRD and CKD-EPI. Furthermore, we developed a DNN model with three hidden layers. The first, second, and third hidden layers included 40, 20, and 10 nodes respectively. We compared GFR values of MDRD, CKD-EPI, and DNN model against standard GFR values from renogram in various statistical ways.
Results: The mean differences of GFR value from MDRD, CKD-EPI, and DNN methods with standard GFR were 2.35, 2.86, and 1.87 mL/min respectively. The root-mean-square-error values of MDRD, CKD-EPI, and DNN methods against standard GFR were 19.45, 18.9, and 16.78 (mL/min)² respectively suggesting that the GFR values of DNN model are closest to standard GFR values. When estimating the accuracy in classifying CKD stages, the degree of error or reduced eGFR for 3 months. The definition of reduced eGFR was <60 mL/min/1.73 m² according to the standard KDIGO criteria, ≥65 years.

Conclusions: GFR measurement using DNN model is believed to be useful and accurate.

TH-PO390

Comparison of Standard and Age-Adapted GFR Criteria for Determination of CKD Prevalence
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Background: Inclusion of age-adjusted GFR criteria in the definition of chronic kidney disease (CKD) has been proposed to avoid overdiagnosis in the elderly and underdiagnosis in the young. The aim of this study was to estimate the prevalence of CKD based on age-adapted glomerular filtration rate (GFR) criteria compared with a standard cut-off of GFR value of 60 mL/min/1.73 m².

Methods: In this retrospective study, we obtained all serum creatinine (SCr) values and standard SCr were 2.35, 2.86, and 1.87 mL/min respectively. The root-mean-square-error values of MDRD, CKD-EPI, and DNN methods against standard GFR were 19.45, 18.9, and 16.78 (mL/min)² respectively suggesting that the GFR values of DNN model are closest to standard GFR values. When estimating the accuracy in classifying CKD stages, the degree of error or reduced eGFR for 3 months. The definition of reduced eGFR was <60 mL/min/1.73 m² according to the standard KDIGO criteria, whereas the age-adjusted eGFR definition was <75 mL/min/1.73 m² for age <60 years, <60 mL/min/1.73 m² for 40-65 years and <45 mL/min/1.73 m² for age >65 years.

Results: We obtained 2,120,232 SCr values for 218,437 individuals. The median age was 46 (range, 18-107) years; 47% were men. The age-adjusted mean annual prevalence of CKD per 100,000 men and women, respectively, was 4420 (95%CI, 4370-4470) and 5500 (95%CI, 5440-5550) using standard GFR criteria, compared with 2844 (95%CI, 2805-2883) and 3232 (95%CI, 3190-3274) using age-adjusted criteria. In men, the prevalence of CKD per 100,000 using standard vs age-adjusted GFR criteria was 505 vs 591 in the age group 18-44 and 54,454 vs 31,958 in the age group 85+. In women, the prevalence per 100,000 was 908 vs 1078 and 48,868 vs 26,157 for the same age groups, respectively (Figure 1).

Conclusions: Compared with the conventional GFR cut-off, age-adjusted GFR thresholds for definition of CKD yield a slightly higher prevalence in the young age groups, but a markedly lower prevalence among older people.

TH-PO391

Normalizing Urine Albumin to Urine Creatinine, Osmolality, or Not at All: Insights from NHANES
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Background: The concentration of urinary metabolites and proteins such as albumin is influenced by water excretion and urinary concentration, which varies across individuals and diurnally within individuals. To account for this variability, measures like albuminuria are often reported as normalized ratios. We hypothesized that the method of expressing urinary albumin – whether as a raw concentration or normalized to urine creatinine or osmolality – would influence observed associations with mortality due to confounding from determinants of urine protein excretion and osmolality, such as muscle mass, solute intake, and concentrating ability of the kidney.

Methods: We used data from the National Health and Nutrition Examination Survey 2009-2010 to model associations of albuminuria with mortality using Cox proportional hazards models. We used measurements on spot urine samples from 5,681 adults (age 42 ± 17 years) who had follow-up information on vital status (377 deaths) over 6 years. Results: Median estimated glomerular filtration rate was 97 (range, 7-170) mL/min/1.73 m², and median albumin:creatinine ratio was 5.9 (range 0.3-17,788) mg/g. The Table shows the associations of albuminuria with the risk of death. The strongest association was observed with urine albumin after multivariable adjustment for urinary creatinine.

Conclusions: While all methods of modeling urine albumin showed that elevated levels were independently associated with mortality, we found that associations were stronger when adjusted rather than normalized for urine creatinine and osmolality. Normalizing urinary biomarkers to urine creatinine may not be the optimal approach to distinguish urinary biomarker associations with health outcomes.

Multivariable-adjusted (MV) hazard ratios (95% confidence intervals) for different measures of albuminuria quartiles and the risk of death. Models were adjusted for age, sex, race/ethnicity, hypertension, cardiovascular disease, diabetes mellitus, body mass index, and estimated glomerular filtration rate.

TH-PO392

Conversion of Urine Protein-Creatinine to Albumin-Creatinine Ratio for Use in CKD Risk Equations

Background: Urine albumin-creatinine ratio (ACR) is a core component of CKD staging and used in equations to predict adverse outcomes. However, many cohorts and health systems preferentially measure urine protein-creatinine ratio (PCR) rather than ACR. These assays measure different protein components and the degree to which levels are often reported as normalized ratios. We hypothesized that the method of expressing urinary albumin – whether as a raw concentration or normalized to urine creatinine or osmolality – would influence observed associations with mortality due to confounding from determinants of urine protein excretion and osmolality, such as muscle mass, solute intake, and concentrating ability of the kidney.

Methods: We used data from the National Health and Nutrition Examination Survey 2009-2010 to model associations of albuminuria with mortality using Cox proportional hazards models. We used measurements on spot urine samples from 5,681 adults (age 42 ± 17 years) who had follow-up information on vital status (377 deaths) over 6 years. Results: Median estimated glomerular filtration rate was 97 (range, 7-170) mL/min/1.73 m², and median albumin:creatinine ratio was 5.9 (range 0.3-17,788) mg/g. The Table shows the associations of albuminuria with the risk of death. The strongest association was observed with urine albumin after multivariable adjustment for urinary creatinine.

Conclusions: While all methods of modeling urine albumin showed that elevated levels were independently associated with mortality, we found that associations were stronger when adjusted rather than normalized for urine creatinine and osmolality. Normalizing urinary biomarkers to urine creatinine may not be the optimal approach to distinguish urinary biomarker associations with health outcomes.

Multivariable-adjusted (MV) hazard ratios (95% confidence intervals) for different measures of albuminuria quartiles and the risk of death. Models were adjusted for age, sex, race/ethnicity, hypertension, cardiovascular disease, diabetes mellitus, body mass index, and estimated glomerular filtration rate.

Multivariable-adjusted (MV) hazard ratios (95% confidence intervals) for different measures of albuminuria quartiles and the risk of death. Models were adjusted for age, sex, race/ethnicity, hypertension, cardiovascular disease, diabetes mellitus, body mass index, and estimated glomerular filtration rate.
RMSE 0.83). Relationships between PCR and ACR were similar across cohorts (Figure), as well as demographics, and hypertension, cardiovascular disease, and diabetes status. Conclusions: Guidelines recommend measurement of ACR. However, when ACR is not available, we developed an equation to convert PCR levels >50mg/g to ACR for use in risk equations. Lower levels of PCR were not amenable to harmonization.

Funding: NIDDK, Support, Private Foundation Support

TH-PO393
High-Normal Albuminuria Is Strongly Associated with Incident CKD in a Nonobdiant Population with Normal Kidney Function
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Background: Several studies have reported that high albuminuria within the normal range (high-normal albuminuria) is associated with chronic kidney disease (CKD). This study aimed to clarify the association between high-normal albuminuria and the risk of incident CKD, particularly in a nondiabetic population with normal kidney function.

Methods: A 10-year follow-up, retrospective cohort study was performed involving 317 Japanese men (mean age, 42 years) with an eGFR ≥ 90 mL/min/1.73 m2 and urine albumin-to-creatinine ratio (UACR) < 30 mg/gCr. Patients were free of diabetes mellitus. We calculated the cut-off value of the UACR from receiver-operating characteristic curves, and the value of ≥ 7.0 mg/gCr was defined as high-normal albuminuria. Multivariate stepwise analysis and logistic regression approaches were used to assess independent predictors of the incidence of CKD.

Results: Twenty-nine (9%) participants developed CKD through 10 years of follow-up. At the baseline examination, blood pressure, the UACR, and BUN values were higher in participants who developed incident CKD than in those with normal renal function. After adjustment for confounders, high-normal albuminuria was associated with an increased risk of incident CKD. Logistic regression analyses showed that subjects with a UACR ≥ 7.0 mg/gCr had an increased risk of new-onset CKD 10-years later compared with a UACR < 7.0 mg/gCr (odds ratio, 16.61; 95% confidence interval, 6.45–42.78; P < 0.01). This difference persisted after adjustment for age, BMI, hypertension, smoking status, and dyslipidemia.

Conclusions: High-normal albuminuria is associated with incident CKD in a nondiabetic population with normal kidney function.

TH-PO394
eGFR Trajectory in Old Age
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Background: Longitudinal data about the natural course of estimated glomerular filtration rate (eGFR) among older adults over several years are scarce. The Berlin Initiative Study (BIS) aims to fill this gap by evaluating repeat assessments of eGFR over time and potential risk factors for GFR decline in older adults.

Methods: The BIS is a prospective population-based cohort study initiated in 2009 whose participants are members of a German insurance company with the biggest fraction of older adults. Participants were interviewed face-to-face biannually using a standardized questionnaire recording clinical, laboratory and patient reported outcomes. eGFR was calculated with the BIS2(crea/cysC) formula. The course of eGFR was analyzed with a linear mixed-effects model, comprising age, sex, diabetes mellitus (DM), smoking status, body mass index (BMI), systolic blood pressure (systBP), albumin-creatinine ratio (ACR), serum creatinine, cystatin C, ACE inhibitors, AT1 antagonists, NSAID, number of regular drugs, and myocardial infarction (all time-dependent), applying multiple imputation for missing data.

Results: As of May 06, 2019, 2,069 participants (47.4% male, mean age 80.4 years at inclusion) were followed for a median of 6.0 years. Of those, 1,699 (82%) had at least 2 eGFR assessments. We observed higher eGFR values in men. Crude linear regression lines of the eGFR course suggested a continuous decline, which decreased with rising age. In the mixed linear effects model, age, sex, BMI, myocardial infarction, current smoking, systBP, use of sartanes and the number of regular drugs had a significant impact on eGFR.

Conclusions: Taking into account the potential impact of clinical, therapeutically and behavioral variables, we still observed an age-dependent decrease of eGFR, suggesting a naturally declining course in older age. The mixed model reveals that the expected mean eGFR for men aged ≥79 and women ≥78 is below 60, defining deficient kidney function when using the current classification system.

Funding: Private Foundation Support

TH-PO395
Sex Differences in the Risk of ESKD and Death Among Patients with Moderate to Advanced CKD Followed Up in Renal Clinics
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Background: Data on sex-specific differences in the epidemiology of CKD may help nephrologists to better tailor treatments for their patients. However, studies evaluating the association of sex with CKD progression have provided conflicting results.

Methods: We pooled four observational cohort studies including consecutive CKD patients (not dialysis/transplant) under stable Nephrology care for ≥6 months. Out of 3,212 unique patients, we selected 1,311 men and 1,024 women with eGFR<45 mL/min/1.73m2. Primary outcome was ESKD (chronic dialysis or renal transplantation), all-cause mortality and eGFR decline were secondary outcomes. We used multivariable Cox proportional hazard analysis to estimate relative risk of ESKD and all-cause mortality, and linear mixed models to estimate the rate of eGFR decline.

Results: Age (67±14 y), systolic BP (139±20 mmHg), use of RAS inhibitors (69%), antihypertensive drugs (2.3±1.2) and statins (30%) were similar in men and women. Compared to men, women had lower eGFR (26.1±28±10 mL/min/1.73m2, P=0.001) and lower proteinuria (0.45 g/dI IQR 0.14-1.10 vs 0.69 g/d, IQR 0.19-1.60, P=0.001). During a median follow-up of 4.2 years, 757 developed ESKD (507 women) and 471 died (196 women). Table reports the adjusted risk (HR and 95%CI) of ESKD and all-cause mortality overall and by CKD stages. We found a significant interaction between sex and proteinuria with the risk of ESKD in men becoming significantly greater at a level of proteinuria ≥0.5 g/d. Rate of eGFR decline (mL/min/year) was greater in men than in women (2.1±1.5 vs 1.4±1.2, P=0.001) with no difference across CKD stages (P=0.28). The difference in slopes between men and women was progressively larger with proteinuria levels ≥0.5 g/d (P=0.04).

Conclusions: Our study highlights an excess of renal risk in men possibly related, at least in part, to the higher levels of proteinuria in men compared to women.
Performance of Creatinine-Based GFR Estimates in Patients on Ritonavir-Boosted Protease Inhibitors

Juli Chaudhari,1 Christina M. Wyatt,2 Shiuyuan Miao,3 Ziporah Krishnasami,3 Andrew S. Levey,1 Michael J. Ross,3 Lene Ryom,1 Amanda Mocroft,4 Laurence Brunet,1 Jennifer S. Fusco,1 Lesley Inker.2 Tufts Medical Center, Boston, MA; 3Duke University School of Medicine, Durham, NC; 4Epidemic, Inc., Durham, NC; 5University College London, London, United Kingdom; 6Bethesda, MD; 4Centers for Disease Control and Prevention, Atlanta, GA.

Background: The pharmacoenhancer ritonavir has been shown to inhibit tubular transport of creatinine in vitro. We aimed to determine whether use of ritonavir-boosted protease inhibitors (PI) affects the performance of creatinine-based GFR estimates.

Methods: We previously measured GFR (mGFR) in 200 HIV-positive adults on stable antiretroviral therapy using plasma iohexol clearance. We evaluated performance of the CKD-EPI creatinine equation (CKD-EPI_eq), MDRD Study equation, and Cockcroft-Gault creatinine clearance (indexed to 1.73 m² body surface area) versus mGFR. We compared bias (median difference between mGFR and estimated GFR) and accuracy (percent of estimates within 30% of mGFR, with large errors indicated by 1 - P30). Statistical significance of the differences in bias and accuracy were tested by Wilcoxon two-sample test and chi-square test, respectively.

Results: 73% of the population was male, 52% of Black race, and 34% over the age of 50 years. 61% were virologically suppressed and 44% were on a PI. No participants were taking other antiretrovirals known to inhibit creatinine secretion. The CKD-EPI equation performed better than other equations. There were no clinically or statistically significant differences in the performance of any equation between the PI and no-PI1 groups (Figure).

Conclusions: Use of PI may not have a significant impact on the performance of creatinine-based GFR estimates as compared to mGFR. Declines in eGFR with the use of PI may reflect real changes in kidney function.

Funding: Other NIH Support - Supported by the National Center for Research Resources; the National Center for Advancing Translational Sciences, National Institutes of Health Grant UL1 TR000375 (Tufts Medical Center) and UL1 RR028887 (Mount Sinai School of Medicine); and the New York City Department of Health Grant UL1 RR002577 (University of Alabama at Birmingham), Commercial Support - Supported by Gilead Sciences, Inc under an investigator-initiated protocol NCCR LIR025752.

Performance of creatinine-based estimating equations in patients on PI versus no PI based on right accuracy: PI; ritonavir-boosted protease inhibitor; GFR, glomerular filtration rate; CKD-EPI_eq, GFR by CKD-EPI creatinine equation; MDRD, GFR by MDRD Study equation; CG, creatinine clearance by Cockcroft-Gault equation indexed to 1.73 m² body surface area. Error bars represent 95% confidence intervals.

TH-PO398

State-Level Kidney Disease Surveillance Using Medicaid Data in Michigan and California

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Background: Medicaid provides health insurance for low-income individuals, including children. Coverage varies by state. We examined the feasibility of using state-level Medicaid data for chronic kidney disease (CKD) surveillance in a disadvantaged, low income, and younger US population.

Methods: The 2012 Medicaid Analytic eXtract data for the states of Michigan (MI) and California (CA) were evaluated. Patients with >3 months of Medicaid eligibility aged ≤ 21 were included. CKD was defined by two outpatient or one inpatient ICD-CM codes. Descriptive analyses were conducted for children (age <22) and adults (age ≥ 22).

Results: The study population for MI (n=1,700,044) included 989,834 (58%) children and for CA (n=7,457,920) included 3,661,569 (49%) children. CKD was diagnosed in 0.9% of children (9,160) and 3.7% of adults (26,580) in MI, and 0.7% of children (24,090) and 3.0% of adults (114,183) in CA. There was geographic variation in prevalence of diagnosed CKD (Figure 1). Higher proportions of diabetes (DM) and hypertension (HTN) were seen in those with CKD (vs. non-CKD) in MI (DM: children 3.9% vs. 0.7%, adults 41.3% vs. 11.7%; HTN: children 7.6% vs. 0.6%, adults 62.4% vs. 17.2%) and CA (DM: children 2.2% vs. 0.4%, adults: 40.6% vs. 7.9%; HTN: children 6.6% vs. 0.2%, adults 47.7% vs. 11.1%). Emergency department use was higher among CKD patients (vs. non-CKD) in both MI (children 59.4% vs. 40.5%; adults 65.9% vs. 40.9%) and CA (children 69.5% vs. 28.8%; adults 41.6% vs. 21.4%).

Conclusions: We demonstrate the feasibility of using Medicaid data from two states for CKD surveillance efforts. There is substantial geographic variation of diagnosed CKD in both MI and CA with higher prevalence mostly in urban areas. Children and adults with CKD had a higher prevalence of comorbidities and ED use compared to those without CKD. This work serves as a foundation for future analyses of other state and longitudinal data to guide upstream disease prevention and management for a young and socioeconomically disadvantaged population.

Funding: Other U.S. Government Support

Prevalence of Chronic Kidney Disease (per 1000 patients) in Michigan (A) and California (B), by county.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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TH-PO399

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Background: Although chronic kidney disease (CKD) is common in the Irish health system, few data exist on longitudinal trends and future growth. To better inform strategic planning of renal services, we determined future trends in CKD burden in the Irish population.

Methods: Data from the National Kidney Disease Surveillance System (NKSS) determined age and sex standardised prevalence of CKD among adults > 18 yrs, in Midwest and Northwest regions from 2005-2014. CKD was defined as eGFR < 60 mL/min per 1.73 m² using the CKD-EPI equation. Four forecasting models (naïve with trend, exponential smoothing, Holt’s linear trend, and autoregressive integrated moving average (ARIMA)) estimated future prevalence of CKD beyond 2015 to 2024. The population at risk was derived from national census data in 2006 and 2011.

Results: Study included 478,251 participants, average age 55.5 (18.8) years with 53% female. From 2005 to 2014, overall prevalence increased significantly from 6.72% (95% CI 6.17-7.24%) to 9.20% (95% CI 8.66-9.75%); men 9.40% (95% PI: 8.81, 9.99); and women 9.06% (95% PI: 8.31, 9.80). The largest growth occurred in the elderly age 75+, p-value <0.001, [5.81 (5.78,5.85) to 7.28 (7.25,7.32), p< 0.001]) than for women [7.62% (7.59,7.66%)] than for men [7.05% (6.96, 7.16%)] to 7.73% (7.71-7.46%), with significantly greater increases for men (p-value <0.001), while prevalence fell in all other age groups, p value <0.001 for each. By 2024, overall prevalence was predicted to increase to 9.20% (95% PI 8.66, 9.75); men 9.40% (95% PI: 8.81, 9.99); and women 9.06% (95% PI: 8.31, 9.80).

Conclusions: In line with current trends, we forecast continued growth in CKD burden up to 2024. These are driven principally by increases in the elderly. Given the risk implications on rates of kidney failure, morbidity and mortality, actionable policies that promote better CKD prevention and treatment strategies should be vigorously pursued.

Funding: Government Support - Non-U.S.

TH-PO400

The Prevalence, Awareness, and Treatment of CKD in Korean Adults
Kyeong Min Kim, Eunjii medical center; Daejeon, Republic of Korea.

Background: Chronic kidney disease (CKD) is a global public health problem, and its prevalence has dramatically increased with an increasing old aged and their chronic diseases. It is known that the rate of recognition and treatment of chronic renal failure is very low. But there is a lack of data on prevalence, awareness, treatment of CKD that is representative of the Korean population. Our objective was to investigate the prevalence, awareness and treatment in Korean CKD patients.

Methods: Among adults aged ≥ 19 years who participated in the Korea National Health and Nutrition Examination Survey (KNHANES) between 2013 and 2014, a total of 15,568 subjects were analyzed. CKD prevalence was defined as an eGFR < 60 mL/min/1.73m2 or spot urine albumin to creatinine ratio a 30 mg/g.

Results: A total of 9,550 incident CKD patients between 2013 and 2014 were included in the analysis. The prevalence of CKD was 8.66%. Of the total patients, 341 patients (3.78%) were in the stage 1 of CKD, 316 patients (2.52%) in the stage 2, 311 patients (2.15%) in the stage 3, 15 patients (1.16%) in stage 4 and 4 patients (0.04%) in the stage 5. The rate of awareness and the treatment of CKD were 2.19% and 1.35%, respectively.

Conclusions: In this nationally representative KNHANES data, very low awareness and treatment observed for Korean patients with CKD. And we analyzed the prevalence of chronic kidney disease in Korean adults using the most up-to-date data available. The present findings provide meaningful epidemiological data.

Table 1. Awareness of CKD in South Korea

<table>
<thead>
<tr>
<th>Diagnosis of CKD by Doctor</th>
<th>Non-CKD</th>
<th>CKD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>500 (94.5)</td>
<td>100 (95.4)</td>
<td>600 (99.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>100 (5.5)</td>
<td>6 (4.6)</td>
<td>66 (9.7)</td>
</tr>
<tr>
<td>Unknown or Refused to Answer</td>
<td>20 (4.0)</td>
<td>4 (3.3)</td>
<td>24 (4.0)</td>
</tr>
</tbody>
</table>

Figure 1. Prevalence of CKD in South Korea

TH-PO401

Histopathologic and Demographic Features Associated with ESRD and Death
Tae-Hwi Schwantes-An, Ranjani N. Moonthri, Carrie L. Phillips, Michael T. Eadon. Indiana University School of Medicine, Indianapolis, IN.

Background: The ability to stratify risk for developing end-stage renal disease and death in those who undergo a kidney biopsy allows us to better prognosticate patients who are at higher risk. We hypothesize that histopathologic features in kidney biopsy specimens augment risk stratification for ESRD and death and over above a fully adjusted demographic and clinical model.

Methods: Data from 2,720 individuals who underwent a kidney biopsy from 2001 to 2015 from the Biobank Biopsy Cohort of Indiana were obtained. Natural language processing facilitated annotation of histopathologic features and discrete clinical data was added using bioinformatics methods. Primary outcome was defined as time to ESRD or death, whichever occurred earlier. Censoring was done at 5 year follow up. Using Cox proportional hazard models, we studied relationship between demographic variables, comorbidities, baseline clinical features, primary diagnosis, and histopathologic features.

Results: Within 5 years of biopsy, 625 (23.0%) patients reached the primary endpoint of ESRD or death. Survival analysis with demographic and clinical variables as covariates and stratification by baseline renal function, glomerular obsolescence (Hazard Ratio 1.81, 95% CI, 1.42 to 2.32, Pvalue < 0.001), interstitial fibrosis and tubular atrophy (HR 1.61, 95% CI, 1.30 to 2.0, Pvalue < 0.001), arteriolar hyalinosis (HR 1.46, 95% CI, 1.15 to 1.85 Pvalue < 0.001), and nodular mesangial sclerosis (adjusted HR 1.44, 95% CI, 1.15 to 2.82 Pvalue <0.01).

Conclusions: Histopathologic features on kidney biopsy specimens further augmented risk prediction for ESRD and death when compared to models with demographic and clinical variables alone. Inclusion of histopathologic features in ESRD and death risk models facilitates improved prognostication.

Funding: NIDDK Support
The Histological Spectrum of CKD in HIV-Infected Black Patients: A Single-Centre Experience
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Background: HIV infection has become one of the world’s most serious health and developmental challenge affecting 36.9 million people. Kidney disease is the 4th most common cause of death among HIV-infected patients. HIV-Associated Nephropathy (HIVAN) has been documented as the most common cause of chronic kidney disease (CKD) in HIV-seropositive patients. Although 9% of world’s HIV-infected patients live in Nigeria, data on spectrum of kidney diseases affecting HIV-infected patients are still paltry. The study was undertaken to determine the histological spectrum of CKDs in HIV-infected patients.

Methods: Fifty-eight adequate biopsy samples from 72 adult HIV-infected patients with ages ≥ 15 years, were included. Patients were aged 21-65 years. Mean age was 43.86 ± 9.83 years. Forty-three (74.1%) patients had WHO clinical asymptomatic disease. Only 9/58 (15.5%) patients had CD4 cell count < 200 cells/mm³.

Results: There were 25 (43.1%) males and 33 (56.9%) females. Participants were aged 21-65 years. Mean age was 43.86 ± 9.83 years. Forty-three (74.1%) patients had WHO clinical asymptomatic disease. Only 9/58 (15.5%) patients had CD4 cell count < 200 cells/mm³. Histology showed 13(22.4%) HIVAN, 8(13.8%) normal histology and 37(63.8%) non-HIVAN lesions including: 12(20.7%) FSGS (NOS), 7(12.1%) focal glomerulosclerosis, 6(10.3%) chronic interstitial nephritis, 4(6.9%) minimal chronic damage, 4(6.9%) arteriorenopelrosisclerosis, 3(5.2%) FSGS (cellular variant) and 1(1.7%) BK-virus nephropathy.

Conclusions: Although HIVAN remains the predominant histology finding in HIV-infected patients with CKD, its prevalence in this study is less than previous reports emphasizing the need for kidney biopsy for accurate diagnosis of CKD in HIV-infected patients.

Funding: Private Foundation Support

Citation: Onu UC, Adu D, Ojo AO, Ulasu IL. TH-PO402. J Am Soc Nephrol 30: 2019

Clinical and Pathological Characterization of Patients with ESKD from a Potential Mexican CKD of Undetermined Etiology (CKDu) Hotspot
Sofia De Arreguiaguna,1 Marco A. Ascencio Martinez,1 Laura Crespo Ortega,1 Gregorio Villarreal,2 Gregorio T. Obrador,3 Antonio Villa,1 Diego J. Aguilar-Ramirez,2 Madgalena Madero,1 1Universidad Panamericana, School of Medicine, Mexico City, Mexico; 2University of Oxford, Oxford, United Kingdom; 3Instituto Nacional de Cardiologico, Mexico, Mexico.

Background: Mesosamerican nephropathy (MeN) – the chronic kidney disease of unknown etiology (CKDu) identified in Central American hotspots – affects mostly young, male farmers without traditional risk factors (TRF) for kidney disease. To date, CKDu hotspots have not been described in Mexico. Between 1991 and 2018, 57 patients from a sugarcane region in Tierra Blanca, Veracruz (Mexico) were referred to our Institution for kidney transplantation. The aim of this study was to identify the clinical characteristics and risk factors for CKDu in these patients and compare their histopathological findings with others previously reported.

Methods: Socio-demographic, clinical, laboratory and pathological data were collected from medical records. Patients were categorized as having TRF for CKD (diabetes mellitus and/or hypertension) or not (CKDu). Descriptive statistics were used and multivariate logistic regression models were built to identify CKDu associated risk factors.

Results: The mean age of the 57 patients was 26.9 ± 9.7 years, 70% were male, and 44% farmers. Mean BMI was 23.0 ± 4.17, and 39% had a positive family history for CKD. Thirty (53%) patients met CKDu criteria. In the multivariate logistic regression model, agricultural work and family history of CKD were independent risk factors for CKDu, while high BMI conferred protection. Of the six patients who underwent kidney biopsy, 5 showed atrophy, mild sclerosis, tubulointerstitial nephritis, and inflammatory infiltrate, all compatible with previously reported MeN findings.

Conclusions: The clinical and pathological characteristics of this group of patients suggest that Tierra Blanca, Veracruz (Mexico) may be a potential CKDu hotspot. This conclusion is further supported by another study done by our group that showed a high prevalence of CKD in this region. Further research is needed to confirm our findings.

Table 1. Logistic regression model for CKDu

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in Years (yr)</td>
<td>1.00 (0.99-1.01)</td>
<td>0.72</td>
</tr>
<tr>
<td>Sex</td>
<td>0.50 (0.42-0.61)</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.81 (0.58-1.21)</td>
<td>0.35</td>
</tr>
<tr>
<td>Agricultural work</td>
<td>4.89 (1.28-18.31)</td>
<td>0.02</td>
</tr>
<tr>
<td>Family History of CKD</td>
<td>0.01 (0.00-2.41)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Illustrative graphs of the stage 2 process

Evaluation of Kidney Fibrosis Based on Imaging and Histologic Analysis
Fiona Zhang,1 Tang Xiong,2 Xiaoshuang Liu,3 Long jiang Zhang,2 Zhihong Liu.1 1National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China; 2Nanjing University, Nanjing, China; 3Jinling Hospital, Nanjing, China; 4Ping An Health Technology, Beijing, China.

Background: Increased institial extracellular matrix (EM) and peritubular capillary (PTC) dropout are two key pathologic features of the fibrosing kidney. There is absence of enale multiple dimensional pictures to show fibrotic kidney from function, imaging and morphology. Methods: We derived a represented model for EM ratio and PTC densities using intravoxelcoherent motion diffusion weighted imaging (IVIM-DWI), magnetic resonance elastography (MRE) and glomerular filtration rate (estimate GFR). 97 patients with chronic kidney diseases from stage 1 to 4 were studied. EM ratio and kidney microcirculation were evaluated by pathology. A multi-dimensionals perspective and relationship of kidney fibrosis based on histology, imaging and GFR were established. Multiple linear regression and ROC were performed.

Results: The cortex EM ratios were linear with the nature logarithm of MRE and eGFR, which were both negatively associated with EM ratios. The best fitted model was as below: EM ratio= ln[(MRE-18.499)+18.499]+18.42]>EM ratio (Figure 1). The PTC densities were linear with DWI-Fraction and eGFR, which were both positively related with PTC. The best fitted model was as below: PTC density=17.914+9.403(DWI-Fraction)+0.112<eGFR (Figure 2).

Conclusions: Our study firstly provides histological evidences to support that IVIM-DWI and MRE can effectively evaluate the EM ratio and PTC densities. These findings delineate the multi-dimensional picture of kidney fibrosing.
Reproducibility of the SOMAscan Proteomic Assay in CKD: A Pilot Study in the Chronic Renal Insufficiency Cohort (CRIC) for the CKD Biomarkers Consortium

Ruth F. Dubin,1 Rajat Deo,2 Yue Ren,2 Haochang Shou,2 Harold I. Feldman,2 Eugene P. Rhee,1 Josef Coresh,3 Paul L. Kimmel,1 Peter Ganz,2 1UCSF, San Francisco, CA; 2University of Pennsylvania, Philadelphia, PA; 3Massachusetts General Hospital, Newton, MA; 4National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Bethesda, MD; 5University of California, San Francisco, San Francisco, CA; 6Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD.

Background: The Slow Off-rate Modified Aptamer proteomic assay (SOMAscan) is a transformative tool used increasingly in medical research as it affords the opportunity to measure 4,933 unique proteins in 150μl of plasma. In prior studies, mostly outside of the setting of chronic kidney disease (CKD), these assays have low levels of analytical variability, with median inter- and intra-assay coefficients of variation (CV) of 4–6%. Whether the biochemical alterations present in CKD impact the assay’s precision is unknown. We examined the reproducibility of these assays in participants with CKD.

Methods: Cryopreserved blinded split duplicate plasma samples from 24 CRIC participants were assayed at SomaLogic (Boulder, CO). Among these 24, 8 were from each of CKD Stages IIIa, IIIb, and IV. Within each stage, 4 had diabetes, and 4 had history of CVD. Using the SOMAscan v.4, 4933 unique proteins were quantified in each paired sample in fluorescent units. Measurement of 4,993 unique proteins with SOMAscan in plasma samples of patients with CKD was achieved with low levels of analytical variability. These data demonstrate that the SOMAscan assay is suitable for large-scale proteomic studies of individuals with CKD.

Results: Prior to unblinding, 1 sample was excluded for having a technical error. For the remaining 23 paired samples, the median intra-assay CV for all proteins was 7%; 95.6% of all 4,993 proteins had CV ≤10% and 99.8% had a CV ≤20%. The distribution of CV’s did not differ by CKD stage (Figure).

Conclusions: Measurement of 4,993 unique proteins with SOMAscan in plasma samples of patients with CKD was achieved with low levels of analytical variability. These data demonstrate that the SOMAscan assay is suitable for large-scale proteomic studies of individuals with CKD.

Funding: NIDDK Support
Association of Serum Uromodulin with Mortality, Cardiovascular Disease, and Kidney Function Decline in CKD Patients: The GCKD Study

Dominik Steubl, Markus P. Schneider, Heike Meiselbach, Jennifer Nadal, Turgay Saritas, Vera Krane, Claudia Sommerer, Scena Baid-Agrawal, Anna Kottgen, Kai-Uwe Eckardt, Juergen E. Scherberich.

Klinikum rechts der Isar, Munich, Germany; 2Division of Nephrology, Tufts Medical Center, Boston, MA; 3Klinikum Nuremberg, Nuremberg, Germany; 4Nephrology and Hypertension, Erlangen, Germany; 5University of Wuerzburg, Wuerzburg, Germany; 6Medical Center - University of Freiburg, Freiburg, Germany; 7Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden; 8Charité – Universitätsmedizin Berlin, Berlin, Germany; 9Nephrology, RWTH Aachen University, Aachen, Germany; 10University of Heidelberg, Heidelberg, Germany; 11IMBIE, Bonn, Germany; 12University Munich Klinikum Muenchen Harlaching, Muenchen Gruenwald, Germany.

Background: Uromodulin is exclusively produced by tubular cells and released into both urine and serum. Lower sUMOD has been associated with end-stage renal disease (ESRD) in Chinese chronic kidney disease (CKD) patients and with higher risk for mortality in patients undergoing coronary angiography. The association of sUMOD with cardiovascular (CV) events and ESRD in Caucasian CKD patients is unknown.

Methods: We measured sUMOD in 5143 participants enrolled in the German Chronic Kidney Disease (GCKD) study. The associations of baseline sUMOD with all-cause mortality, major adverse CV events (MACE; a composite of fatal CV event, non-fatal myocardial infarction or stroke, or incident peripheral vascular disease) and ESRD (dialysis or transplantation) were evaluated using multivariable Cox regression analyses, adjusting for demographics, estimated glomerular filtration rate (eGFR), albuminuria, CV risk factors and medication.

Results: The mean age was 60±12 years, 60% were male. sUMOD level was 98±60 ng/ml, eGFR was 47±17 ml/min/1.73 m² and 78% had eGFR<60 ml/min/1.73 m². Patients in the lower sUMOD quartiles had lower eGFR, hypertension, coronary artery disease and stroke at baseline were more frequent in lower sUMOD quartiles. During a follow-up of 4 years, 319 patients died, 398 developed MACE and 216 ESRD (Table 1). In multivariable analysis, higher sUMOD was significantly associated with lower hazard for mortality (HR 0.238 [0.174-0.32] [0.13-0.18] for the highest versus lowest quartile, MACE (HR 0.632 [0.445-0.898]) and ESRD (HR 0.238 [0.103-0.547]), Table 1).

Conclusions: Higher sUMOD is independently associated with lower risk for mortality, CV events and ESRD in Caucasian CKD patients. A better understanding of the underlying mechanisms may lead to therapies offering both renal and CV protection in CKD patients.

Table 1: Associations of serum uromodulin (sUMOD) with mortality, end-stage renal disease and cardiovascular disease

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Mortality HR (95% CI)</th>
<th>CV events HR (95% CI)</th>
<th>ESRD HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Q1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Q2</td>
<td>1.12 [0.89-1.41]</td>
<td>1.07 [0.82-1.40]</td>
<td>1.00</td>
</tr>
<tr>
<td>Q3</td>
<td>1.08 [0.82-1.43]</td>
<td>1.08 [0.82-1.43]</td>
<td>1.00</td>
</tr>
<tr>
<td>Q4</td>
<td>1.40 [1.10-1.79]</td>
<td>1.10 [0.82-1.48]</td>
<td>1.00</td>
</tr>
</tbody>
</table>

TH-PO408

Association of Serum Uromodulin with Mortality, Cardiovascular Disease, and Kidney Function Decline in CKD Patients; The GCKD Study

Dominik Steubl, Markus P. Schneider, Heike Meiselbach, Jennifer Nadal, Turgay Saritas, Vera Krane, Claudia Sommerer, Scena Baid-Agrawal, Anna Kottgen, Kai-Uwe Eckardt, Juergen E. Scherberich.

Klinikum rechts der Isar, Munich, Germany; 2Division of Nephrology, Tufts Medical Center, Boston, MA; 3Klinikum Nuremberg, Nuremberg, Germany; 4Nephrology and Hypertension, Erlangen, Germany; 5University of Wuerzburg, Wuerzburg, Germany; 6Medical Center - University of Freiburg, Freiburg, Germany; 7Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden; 8Charité – Universitätsmedizin Berlin, Berlin, Germany; 9Nephrology, RWTH Aachen University, Aachen, Germany; 10University of Heidelberg, Heidelberg, Germany; 11IMBIE, Bonn, Germany; 12University Munich Klinikum Muenchen Harlaching, Muenchen Gruenwald, Germany.

Background: Uromodulin is exclusively produced by tubular cells and released into both urine and serum. Lower sUMOD has been associated with end-stage renal disease (ESRD) in Chinese chronic kidney disease (CKD) patients and with higher risk for mortality in patients undergoing coronary angiography. The association of sUMOD with cardiovascular (CV) events and ESRD in Caucasian CKD patients is unknown.

Methods: We measured sUMOD in 5143 participants enrolled in the German Chronic Kidney Disease (GCKD) study. The associations of baseline sUMOD with all-cause mortality, major adverse CV events (MACE; a composite of fatal CV event, non-fatal myocardial infarction or stroke, or incident peripheral vascular disease) and ESRD (dialysis or transplantation) were evaluated using multivariable Cox regression analyses, adjusting for demographics, estimated glomerular filtration rate (eGFR), albuminuria, CV risk factors and medication.

Results: The mean age was 60±12 years, 60% were male. sUMOD level was 98±60 ng/ml, eGFR was 47±17 ml/min/1.73 m² and 78% had eGFR<60 ml/min/1.73 m². Patients in the lower sUMOD quartiles had lower eGFR, hypertension, coronary artery disease and stroke at baseline were more frequent in lower sUMOD quartiles. During a follow-up of 4 years, 319 patients died, 398 developed MACE and 216 ESRD (Table 1). In multivariable analysis, higher sUMOD was significantly associated with lower hazard for mortality (HR 0.238 [0.174-0.32] [0.13-0.18] for the highest versus lowest quartile, MACE (HR 0.632 [0.445-0.898]) and ESRD (HR 0.238 [0.103-0.547]), Table 1).

Conclusions: Higher sUMOD is independently associated with lower risk for mortality, CV events and ESRD in Caucasian CKD patients. A better understanding of the underlying mechanisms may lead to therapies offering both renal and CV protection in CKD patients.
Figure. Adjusted Hazard Ratio for the Kidney Endpoint per Doubling in Plasma Biomarker.

TH-PO412
Attenuation of Estimated Glomerular Filtration Rate Decline After Arteriovenous Fistula Creation in Pre-Dialysis Marie-Eve Dupuis,1 Louis-Philippe Laurin,1 Naouel Eliftouh,1 Vincent Pichette,1 Remi Goupil,2 Jean-Philippe Lafrance,1 Annie-Claude Nadeau-Fredette,1 1Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; 2Hopital du Sacre-Coeur de Montreal, Montreal, QC, Canada.

Background: Arteriovenous fistula (AVF) placement has been associated with potential attenuation of eGFR decline. Uncertainty remained as to whether this association is specifically related to AVF or rather involves confounding such as natural change in eGFR decline. We sought to assess CKD-EPI eGFR changes before and after AVF creation using a comparator group of peritoneal dialysis (PD) oriented patients.

Methods: This observational study included incident patients followed in a CKD clinic between 2000 and 2017. Patients with AVF placement were matched 1:1 (using age, sex, race, diabetes and eGFR) with patients who underwent PD catheter installation. Time zero/match-point was defined by AVF creation date (AVF group) or date when eGFR was closest to their ‘AVF-par’ eGFR at time of AVF creation (PD-matched group). Mixed effect linear regression models were built to predict eGFR in the AVF and PD-matched groups. Estimated-GFRs were calculated using the CKD-EPI equation.

Results: Baseline characteristics of the 47 patients with AVF and 47 patients with PD catheter installation were globally similar. Median eGFR at time of AVF creation was 11.4 mL/min/1.73m² (and 11.9 mL/min/1.73m² in matched PD group). Predicted eGFR decreased by 0.4 mL/min per month in both groups. There was an attenuation in eGFR decline each additional month after AVF creation/match-point (B = 0.23, p = 0.001 AVF group, B = 0.13, p = 0.001 PD matched group). However, the period after AVF creation (or match-point) was associated with a fixed increase in predicted eGFR only for the AVF group (B = 0.1, p = 0.001).

Conclusions: In this matched cohort study, placement of AVF was associated with an increase in predicted eGFR in the AVF group only. There was however, an attenuation of monthly eGFR decline in both groups with progression of advanced CKD. Overall, this study supports other findings suggesting a contribution of AVF in the stabilisation of eGFR decline.

TH-PO413
Prevalence of Kidney Failure Among Adult Population in Madagascar Ranivoharisoa E, Mikkelson A, Antso hasina Raherinandrasona Z, Ziad Massy J, Julio Rakotomininana H, Harilalaina W. Randriamarotia, Befelatanana Nephrology’s Team 1University Hospital of Befelatanana, Antananarivo, Madagascar; 2University Hospital of Care and Public Health Analaky, Antananarivo, Madagascar; 3Ambroise Pare University Hospital and Inserm U1018 EqP, Boulogne Billancourt/ Paris cedex, France.

Background: Kidney Failure becomes a public worldwide health problem mainly in a developing country. Few data is available in most of countries in Africa to specify the prevalence of CKD. We assessed the prevalence and risk factors of kidney failure among population in Madagascar.

Methods: We conducted a randomized, multicenter, cross sectional study among four provinces in the island. It includes Tananarive, Majunga, Fianarantsoa and Tananarive. Kidney function was evaluated by capillary creatinine using strip test and creatinine meter. We defined kidney failure if the glomerular filtration rate calculated with the Equation of Chronic Kidney Disease Epidemiology was under than 60mL/min/1.73m². Cluster sample was used to characterise the study population.

Results: A total of 808 patients were included. Prevalence of kidney failure was 12.5%. Mean age 38 years old (±15). Sex ratio was 0.84. Patients aged 45-55 years old was 62.1%. Normal socioeconomic class was found in 64% of the cases. Hypertension and diabetes were identified respectively in 30.3% and 7.7% in studied population. During screening, mean creatinine level was 99μmol/L (±25) and mean post prandial glycemia was 1.16g/dl (±0.3). According to KDIGO classification, patients were classified in Stage 3, 4 and 5 of CKD respectively in 10.76% (N=87), 0.7% (N=6) and 1% (N=8). In mono variable analysis, kidney failure was related with gender (p = 0.078), age (p = 0.001), socioeconomic class (p = 0.005), familial background of hypertension (p = 0.04), personnel background (p = 0.001) and diabetes (p = 0.05). There was no association of blood pressure during examination (p = 0.088), glycemia (p = 0.003) and body mass index (p = 0.003). In multiple variable analysis, it was related with female gender (OR = 0.57; IC = 0.35-0.92), age > 54 years old (OR = 1.04; IC = 0.52-2.37), rural socio economic class (OR = 2.8; IC = 1.03-7.81), overweight (OR = 2.5; IC = 1.08-4.92) and obesity (OR = 2.3; IC = 1.13-5.73).

Conclusion: This is the first study in Africa which evaluates the kidney failure by using creatinine strip test. The prevalence is high compare another african countries. Almost of the patients were seen lately over Stage 3 of CKD requiring a specialized medical follow-up. Prevention of all risk factors should be first of all the best solution.

TH-PO414
Estimated Glomerular Filtration Rate Decline and Incidence of Major Surgery: A Population-Based Cohort Study Tyrone Harrison,1 Matthew T. James,1 Kelly B. Zarrke,2 Zhiiha Ma,1 Shannon M. Ruzyczki,1 Brenda Hemmelgarn.1 University of Calgary, Calgary, AB, Canada.

Background: Approximately 1 in 9 Canadian adults have a surgical procedure each year, however whether the rates of major surgical procedures vary by level of estimated glomerular filtration rate (eGFR) is unknown. We aimed to quantify the incidence of major surgery by varying degrees of impaired kidney function.

Methods: We identified 1,455,565 adults in Alberta, Canada that had at least one outpatient serum creatinine measure or were in receipt of chronic dialysis between 2008 and 2009. As in prior studies, incident major surgical procedures were identified and categorized into 13 major surgical subtypes using procedure codes and physician claims; major surgery was defined by requiring hospital admission for at least one day. Surgical subtypes included musculoskeletal, intra-abdominal, lower urogynecologic, head and neck, vascular, skin and soft tissue, cardiac, breast, neurosurgery, retroperitoneal, thoracic, anorectal, and ophthalmologic. Only the first event per surgical subtype was included. Patients were follow-up from January 1 2010 to December 31 2016, and were censored at kidney transplantation, outmigration or death. Incidence rates by eGFR strata were estimated using negative binomial regression and adjusted for age, sex, income, location, proteinuria, and comorbidities.

Results: The median age of the cohort was 51.6 years (IQR 39.4, 63.4) with the majority female (57.0%). Most patients had an eGFR ≥60mL/min/1.73m² (92.2%), with 0.1% having an eGFR <15mL/min/1.73m² not on dialysis. Over a median follow up of 7.00 years, musculoskeletal surgeries were the most common across all eGFR strata, with adjusted incidence rates between 9.88 per 1000 person-years (95%CI: 9.39, 9.56) for those with eGFR ≥60mL/min/1.73m² and 74.81 per 1000 person-years (95%CI: 65.60, 85.32) for dialysis patients. Similar trends of increasing surgical incidence for those with lower eGFR were noted for all surgical types except for breast and lower urogynecologic.

Conclusion: In a large population-based cohort, incidence rates of major surgical procedures increased with decreasing eGFR, and were highest among dialysis-dependent patients. Further research is needed to investigate whether differences exist in perioperative outcomes and costs for those with varying degrees of kidney function.

TH-PO415
Clinical Significance of Creatinine Variability and Its Impact on Cardiovascular Outcomes in the General Population Sooin Lee1, Min woo Kang2, Semin Cho3, Yaerim Kim1, Jung Pyo Lee3, Chun Soo Lim1, Kwon Wook Joo1, Youn Su Kim1, Dong Ki Kim1.1 Seoul National University Hospital, Seoul, Republic of Korea; 2Seoul National University Boramae Medical Center, Seoul, Republic of Korea; 3Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Linear decline of glomerular filtration rate (GFR) is unknown. We aimed to quantify the incidence of major surgery by varying degrees of impaired kidney function.

Methods: We identified 1,455,565 adults in Alberta, Canada that had at least one outpatient serum creatinine measure or were in receipt of chronic dialysis between 2008 and 2009. As in prior studies, incident major surgical procedures were identified and categorized into 13 major surgical subtypes using procedure codes and physician claims; major surgery was defined by requiring hospital admission for at least one day. Surgical subtypes included musculoskeletal, intra-abdominal, lower urogynecologic, head and neck, vascular, skin and soft tissue, cardiac, breast, neurosurgery, retroperitoneal, thoracic, anorectal, and ophthalmologic. Only the first event per surgical subtype was included. Patients were follow-up from January 1 2010 to December 31 2016, and were censored at kidney transplantation, outmigration or death. Incidence rates by eGFR strata were estimated using negative binomial regression and adjusted for age, sex, income, location, proteinuria, and comorbidities.

Results: The median age of the cohort was 51.6 years (IQR 39.4, 63.4) with the majority female (57.0%). Most patients had an eGFR ≥60mL/min/1.73m² (92.2%), with 0.1% having an eGFR <15mL/min/1.73m² not on dialysis. Over a median follow up of 7.00 years, musculoskeletal surgeries were the most common across all eGFR strata, with adjusted incidence rates between 9.88 per 1000 person-years (95%CI: 9.39, 9.56) for those with eGFR ≥60mL/min/1.73m² and 74.81 per 1000 person-years (95%CI: 65.60, 85.32) for dialysis patients. Similar trends of increasing surgical incidence for those with lower eGFR were noted for all surgical types except for breast and lower urogynecologic.

Conclusion: In a large population-based cohort, incidence rates of major surgical procedures increased with decreasing eGFR, and were highest among dialysis-dependent patients. Further research is needed to investigate whether differences exist in perioperative outcomes and costs for those with varying degrees of kidney function.
Participants with higher creatinine variability were significantly associated with elevated risk of MI (hazard ratio (HR) (95% confidence interval (95% CI)) 1.11 (1.04-1.18), stroke (HR (95% CI) 1.06 (1.00-1.13)) and death (HR (95% CI) 1.15 (1.09-1.21)), compared to those with the lowest quartile of creatinine variability.

Conclusions: Increased creatinine variability exhibited association with elevated risk of MI, stroke and death. In general population, whose renal function is prior to CKD development, monitoring of creatinine variability needs to be considered as the parameter of predicting the adverse outcomes, in addition to the decline of GFR.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

TH-PO416
Progressive Kidney Failure: An Overlooked Feature of Down Syndrome
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Background: Life expectancy of patients with Down syndrome (DS) has increased significantly in the last decades. DS is associated with a fourfold risk of urinary tract abnormalities, still data on renal dysfunction in DS patients are conflicting. The present study was set out to assess kidney function in a large pediatric tertiary DS clinic.

Methods: Retrospective analysis of data collected during routine visits at the DS clinic of the VU medical center. All patients aged between 2 and 18 years in whom serum creatinine had been measured were eligible for inclusion. Exclusion criteria were glucocorticosteroid use, neuromuscular disease or primary referral to a nephrologist or urologist. Kidney function was assessed using the full-age spectrum equations, i.e. eGFRcrea = (107.3/[sCr (mg/dL)/Q (age- or height-based normal value)]) and eGFRcys = (107.3/[sCys (mg/L)/0.82]).

In a subgroup of 74 patients, a total of 374 serial creatinine measurements were analyzed by linear mixed modelling.

Results: Serum creatinine was available in 189 patients (63% boys), aged 10.8 ± 5.0 years, with a median [IQR] of 0.70 µmol/L [0.55-1.01]. Mean eGFRcrea was 83.6 ± 16.7 mL/min/1.73m², mean eGFRcys = 87.3 ± 12.0 mL/min/1.73m². Based on eGFRcrea, 32% of patients had CKD stage 1, 62% stage 2 and 6% stage 3. There was no relation between kidney function and co-morbidity (i.e. celiac disease, congenital heart disease, hypothyroidism and history of leukemia). Serial measurements showed a significant decline of eGFRcrea (slope -2.01 mL/min/1.73m²/yr [95%CI -2.99 to -1.04] (p < 0.0001).

Conclusions: Mildly to moderately impaired renal function is a common finding in children with Down syndrome. The progressive loss of GFR is troublesome and calls for regular monitoring of kidney function both in children and in adults with DS to identify potentially treatable risk factors for disease progression such as hypertension and microalbuminuria.

Serial measurements of eGFR

TH-PO417
Incidences of ESKD and Death Before ESKD Among US Veterans with New-Onset CKD
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Background: Epidemiologic data on competing-risks events of progressing to ESKD or death before ESKD are limited due to prevalent cohorts used. Using a recently constructed national incident CKD cohort, we report the 5-year incidence of these two events following new CKD onset by demographics, kidney function and comorbidity conditions.

Methods: The cohort included 534,972 subjects with new onset CKD (stage 3-5) between 2002 and 2011 in the U.S. Veteran affairs database. CKD onset was determined by two eGFRs (based on CKD-EPI equation) <60 mL/min/1.73 m² at >90 days apart. We excluded subjects in the database who had <2 years before the first eGFR <60 or had prior ESKD. As such, the index date identified was very close to new onset CKD. All subjects were followed for 5 years.

Results: The three groups had similar mean eGFRs at onset (range 49-50 mL/min/1.73 m²) and gender distributions (97%-98 male). Blacks had younger onset age (mean 67 years) than Hispanics (71 years) and whites (74 years). Over the course of 5 years after onset, approximately two-thirds of the initial cohort remained alive in pre-ESKD, with Blacks having a lower percentage (65%) than Hispanics and Whites (68%). Among the one-third who progressed, Blacks and Hispanics had greater percentages who progressed to ESKD than Whites (10%, 7%, and 2%, respectively), whereas they had smaller percentages of dying before ESKD (25%) than Whites (30%). Males were more likely than females to develop these two events. The relative likelihood of the two events also varied by age and GFR (Table), as well as comorbidities such as diabetic and hypertensive status and cardiovascular diseases (not shown).

Conclusions: Improving outcomes for patients with CKD could be more effective by identifying risk factors associated with differential risks of developing ESKD and dying before ESKD.

Funding: NIDDK Support

Percentages of events within 5 years of CKD onset

TH-PO418
Survival ofPatients with CKD Stages 1-5 in Iceland
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Background: Studies on survival of patients with chronic kidney disease (CKD) employing the KIDIOB definition and classification system with repeated serum creatinine (SCr) and proteinuria measurements were scarce. The present study was to estimate hazard ratio (HR) for death in patients with CKD stages 1-5 in Iceland.

Methods: In this retrospective study, we obtained all SCr values and urine protein measurements from every clinical laboratory in Iceland in 2008-2016. Clinical information, including ICD-10 diagnosis codes indicating kidney disease or proteinuria, or as eGFR <60 mL/min/1.73m² for ≥3 months. Cox regression was used for survival analysis with CKD stage as a time-dependent variable and adjustments for age at study entry, sex, number of SCr measurements, initial eGFR, multiple co-morbid conditions and by CKD detection criteria, i.e. proteinuria, kidney specific diagnosis or reduced eGFR, either by a single criterion or various combinations.

Results: We obtained 2,120,232 SCr values for 218,437 individuals and information on proteinuria for 84,364 individuals. A total of 4972 had persistent proteinuria, 5286 had kidney disease diagnoses and 20131 had eGFR <60 mL/min/1.73 m². The median age was 46 (range, 18-167) years and 47% were men. Compared with individuals without CKD, the hazard ratios (95%CI) for patient survival were 10.39 (7.62-14.17), 3.92 (3.8-8.85), 1.43 (1.31-1.56), 2.00 (1.83-2.20), 3.15 (2.78-3.57) and 11.88 (9.63-13.95) for CKD stages 1, 2, 3a, 3b, 4 and 5, respectively.

Conclusions: This nationwide study on survival of patients with CKD, incorporating kidney disease diagnoses and albuminuria and CKD and SCr values over time, suggests increased risk of death for all CKD stages. While this finding supports current criteria for definition of CKD, a more detailed analysis of the influence age is needed.

TH-PO419
eGFR Decline in Patients with CKD and at Risk for CKD by Age, Gender, and Race/Ethnicity in Two Large Health Systems
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Background: Comparisons in eGFR decline in patients with CKD and At-risk for CKD have not been described. We completed an analysis of eGFR trajectories (eGFR-T) in CKD and At-risk for CKD patients from the UCLA-PHSI CKD Registry.
Methods: The cohort: >2.6 million adults (2006-2017) based on labs and/or diagnoses of CKD, hypertension (HTN), diabetes mellitus (DM), or pre-DM from administrative codes. We analyzed CKD (N=84,150) and At-risk CKD (N=807,211) patients with ≥3 eGFRs ≥15%/min/1.73m2 followed for an average (SD) of 5.4±2.4 years. We identified non-decliners, moderate and severe decliners (≥2%/y; 2-5%/y; ≥5%/y/min/1.73m2/ year), by least-squares fit for individual eGFR-T: Linear mixed effects (LME) models compared eGFR-T in moderate and severe decliners across gender and race/ethnicity groups, stratified by CKD vs. At-risk for CKD.

Results: Most patients were 45-64 yrs (41%), female (56%) and White Non-Latino (83%). CKD vs. At-risk CKD patients were 665 years (72% vs 36%), and had more DM (18% vs 106%) and HTN (25% vs 18%), p<0.001. Severe (vs. non- and moderate-) decliners had higher baseline eGFR and 27% of At-risk CKD progressed to eGFR <60ml/min/173m2. eGFR-T were steepest for CKD 18-44 yrs: -5.22 (95%CI= -5.38, -5.11) and -5.18 (95%CI= -5.38, -5.01), vs. 18% of CKD patients were moderate decliners (p<0.001) and declined in female vs. male CKD patients (p=0.025) and At-risk CKD (p=0.001) patients. eGFR-T were steepest for CKD American Indian/Alaska Native (p=0.007) and At-risk Native Hawaiian/Pacific Islander (p=0.001) vs. White Non-Latino. Similar results were obtained in fully adjusted LME models.

Conclusions: Patients with CKD are older, have more DM and HTN, lower baseline eGFR, and more rapid renal function decline compared to At-risk CKD patients. CKD and At-risk CKD severe decliners were youngest, with the highest baseline eGFR. The study results suggest a subset of young patients with high baseline eGFR may be important to target to prevent rapid renal function decline.

Funding: Private Foundation Support

TH-PO420

Progression of Kidney Disease in Patients with CKD of Undetermined Etiology in Sri Lanka: Disease Natural History and Association with Water Source

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Background: Chronic kidney disease of unknown etiology (CKDu) is occurring at high rates in Sri Lanka, without an identified cause or risk factors for progression. Prior GIS mapping and case-control studies have implicated shallow water well use as potentially causative, since water here could be contaminated with irrigation fields. We recruited a cohort of patients with CKDu from an endemic region in Sri Lanka to determine 1) natural history of disease, and 2) identify any modifiable risk factors for disease progression, with the hypothesis that persons experiencing faster progression may have ongoing or higher dose exposure to other causative agent(s).

Methods: We recruited 302 persons with CKDu, with the clinical criteria: CKD-EPI eGFR < 60 ml/min/1.73m2 on two tests at least 3 months apart, none to trace proteinuria on urine dipstick, and no self-reported diagnosis of diabetes. In addition to extensive baseline questionnaire and groundwater sampling, we undertook quarterly IDMS-calibrated serum creatinine testing. We used linear mixed models to test the association of the three putative risk factors with eGFR decline over time, accounting for age and sex.

Results: Over a median follow up 9.8 (25%-75% percentile 9.6, 10.7) months, 293 participants provided at least one serum test for eGFR assessment, with median eGFR slope -0.68 (25%-75% percentile -3.14 to 1.00) ml/min/1.73m2/year. 48 (16.4%) participants experienced eGFR decline > 5 ml/min/1.73m2/year. Participants who had never used water from a dug well had slower decline (eGFR slope 6 ml/min/1.73m2 higher (95%CI: 0.3-12.3 ml/min/1.73m2, p value: 0.04) (Figure 1).

Conclusions: Kidney function decline in surviving patients with CKDu in Sri Lanka is slow. No exposure to dug well water was associated with slower decline, and could be investigated as potential cause(s) or disease modifiers.

Funding: Other NIH Support - NIH grant number- grant 12102751

TH-PO421

Urinary Molybdenum Levels and CKD: National Health and Nutrition Examination Survey (1999-2016)

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Background: Molybdenum is both a metal and a micronutrient needed for enzymatic reactions in the carbon, sulfur, and nitrogen metabolism. However, their effects on kidney functions are not well investigated. We aimed to investigate the association of urinary molybdenum levels with chronic kidney disease (CKD) according to increased urinary albumin-to-creatinine ratio (ACR), decreased glomerular filtration rate (GFR), and composite outcomes.

Methods: Population-based cohort study. A total of 16,294 adult aged above 18 years old participants, who participated in the NHANES surveys over 18 years, were enrolled. We used multivariable linear regression adjusting age, sex, ethnicity, diabetes mellitus, hypertension, and body mass index to analyze the association between log-transformed standardized (standard deviation converted to 1) urinary molybdenum levels and urinary ACR and GFR. The association between log-transformed standardized urinary molybdenum levels and CKD was investigated by multivariable logistic regression methods. CKD was defined as three categories; urinary ACR above 30 mg/g (CKD ACR30), GFR below 60 ml/min/1.73m2 (CKD GFR60), and composite of CKD ACR30 or CKD GFR60 (CKD ACR30 GFR60).

Results: Mean age of participants was 47.1 ± 19.3 years old, and male participants were 7,978 (49.0%). Mean urinary ACR was 42.6 ± 326.5 mg/g and GFR was 94.4 ± 24.7 ml/min/1.73m2. Diabetic patients were 2,162 (13.3%) and participants with hypertension were 6,314 (38.8%). Number of patients with CKD GFR60, CKD ACR30, and CKD ACR30 GFR60 was 1,401 (8.6%), 1,983 (12.2%), and 2,922 (17.9%). Log-transformed standardized urinary molybdenum levels were significantly associated with the GFR (β = 3.093, P-value < 0.001), but not with urinary ACR (β = 2.761, P-value = 0.289). Prevalence of CKD GFR60 and CKD ACR30 GFR60 decreased significantly according to the increased urinary molybdenum levels (P-value < 0.001 and 0.03, respectively).

Conclusions: Urinary molybdenum levels are positively correlated with GFR, risk of CKD (CKD GFR60 and CKD ACR30 GFR60) decreased according to the increased urinary molybdenum levels.

TH-PO422

A Newly Recognized Endemic Region of CKD of Undetermined Etiology in South India: The Tondaimandalam Nephropathy

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Background: There are some regions with high incidence of unexplained CKD, referred to as CKD of Undetermined etiology (CKDu), predominantly affecting underprivileged farming populations in tropical climates in Sri Lanka & Latin America. Similar CKD cluster was reported from Andhra Pradesh, India. Many patients exhibiting characteristics of CKDu seek treatment at our tertiary care center in South India & we explored whether a similar burden of CKDs exist in our region as well.

Methods: All consecutive incident adults with CKD per KDIGO criteria presenting to the renal clinic between 1st January 2015 and 31st December 2018 were prospectively recruited in this observational study. Case definition of CKDu by WHO was used. We define a new endemic area of CKD (Tondaimandalam) in Tamil Nadu, India, accounting for 56.2% of CKD.

Conclusions: We define a new endemic area of CKDu (Tondaimandalam) in Tamil Nadu, India, accounting for 56.2% of CKD.

Funding: Private Foundation Support, Government Support - Non-U.S.
TH-PO423

Associations Between Long-Term Ambient PM$_{2.5}$ Exposure and Prevalence of CKD: An Analysis Based on the China National Survey of CKD

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Background: Our aim is to explore the associations between long-term exposure to ambient PM$_{2.5}$ and prevalence of chronic kidney disease (CKD) based on the China National Survey of CKD.

Methods: A sample of 47,204 people representing general adult population in China were recruited from January 2007 to October 2010. Annual exposure to satellite derived PM$_{2.5}$ (obtained from the Aerosol Optical Depth Database) prior to the survey date (2 years range) was estimated at each participant’s address using validated satellite-based spatiotemporal model with 10km x 10km resolution. Participants with estimated glomerular filtration rate <60 mL/min/1.73 m$^2$ and/or urinary albumin creatinine ratio $>30$mg/g were defined as CKD. Generalized additive mixed effects models were used to estimate the associations, and the influence of the potential modifiers were also analyzed.

Results: Across all participants (mean age 24.8 years) at baseline 87% of men and 95% of women had an eGFR<90mL/min/1.7m$^2$, but despite excluding those self-reporting CKD, 2.9% of males had an eGFR<60mL/min/1.7m$^2$. In the original cohort, 90% participants attended 2 of the 7 study visits. eGFR varied substantially visit-to-visit such that 42% of men (Figure) and 54% of women had an eGFR<90mL/min/1.7m$^2$ at some point during the 4-year follow-up. Furthermore, among men (but not women), 11% had an eGFR<60mL/min/1.7m$^2$ (at ≥1 visit), 3.8% developed new CKD, and 0.8% (n=2) died from kidney failure over the follow-up.

Conclusions: Within person eGFR varies substantially in this population at high-risk of CKD. This likely reflects important biological effects, as well as analytical variation, making longitudinal studies critical for disease insight. Nonetheless there is both a substantial loss of eGFR and unprecedented rates of incident CKD among young men in the region. 1. Gonzalez-Quiroz et al. JASN 2018

Funding: Private Foundation Support

TH-PO424

Incident CKD over 4 Years in a Population-Based Study of Apparently Healthy Young Adults at Risk of Mesoamerican Nephropathy (MeN)

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Background: MeN has led to the death of tens of thousands of young adults across rural Central America. We recently reported eGFR decline of over 30mL/min/1.7m$^2$ over 2 years among substantial numbers of apparently healthy young adults from rural communities in northwest Nicaragua. The consequences of this early loss of eGFR is not known.

Methods: The original 350 participants (a rural, population-based sample, aged 18-30 years, male/female ratio 3:1, without reported diabetes, hypertension or CKD) from the study have been followed-up annually for a further 2 years. An additional 417 men and women (ratio 1:1) were recruited in October 2018. Serum creatinine was measured at UNAN-Leon after each study visit and eGFR was calculated by CKD-EPI formula. de novo CKD was defined as those participants from the original cohort with an eGFR<60mL/min/1.7m$^2$ at baseline who developed an eGFR<60mL/min/1.7m$^2$ on at least two serial measurements without recovery.

Results: Across all participants (mean age 28.4 years) at baseline 87% of men and 95% of women had an eGFR<90mL/min/1.7m$^2$. In the original cohort, 42% of men (Figure) and 54% of women had an eGFR<90mL/min/1.7m$^2$ at some point during the 4-year follow-up. Furthermore, among men (but not women), 11% had an eGFR<60mL/min/1.7m$^2$ (at ≥1 visit), 3.8% developed de novo CKD, and 0.8% died from kidney failure over the follow-up.

Conclusions: Within person eGFR varies substantially in this population at high-risk of MeN. This likely reflects important biological effects, as well as analytical variation, making longitudinal studies critical for disease insight. Nonetheless there is both a substantial loss of eGFR and unprecedented rates of incident CKD among young men in the region. 1. Gonzalez-Quiroz et al. JASN 2018

Funding: Government Support - Non-U.S.
Background: In several countries, including India, Sri Lanka, and Mesoamerica, there are notable differences as well. Individuals affected in Mesoamerica are younger (aged 20-40 as opposed to 20-60). Both regions show a higher male-to-female ratio, and potential concordance. Affected individuals largely live in poverty. Most work in agriculture and live in rural areas, although not all. In Mesoamerica, the clinical presentation of CKDu is different, with a higher prevalence of AKI and CKD compared to Sri Lanka and India. Clinical management in early stages of CKDu focuses on appropriate hydration with clean water, minimizing exposure to heat and agrichemicals, and correction of electrolyte disturbances. Timely diagnosis and establishment of nephrology care appears to improve outcomes.

Conclusions: More studies on the clinical aspects and management of CKDu are desperately needed; to date there is little published guidance for clinicians and health care providers. Nevertheless, based on our experience there are concrete actions which can be taken by both healthcare providers and governments to care for people affected by CKDu.

Funding: NIDDK Support

TH-PO246 MicroRNA Profiling of Urinary Exosomes to Identify Appropriate Housekeeping Genes and Early Biomarkers of CKD in Humans

Background: In the last decade or so the CKD mortality increased by almost 30%, with diabetic kidney disease increasing 40% throughout the globe. Regular screening for kidney disease onset can lessen this burden. The potential of urinary exosome (UE) as a non-invasive source for kidney disease biomarkers has gained enormous research attention. However, the lack of optimal endogenous control for normalizing gene-expression analysis has hampered translation into clinical practice.

Methods: Using microarray, we compared the microRNA profile of UE from early kidney disease subjects [with and without diabetes, serum creatinine < 2.0 mg/dl] with matched healthy controls. taqman-based RT-PCR was done for validation.

Results: Around fifteen hsa-miRs were found constitutively expressed across the three groups. Out of these, four abundant miRs were validated by TaqMan-based RT-PCR (n=10-20/group). Also, we found twenty-seven differentially expressed miRs in the UE among the three groups. Pathway analysis revealed VEGF signaling, focal adhesion, and cytokine-cytokine receptor interaction pathways as major targets of the differentially expressed miRs. Among the the differentially expressed miRs, mir-200c-3p, let-7i-3p, miR-6812 and miR-320 were validated by TaqMan-based RT-PCR (n=10-20/group). Also, we found twenty-seven differentially expressed miRs in the UE with the potential to serve as a non-invasive source for kidney disease biomarkers with high clinical relevance.

Funding: Government Support - Non-U.S.

TH-PO247 Clinical Considerations Surrounding CKD of Undetermined Etiology (CKDu): Expert Consensus from the Third International Workshop on CKDu

Background: CKDu is a term that describes a pattern of endemic, non-diabetic, non-hypertensive kidney diseases characterized by reduced GFR without nphrotic range proteinuria or features of glomerulonephritis. It has been described most extensively in rural communities in Mesoamerica, Sri Lanka, and India, although the global extent is unknown. The underlying etiology or etiologies of CKDu remains incompletely understood, and there are no consensus guidelines for CKDu management.

Methods: The Third International Workshop on CKDu was held March 20-22, 2019 in San Jose, Costa Rica. Our working group, comprised of clinicians who care for CKDu patients in India, Sri Lanka, and Mesoamerica as well as CKDu researchers, developed an expert consensus on the clinical features and management of the disease.

Results: While there are many similarities in the clinical aspects of CKDu in India, Sri Lanka, and Mesoamerica, there are notable differences as well. Individuals affected in Mesoamerica are younger (aged 20-40 as opposed to 20-60). Both regions show a higher male-to-female ratio, and potential concordance. Affected individuals largely live in poverty. Most work in agriculture and live in rural areas, although not all. In Mesoamerica, the clinical presentation of CKDu is different, with a higher prevalence of AKI and CKD compared to Sri Lanka and India. Clinical management in early stages of CKDu focuses on appropriate hydration with clean water, minimizing exposure to heat and agrichemicals, and correction of electrolyte disturbances. Timely diagnosis and establishment of nephrology care appears to improve outcomes.

Conclusions: More studies on the clinical aspects and management of CKDu are desperately needed; to date there is little published guidance for clinicians and health care providers. Nevertheless, based on our experience there are concrete actions which can be taken by both healthcare providers and governments to care for people affected by CKDu.

Funding: NIDDK Support

TH-PO248 Association of Urine Biomarkers of Kidney Tubule Health with Incident CKD in the REGARDS Cohort

Background: Novel biomarkers have been identified that associate with the onset or progression of CKD in specific populations. Within the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, we evaluated whether 5 proteins, measured in stored urine specimens, were associated with the subsequent development of CKD among persons without diabetes at baseline.

Methods: The REGARDS Study recruited Black and White participants from the continental US with emphasis on the Southeast US stroke belt. Candidate participants for this ancillary study had a stored urine specimen from baseline, had a stored urine specimen from baseline, and an estimated glomerular filtration rate (eGFR) ≤ 60 ml/min/1.73 m², had a stored urine specimen from baseline, and an eGFR repeated at the follow-up visit 9 years later. Incident CKD was defined as the onset of an eGFR <60 ml/min/1.73 m² and a ≥40% decline in eGFR. The case-cohort design included a subcohort of 574 participants, all of whom had 57 urine specimens, and 431 additional cases of incident CKD. Weighted multivariable proportional hazards analyses modeled biomarkers both as continuous variables (log2) and in quartiles.

Results: The mean age of the subcohort was 63.8 years, 58% were women, and 30% were hypertensive. On multivariate SD) and eGFR was 89a/14 ml/min/1.73m² and median (IQR) albumin-to-creatinine ratio of 6.1 (4.2 – 9.7) mg/g. In unadjusted models, only higher urine EGF was associated with incident CKD (HR per two-fold increment 1.20; 95% CI: 1.02-1.41); this
association was attenuated after adjustment. No other biomarker approached statistical significance in any analysis (Table).

**Conclusions:** Among REGARDS Study participants without diabetes or CKD at baseline, none of the 5 urine biomarkers studied was independently associated with incident CKD.

**Funding:** NIDDK Support

**TH-PO429**

**Longitudinal Follow-Up and Outcomes for Patients with CKD in China: Results from the C-STRIDE Study**

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**Background:** We aimed to evaluate the longitudinal prognosis of chronic kidney disease (CKD) in China by comparing incidence rates of end-stage kidney disease (ESKD), cardiovascular disease (CVD) and death.

**Methods:** Totally, 3,700 participants of the C-STRIDE study, an ongoing cohort study with stage 1-4 CKD, were included. The outcomes were occurrence of ESKD, CVD, and death. Crude incidence rates were computed and expressed as the number of events per 100 patient-years. Cumulative incidence curves were depicted for the outcomes stratified by age, eGFR and ACR, with the adjustment for other risk factors. Fine and Gray model was used in computing the cumulative incidence of ESKD and CVD.

**Results:** The participants were 49.9 ± 5.5 years old. No significant differences were observed for CVD and death (all p-values>0.05). Higher cumulative incidence rate of ESKD was observed in those with eGFR<60ml/min/1.73m² and 55.5% with ACR 300mg/g, while no other biomarker approached statistical significance. No other biomarker approached statistical significance. No other biomarker approached statistical significance. No other biomarker approached statistical significance.

**Conclusions:** Our study found a higher rate of ESKD than CVD or death in a prospective cohort study of patients with CKD in China. Advanced age was shown as protective factors for the risk of ESKD, while reduced eGFR and presence of albuminuria exacerbate the risk of ESKD, compared with their effect on the risk of CVD and death.

**Funding:** Government Support - Non-U.S. 

**TH-PO430**

**Associations of Plasma YKL-40 with Kidney Disease Progression, Mortality, and Histopathologic Lesions in Native Kidney Biopsies**

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**Background:** YKL-40 is a chitinase-like protein and important regulator of renal tissue injury and apoptosis. We evaluated the association of plasma YKL-40 with progression to ESRD and all-cause mortality among patients with diverse kidney diseases. Furthermore, we tested whether YKL-40 is associated with specific clinicopathologic diagnoses and histopathologic lesions in human kidney biopsies.

**Methods:** We measured plasma YKL-40 levels in 490 participants of the Boston Kidney Biopsy Cohort—a prospective cohort study of patients undergoing native kidney biopsies. Biopsies were reviewed by renal pathologists and adjudicated for histopathologic findings. Cox proportional hazard models tested the association between YKL-40 and the risks of progression to ESRD and all-cause mortality. Multivariable linear regression models were used to assess the relationship between YKL-40, histopathologic lesions, and clinicopathologic diagnoses. Models were adjusted for age, sex, race, BMI, serum albumin, smoking, CHD, stroke, albuminuria, and eGFR.

**Results:** YKL-40 correlated positively with proteinuria and inversely with eGFR (r=0.27, r=0.51; p<0.0001, respectively). During a median follow-up time of 25 months, higher YKL-40 levels were independently associated with an increased risk for progression to ESRD (adjusted HR per 1-SD increase of natural log-transformed YKL-40=1.59, 95% CI (1.10-2.31) and all-cause mortality (adjusted HR=2.80, 95% CI (1.44-4.62)). YKL-40 levels were significantly higher in non-nephrotic glomerulopathies (adjusted β=0.48 [ref=normal or thin basement membrane], 95% CI (0.16-0.79), p=0.003) and significantly associated with more severe arterial sclerosis (adjusted β=0.16 [ref=no sclerosis], 95% CI (0.05-0.32), p=0.043).

**Conclusions:** YKL-40 is independently associated with increased risks of all-cause mortality and progression to ESRD in patients with a diverse spectrum of kidney diseases. Higher levels of YKL-40 were seen in non-nephrotic glomerulopathies and biopsies with more severe arterial sclerosis.

**Funding:** Other NIH Support - R01DK093574

**TH-PO431**

**Urinary Calprotectin, Neutrophil Gelatinase Associated Lipocalin (NGAL), and KIM-1 in the Differentiation of Inflammatory vs. Non-inflammatory CKD**

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**Background:** It has been demonstrated that urinary neutrophil gelatinase-associated lipocalin (NGAL) and calprotectin are helpful biomarkers in the differentiation of intrinsic and prerenal acute kidney injury. The present cross-sectional study investigates, whether urinary biomarkers are able to differentiate primarily inflammatory from non-inflammatory entities in chronic kidney disease (CKD).

**Methods:** Urinary calprotectin, NGAL and kidney injury molecule-1 (KIM-1) concentrations were assessed in a study population of 143 patients with stable CKD and 29 healthy controls. Stable renal function was defined as an eGFR fluctuation 5ml/ min/1.73m² in the past 12 months. Pyuria, metastatic carcinoma and renal transplantation were regarded as exclusion criteria. Diabetic nephropathy, hypertensive nephropathy, and polycystic kidney disease were categorized as “non-inflammatory renal diseases”, whereas glomerulonephritis and vasculitis were regarded as “inflammatory renal diseases”.

**Results:** Urinary calprotectin and NGAL concentrations significantly differed between CKD and healthy controls (p<0.05 each), whereas KIM-1 concentrations did not (p=0.84). Urinary calprotectin concentrations were numerically highest in glomerulonephritis/vasculitis (155.7 ng/ml), NGAL concentrations in diabetic and hypertensive nephropathy (18741 pg/ml), and KIM-1 concentrations in polycystic kidney disease (1556 pg/ml).

**Conclusions:** The three biomarkers did not show significant differences in-between the individual entities, nor the two categories of inflammatory vs. non-inflammatory renal diseases (calprotectin 155.7 vs. 96.99 ng/ml, NGAL 14896 vs. 11977 pg/ml, KIM-1 1388 vs. 1009 ng/ml; p>0.05 each).

**Funding:** The conclusions of this biomarkers calprotectin, NGAL and KIM-1 have no diagnostic value in the differentiation of inflammatory vs. non-inflammatory etiologies of CKD.
TH-PO432
A Phase 1 Randomized, Double-Blind, Placebo-Controlled, Cohort Dose-Ascalation Study of a Human Monoclonal Antibody to IL-6 in Patients with CKD
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Background: Chronic systemic inflammation is highly prevalent in patients with CKD (measured as an elevated high-sensitivity C-reactive protein [hsCRP]) and independently associated with cardiovascular events and mortality. Use of an interleukin-6 (IL-6) blocker to suppress inflammation represents a potential new paradigm to reduce cardiovascular risk in patients with CKD.

Methods: COR-001 is a fully human monoclonal antibody against IL-6. A Phase I trial of COR-001 was conducted in patients with moderate-to-severe non-dialysis dependent CKD (estimated glomerular filtration rate [eGFR] 20-60 ml/min/1.73 m2) and evidence of chronic inflammation (hsCRP level >2 mg/L over two consecutive measurements). Three cohorts of n=4 (3:1 active vs. placebo) were randomized in a blindfaced to single dose of COR-001 (5 mg, 15 mg, and 50 mg subcutaneous injection) and followed for 12 weeks for safety, and pharmacokinetic and pharmacodynamics assessments.

Results: Participants were 67±11 years with a baseline GFR of 40±13 ml/min/1.73 m2 and hsCRP of 5.1±2.6 mg/L. Throughout the 12-week study period, dose escalation was approved and all adverse events were within the expected range for a CKD population selected based on the presence of inflammation. hsCRP levels were substantially reduced with COR-001 treatment. 100% of participants achieved suppression of hsCRP to <2mg/L with the 15 mg and 50 mg dose, and several subjects had undetectable levels of hsCRP with the 50 mg dose (Figure). No SAEs were reported in any cohort. The pharmacokinetic data suggested a half-life of 38-52 days in these patients.

Conclusions: IL-6 inhibition with COR-001 was safe and highly effective at suppressing hsCRP over a long period with a single injection, in adults with moderate-to-severe CKD and evidence of chronic inflammation.

Funding: Commercial Support - Corvidia Therapeutics, Inc.

TH-PO434
Protein-Bound Uremic Toxins Lowering Effect of Sevelamer in Pre-Dialysis CKD Patients with Hyperphosphatemia: A Randomized Controlled Trial
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Background: P-cresol (pCS), the protein-bound uremic toxins, is strongly associated with cardiovascular events and mortality in chronic kidney disease(CKD). However, effectively therapeutic reduction of this toxin is still limited. This is the first study to evaluate the pleiotropic effects of sevelamer on decreasing of pCS in predialysis CKD patients with hyperphosphatemia.

Methods: This was a randomized controlled trial comparing sevelamer with calcium carbonate in predialysis CKD patients with persistent hyperphosphatemia. After 2 weeks of run-in period, patients were randomly assigned to receive either daily 2,400 mg of sevelamer (n=12) or 3,000 mg of calcium carbonate (n=12) for 12 weeks. Plasma pCS, high sensitivity C-reactive protein (hs-CRP), lipid profiles and renal function were evaluated at baseline and 12 weeks after treatment. The study was registered with the Thai Clinical Trials Registry (TCTR20181010003).

Results: The baseline characteristics were not different. The significant reduction of log plasma pCS, hs-CRP, LDL-cholesterol, and serum phosphate were demonstrated in sevelamer group, whereas non-significant changes were observed in calcium carbonate group (Table1). Interestingly, there was significantly greater renal function progression in calcium carbonate group compared with sevelamer group (mean difference of eGFR -2.71±1.04 mL/min/1.73m2, p=0.018).

Conclusions: This is the first study to demonstrate benefit effect of sevelamer on decreasing pCS and retarding renal impairment in predialysis CKD patients with hyperphosphatemia. These effects of sevelamer might be considered as treatment for slowing CKD progression and decreasing the risk of cardiovascular events in CKD patients.

Funding: Private Foundation Support

TH-PO435
Utility of D-Serine in the Estimation of GFR and the Diagnosis of Kidney Disease
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Background: Glomerular filtration ratio (GFR), measured by inulin clearance, is rarely used in clinics due to its methodological complexity. As a replacement, estimated GFR (eGFR), calculated from either serum creatinine or serum cystatin C, is widely used currently, but it has some limitations such as the accuracy. D-Amino acids, long-term undetected emantniers of L-amino acids, is now emerging as a potential biomarker of...
especially in kidney diseases. Here we investigated the potential of D-serine as a biomarker for kidney function and diseases.

**Methods:** Insulin clearance and chiral amino metabolomics were simultaneously performed in 11 CKD patients and 15 non-CKD participants. The association between chiral amino acids and clinical parameters was analyzed using either unsupervised principal component analysis (PCA) or supervised orthogonal partial least squares (OPLS) analysis. Additionally, D-serine was monitored in one patient with systemic erythematous lupus nephritis during its recovery phase.

**Results:** The plasma level of D-serine correlated well with the actual GFR, and this correlation was compatible with those of serum creatinine and cystatin C. Fractional excretion (Fe) of D-serine in non-CKD was much higher than those of L-serine, but its variance was maintained within a certain limited range. Although Fe of D-serine was uncorrelated with GFR, it reflected the presence of CKD. The combination of plasma and Fe of D-serine effectively separated the CKD from non-CKD participants. This concept was exemplified in a patient with SLE, in which the combination of plasma and Fe of D-serine well-reflected its recovery phase.

**Conclusions:** D-serine would benefit patients with kidney diseases via accurate estimation of GFR and estimation of disease activities.

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**TH-PO436**

**High Serum Adiponectin Is Associated with Renal Outcome in CKD:**

**Results:** The plasma level of D-serine correlated well with the actual GFR, and this correlation was compatible with those of serum creatinine and cystatin C. Fractional excretion (Fe) of D-serine in non-CKD was much higher than those of L-serine, but its variance was maintained within a certain limited range. Although Fe of D-serine was uncorrelated with GFR, it reflected the presence of CKD. The combination of plasma and Fe of D-serine effectively separated the CKD from non-CKD participants. This concept was exemplified in a patient with SLE, in which the combination of plasma and Fe of D-serine well-reflected its recovery phase.

**Conclusions:** D-serine would benefit patients with kidney diseases via accurate estimation of GFR and estimation of disease activities.

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**TH-PO437**

**Deoxycholic Acid and Mortality, ESRD, and Cardiovascular Events in Patients with CKD**

**Results:** The plasma level of D-serine correlated well with the actual GFR, and this correlation was compatible with those of serum creatinine and cystatin C. Fractional excretion (Fe) of D-serine in non-CKD was much higher than those of L-serine, but its variance was maintained within a certain limited range. Although Fe of D-serine was uncorrelated with GFR, it reflected the presence of CKD. The combination of plasma and Fe of D-serine effectively separated the CKD from non-CKD participants. This concept was exemplified in a patient with SLE, in which the combination of plasma and Fe of D-serine well-reflected its recovery phase.

**Conclusions:** D-serine would benefit patients with kidney diseases via accurate estimation of GFR and estimation of disease activities.

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
TH-PO438

Differences in Urinary Potassium and Acid-Base Handling in African American vs. Non-African American CKD Patients

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Background: African American (AA) patients with chronic kidney disease (CKD) have faster progression to end stage renal disease (ESRD) than non AA CKD patients. The underlying etiology is multifactorial related to genetics (APOL1), renal disease pathology, co-morbidities or underlying physiologic differences. Physiologic differences include potassium (K+) and acid/base metabolism within the CKD population, specifically racial differences between AA and non AA patients with CKD. Correction of metabolic acidosis in CKD patients has shown to slow progression of CKD, but few studies have examined differences between acid/base metabolism in AA and non AA. No studies have examined differences in urinary K+ excretion in these populations but studies that have shown AA CKD patients maintain lower serum K+ compared to non AA CKD patients. Our object is to identify differences in K+ handling and acid/base metabolism in AA vs non AA CKD patients.

Methods: We studied a cohort of 107 patients with CKD Stage 3-5 who had collected 24-hr urine and serum studies as part of routine clinical care between 2009-2018. Results: Urinary K+ excretion in AA patients was much lower (50±3 mEq and 38±5 mEq, early and late CKD respectively; p=0.05) compared to non AA patients (64±3 mEq and 77±7 mEq, early and late CKD respectively; p value <0.01). Examination of acid/base metabolism using “GI anion”, a measure of net dietary alkaline load, found late stage CKD non AA male patients had more urinary alkali excretion (71±12, p value <0.01) compared to early stage non AA patients (27±5) and all stages of AA patients (32±4 and 25±7 mEq, early and late CKD respectively). Also, within each CKD stage, protein catabolic rate (PCR) in non AA patients was much higher (1.00±0.03 and 1.03±0.07, early and late CKD respectively; p value <0.01) than AA patients (0.8±0.03 and 0.71±0.04, early and late CKD respectively).

Conclusions: AA patients with CKD handle K+ excretion and acid/base metabolism differently than non AA patients. The mechanism and impact of these racial disparities in CKD warrant further investigation.

Funding: NIDDK Support

TH-PO439

Association Between Income Disparities and Risk of CKD: A Nationwide Cohort Study of 7 Million Adults in Korea

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Background: Income disparities may have bearing on public health problems. However, longitudinal studies of the relationship between income level and incident chronic kidney disease (CKD) are scarce.

Methods: To examine the association between income level and incident CKD in a national cohort comprised of 7.4 million adults who underwent National Health Insurance Service health examinations between 2009-2015 with baseline estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m². Incident CKD was defined as de novo development of eGFR <60 mL/min per 1.73m² (model 1) or ≥25% decline in eGFR from the baseline values accompanied by eGFR <60 mL/min/1.73m² (model 2).

Results: During a median follow-up of 4.8 years, there were a total of 122,032 (1.65%) and 55,779 (0.75%) incident CKD events based on model 1 and 2 definitions, respectively. Compared with income levels in the lowest income decile, there was an inverse association between lower income level and higher risk of CKD up to fourth decile, above which no additional reduction (model 1) or slightly higher risk of CKD (model 2) was observed at higher income levels. The multivariable-adjusted hazard ratios (95% confidence interval) from the lowest to fourth deciles were 1.30 (1.26-1.33), 1.16 (1.13-1.19), 1.07 (1.05-1.10), and 1.06 (1.03-1.09) in model 1 and 1.32 (1.27-1.37), 1.18 (1.14-1.22), 1.08 (1.04-1.13), and 1.05 (1.01-1.09) in model 2, respectively. These associations persisted across various subgroups of age, sex, and comorbidity status.

Conclusions: In this large nationwide cohort, lower income levels were associated with higher risk of incident CKD.

Funding: NIDDK Support
Aldosterone Antagonists for Preventing the Progression of CKD: An Updated Cochrane Review

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Background: Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) reduce proteinuria and retard loss of kidney function in patients with chronic kidney disease (CKD), though resolution of proteinuria may be incomplete. We evaluated whether addition of an aldosterone antagonist may further prevent progression of CKD.

Methods: We searched the Cochrane Kidney and Transplant Register of Studies through to 3 September 2018 for randomized controlled trials comparing aldosterone antagonists to standard care for patients with proteinuric CKD. We included studies with at least 12 months of follow-up. Two independent authors extracted data for end-stage kidney disease (ESKD), major cardiovascular events, mortality, proteinuria, glomerular filtration rate (GFR), blood pressure, hyperkalemia, acute kidney injury and retained cystic glomeruli. Risk of bias was assessed using the Cochrane tool. Evidence certainty was assessed using GRADE.

Results: Forty-three studies (5171 participants) were eligible. Risk of bias in the evaluated methodological domains was unclear or high in most studies. Aldosterone antagonists had uncertain effects on risk of ESKD (2 studies, 84 participants, risk ratio [RR] 3.00, 95% confidence interval [CI] 0.13 to 76.65, very low certainty evidence), mortality (3 studies, 421 participants, RR 0.58, 95%CI 0.10 to 3.50, low certainty evidence), cardiovascular events (3 studies, 1067 participants, RR 0.95, 95%CI 0.26 to 3.56, low certainty evidence) and GFR (12 studies, 861 participants, MD -2.25 ml/min/1.73 m2, 95%CI -4.76 to 0.25, low certainty evidence); may reduce proteinuria (14 studies, 910 participants, standardized mean difference [SMD] -0.53, 95%CI -0.86 to -0.19, very low certainty evidence) but probably increases risk of hyperkalemia (17 studies, 2683 participants, RR 2.10, 95%CI 1.42 to 3.13, moderate certainty evidence), AKI (4 studies, 1088 participants, RR 2.02, 95%CI 1.02 to 4.02, moderate certainty evidence) and gynecomastia (4 studies, 281 participants, RR 5.14, 95%CI 1.14 to 23.23, moderate certainty evidence) compared to standard care or placebo.

Conclusions: Aldosterone antagonists when added to ACEI or ARB (or both) may reduce proteinuria but have uncertain effects on major cardiovascular events or ESKD and may incur excess hyperkalaemia, acute kidney injury and gynecomastia.

TH-PO441

Comprehensive Profiling of the Clinical Nephropathies in Participants of the H3Africa Kidney Disease Research Network Project Cohort Study

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Background: It is estimated that more than greater than 50 million African Blacks have Chronic Kidney Disease (CKD) due to clinically defined nephropathies. A significant fraction of these will progress to ESRD. Despite the high rate of CKD progression among individuals of African ancestry, the molecular and clinical factors underlying this high burden is not completely understood. The ongoing H3Africa Kidney Disease Cohort study aims to evaluate the independent contribution of risk variants in the APOL1 genes to the progression of clinically defined nephropathies among 3,000 African Blacks. This abstract described the baseline characteristics of the participants of the study

Methods: A longitudinal study of 3,000 African black with clinical defined nephropathies. It involves baseline and follow up visits. At the baseline, relevant clinical information was obtained while blood and urine specimens were collected for the assays. Biological specimens were processed, stored, packaged and shipped to the central repository for analysis. Information obtained from participants were demographics, contact information and medical history and blood was collected for DNA, RNA, whole blood, serum creatinine, full blood count and anthropometric measures. Where clinically indicated, a kidney biopsy was performed and kidney tissue examined

Results: A total of 2,192 participants were included in this analysis, and the clinical nephropathies include hypertensive nephropathy 1194 (54.5%), diabetic nephropathy 558 (25.5%), sickle cell nephropathy 632 (2.9%) and CKD of unknown aetiology 326 (1.4%). The mean creatinine among participants were 53.84±14.41, 53.86±14.41, 53.84±14.41 and 53.86±14.41 μmol/L at 13±6.7 and 37.08±15.97 years for hypertensive, diabetic and sickle cell nephropathies and CKD of unknown aetiology respectively. Albumin-Creatinine Ratio was higher among participants with CKD of unknown aetiology (165.09±302.49mg/Mmol) and sickle cell nephropathy (109.13±111.18mg/mmol) compared to hypertensive nephropathy 62.68±184.32mg/mmol and diabetic nephropathy (78.71±144.61mg/mmol).

Conclusions: Hypertensive nephropathy, diabetic nephropathy and CKD of unknown aetiology are the leading clinically defined nephropathies among the sub-Saharan African populations.

Funding: NIDDK Support

TH-PO443

Design and Patient Characteristics of a Study to Assess the Renoprotective Effects of the SGLT2 Inhibitor Dapagliflozin in Non-Diabetic Proteinuric Kidney Disease (DIAMOND)

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Background: Sodium glucose co-transporter 2 (SGLT2) inhibition decreases albuminuria and reduces the risk of kidney disease progression in patients with type 2 diabetes. These beneficial effects are likely mediated by activation of tubuloglomerular feedback by natriuresis, leading to decreased intraglomerular hypertension. Since non-diabetic kidney diseases are also characterized by glomerular hypertension, we tested the hypothesis that in patients with non-diabetic proteinuric kidney disease, SGLT2 inhibition with dapagliflozin reduces proteinuria and acutely and reversibly reduces glomerular filtration rate (GFR).

Methods: We designed a multicenter double-blind randomized placebo controlled 6-week cross-over study to assess the change from baseline in 24-hour proteinuria with dapagliflozin 10 mg/day in patients with proteinuric kidney disease without diabetes (ClinicalTrials.gov identifier: NCT03190694). The secondary endpoint was the change in iohexol-derived GFR. The main inclusion criteria were: urinary protein excretion >500 mg/24hr and <3500 mg/24hr, GFR ≥25 ml/min/1.73m2; stable dose of RAAS inhibitors.

Results: Patients with non-diabetic kidney disease were enrolled between November 2017 and April 2019. A total of 58 patients were screened of whom 53 patients were randomized in this ongoing study. The mean age at screening was 51 (SD 13) years and 32% were female. Mean screening GFR was 59 (29) ml/min/1.73m2 and median proteinuria was 25% (25% to 75%) percentile 810 -1400 mg/24hr Overall, blood pressure was well controlled (SBP/DBP 128 (15) /78 (8) mmHg) and mean body weight was 83.0 (20) kg. Mean HbA1c was 5.6 (0.4) % and mean hemoglobin level 138 (20) g/L. All patients were receiving a RAAS inhibitors.

Conclusions: This is the first placebo controlled clinical trial to examine the effects of an SGLT2 inhibitor in a non-diabetic population at risk for progressive kidney function loss. Final study results are expected in December 2019.

Funding: Commercial Support - AstraZeneca

TH-PO444

Effect of Barbados Methyl on Kidney Events in Patients with CKD Stage 4 and Type 2 Diabetes at High Risk of Adverse Kidney Outcomes

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Background: Increases in kidney function, including increases in inulin-clearance and estimated glomerular filtration rate (eGFR), have been observed with barbados methyl (Bard) in 11 studies enrolling approximately 3,000 patients with chronic kidney disease (CKD). The largest of these studies was Barbados Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes (BEACON), a multinational, randomized, double-blind, placebo-controlled phase 3 trial, which enrolled patients with type 2 diabetes and stage 4 CKD. We performed a post-hoc analysis of BEACON to characterize changes

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in kidney function induced by Bard in subgroups of patients at particularly high risk of adverse kidney outcomes, including those with baseline eGFR below 22 mL/min/1.73 m² or with a urine albumin to creatinine ratio (UACR) > 300 mg/g.

Methods: Patients in BEACON (n=2185; NCT01351675) were randomized 1:1 to receive once-daily bardoxolone methyl (20 mg) or placebo. For the subsets of patients with baseline eGFR < 22 mL/min/1.73 m² (n=503 for Bard, n=514 for placebo) or baseline UACR > 300 mg/g (n=540 for Bard, n=578 for placebo), we compared the effects of Bard and placebo on a post-hoc composite kidney endpoint consisting of a sustained ≥30% decline from baseline in eGFR, sustained eGFR <15 mL/min/1.73 m², and end-stage kidney disease events.

Results: Patients with baseline eGFR < 22 mL/min/1.73 m² randomized to Bard were significantly less likely to experience the composite kidney endpoint than patients randomized to placebo: 45/503 (9%) Bard patients experienced an event compared to 111/514 (22%) placebo patients (hazard ratio 0.39; 95% CI, 0.28-0.55; p<0.001). For patients with baseline UACR > 300 mg/g, 58/540 (11%) Bard patients experienced an event compared to 105/578 (18%) placebo patients (hazard ratio 0.58; 95% CI, 0.42-0.80; p<0.001). For the subsets of patients enrolled in BEACON who were at greatest risk of progression to kidney failure, the increases in eGFR with Bard were associated with a significant reduction in the likelihood of an end-stage kidney disease composite endpoint.

Funding: Commercial Support - Trial sponsored by Reata Pharmaceuticals Inc.

TH-PO445
Effect of Aspirin on Cardiovascular Events, Mortality, and Bleeding Outcomes in Older Individuals with CKD
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Background: The primary efficacy and safety of aspirin (ASA) in older people with chronic kidney disease (CKD) is unclear. Aspirin in Reducing Events in the Elderly (ASPREE), a large binational (Australia, US) RCT in elderly participants free of diagnosed CVD or disability, found no benefit of aspirin for primary prevention. The ASA To Target Arterial Events In CKD (ATTACK) trial is underway with a primary endpoint of major adverse cardiovascular events (MACE) in patients with CKD. To provide insights into whether ATTACK should consider exclusion of individuals aged >70 years, we examine the effects of daily 100mg ASA on outcomes in ASPREE participants with CKD.

Methods: ASPREE participants with eGFR <60, or AST-120 6 gram/day was orally administered as patients with high amount of proteinuria (over 1.0g/gCr). We next divided into five groups according to the initial median eGFR at baseline (G1: n=718, G2: n=722, G3: n=720, G4: n=14, and G5: n=3)). Monthly decline in renal function (slope of 1/eGFR) and IS-lowering therapy could improve microcirculatory impairment in non-diabetic pre-dialysis CKD patients.

Conclusions: IS-lowering therapy significantly improved micro-circulatory impairment in non-diabetic pre-dialysis CKD patients.

Funding: Government Support - Non-U.S.

TH-PO446
Oral Adsorbent AST-120 Improves Microcirculatory Impairment in Patients with CKD
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Background: Microcirculatory impairment plays an important role at an earlier stage for peripheral arterial disease (PAD) in patients with chronic kidney disease (CKD). To treat PAD as early as possible is mandatory to avoid lower limbs’ amputation. Therefore, we evaluated whether uremic toxin-lowering therapy could improve microcirculatory impairment in patients with CKD.

Methods: Oral charcoal adsorbent AST-120 (Kremezin, Kureha Corporation, Tokyo, Japan) adsorbs indole, a precursor of indoxyl sulfate (IS), in the gastrointestinal tract so that IS does not accumulate in the body. We performed a prospective interventional clinical trial whether AST-120 could improve arteriosclerotic surrogates in CKD patients (UMIN no. 000013577). As a primary endpoint, skin perfusion pressure (SPP) of lower limbs, and flow mediated dilation (FMD) were evaluated as surrogate of microcirculatory and macrocirculatory status, respectively. They were evaluated at baseline, 3, 6, and 12 months after AST-120 administration. Serum levels of total IS (free IS and protein-binding IS) and renal function (serum creatinine (cCr), 1/cCr) were also evaluated at baseline, 3, 6, and 12 months after AST-120 administration. Total IS was evaluated using HPLC method and expressed as µM.

Results: We enrolled 33 non-diabetic CKD patients (CKD stage; G3a (n=4), G3b (n=9), G4 (n=14), and G5 (n=3)), and AST-120 6 gram/day was orally administered for 12 months. Serum creatinine (cCr) levels and 1/cCr at baseline were 2.0±0.85 mg/dL and 0.587±0.226 dL/mg (meansSD), respectively. Monthly decline in renal function (slope of 1/eGFR) after AST-120 administration did not change compared to that in pre-treatment period. However, serum total IS significantly decreased at 3 months after AST-120 administration (baseline: 11.7±8.6 µM to 3 months: 6.9±5.0 µM, p<0.01). Serum IS levels continued to be decreased for 12 months (p<0.01). Although FMD did not change during study period, SPP values in lower limbs constantly elevated, and was significantly improved at 12 months after AST-120 administration compared to baseline values (69.7±14.6 vs. 78.8±18.9 mmHg, p<0.05).

Conclusions: IS-lowering therapy significantly improved micro-circulatory impairment in non-diabetic pre-dialysis CKD patients.

Funding: Government Support - Non-U.S.
TH-PO448
Randomized Controlled Trial of Long-Term Safety and Efficacy of Veverimer for Treatment of Metabolic Acidosis

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Background: Metabolic acidosis in CKD is associated with accelerated GFR decline, augmented muscle catabolism and increased mortality. Veverimer, an oral, non-absorbed, counterion-free, polymeric drug candidate, selectively binds and removes HCl from the GI lumen.

Methods: We report a multicenter, randomized, blinded, placebo-controlled, 40-wk extension (n=196) of a 12-wk parent study (n=217) in patients with CKD (GFR 20-59 mL/min/1.73m²) and metabolic acidosis (serum bicarbonate 12-20 mM/L) randomly assigned (4:3) to veverimer or placebo. The primary endpoint was safety; secondary endpoints were effect on bicarbonate level, patient-reported physical function (Kidney Disease and Quality of Life Physical Functioning Domain [KDQOL-PFD]) and objectively measured physical function (repeated chair stand [RCS] test). A pre-specified time to event analysis for the composite outcome of death, RRT or eGFR decline ≥50% was also performed.

Results: Fewer patients on veverimer than placebo discontinued treatment prematurely (2.6% vs 9.8%) or experienced a serious adverse event (1.8% vs 4.9%). No patients on veverimer died (vs 2 on placebo) or discontinued due to an adverse event (vs 1 on placebo) and the frequencies of common adverse events were comparable between groups. More patients on veverimer than placebo had an increase in bicarbonate (≥3 mM/L or normalization) at Week 52 (62.7% vs 37.8%, p=0.001) and higher bicarbonate levels were observed on veverimer at all time points (p<0.001). The KDQOL-PFD score improved on veverimer vs. placebo, with a mean placebo-subtracted (SE) change at end of treatment of 12.1 (3.3) points (p<0.0001). Veverimer specifically improved physical function to 1.4 (0.6) points of the RCS test. A change >4 points from baseline at end of treatment was observed in 42% of veverimer vs 12% of placebo, p=0.023.

Conclusions: Veverimer safer and effectively improved metabolic acidosis in patients with CKD. Our multicenter, randomized, controlled trial adds to the evidence that veverimer reduces mortality and improves quality of life.

Funding: Commercial Support - Tricida, Inc. San Francisco, CA, USA

TH-PO449
PHYOX: A Safety and Tolerability Study of DCR-PHXC in Primary Hyperoxaluria Types 1 and 2

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Background: Primary hyperoxaluria (PH) is characterized by hepatic overproduction of oxalate, leading to three distinct genetic mutations. DCR-PHXC is an investigational RNA therapeutic targeting the LDHA enzyme, which is involved in the final step of hepatic oxalate production.

Methods: Preliminary data from the ongoing PHYOX study (ClinicalTrials.gov: NCT03938960), a two-wk single-ascending dose study conducted in 7 Healthy Volunteers (IVs, Groups A and 18 PH patients (Group B, reported here). Eligible PH patients have PH1 or PH2, urinary oxalate (Uox) ≥70mmol/24Hr, and eGFR ≥30 mL/min/1.73m². Group B is open label and has three PH1 Cohorts dosed at 1.5, 3, and 6 mg/kg and 1 PH2 Cohort (1.5 and 3 mg/kg DCR-PHXC). The primary objective is safety. Change in 24Hr Uox from baseline (the mean of two screening 24Hr urine collections) was assessed.

Results: Safety Results: Group A is complete with no clinical meaningful safety signals. Two serious adverse events (SAEs) were reported. One patient withdrew consent; another had an imaging site reaction (IRS) occurred. Group B: Fifteen adult and three adolescent patients have been dosed. Four SAEs have occurred in three participants. Two SAEs of reoccurring fever, but unrelated to study drug, occurred in one participant. An SAE of ureteral stone occurred in a different participant and was unrelated to study drug. A fourth SAE of appendicitis was reported in a patient who also unrelated to study drug. All four SAEs are resolved. Seven participants experienced mild or moderate IRS and all resolved within 96 hours. Efficacy Results: Group B: Preliminary results following a single administration of DCR-PHXC appear in table 1. At fng/kg one participant experienced undetectable levels of Uox at Days 57 and 85. Conclusions: Observed reduction of 24Hr Uox following a single administration of DCR-PHXC in both PH1 and PH2 participants is a promising sign of DCR-PHXC’s potential potency and duration of action.

Funding: Commercial Support - Dicerca Pharmaceuticals

TH-PO450
Levothyroxine in Proteinuric CKD Patients Decreases Proteinuria and Improves Kidney Function: A Randomized, Double-Blind, Clinical Trial

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Background: Thyroid hormones can affect kidney function. Elevated levels of TSH in CKD patients is associated to proteinuria, decrease in GFR, and progression to ESRD. We hypothesized that the use of levothyroxine (LTX) in proteinuric CKD patients with TSH levels between 2.5-9.9 µIU/mL and normal FT4, decreases proteinuria and improve kidney function. Clinical trial registration number: NCT03898622

Methods: A double-blind, phase 2 randomized clinical trial, in proteinuric CKD patients, stage 3-5, not on dialysis, with TSH levels between 2.5-9.9 µIU/mL, and FreeT4 in a range of 0.7-1.8 ng/dL. All patients were already on ACE inhibitors or ARBs. Patients were randomized 1:1 to receive LTX (25-50mcg/day) or placebo for 12 weeks. The main outcomes were change in proteinuria, sCr, eGFR, TSH, and tolerability and safety of LTX.

Results: 163 patients were assessed for eligibility; 119 were excluded; 32 patients were randomized (16 LTX; 16 placebo). Fewer patients on LTX than placebo discontinued treatment prematurely (2.6% vs 9.8%) or experienced a serious adverse event (1.8% vs 4.9%). No patients on LTX died (vs 2 on placebo) or discontinued due to an adverse event (vs 1 on placebo) and the frequencies of common adverse events were comparable between groups. At 12 weeks, mean change in proteinuria (LTX vs placebo) was –1.1 (-4.1 to +0.9) g/day vs –0.20 (-0.4 to +2.1) g/day (p=0.001); sCr –0.20 (-0.7 to +0.5) mg/dL vs +0.05 (-0.5 to +1.49) mg/dL (p=0.032); eGFR +0.04 (+9.8 to -2.0) ml/min/1.73m² vs -1.96 (-6.2 to 2.9) ml/min/1.73m² (p<0.001). LTX in proteinuric CKD patients decreased proteinuria and improved kidney function. Further studies are needed to determine the long-term impact of exogenous thyroid hormone treatment on proteinuria and CKD progression.

Funding: Commercial Support - Dicerna Pharmaceuticals

TH-PO451
Levophedrine in Proteinuric CKD Patients Decreases Proteinuria and Improves Kidney Function: A Randomized, Double-Blind, Clinical Trial

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RESULTS: Of 167 patients randomized (FM 111, PL 56), 125 started open-label FM, and 92 completed 52 weeks. Improvements in Hb and iron indices with FM during double-blind treatment were maintained with OL FM to Week 52, while changes in Hb and iron indices for those moving from PL to FM mirrored the changes seen with FM during double-blind treatment (Figure). Drug-related AEs (mostly gastrointestinal) were recorded in 24 patients in the OL phase. Eleven patients discontinued treatment because of AEs during the OL phase.

CONCLUSIONS: Long-term treatment with FM was associated with sustained and clinically meaningful increases in Hb and iron indices, further confirming efficacy of oral FM for treating IDA in patients with stage 3/4 CKD. There were no new safety signals with up to 52 weeks' treatment.

Funding: Commercial Support - Shield Therapeutics plc

TH-PO453
A Metabolome-Wide Association Study of Kidney End Points in CKD Patients: Results from the GCKD Study
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Background: Chronic kidney disease (CKD) affects >10% of the adult population and is associated with increased risk of end-stage kidney disease (ESKD) and mortality. The underlying mechanisms are incompletely understood. A comprehensive screen of metabolites whose levels in urine are associated with kidney endpoints can identify novel biomarkers for CKD progression and may provide pathophysiological insights.

Methods: We performed Cox Proportional Hazards analyses relating incident kidney endpoints to levels of 1487 urinary metabolites quantified in 5088 participants of the German Chronic Kidney Disease (GCKD) study in a randomly selected discovery (N=3392) and replication (N=1696) sample adjusted for age, sex, eGFR and UACR at baseline. Main endpoints were time to ESKD (dialysis or transplantation) or renal death (eGFR ≤ 24ml/min1.73m2) and a composite endpoint that additionally included acute kidney injury AKIN stage 3 (“Composite”, Nevents=382). Urinary metabolites were measured using the Metabolon HD4 platform, log-transformed and analyzed when quantified in at least 30 patients with an event. Cause-specific hazard (CSH) regression as well as subdistribution hazard (SH) analyses with death of other causes as a competing event were performed. Statistical significance was defined using a Bonferroni correction for the number of tested metabolites in both the discovery and replication setting.

Results: Median follow-up time was 4.0 years. CSH analyses of the Composite and the ESKD event identified and replicated 20 and 8 significant metabolites, respectively. For the Composite event, there were both protective and harmful metabolites, with cause-specific hazard ratios ranging from 0.63 to 2.75 per doubling of metabolite levels. Many replicated metabolites have not yet been implicated in ESKD. They belong to different biochemical classes, with evidence for enrichment in one sub-pathway. Most associations remained after adjusting for additional clinical covariates. SH analyses showed almost identical results.

Conclusions: We identified 20 urinary metabolites significantly associated with adverse kidney events in a cohort of CKD patients, potentially providing new insights into the mechanisms of kidney disease progression.

Funding: Government Support - Non-U.S.

TH-PO454
A Randomized Controlled Trial of the Effects of Febuxostat Treatment on Markers of Endothelial Dysfunction and Renal Progression in Patients with CKD

Background: Hyperuricemia relates to chronic kidney disease (CKD) progression, systemic inflammation and impaired endothelial function. Febuxostat, a novel nonpurine selective xanthine oxidase inhibitor, is potent and effective for decreasing serum uric acid levels. The study aimed to evaluate the effect of oral febuxostat on markers of endothelial dysfunction and renal function in CKD patients.

Methods: A total of 84 CKD stage III-IV patients with asymptomatic hyperuricemia were randomly assigned to either the febuxostat (40 mg/day, N=40) or the matching control (N=44) for 8 weeks. Serum uric acid, estimated glomerular filtration rate (eGFR), urine albumin, serum asymmetric dimethylarginine (ADMA), and high sensitivity C-reactive protein (hsCRP) were measured at baseline and at the end of the study.

Results: Febuxostat administration significantly reduced the serum uric acid concentration in patients with CKD when compared with control [-3.40 (95% CI -4.19 to -2.62) vs. -0.35 (95% CI -0.76 to 0.06) mg/dL; P<0.001, respectively]. No significant difference in the changes in serum ADMA, hsCRP, eGFR and albuminuria, was identified between the two groups. Subgroup analysis in patients with decline serum uric acid after treatment, mean eGFR showed a significant increase in the febuxostat group (P=0.022), but no significant change in the placebo group (P=0.802). The difference GFR change between groups was 1.97 ml/min/1.73 m2 with 95%CI 0.15 to 4.64 at 8 weeks (P=0.03).

Adverse events specific to febuxostat were not observed.

Conclusions: Febuxostat effectively reduced serum uric acid in the population of CKD without effect to endothelial dysfunction and systemic inflammation. It was able to preserve renal function in subgroup CKD patients with lower serum uric acid level after treatment.
TH-PO455
Long-Term Impact of Bariatric Surgery on Renal Outcomes at a Community-Based Publicly Funded Bariatric Program
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Background: Obesity is recognized as an independent risk factor for chronic kidney disease (CKD) through multiple direct and indirect biological pathways. Bariatric surgery is a proven, effective method for sustained weight loss. However, there is a relative paucity of data on the impact of bariatric surgery on renal outcomes.

Methods: 471 consecutive obese adult patients who underwent bariatric surgery between 2008-2015 were included in this observational retrospective cohort study. The patients were followed for two years post surgery at the Proventricul Surgery Clinic, Regina General Hospital, Saskatchewan. The primary objective was to evaluate the change in urine albumin/creatinine ratio (ACR) at the time of surgery and at 12 months post procedure. Secondary objectives were to determine the changes in ACR (6 and 24 months), estimated glomerular filtration rate (eGFR) (6, 12 and 24 months), and HbA1c (12 and 24 months) post procedure. The change in body mass index (BMI), and metabolic outcomes (fasting glucose, total cholesterol, LDL, triglycerides, HbA1c) were also measured.

Results: Patients were predominantly female (81%) with a mean age (±SD) of 46 ± 10 years. The majority of patients (87%) had a BMI >40 kg/m2 and 81 % of the patients underwent Roux-en-Y gastric bypass. The mean BMI decreased from 47.7 ± 7.8 kg/m2 at baseline to 37.1 ± 7.9 kg/m2 at 6 months and 34.8 ± 8.8 kg/m2 at 12 months. In patients with microalbuminuria, ACR showed an improvement from a median [IQR] value of 5.1 [3.7-7.5] mg/mmol at baseline to 2.3 [1.2-3.6] mg/mmol at 6 months (p<0.001), to 1.4 [0.9-3.7] mg/mmol at 2-year follow-up (p<0.001). Similarly, eGFR increased in patients with microalbuminuria from 109 ± 10 mL/min/1.73m2 at baseline to 120 ± 36 mL/min/1.73m2 at two-year follow-up (p<0.013). There were statistically significant reductions in triglycerides, fasting glucose, and HbA1c.

Conclusions: The results of our study suggest bariatric surgery significantly decreased weight and consequently improved renal outcomes. There was a significant improvement in albumin excretion rates and improvement in filtration rates. An improvement in metabolic outcomes was also seen (fasting glucose, cholesterol, and triglycerides) in patients with elevated BMI.

TH-PO456
Advanced CKD Is Associated with Higher and Not Lower Insulin Use
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Background: Obesity is recognized as an independent risk factor for chronic kidney disease (CKD) through multiple direct and indirect biological pathways. Bariatric surgery is a proven, effective method for sustained weight loss. However, there is a relative paucity of data on the impact of bariatric surgery on renal outcomes. Bariatric surgery is a proven, effective method for sustained weight loss. However, there is a relative paucity of data on the impact of bariatric surgery on renal outcomes.

Methods: We evaluated 3,416 participants from the Chronic Renal Insufficiency Cohort (CRIC) Study. We estimated the kidney clearances of 11 endogenous solute clearances based on their measured concentrations in paired 24-hour urine and plasma samples at baseline using targeted mass spectrometry. CKD progression was defined by a 50% decline in the estimated glomerular filtration rate (eGFR), initiation of maintenance dialysis, or kidney transplantation. We used Cox proportional hazards regression to test associations of secretory solute clearances with CKD progression and all-cause mortality, adjusting for eGFR, albuminuria, and other potential confounders.

Results: There were 1,206 CKD progression events and 1,004 mortality events over a median follow-up of 6.0 and 9.6 years, respectively. Adjusted for eGFR, albuminuria, and other risk factors, lower kidney clearances of six secretory solutes (cinnamoylglycine, indoxyl sulfate, isovalerylglucine, kynurenic acid, pyridoxic acid, and xanthosine) were associated with greater risks of CKD progression (11%-21% greater risk per 50% lower secretory clearance). Lower clearances of four solutes (hippurate, isovalerylglucine, tyglycine, and trimethylacid) were associated with all-cause mortality after adjustment.

Conclusions: Lower proximal tubular secretory solute clearance is associated with greater risks of CKD progression and all-cause mortality independent of eGFR and albuminuria. These findings suggest that estimates of tubular secretory clearances may provide complementary information to existing measures of glomerular filtration and integrity.

Funding: NIDDK Support

TH-PO457
Proximal Tubular Secretory Clearance Is Associated with the Progression of CKD: The CRIC Study
Yan Chen,1 Leila R. Zeltnick,2 Ke Wang,1 Chi-yuan Hsu,4 Alan S. Go,4 Harold I. Feldman,1 Rupal Mehta,6 James P. Lash,1 Sushrut S. WaiK,1 L. Lee Hamm,7 Tariq Shafi,10 Stephen L. Seliger,11 Michael Shlipak,12 Mahboob Rahman,13 Bryan R. Kestenbaum,14 University of Washington, Seattle, WA; 2Kidney Research Institute, Seattle, WA; 3University of California San Francisco, San Francisco, CA; 4Kaiser Permanente Northern California, Oakland, CA; 5University of Pennsylvania, Philadelphia, PA; 6Northwestern University, Feinberg School of Medicine, Chicago, IL; 7Harvard Medical School, Boston, MA; 8Tulane University School of Medicine, New Orleans, LA; 9University of Mississippi Medical Center, Jackson, MS; 10University of Maryland School of Medicine, Baltimore, MD; 11San Francisco VA Medical Center, San Francisco, CA; 12Case Western Reserve University, Cleveland, OH.

Background: The secretion of organic solutes by the proximal tubules is an essential intrinsic kidney function. The clinical significance of tubular secretory clearance is uncertain.

Methods: We evaluated 3,416 participants from the Chronic Renal Insufficiency Cohort (CRIC) Study. We estimated the kidney clearances of 11 endogenous solute clearances based on their measured concentrations in paired 24-hour urine and plasma samples at baseline using targeted mass spectrometry. CKD progression was defined by a 50% decline in the estimated glomerular filtration rate (eGFR), initiation of maintenance dialysis, or kidney transplantation. We used Cox proportional hazards regression to test associations of secretory solute clearances with CKD progression and all-cause mortality, adjusting for eGFR, albuminuria, and other potential confounders.

Results: There were 1,206 CKD progression events and 1,004 mortality events over a median follow-up of 6.0 and 9.6 years, respectively. Adjusted for eGFR, albuminuria, and other risk factors, lower kidney clearances of six secretory solutes (cinnamoylglycine, indoxyl sulfate, isovalerylglucine, kynurenic acid, pyridoxic acid, and xanthosine) were associated with greater risks of CKD progression (11%-21% greater risk per 50% lower secretory clearance). Lower clearances of four solutes (hippurate, isovalerylglucine, tyglycine, and trimethylacid) were associated with all-cause mortality after adjustment.

Conclusions: Lower proximal tubular secretory solute clearance is associated with greater risks of CKD progression and all-cause mortality independent of eGFR and albuminuria. These findings suggest that estimates of tubular secretory clearances may provide complementary information to existing measures of glomerular filtration and integrity.

Funding: NIDDK Support

Table 1. Adjusted associations between secretory solute clearances and outcomes.

<table>
<thead>
<tr>
<th>Solute</th>
<th>CKD Progression</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>xanthosine</td>
<td>1.3 (1.09-1.05) *</td>
<td>0.97 (1.03-1.01)</td>
</tr>
<tr>
<td>trimethylacid</td>
<td>1.03 (0.97-1.09)</td>
<td>1.07 (1.02-1.13)</td>
</tr>
<tr>
<td>isovalerylglucine</td>
<td>1.09 (1.01-1.18)</td>
<td>1.07 (1.01-1.14)</td>
</tr>
<tr>
<td>tyglycine</td>
<td>1.09 (1.01-1.18)</td>
<td>1.10 (1.05-1.16)</td>
</tr>
<tr>
<td>pyridoxic acid</td>
<td>1.04 (1.01-1.08)</td>
<td>1.09 (1.04-1.14)</td>
</tr>
<tr>
<td>kynurenic acid</td>
<td>1.21 (1.10-1.32)</td>
<td>1.14 (1.07-1.23)</td>
</tr>
<tr>
<td>indoxyl sulfate</td>
<td>1.15 (1.06-1.27)</td>
<td>1.14 (1.06-1.23)</td>
</tr>
<tr>
<td>cinnamoylglycine</td>
<td>1.19 (1.06-1.33)</td>
<td>1.14 (1.06-1.23)</td>
</tr>
<tr>
<td>hippurate</td>
<td>1.01 (0.95-1.05)</td>
<td>1.07 (1.01-1.11)</td>
</tr>
</tbody>
</table>

* P < 0.05. 

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Low for hypertension without diabetes, even in the presence of reduced eGFR. Consistent with recommendations from clinical guidelines. uACR measurement rates in patients with diabetes). When limiting to patients with hypertension but no diabetes, 24.8% using the 3-year measurement period. Rates varied considerably across HCOs for CKD, reduced LEF/TCF-dependent transcription in PT cells (Topflash and Axin2 mRNA) reportedly switches b-catenin transcriptional binding partners from LEF/TCF to FoxO, suggesting that b-catenin signaling in the PT is protective. Cortical tubular apoptosis was increased in KIM-1 positive conditional mice compared to their controls, in vitro studies.

Using a large, geographically diverse clinical dataset from 27 health care organizations (HCOs), 580,950 patients with diabetes and 1,558,525 patients with hypertension were identified, among a population aged 18-85, with hypertension, with eGFR listed as a basic test, and uACR optional.

Methods: This is the first study to evaluate the importance of TDM in ND-CKD patients received vancomycin. In real practice, the application of TDM of vancomycin was even unexpectedly low in ND-CKD patients. Our results show ND-CCKD patient with TDM of vancomycin is associated with reduced risk of mortality. The TDM of vancomycin in ND-CCKD patients cannot be overemphasized.
and augmented FoxO3 activity. Co-IP studies showed that oxidative stress plus Wnt3a significantly increases nuclear β-catenin interactions. In the AAN model, injured and conditioned β-catenin mice have augmented nuclear FoxO3 expression in proximal tubules. Furthermore, FoxO3 was required for β-catenin’s protective effect as mice with PT-specific β-catenin stabilization and FoxO3 deletion (using gOT-Cre) lost the protective effect of AN. RNAseq on PT cells was performed and identified 19 novel β-catenin and FoxO3 targets.

**Conclusions:** In conclusion, β-catenin signaling within the proximal tubule mitigates AKI to CKD transition through its interaction with FoxO3. Ongoing efforts are examining this β-catenin effect in the IRI and validating novel targets in vivo.

**Funding:** Veterans Affairs Support

### TH-PO462

#### Inhibition of Nα-Acetylasparatylase Attenuates Renal Interstitial Fibrosis via Modulation of Epithelial-to-Mesenchymal Transition and Inflammation

**Joung Soh,1 Sungjin Chung,2 Seok Joon Shin,3 Chool Whee Park,2 Chul Woo Yang,2 Eun Sil Koh.2 The Catholic University of Korea Yeouido St. Mary’s Hospital, Seoul, Republic of Korea; 3The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; 1Incheon St. Mary’s Hospital, The Catholic University of Korea, Incheon, Incheon, Republic of Korea.**

**Background:** Nα-acetylasparatylase 10 (Naa10), the catalytic subunit of N-acetylasparatylase A, has been reported to be involved in the regulation of telomerase activity, DNA damage response, cell cycle, cytoskeleton, nuclear microtubule reorganization and histone acetylation. This study was designed to investigate whether the pharmacological inhibition of Naa10 could affect the progression of renal tubulointerstitial fibrosis.

**Methods:** Remodelin 1mg/kg, a Naa10 inhibitor, was administered to the mice for 3 or 7 days following unilateral partial obstruction (UPO).

**Results:** Renal Naa10 expression after UUO was significantly enhanced but reduced by the Naa10 inhibitor remodelin. Masson trichrome and Sirius red staining demonstrated that Naa10 inhibition led to a decrease in renal interstitial fibrosis induced by UUO. In addition, the α-SMA- and TUNEL-positive cells were apparently decreased in obstructed kidneys with administration of remodelin. Furthermore, remodelin inhibited the increase in the mRNA levels of α-SMA, fibronectin, MMP-2, IL-1β, IL-6, TNF-α, TGF-β1 and CollIV without significant changes in mRNA levels of vimentin, E-cadherin and VE-cadherin and protein expressions of Nox1, Nox2, Nox4, SOD1, HO-1, NQO1 and catase in obstructed kidneys. All these findings were apparent at day 7 after UUO. Collectively, these results indicate that long-term treatment of remodelin mitigates UUO-induced renal interstitial fibrosis by affecting epithelial-to-mesenchymal transition (EMT) and inflammation.

**Conclusions:** Current study suggests that Naa10 inhibition could attenuate renal fibrosis through regulation of certain EMT- and inflammation-related factors.

**Funding:** Government Support - Non-U.S.

### TH-PO463

#### Proximal Tubule-Derived Amphiregulin Amplifies and Integrates Profibrotic EGFR Signals in Kidney Fibrosis

**Eirini Kefalogianni,1 Manikanda raja Keerthi raja,4 Julian Schumacher,3 Sushir S. Waiker,3 Andreas Herrlich,1 Washington University School of Medicine, St. Louis, MO; 2Harvard Medical School, Boston, MA; 3Washington University in St. Louis, St. Louis, MO; 4University of South Carolina, Columbia, SC.**

**Background:** Sustained activation of epidermal-growth-factor-receptor (EGFR) in proximal-tubule-cells (PTCs) is a hallmark of progressive kidney fibrosis after acute kidney-injury (AKI) and in chronic kidney-disease (CKD), but the molecular mechanism(s) and particular EGFR ligands involved are unknown.

**Methods:** We studied EGFR activation in PTCs and in primary tubular cells isolated from injured kidneys in vitro. To determine the role of amphiregulin (AREG), a highly injury-upregulated low-affinity EGFR ligand in vivo, we used ischemia-reperfusion-injury (IRI) or unilateral-ureteral-obstruction (UO) in AREG PTC-KO mice, or injection of soluble AREG (sAREG) into mice with PTC-KO of its releasing enzyme, a disintegrin and metalloproteinase-17 (ADAM17), and into ADAM17 hypomorphic mice. Serum AREG was measured by ELISA in a CKD patient cohort.

**Results:** We show that Yes-associated-protein-1 (YAP1)-dependent upregulation of AREG transcript and protein amplifies AREG signaling in a positive feedback loop and integrates signals of other moderately injury-upregulated low-affinity EGFR ligands (epiregulin, epigen, TGF-α), which we show also require sAREG and YAP1 to induce sustained EGFR activation in PTCs in vitro. In vivo, sAREG injection sufficed to reverse protection from fibrosis after IRI in ADAM17 hypomorphic mice, and to reverse the corresponding protective PTC phenotype in injured ADAM17 PTC-knockout mice. AREG was necessary for the development of fibrosis, as AREG PTC-knockout mice were protected from fibrosis after IRI or UO. In a nephrectomy cohort (n=78) of CKD patients, serum sAREG negatively correlated with kidney function.

**Conclusions:** Our results identify AREG as a key player in injury-induced kidney fibrosis and suggest therapeutic or diagnostic applications of sAREG in kidney disease.

**Funding:** NIDDK Support

### TH-PO464

#### Graphene Quantum Dots Suppress Kidney Fibrosis After AKI by Affecting the Pericyte-Myofibroblast Transition

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**Background:** Renal pericytes are important in the pathogenesis of kidney disease. They are key to vascular survival can contribute to glomerular and interstitial fibrosis. Graphene quantum dots (GQDs) are novel nanomaterials with excellent biocompatibility. They have anti-oxidative, anti-inflammatory and immune regulatory effects. The purpose of this study is to demonstrate that GQDs can inhibit pericyte activation and reduce the conversion of pericytes into myofibroblasts, thereby suppress kidney fibrosis after acute kidney injury.

**Methods:** Unilateral ischemia-reperfusion injury (UIRI) was induced in 7- to 8-week-old male wild-type C57BL6 mice. GQDs were injected in kidney fibrosis models through the tail vein and the animals were observed for 6 wk. Histopathological examination was performed on the kidneys using Masson’s trichrome staining, and pericyte detection in tissue by Immunofluorescence technique. rhTGF-β1 was used in vitro experiments to induce pericyte-myofibroblast transition. Western blot analysis was used to detect the expression of fibroblast markers.

**Results:** At 6 wk after UIRI, GQDs treatment significantly attenuated interstitial fibrosis in UIRI models. GQDs administration significantly reduced the expression of -smooth muscle actin, collagen I/III, fibronectin, vimentin, TGF-β1, Hsp27, and increased the expression of E-cadherin, smad7, and becl2. In addition, the expression of PDGF in the UIRI group was significantly increased compared with the control group, only a small part overlapped with NG2, and the overlap was significantly less than that of the control group and away from the endothelial cells. Compared with the UIRI group, the expression of PDGF was significantly decreased after GQDs treatment, and the overlap of PDGF and NG2 was increased, and the signs of pericytes away from endothelial cells were improved. rhTGF-β1 was used in vitro experiments to induce pericyte injury, and cell deletion of NG2, ESA, TGF-β, and collagen 1α1 was increased compared with the control group, and the dose-dependent decrease was observed after treatment with various concentrations of GQDs.

**Conclusions:** We found that non-toxic doses of GQDs protect pericyte damage and inhibit the transformation of pericytes into myofibroblasts, there by plays an important role in anti-fibrosis processes after acute kidney injury.

**TH-PO465**

#### The Deletion of Akt1 Exacerbates the Renal Fibrosis Via Transforming Growth Factor β1 Induction

**Il Young Kim,1 Byung Min Ye,1 Dong Won Lee,1 Soo Bong Song,2 Eun Young Seong,3 Sang Hoon Song,2 Pusan National University Yangyang Hospital, Yangyang, Republic of Korea; 2Pusan National University Hospital, Busan, Republic of Korea.**

**Background:** Renal fibrosis is the hallmark of all progressive kidney disease. However, the mechanisms of renal fibrosis are poorly understood. Previous studies have found the increased Akt activity in experimental renal fibrosis. In this study, we investigated the role of Akt1, one of the three Akt isoforms, in renal fibrosis using the murine model of unilateral ureteral obstruction (UUO).

**Methods:** In vivo, we subjected the wild type and Akt1−/− mice to UUO. In vitro, gene silencing of Akt1 was achieved using the short hairpin RNA delivered by the lentiviral vector in immortalized human proximal tubular cells (HK2 cells) and rat kidney fibroblasts (NRK-49F cells). Western blot and immunohistochemical stain were used to investigate the mode of action of Akt1 in vivo and in vitro.

**Results:** In immunohistochemical stain, the expression of Akt1 was significantly higher in obstructed kidneys of wild type mice compared with control sham kidneys and increased gradually as UUO progressed. The fibronectin, type I collagen, and heat shock protein 47 (HSP47) were markedly more expressed in obstructed kidneys of Akt1−/− mice than in those of the wild type mice. Transforming growth factor β1 (TGFβ1) was highly induced within 1 day of UUO in obstructed kidneys of Akt1−/− mice and the expression of TGFβ1 was significantly higher in the Akt1−/− mice than in the wild type mice as UUO progressed. Western blot showed that silencing of Akt1 increased the expression of TGFβ1, which was enhanced by angiotensin II stimulation in HK2 cells, but not in NRK-49F cells. Immunohistochemical stain demonstrated that the expression of cleaved caspase-3 in renal tubules was significantly higher in the Akt1−/− mice than in the wild type mice. Western blot showed that silencing of Akt1 increased the expression of cleaved caspase-3 in HK2 cells, but not in NRK-49F cells.

**Conclusions:** TGFβ1 gene silencing was induced in vivo and in vitro by the genetic deletion of Akt1. Our findings suggest that deletion of Akt1 might contribute to renal fibrosis and tubulointerstitial apoptosis via TGFβ1 induction.
TH-PO466

Knockout of Interleukin-36 Receptor Ameliorates AKI-to-CKD Transition via Prevention of Fibrosis and Inflammation

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Background: IL-36, a newly named member of the IL-1 cytokine family, includes 3 isoforms, IL-36α, IL-36γ, and IL-36ε, all of which bind to a heterodimer containing IL-36 receptor (IL-36R). Little is known about the role of the IL-36 axis in fibrosis during AKI to CKD transition. We examined IL-36 function using mice AKI to CKD models and clinical samples.

Methods: We evaluated IL-36 function in two models of AKI to CKD transition by using IL-36R knockout (KO) and wild-type (WT) mice. First model, left renal ischemia was performed for 35 min and right kidney was removed 2 days later, and left kidney examined at 28 days (IRI). Second model, we used aristolochic acid toxic nephropathy (AAN) in mice at 28 days. In both conditions, we analyzed IL-36 expression, function and histological analysis of KO and WT mice in both models. Fibrotic changes and inflammation were evaluated by RT-PCR, Western blot analysis. Immunohistochemical analysis of collagen type IV, CTGF, and Masson trichrome staining were performed. In clinical study, we performed immunohistological examination of IL-36α in AKI to CKD, and renal biopsy sample.

Results: IL-36α was found to be expressed in the kidney mainly in proximal tubules in WT mice. IL-36R KO mice had significantly lower Cr and BUN at 28 days compared to WT mice in both models. IL-36R KO mice developed less renal fibrosis and tubular cell injury, compared to WT mice in both models. IL-36R KO mice had significantly lower Cr and BUN at 28 days compared to WT mice in both models. IL-36R KO mice developed less renal fibrosis and tubular cell injury, compared to WT mice in both models. IL-36R KO mice had significantly lower Cr and BUN at 28 days compared to WT mice in both models. IL-36R KO mice developed less renal fibrosis and tubular cell injury, compared to WT mice in both models.

Conclusions: Our results demonstrate that IL-36α is up-regulated in renal tissues in both mouse and human AKI to CKD transition, and that IL-36α stimulates collagen type IV, CTGF, and inflammashome in AKI to CKD transition models. Thus, IL-36α/IL-36R blockage could serve as a potential therapeutic target in AKI to CKD transition.

TH-PO467

The Novel NQO1 Donor Reduced Renal Fibrosis in Unilateral Ureteral Obstruction Mice

Dae Fun Choi, Tae Woong Hwang, Da Bi Kim, Eunji Kim, Jin young Jeong, Jwajin Kim, Jae Ri Kim, Jae wan Na, Kang Wook Lee, Wonjung Choi, Yoon-Kyung Chang, Department of Medical Science, Chungnam National University, Daejeon, Republic of Korea.

Background: Reactive oxygen species (ROS) are thought to be a major factor in the development of acute renal injury and renal fibrosis in unilateral ureteral obstruction (UUO). NAD(P)H: quinone oxidoreductase 1 (NQO1) is a well-known antioxidant protein that regulates ROS generation. We generate the NQO1 donor, KL1333 and investigate whether KL1333 modulates the renal injury in UUO mice.

Methods: Adult male mice were divided 4 groups as following, sham, sham with KL1333, UUO, UUO with KL1333. KL1333 was treated oral route, 10mg/kg, daily. UUO were generated by tying left ureter, and after 7 days, the mice were sacrificed and kidney tissue were collected. In vitro, TGF beta treated HK2 cell were used. We analyzed renal injury using various stains, oxidative stress and tubular apoptosis using western blot and immunohistochemical stains.

Results: UUO mice kidney showed increased alpha SMA, collagen, masson trichrome stained area, and renal inflammation, compared to sham kidney. The KL1333 treatment decreased alpha SMA, collagen, masson trichrome stained area, and renal inflammation in UUO mice kidney. In addition, KL1333 increased the levels of HO-1, catlease, UCPI2 in UUO mice kidney. Also, KL1333 increased NQO1, p-sirt1, and NAD+/NADH ratios in UUO mice. These finding indicate that KL1333 decreased UUO-induced oxidative stress and renal fibrosis.

Conclusions: NQO1 activation using KL1333 might be beneficial for ameliorating renal injury induced by UUO mice.

TH-PO468

Regulation of Renal Fibroblast Functions by Myocardin-Related Transcription Factor Focal Adhesion in Response to TGFβ1

Norihiko Sakai, Koichi Sato, Hisayuki Ogura, Taro Miyagawa, Shiji Kitajima, Tadashi Toyama, Akinori Hara, Yasunori Iwata, Miho Shimizu, Kengo Furutachi, Takashi Wada, Division of Blood Purification, Kanazawa University Hospital, Kanazawa, Japan, Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan, Department of Nephrology, Kanazawa Medical University, Kahoku-Gun, Japan.

Background: Renal fibrosis is a common pathway resulting in end-stage renal disease regardless of their etiologies. As pathological findings, tissue fibrosis is characterized by the accumulation of fibroblasts and the excessive deposition of extracellular matrix (ECM). In general, cells can contact with ECM via multiprotein structures called focal adhesion composed of various cytoskeletal proteins and integrins. We have previously found the lipid mediator lysophosphatidic acid (LPA) and one of its receptors, LPA1, contributes to the development of renal fibrosis through connective tissue growth factor (CTGF) expression, at least in part, via myocardin-related transcription factors (MRTFs; MRTF-A and MRTF-B). Recently, TGFβ1 has also been reported to be involved in MRTFs pathway; however, the precise mechanisms how TGFβ1, MRTFs signaling contributes to the regulation of renal fibroblast activities through focal adhesion formation remain to be investigated.

Methods: In this study, we focused on the effects of TGFβ1, signaling on the activities of renal fibroblasts, especially through MRTFs signaling. Cultured renal fibroblasts were used to examine the activation of MRTFs signaling using promotor assays and the expressions of molecules in response to TGFβ1. Renal fibroblasts were transfected with either siRNA targeting MRTFs or focal adhesion components to determine the impact of MRTFs-focal adhesion on renal fibroblast behaviors.

Results: Promoter assay showed the activation of MRTFs signaling by TGFβ1, in a dose- and a time-dependent manner in renal fibroblasts. The stimulation of renal fibroblasts with TGFβ1, increased CTGF expression, while siRNA treatment targeting MRTFs suppressed it. In addition, TGFβ1 enhanced fibronectin, various integrins (αvβ1 and α5β1) and cytoskeletal proteins such as αv and αtalin, all of which were MRTFs-dependent. The treatment of renal fibroblasts with integrin αv siRNA or integrin-linked kinase inhibitor attenuated CTGF expression in response to TGFβ1. Finally, TGFβ1 stimulated the proliferation of renal fibroblasts, however, TGFβ1 siRNA treatment suppressed it.

Conclusions: Our results suggest that MRTF signaling mediates renal fibroblasts biologies through focal adhesion formation in response to TGFβ1.

Funding: NIDDK Support, Government Support - Non-U.S.
TH-PO470

LOXL4 Promotes Renal Fibrosis via Triggering Coll1 Production

Saiya Zhu, Chen Yu, Shanghai Tongji Hospital, Shanghai, China.

Background: Renal fibrosis characterized by excessive deposition of extracellular matrix (ECM) represents a feature of end stage of kidney disease. ECM consists of collagen, fibronectin, elastin and so on. Over crosslinking of extracellular matrix acts as a key role in the process of fibrosis. Lysyl oxidase (LOXs) facilitates the crosslinking of collagen and elastin. Lysyl oxidase-like protein 4 (LOXL4) is the latest member of the LOXs family. Till now, there is no report about the pathogenesis of LOXL4 during renal fibrosis. The aim of the current study is to uncover the role of LOXL4 in renal fibrosis.

Methods: Human renal specimens were obtained from renal biopsy and normal renal tissue adjacent to renal cancer after nephrectomized kidneys. Fibrosis in the kidney specimens was assessed by Masson’s trichrome staining, and LOXL4 expression was examined by using IHC staining. We used unilateral ureteral ligation (UUO) kidney in vivo and used a cell line of rat fibroblast (NRK-49F) in vitro to demonstrate the underlying mechanism of LOXL4 during renal fibrosis by immunofluorescence and western blot analysis. We investigated the biological role of LOXL4 after over-expression or silencing its expression in NRK-49F.

Results: LOXL4 deposited in the fibrotic renal tissue in patients with diabetic nephropathy, which were significantly higher compared with that in renal tissues adjacent to renal cancer after nephrectomized kidneys and minimal changed disease. Compared with sham group, the expressions of LOXL4 and Coll1 in the kidney of UUO group were extremely upregulated (p<0.05, n=5). TGF-β1 significantly increased the expression of LOXL4 and Coll1 (p<0.05, n=5) in NRK-49F. After transfecting with LOXL4 overexpression plasmid, the Col1 expression was significantly increased. There was sharply reduction of Coll1 in NRK-49F cells after transfected with LOXL4 siRNA.

Conclusions: LOXL4 was significantly increased in human and rat tissue, and fibrogenesis. LOXL4/GFP fl/fl mice were crossed with mice expressing Cre-LoxP to generate LysM-Cre-C5aR1GFP fl/fl mice by flow cytometry following UUO-injury and we performed RNA seq.

TH-PO471

Macrophages Mediate Renal Fibrosis via C5AR1 Signaling

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Background: Macrophages regulate innate immunity, inflammation, metabolism and tissue repair. We reported increased expression of intracellular complosome components, C1q, C3, C5 and anaphylatoxins receptors C3aR1 and C5aR1 in macrophages isolated from kidney tissue of mice receiving folic acid (FA) or unilateral ureteral obstruction (UUO). Recently, single cell transcriptomic study performed in UUO mice identified new proximal tubule sub clusters, but also increased expression of C5aR1 in UUO macrophages. We hypothesized that deletion of C5aR1 in macrophages reduces kidney fibrosis.

Methods: C5aR1GFP+ mice were generated by inserting LoxP sites flanking exon 2 as previously described. C5aR1GFP fl/fl mice were crossed with mice expressing Cre recombinase under control of the LysM promoter to generate LysM-Cre-C5aR1GFP fl/fl mice. LysM-Cre-C5aR1GFP fl/fl mice and C5aR1GFP +/+ control mice were intraperitoneal injections of either vehicle (sodium bicarbonate) or FA in sodium bicarbonate. Two weeks later kidney tissue was harvested for analysis. Macrophages expressing C5aR1 fl and C5aR1 negative control macrophages were isolated from C5aR1GFP +/+ mice by flow cytometry following UUO-injury and we performed RNA seq analysis of their transcriptome.

Results: Flow-analysis detected confocal microscopy using C5aR1GFP reporter mice confirmed that macrophages are the dominant expressors of C5aR1 in both models of fibrosis, RNAseq analysis of GFP+ macrophages isolated from C5aR1GFP +/+ mice subjected to UUO confirmed increased expression of C5aR1 mRNA, as well as increased transcript encoding of inflammation, including Tlr4 and C3aR1. GFP+ macrophages also exhibit increased expression of iron homeostatic genes, iron transporters and iron-recycling transcription factors. Immunohistochemistry, flow cytometry, qRT-PCR and western blots demonstrated reduced inflammation and fibrosis in whole kidney tissues from mice with selective deletion of C5aR1 in macrophages (LysMCreC5aR1GFP fl/fl) compared to control mice treated with FA.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
activation was inhibited by GSPE via TGF-β1 /Smad2/3 signaling pathways in normal rat kidney fibroblasts (hNRK-49F).

**Conclusions:** Taken together, these observations provide that GSPE alleviates renal fibrosis by inhibiting the activation of C3/1 HMGB1 / TGF-β pathway and could thus lead to find the potential therapy for the suppression of renal fibrosis.

**TH-PO474**

A Water-Soluble Extract from Actinidia arguta (PG102) Can Inhibit Kidney Fibrosis

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**Background:** PG102 is a water-soluble extract of hardy kiwifruit Actinidia arguta. We aimed to investigate whether treatment with PG102 can attenuate kidney fibrosis.

**Methods:** Male C57BL/6 mice (7-week-old, n = 14) were purchased. Treatment group (n = 7) was administered with PG102 per oral using Zonde needle at dosage of 100 mg/kg daily for 10 days. Control group (n = 7) was fed with distilled water. After this pre-treatment, unilateral ureteral obstruction operation performed, and mice were administered with PG102 or distilled water at the same dose for 10 days. After 10 days, mice were sacrificed. In addition, human kidney proximal tubular cells were cultured and challenged with TGF-β (2 ng/ml) with or without PG102 (2.5 and 5 µg/ml).

**Results:** Mice in both groups showed similar body weight and similar serum creatinine levels between groups. In the histopathologic specimen of Masson’s trichrome stain, areas of kidney interstitial fibrosis attenuated in the treatment group (3.6 ± 0.9 % area vs. 8.7 ± 3.0 % area, P = 0.03). In the western-blot analysis, protein abundance of α-smooth muscle actin (30.6% of control), fibronectin (47.8% of control), p53 (30.8% of control) decreased, and protein abundance of e-cadherin increased (325.1% of control) in the treatment group. In immunohistochemical stain of phospho-p38, PG102 treated group showed decreased expression of phospho-p38 (0.9 ± 0.9 % area vs. 8.7 ± 3.0 % area, P = 0.03). In the western-blot analysis, protein abundance of α-smooth muscle actin (47.8% of control), and phospho-p38 (51.5% of control).

**Conclusions:** PG102 attenuates kidney fibrosis in the unilateral ureteral obstruction model and TGF-β-treated human kidney proximal tubular cells, p38 MAPK pathway is inhibited after treatment of PG102.

**TH-PO475**

Suppression of Transcription Factor OASIS Ameliorated Kidney Fibrosis

Masanori Kato,1 Lilin Li,2 Jung Pyo Lee.1 Halhym University Hangang Sacred Heart Hospital, Seoul, Republic of Korea; 2Seoul National University College of Medicine, Boramae Medical Center, Seoul, Republic of Korea; 1Seoul National University Boramae Medical Center, Seoul, Republic of Korea.

**Background:** OASIS (2′-5′-OAS) is a member of the RNA-dependent activator of the transcription factor 2. Through Inhibition of FAK Pathway in the Tubular Epithelium

Hiroaki Amano, Tsutomu Inoue, Hirokazu Okada. Department of Nephrology, Saitama Medical University Saitama Medical University, Saitama, Japan.

**Methods:** OASIS expression was investigated by immunohistochemistry, immunoblotting and quantitative PCR. To assess the functions of OASIS in in (myo) fibroblast, NRK-49F cells, rat renal fibroblasts, were transduced with the lentivirus encoding OASIS shRNA, followed by TGF-β1 treatment. Twenty-four hours after TGF-β1 treatment, wound healing assay and proliferation assay were performed. To examine the effects of OASIS on kidney fibrosis, OASIS knockout (KO) mice were subjected to unilateral ureteral obstruction (UUO). At day 7 after UUO, Masson’s trichrome stain and hydroxyproline assay were performed. To explore the downstream molecules of OASIS, DNA microarray was performed on OASIS KO myofibroblasts. Anti-bone marrow stromal antigen (Bs2) antibody was injected into mice at day 1 after UUO.

**Results:** The protein level of OASIS was increased in human fibrotic kidney. Consistently, mRNA and protein levels of OASIS were upregulated in UUO-induced murine fibrotic kidney. In addition, the number of OASIS-expressed myofibroblasts were elevated after UUO. OASIS expression was induced by TGF-β1 in NRK-49F cells. OASIS knockdown suppressed TGF-β1-induced migration and proliferation of NRK-49F cells. Moreover, kidney fibrosis was attenuated in OASIS KO mice (HP content [mg/g]: Wild-type-UUO; 0.48 ± 0.05, OASIS KO-UUO; 0.38 ± 0.05, n = 7, p < 0.05). DNA microarray revealed that Bs2 was a candidate downstream molecule of OASIS. Finally, antibody blockade of Bs2 ameliorated kidney fibrosis after UUO (HP content [mg/g]: control IgGx; 0.60 ± 0.08, anti-Bs2 antibody; 0.49 ± 0.09, n = 6, p < 0.05).

**Conclusions:** OASIS exacerbated kidney fibrosis in part by increased Bs2 expression. Suppression of OASIS could be a novel therapeutic strategy against chronic kidney disease.
were also lowered (p-Akt/Akt: 7.0±1.4 vs. 2.5±0.3, p<0.05; p-GSK-3b/ GSK-3b: 3.2±0.3 vs. 1.6±0.6, p<0.05). Among MAPKs, only the levels of p-p38 were lowered by DC5. 

Conclusions: DCs likely suppressed FAK-mediated renal fibrogenesis in mice. This finding is similar to that observed in the in vitro experiments, suggesting that these DCs may have a therapeutic potential for the intervention between M4 and integrin in TEC. The in-vitro experiments showed that down-stream signals activated by CCN2-M4-Integrin-FAK pathway were P38-Akt-mediated phosphorylation of GSK-3b and p38 in TECs. The CCN2M4-Integrin-FAK pathway seems to be a promising, therapeutic target for attenuating renal fibrogenesis.

TH-PO478

Suppression of the Hippo Pathway in Tubular Cells Leads to Renal Fibrosis in Mice
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Background: The Hippo pathway controls organ size and tumorigenesis. The core components of the Hippo pathway consist of Mammalian Ste20-like kinases 1/2 (MST1/2) and their scaffold protein Sav1, a large tumor suppressor 1/2 (LATS1/2) and two downstream effectors YAP/TAZ. Several components of the Hippo pathway, including Sav1, LATS1/2, and YAP/TAZ, have been found to be critically involved in embryonic kidney development or kidney disease. However, the role of MST1 and MST2 in kidney remains unknown.

Methods: We generated tubular cell specific Mst1/Mst2 double knockout mice by intercrossing floxed Mst1/Mst2 mice with Kap-Cre transgenic mice. The Hippo pathway is restrained in renal tubular epithelium in Mst1/Mst2 mutant mice.

Results: We showed for the first time that MST1 and MST2 were highly expressed in all nephron segments and collecting ducts in mice kidneys. Deletion of Mst1/ Mst2 in tubular cell specific Mst1/Mst2 (Kap-Cre) in mouse renal tubular epithelium resulted in increased kidney sizes starting from 4 weeks of age, coupled with increased YAP activity and cell proliferation in renal tubules. The Mst1/Mst2 mutant mice developed chronic kidney disease as indicated by progressive increases in tubular damage, inflammation, fibrosis and functional impairment. Deletion of Yap prevented kidney overgrowth and tubular damage in Mst1/Mst2 mutant mice and rescued the expression of many inflammatory factors measured at 4 weeks of age. More importantly, ablation of Yap prevented fibrosis development in Mst1/Mst2 mutant mice at 8 weeks of age.

Conclusions: We found that suppression of the Hippo pathway in renal tubular epithelium results in renal fibrosis via activation of YAP.

Funding: Government Support - Non-U.S.

TH-PO479

The Association Losartan/Erlotinib Is More Effective in Attenuating Renal Fibrosis Formation by Blocking TACE-Dependent EGF Receptor Activation in 5/6-Nephrectomized Rats Under Vitamin D Deficiency
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Background: Hypovitaminosis D has been described as a risk factor for the progression of kidney disease. Among others, overactivity of renin-angiotensin system and renal fibrosis formation (RFF) are hallmarks of CKD. In an alternative RFF pathway, converting enzyme (ACE), which binds to and activates the epidermal growth factor (EGF) receptor (EGFr). Although many studies have focused on the mechanisms underlying RFF, novel anti-fibrotic therapies need to be evaluated in order to retard the progression of CKD. We evaluated the effects of losartan (L) and erlotinib (E) in 5/6-nephrectomized rats under vitamin D deficiency.

Methods: Male Wistar rats were fed a vitamin D-free diet (D) for 90 days and submitted to 5/6 Nx (N) on day 30. We studied four groups: (A) D; (B) D+N; (C) D+E; (D) D+N+E. We submitted to 5/6 Nx (N) on day 30. We studied four groups: (A) D; (B) D+N; (C) D+E; (D) D+N+E. We showed for the first time that losartan (L) and erlotinib (E) were more effective in blocking the TACE-dependent EGF activation pathway demonstrated by lower expression of TACE, ACE, TGF-α, EGFr and p-EGFr. In addition, we observed decreased expression of fibronectin, collagen III, vimentin and α-sm-actin in renal tissue.

Conclusions: Our data indicate that the dual treatment L+E may represent a novel anti-fibrotic strategy for attenuating CKD.

Funding: FAPESP 2018/12297-1; CNPq 302599/2018-5.

TH-PO480

Sphingosine Kinase 2 Deletion in Kidney Pericytes/Fibroblasts Protects Against Kidney Fibrosis via Suppression of Local Interstitial Inflammation
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Background: Sphingosine 1-phosphate (S1P), which is produced by two different kinases, sphingosine kinase (SphK) 1 and 2, is a sphingolipid involved in myriad cell functions. We recently showed that Sphk2-/- mice were protected from renal fibrosis when compared to wild type or Sphk1-/- mice; bone marrow chimera experiments suggested that Sphk2 deletion in hematopoietic cells contributed to the protection (PMID: 27799486). We hypothesized that Sphk2 deletion in renal pericytes/fibroblasts confers the protection from progressive kidney fibrosis.

Methods: We generated Sphk2 KO mice. Male Wistar rats were fed a vitamin D-free diet (D) for 90 days and subjected to unilateral Ureteric Obstruction (UUO) for 14 days. We performed renal fibrosis analysis.

Results: We found that suppression of the Hippo pathway in renal tubular epithelium resulted in renal fibrosis via activation of YAP.

Funding: Government Support - Non-U.S.

TH-PO481

Profiling Histone Modifications in the Normal Mouse Kidney and After Unilateral Ureteric Obstruction
Timothy D. Hewston, Stephen G. Holt, Edward R. Smith. The Royal Melbourne Hospital, Melbourne, VIC, Australia.

Background: Post-translational modification of nucleosomal histones has emerged as a major determinant of chromatin structure and gene activity. In this study, we hypothesised that unilateral ureteric obstruction (UUO), a widely used model of tubulointerstitial injury, would be associated with a distinct pattern of histone (H) modifications (marks) in the kidney.

Methods: Mass spectrometry (MS) was used to profile 61 different histone marks, and their corresponding unmodified amino acid, in normal mouse kidneys and those after 10 days of UUO. A subsequent bioinformatic analysis further examined examples of specific marks that changed significantly after UUO, for which antisera are available. The distribution of marks was compared with markers of pathology and transcription.

Results: Histone marks were much more widely distributed and abundant in the normal kidney than usually appreciated. Although aggregate analysis of the MS results revealed net differences between control and UUO groups, residue-specific variations were subtle. Of 16/63 significant changes (P<0.05), only 8 were quantitatively different by more than 5%. Nevertheless, we identified several not usually examined in the kidney including H2A.Z in the globular domain of core histones (H3K79), linker histones (H1.4) and histone variants (H3.1K27, H3.3K27). In several cases there were complementary changes in different marks on the same amino acid. In situ staining showed compartment specific differences in the distribution of individual marks. Using H3K79Me2 as an example, mark enrichment was heterogeneous, but largely co-localised with tubular hypoxia and transcription, but not proliferation, apoptosis or interstitial pathology.

Data are expressed as mean±SEM. p<0.001, p<0.01, c<0.05 vs DN; d<0.05, e p<0.01, f<0.05 vs DNE; g<0.001, i p<0.01 vs DNL.

Table 1

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<th>Group</th>
<th>ENL</th>
<th>DNL</th>
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<tr>
<td>TACE</td>
<td>10.9±6.2</td>
<td>2.6±1.0</td>
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<tr>
<td>TGF-α (ng/ml)</td>
<td>3.0±0.5</td>
<td>1.6±0.3</td>
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<td>242</td>
<td></td>
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Conclusions: Our study highlights the importance of unbiased screening in examining histone marks. Significant changes in multiple marks on the same amino acid are indicative of a coordinated histone mark signature. The heterogeneous enrichment of marks, even within the same tubule, highlights the importance of regulatory context.

Funding: Government Support - Non-U.S.

TH-PO482
Diabetic Glomeruli Stiffen as They Sear
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Background: Glomerulosclerosis is an important manifestation of diabetic glomerular injury. Studies of mesangial cells (the main producers of scar in the glomerulus) have mostly focused on biochemical stimuli (eg, high glucose, TGF-β). However, increasing evidence suggests that biomechanical stimuli such as extracellular matrix stiffening can also activate mesenchymal cells. In particular, the mechanosensory transcription co-factors YAP and TAZ appear to link matrix stiffness to fibrogenesis. Our goal was to study changes in glomerular stiffness in diabetic injury.

Methods: We studied male Akita+/- Ren-/- mice at early (8 wk old, n = 8) and late (26 wk old, n = 6) time points. These mice develop diabetes and renin-mediated hypertension, resulting in progressive glomerulosclerosis that mimics human diabetic kidney disease. Male non-diabetic, normotensive Akita+/- Ren-/- mice served as healthy controls. Parameters of glomerular stiffness (atomic force microscopy, AFM) and histology (picrosirius red, type 1 collagen, and YAP/TAZ immunostaining) were measured and correlated. Glomerular stiffness was measured in a minimum of 30 glomeruli per kidney.

Results: Mean glomerular stiffness and glomerulosclerosis values increased with age in both the diabetic, hypertensive Akita+/- Ren-/- mice and their non-diabetic, normotensive Akita+/- Ren-/- controls, although at each time point, diabetic, hypertensive Akita+/- Ren-/- glomeruli were significantly stiffer and more scarred than glomeruli in healthy Akita+/- Ren-/- controls (Table 1). At both early and late stages of diabetic kidney injury, stiffness increased with glomerulosclerotic burden. Reflecting this increased stiffness, glomerular cell YAP/TAZ activity was increased in Akita+/- Ren-/- mice at 26 weeks compared to wild type controls, as evidenced by increased YAP/TAZ nuclear localization.

Conclusions: As glomerulosclerosis progresses in diabetes, the stiffness of glomeruli, as well as the activation of the mechanosensitizing, pro-fibrotic transcription co-factors YAP and TAZ, increases. Taken together, our data suggest a novel biomechanical stimulus for glomerulosclerosis progression in diabetes.

TH-PO483
The Protective Effect of Prostacyclin in Renal Fibrosis
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Background: Progressive decline of renal function is a hallmark of CKD, the mechanism of which is incompletely understood. Inadequate repairing process to injury has been reported to play an important role. Mounting evidence suggests that prostaglandins are important in serving as a “buffer” in response to physiological changes or pathophysiologic insults to tissues including the kidney. Underlyingly, under certain conditions such as aging and hypertension, prostacyclin (PGI2), an active production of COX/PGI2 Synthase (PGIS), is reduced. The present study provides data showing that PGI2 plays an important role in maintaining adequate injury repair condition and correlated. Glomerular stiffness was measured in a minimum of 30 glomeruli per kidney biopsies, aiming to provide insight into the mechanisms of progressive CKD.

We confirmed the biological function of PHF14 in PHF14 conditional knockout mice following AKI and fibrotic kidney. Enhanced PGIS expression is associated with progressive kidney disease. Lack of PGIS enhances kidney damage. PGIS/PGI2 is a potential target for CKD.

Funding: Government Support - Non-U.S.

TH-PO484
Plant Homeodomain (PHD) Finger Protein 14 (PHF14) Inhibits Renal Fibrosis via Repressing Connective Tissue Growth Factor Induced by Hypoxia-Inducible Factor 1 Alpha
Sixiu Chen, Linxi Huang, Zhiguo Mao. Division of Nephrology, Kidney Institute of CPLA, Changzheng Hospital, Second Military Medical University, Shanghai, China.

Background: Renal fibrosis is the final common pathological manifestation of chronic kidney diseases progressing to ESRD, while no effective way has been found to reverse it. Chronic hypoxia was thought to play an important role in renal fibrosis. PHF14, a novel histone binding protein, was discovered in our previous studies to be an innate inhibitor of renal fibrosis. However, the mechanism of PHF14 is not unraveled. We hypothesized PHF14 may be induced by hypoxia-inducible factor 1 α (HIF-1α), and repress the over-expression of connective tissue growth factor (CTGF) by regulating histone methylation.

Methods: We confirmed the biological function of PHF14 in PHF14 conditional knockout mice following fibrotic kidney. To examine the potential role of the candidate gene PHMD3 in CKD progression.

Results: 1. Compared with controls, PHF14 conditional knockout mice presented aggravated renal fibrosis and worse renal function (Figure 1A-1C). 2. PHF14 was induced in hypoxia environment in vitro. And PHF14 was upregulated by HIF-1α stimulant DMOG and repressed by HIF-1α inhibitor KC7F2 (Figure 1D). ChiP detected HIF-1α binding on the promoter of PHF14 and CTGF. 3. PHF14 knockdown enhanced CTGF expression following DMOG stimulation in vitro and PHF14 could bind on the promoter of CTGF, which was proved by ChIP. 4. The enrichment of histone methylation in CTGF promoter induced by HIF-1 α was changed in PHF14KO cells. Co-IP validated PHF14 could interact with H3K4me3 and H3K27me3.

Conclusions: Lack of PHF14 deteriorated aristolochic acid nephropathy in mice. PHF14, which was induced by HIF-1α, inhibited CTGF expression via regulating histone methylation in CTGF promoter.

Funding: Government Support - Non-U.S.

TH-PO485
High Throughput Sequencing of Human Kidney Tissue Implicates FRMD3 as Important in the Pathogenesis of Progressive CKD
Ross P. Doyle,1 Caetirriona M. McEvoy,1 Eoin F. Brennan,1 Peter J. Conlon,2 Denise M. Sadlier,3 Catherine Godson,4 1Mater Misericordiae University Hospital, Dublin, Ireland; 2Diabetes Complications Research Centre, University College Dublin, Dublin, Ireland; 3Beaumont Hospital, Dublin 9, Co Dublin, Ireland; 4University Health Network, Toronto, Toronto, ON, Canada; 5The Conway Institute of Biomolecular and Biomedical, Belfield, Dublin, Ireland; 6University College Dublin, Dublin, Ireland.

Background: The global health concern of Chronic Kidney Disease (CKD) is enhanced by the challenge to predict future disease events, particularly progression to End Stage Kidney Disease (ESKD). We examined the transcriptional profile of human kidney biopsies, aiming to provide insight into the mechanisms of progressive CKD. We evaluated the potential role of the candidate gene FRMD3 in CKD progression.

Methods: RNA extracted from kidney biopsy tissue was sequenced using high throughput techniques and gene expression correlated with clinical variables, eGFR and percentage tubudointerstitial fibrosis (%TIF) on kidney biopsy. We identified genes which were differentially expressed in patients experiencing progressive CKD (doubling of serum creatinine or reaching ESKD). Analyses were adjusted for age and sex of the patients, and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
with a FDR cut-off of <0.05. Using established cellular models we examined the impact of knockdown of the gene FRMD3 in human kidney epithelial and podocytes. Results: We examined gene expression in discovery (n=24) and validation cohorts (n=23) and identified a subset of genes which correlated with the clinical variables, eGFR and %TIF, and were associated with CKD progression. Pathways of inflammation and immune system function are heavily represented in our dataset. FRMD3 expression was consistently associated with worse kidney disease, with lower expression seen in patients with higher %TIF and lower eGFR, and in patients with progressive CKD. FRMD3 knockdown enhances the fibrotic responses to TGF-β1, including loss of E-cadherin, upregulation of N-cadherin and CTGF in human kidney epithelial cells, and exaggerated loss of podocin in immortalised human podocytes. Conclusions: Inflammatory cell signaling pathways are driving forces in CKD progression. Loss of FRMD3 is associated with more severe kidney disease and CKD progression.

Funding: Private Foundation Support

TH-PO486
Collecting Duct-Specific Deletion of Renin Attenuates Obstruction-Induced Renal Fibrosis and Inflammation
Renfei Liao, Kevin Yang, Chunmansang Fei, Wei Wang, Tianxiao Yang. Department of Internal Medicine, University of Utah, Salt Lake City, UT.

Background: Increasing evidence demonstrates that renin is synthesized and secreted by the collecting duct (CD) as a component of the intrarenal renin-angiotensin system (RAS). The intrarenal RAS is known to play a role in the development of chronic kidney disease (CKD) in addition to hypertension. However, the precise mechanism of how intrarenal RAS is activated in the disease process is poorly characterized.

Methods: The goal of the present study was to examine the impact of CD-specific deletion of renin on renal fibrosis and inflammation in a mouse model of unilateral ureteral obstruction (UUO). CD-specific renin deletion was generated by crossing aquaporin-2-Cre flox mice and CD renin KO mice. Results: After 3 days of UUO, the renal medullary renin content, renin activity and renin mRNA in obstructed kidneys of flox mice were increased by 4.7-, 2.2- and 7.8-fold, respectively, which were all blocked by CD renin KO mice. In contrast, renal cortical renin was largely unaffected by UUO, irrespective of the genotype. Meanwhile, CD renin KO decreased the α-SMA (51.3±10.9%) and fibronectin (60.4±7.2%) protein expression and increased E-cadherin (2.1-fold) protein expression in obstructed kidneys. The content of hydroxyproline, a major component of the protein collagen, in obstructed kidneys of renin KO mice showed a significant down-regulated expression compared with obstructed kidneys of flox mice. (KO:UOX: 7.7±0.9 vs. flox-UUX: 12.3±1.6 μg/tissue; P<0.05). The Masson’s trichrome staining (MST) data also showed that CD renin KO significantly attenuated UUO-induced morphological deposition and histological damage in the kidney. In parallel, CD renin KO reduced α-SMA (48.2±4.3%), fibronectin (38.9±7.4%), TGF-β (32.9±4.6%), IL-6 (20.6±1.6%) and TNF-α (47.2±5.2%) mRNA expression in obstructed kidneys.

Conclusions: Overall, these results suggest that overactivation of CD renin play an essential role in driving local RAS to promote renal fibrosis induced by obstruction.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO487
Major Vault Protein Contributes to Tubulointerstitial Fibrosis in CKD
Cheuk Yin Wong, Caleb C. Chan, Chi pang Tai, Susan Yang, Daniel Tak Mao Chan. The University of Hong Kong, Hong Kong, China.

Background: Chronic kidney disease (CKD) is a major global issue leading to much morbidity and mortality. Tubulointerstitial fibrosis is the final pathogenic pathway in the progression of CKD to end-stage renal failure. There is currently no effective treatment for kidney fibrosis. We previously reported that major vault protein (MVP), a key component in the vault complex, contributed to fibrogenesis in HK-2 cells in lupus nephritis. We extended our investigations to other causes of CKD.

Methods: MVP expression in renal biopsies from patients with CKD due to various causes was examined with conventional and quantitative immunostaining. Animals were carried out with unilateral ureteral obstruction (UUO) model in wild-type (WT) and MVP knockout (KO) mice, with the contralateral unobstructed kidney serving as control. Mice were sacrificed 14 days after UUO, and the kidneys were harvested and examined. The effect of MVP overexpression in HK-2 cells was investigated.

Results: Kidney biopsies from patients with IgA nephropathy, diabetic nephropathy, or idiopathic membranous glomerulonephritis with CKD showed markedly increased MVP expression, predominately in proximal tubular epithelial cells, compared with renal biopsies from controls. Northern blot analysis showed significantly induced MVP mRNA expression, accompanied by tubular atrophy, increased tubulo-interstitial inflammatory cell infiltration, and matrix protein accumulation including fibronectin and collagen III. MVP KO in UUO mice was associated with reduced immune cell infiltration and decreased tubulointerstitial collagen III and fibronectin expression compared with WT. Further data showed that MVP regulated collagen III at transcriptional level, whereas its effect on fibronectin expression was at the post-transcriptional level. MVP gene editing using CRISPR-Cas9 in HK-2 cells was accompanied by decreased MCP-1 secretion and fibronectin expression.

Conclusions: Our data show increased renal tubulo-interstitial MVP expression in CKD irrespective of original cause, which may contribute to inflammatory and fibrotic processes in CKD progression.

Funding: Government Support - Non-U.S.

TH-PO488
Upregulation of mir-382 Contributes to AKI to CKD Transition via the PTEN/AKT Signaling Pathway
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Background: Acute kidney injury (AKI) is recently considered as a critical factor for the development of chronic kidney disease (CKD). Kidney mechanisms driving AKI to CKD transition remain unclear. Previously we have discovered mir-382 as a novel target in TGF-β1-induced epithelial-mesenchymal transition and the development of tubulointerstitial fibrosis after AKI was accompanied with an overwhelmed activation of mir-382.

Methods: In our recent study of aristolochic acid nephropathy (AAN), we examine the effects of genetic absence or pharmacologic inhibition of mir-382 on the expression of NF-κB/PTEN/AKT signaling pathway and renal pathological changes.

Results: Renal fibrosis developed at 14 days after a single dose of aristolochic acid (AA, 10mg/kg, ip) and renal fibrotic lesions getting even more severe at 28 days after AA treatment. Renal abundance of mir-382 was detected increasing until 28 days post AA administration while inhibition of mir-382 partly reversed renal tubulointerstitial fibrosis. The protective effects of anti-mir-382 treatment against fibrosis was also verified in mir-382 KO mice. Protein expression of phosphatase and tensin homolog (PTEN), a target of mir-382, was down-regulated and subsequently its downstream phosphorylated protein kinase B (AKT) signaling pathway was activated during AA induced AKI to CKD transition. Furthermore, we found the up-regulation of mir-382 of renal epithelial cells was in part mediated by activation of NF-κB signaling secondary to AA exposure, with substantial elevation of pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α. In vivo study revealed that either mir-382 knockdown or mir-382 knockout was protective for inflammation. In vitro experiment confirmed that up-regulation of mir-382 in cultured HK-2 cells under AA exposure could be remarkably reversed by NF-κB siRNA.

Conclusions: These data supported a novel mechanism in which AA induced mir-382 up-regulation via NF-κB activation, therefore targeting PTEN/AKT signaling, contributing to the development of renal fibrosis secondary to acute AA related renal toxicity.

Funding: Government Support - Non-U.S.

TH-PO489
Kinin in Hypertensive Kidney Disease: A Novel Therapeutic Target
Debargha Basuli, Rohan U. Parchek, Srinivasas Srimalau. East Carolina University, Greenville, NC.

Background: Hypertensive kidney disease is the second leading cause of end-stage renal disease (ESRD) following diabetes. While inhibition of the renin-angiotensin system remains the current management of hypertensive kidney disease, we are still spending billions of dollars for hemodialysis and the incidence of ESRD is projected to increase in upcoming years. Thus, elucidating the pathogenesis of hypertensive kidney disease, particularly if there is any non-angiotensin pathway involved is important to formulate newer treatment strategies. Recently, a growing body of evidence suggests a role for kallikrein-kinin system in hypertension and kidney diseases. The effects of kinins are exerted through two G-protein coupled receptors- B1R and B2R. It has been recently shown that B1R regulates neurogenic hypertension in mice. However, the role of B1R in hypertension induced end-organ damage, particularly in the kidney has not been studied. This study examines the significance of B1R induced inflammation and fibrosis in the kidney environment.

Methods: Human kidney sections were used to study the expression pattern of B1R in kidneys by immunohistochemistry. Deoxocorticosterone acetate (DOCA)-salt hypertensive model coupled with a whole body B1R knockout (B1RKO) mice were used for the effect of kinin on hypertensive kidney disease. Hypertension induced renal damage was assessed by measuring the mRNA and protein expression of Kucy - TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
fibrosis markers (collagen I/III, fibronectin, TGF-β). Renal inflammation was assessed by immunohistochemistry and measuring TNF-α, IL-6, IL-1β and inflammatory cell infiltration.

Results: B1R is expressed in human kidneys predominantly in proximal tubular cells. Treatment with DOCA-salt significantly increased blood pressure (p<0.001) in wild-type mice, which was attenuated in B1R KO mice. B1R blockade decreased DOCA-salt induced renal fibrosis. Administration of DOCA-salt-induced increase in renal inflammation was significantly blunted in B1R KO mice.

Conclusions: Our data provide evidence that kinin B1R is expressed in human kidney and may have an important role in the pathogenesis of hypertensive kidney disease. In an animal model, B1R knockdown reduces renal injury by decreasing inflammation and fibrosis. Kinin B1R offers a potential therapeutic target for the treatment of hypertension and hypertensive kidney disease.

TH-PO490
TGFβ and Kidney Disease Progression
Wenjun Ju,1 Kerstin Ebeers,2 Debra L. Walter,3 Sean Eddy,2 Linda Cederblad,1 Víti Nair,2 Rajasree Menon,1 Jeffrey B. Hodgkin,2 Susanna Ekjétill,1 Anna Reznichenko,1 Jenny C. Nystrom,1 Markus Bitzer,1 Matthias Kretzler,2 Julie Williams.1 AstraZeneca, Mölndal, Sweden; 2University of Michigan, Ann Arbor, MI; 3University of Gothenburg, Goteborg, Sweden.

Background: TGFβ was identified as one of the genes whose hypomethylation is associated with chronic kidney disease (CKD) progression. Increased expression of TGFβ is reported in patients with diabetic kidney disease (DKD) and was considered to play a central role in a novel pathway that promotes DKD. However, the molecular mechanism of TGFβ in kidney disease progression remains to be determined.

Methods: Bioinformatic analysis was performed to investigate the association of TGFβ expression with disease association in human and mouse models for kidney disease. Single cell RNAseq analysis, in situ hybridization and IHC were used to determine the cellular localization. Expression of key pathway genes was evaluated in TGFβ treated-human mesangial and podocyte cells by qRT-PCR and IHC.

Results: Higher expression of TGFβ is associated with increased kidney disease severity in transforming growth factor-β1 transgenic mice (Albumin/Tgfb1 Tg), developing focal segmental glomerular sclerosis and tubulointerstitial injury. In patients with various CKD etiologies, TGFβ expression is reversely correlated with glomerular filtration rate (GFR), including DKD and SLE. Single cell RNAseq analysis demonstrated that TGFβ is enriched in immune cells, followed by mesangial cells. In vitro mesangial cells can produce TGFβ and knock down reduces pathogenic proliferation. Treatment of podocytes with TGFβ leads to actin cytoskeletal rearrangement and fibrotic gene expression, suggesting that increased TGFβ expression by mesangial cells may cause the disease. This hypothesis is supported by the observation that Tgfb1 mRNA is reversely associated with podocyte density (r=-0.66, p<0.01) in Tgfb1 Tg mice.

Conclusions: TGFβ is an important player in CKD/CKD progression by initiating podocyte injury which will lead to proteinuria.

Funding: Commercial Support - AstraZeneca.

TH-PO491
The Role of Renal Uric Acid Crystal Granulomas on CKD Progression in Mice
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Background: Tophaceous uric acid (UA) deposits are occasionally found on diagnostic kidney biopsies. Whether UA crystal granulomas are a cause or bystander of CKD is subject of debate. We hypothesized that renal UA granulomas associate with more severe interstitial fibrosis, therefore contribute to CKD progression. UA granulomas are mainly comprised of M1-macrophages. We thought to target a phenotype switch from M1- to M2-macrophages by activating adenosine receptor signaling in a mouse model of CKD with UA granulomas.

Methods: We screened 81,200 diagnostic kidney biopsies for the presence of UA granulomas to determine the prevalence and performed a case-control study to compare biopsies with and without granulomas for morphological abnormalities. Alb-crelERT2 / Glut9Δ/Δ (ki/ki) or Glut9Δ/Δ (control) mice were fed either a high-fat or chow diet with inosine. We assessed UA crystal deposits, GFR and the extent of kidney damage (MALDI-FTICR MS imaging, immunostaining, flow cytometry). Adenosine therapy was started after renal fibrosis had established.

Results: 84 out of 81,200 kidney biopsies showed UA granulomas, which revealed significantly moreglomerulosclerosis and interstitial fibrosis compared to control biopsies. Ki/ki mice on chow diet with inosine developed only hyperuricemia (HU), whereas ki/ki mice on high-fat diet with inosine developed HU + CKD compared to control mice. Urine urea nephropathy caused a significant GFR decline compared to HU or control mice. MALDI-FTICR MS imaging confirmed UA crystal deposits that were associated with tubulointerstitial fibrosis and macrophage infiltration. Histological analysis showed that UA granulomas occur after renal fibrosis had established. Adenosine therapy significantly reduced the number of renal UA granulomas due to less M1- but more M2-macrophages, a process that attenuated CKD progression.

Conclusions: UA granulomas are found in 0,1% of diagnostic kidney biopsies and associated with more renal fibrosis and tubular atrophy. Our in vivo data revealed that UA granulomas form after renal fibrosis had established. M1-macrophages are essential for UA granuloma formation, and interfering with a switch from M1- to M2-macrophages prevents CKD progression. Together, UA granulomas develop secondary to renal fibrosis but contribute to accelerated kidney atrophy and dysfunction.

Funding: Government Support - Non-U.S.

TH-PO492
Dual Suppression of Endothelial Nitric Oxide Synthase and ApoE Gene Accelerates Kidney Fibrosis and Aging After Injury
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Background: Medical advances have made it possible to control diseases such as cancer, autoimmune diseases and infectious diseases, extending life for affected patients worldwide. On the other hand, CKD has become a lifestyle-related disease and lifestyle management is necessary to extend healthy life span. In this study, we clarify the effect of interaction between hypertension and atherosclerosis on renal fibrosis and aging.

Methods: Wild type (WT) mouse, apolipoprotein E-/- (ApoE: KO) mouse, and endothelial nitric oxide synthase (-/-) (E NOS -/- ) and ApoE: -/- (WKO) mouse were obtained by crossing eNOS -/- mouse and ApoE -/- mouse. Unilateral ureteral obstruction (UUO) was performed on 8-10 weeks old male mice after blood pressure and lipid profile were measured. Mice were sacrificed 10 days after UUO. The degree of renal tubular injury, fibrosis, and kidney aging were evaluated by histological analysis.

Results: ApoE KO mice had higher total cholesterol and lower HDL cholesterol than WT mice. WKO mice manifested elevated blood pressure, higher total cholesterol and lower HDL cholesterol than WT mice. Compared with WT mice, ApoE KO and WKO mice showed the highest injury. Injury molecule-lipoprotein lipase (LPL) expression and increased α-smooth muscle actin protein expression was found in WKO mice after UUO. mRNA expression of transforming growth factor-β, connective tissue growth factor and type 1 collagen was increased both in ApoE KO and WKO mice and the highest in WKO mice with statistical significance. The picro-sirius red positive stained kidney area was significantly higher in ApoE KO and WKO mice. The antioxidant, hemoglobin was significantly decreased in WKO mice. Furthermore, mRNA expression of p32, p31 and p16 was increased both in ApoE KO and WKO mice and the highest in WKO mice among three groups with statistical significance. A significant increase in senescence associated β-gal positive tubule area was observed in WKO mice.

Conclusions: Mice at high risk for cardiovascular disease developed kidney fibrosis and aging even in the young mice after injury. Vulnerability to oxidative stress promotes CKD progression. Managing diseases from a young age is important for CKD prevention. This mouse model could be a good tool for elucidating the relationship between bad lifestyle and kidney fibrosis and aging.

Funding: Government Support - Non-U.S.

TH-PO493
Paraoxonase1 Regulation of Renal Inflammation and Fibrosis in CKD Fatehmin K. Khalat1, Chysan J. Mohammed,2 Prabhatchandra Dube,3 Iman Tassavvor,4 Andrew Kleinhenz,2 Apurva Lad,4 Amira F. Gohara,4 Deepak K. Mallotra,5 Steven T. Haller,1 David J. Kennedy.1 1University of Toledo College of Medicine and Life Sciences, Toledo, OH; 2University of Toledo College of Medicine & Life Science, Maumee, OH; 3University of Toledo Health Science Campus, Toledo, OH.

Background: PON1 (PON1) is a hydrolytic lactonase enzyme which is synthesized by the liver and circulates attached to high density lipoproteins. Clinical studies have demonstrated an association between diminished PON1 and progression of CKD however whether decreased PON1 is mechanistically linked to renal disease is unknown. We tested whether absence of PON1 is mechanically linked to progression of renal injury in a Dahl salt-sensitive model of hypertensive renal disease.

Methods: Experiments were performed on Dahl salt-sensitive rats (wild) and PON1 knock-out rats (PON1 KO). Ten week old, male rats were maintained on high salt diet (8% NaCl) for up to 5 weeks to initiate renal disease. Early mortality was observed in 5 out of 12 (41.6%) Pon1 KO rats (mean time until death=33 days), while no mortality was observed in wild type rats. At 4 weeks, Pon1 KO and wild type rats developed similar degrees of hypertension however Pon1 KO demonstrated significantly decreased renal function compared to the wild type rats as assessed by FITC-Sinistrin glomerular filtration rate as well as increases in cystatin C and urinary protein excretion. Upon histological examination, kidneys from Pon1 KO rats showed significant evidence of increased renal injury compared to the wild rats as noted by increased renal fibrosis, glomerular sclerosis, and tubular ischemia. Pon1 KO rats also showed significant increases in renal inflammation vs wild type, as measured by increased recruitment of CD68 positive immune cells in the renal interstitium. Further, expression of the key inflammatory genes (Timp-1, MCP-1, IL-6, COL1A1, and TGF-β) was significantly higher in renal tissue from Pon1 KO rats compared to the wild type rats. Pon1 KO rats also showed significantly increased renal oxidative stress measured by increased renal staining of the oxidative stress marker 8-OHdG as well higher urinary excretion of 8-OHdG vs. wild type. Finally, as activation of Sre kinase has been shown to act as a common integrator of multiple pro-fibrotic signals we noted that, compared to wild type rats, renal tissue from Pon1 KO showed increased activation of Sre kinase.

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CKD: Mechanisms - I

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TH-PO494
TNFα Inhibition Decreases Fibrosis After Ischemia-Reperfusion Injury
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Background: Renal fibrosis is a frequent complication of acute kidney injury (AKI) and sustained EGFR activation in tubule cells is a hallmark of this process. We have previously shown that injury-induced a disintegrin and metalloproteinase 17 (ADAM17) drives maladaptive repair and kidney fibrosis after injury, but the implicated ADAM17 substrates are unknown. At least two of the main physiological substrates of ADAM17 are upregulated by kidney injury, pro-TNFα and pro-EGFR ligands. ADAM17 releases the active forms of these molecules from the cell surface. We examined the individual contribution of TNFα and EGFR-dependent pathways using FDA-approved drugs in mice (murine) Etanercept and Erlotinib.

Methods: FVB-N mice were subjected to severe bilateral ischemia-reperfusion injury (IRI) and assigned to 4 treatment groups: (1) vehicle, (2) murine Etanercept (soluble TNFα inhibitor scavenger), (3) Erlotinib (EGFR kinase inhibitor), (4) Erlotinib plus Etanercept. Treatments were started Day 0. Sham surgeries were performed as additional controls. Kidney injury and fibrosis were assessed by biochemical parameters and kidney tissue stiffness (FibroTest, o-SMA and picrosirius red). GFR was measured by transendubular monitoring of FITC-sinistrin clearance. Phospho-EGFR levels were detected in kidney lysates by western blotting.

Results: All groups showed the same degree of initial kidney injury. Etanercept or Erlotinib individually significantly decreased renal fibrosis by approximately 40% compared to vehicle-treated mice, but there was no additive protective effect when the drug combination was used. In kidney lysates, Erlotinib (alone or in the combination) decreased EGFR phosphorylation, while Etanercept alone had no effect on p-EGFR.

Conclusions: Etanercept treatment significantly reduced fibrosis after AKI without affecting EGFR activation, and additional EGFR inhibition in combinatorial drug treatments did not further improve outcomes. This suggests that TNFα and Etanercept in the context of AKI-induced fibrosis acts downstream of EGFR. This opens a potentially new therapeutic window for etanercept, a well-tolerated FDA-approved drug, in human AKI.

NIDDK Support

TH-PO495
The Competing Endogenous RNA Network in Renal Aging
Jie Li,1 Hongli Jiang,2 Hongping Su,1 Hongli Jiang,2

Background: It is well known that aging is a continuous and gradual process that causes the physiological functions of all organ systems in the human body to gradually decline. There is no generally accepted definition, definition, of what metaologically active organ, is extremely susceptible to aging. The mechanisms of kidney aging is unclear. MicroRNAs (miRNAs) are a highly conserved non-coding RNA of 18-25 nucleotides in length that inhibits protein expression at the post-transcriptional level or degrades target genes to regulate gene expression. Long-chain non-coding RNA 106 is a non-coding RNA consisting of 200 nucleotides. It is generally considered that they do not encode proteins, but are expressed in various forms at the mRNA level. In ccr3 knockouts, IncRNAs bind to miRNAs via miRNA response elements (MREs), and miRNAs can also bind to the corresponding mRNA 3UTR through specific binding sites, inhibiting the level of protein expression.

Methods: Analyse the IncRNA expression profiles in different ages mouse using a microarray array. And predicted miRNAs and microRNAs that interact with IncRNAs. SAgal-gal staining and immunohistochemistry were performed for the detection of the p33, p16 expression in different ages. Then we use Masson and PAS staining to assess the degree of fibrosis in the kidney.

Results: Bioinformatics analysis results show that the expression of some IncRNAs decreased with age, and the corresponding miRNAs expression increased accordingly. With the increase of age, we detected that the expression of sense-association galactosidase gradually increased, the expression of p16 and p53 gradually increased, and the renal fibrosis gradually worsened.

Conclusions: With the increase of age, the expression of sense-association galactosidase gradually increased, the expression of p16 and p53 gradually increased, and the renal fibrosis gradually worsened. ccr3 network plays an important role in kidney aging.

TH-PO496
Impairment of CPT-1α and Fatty Acid Metabolism Aggravates Renal Fibrosis During Aging
Qi Yuan,1 Yang Zhou,1 Junwei Yang.1

Background: Defects in renal fatty acid metabolism (FAM) pathway have been implicated in the development of renal fibrosis. Aged kidneys show significantly increased fibrosis with impaired kidney function. The mechanisms underlying the effects of FAM on renal fibrosis and FAM have not been investigated. In the present study, we analyzed cardiac palmitoyltransferase-1α (CPT-1α) and FAM pathway as regulators of age-associated renal fibrosis.

Methods: Renal biopsy samples from 126 patients were examined by masson staining and Toluidine blue staining. The expression of CPT-1α was analyzed by immunohistochemistry (IHC). To evaluate the effects of CPT-1α deficiency on age-associated renal fibrosis, aged mice were treated with specific CPT-1α inhibitors.

Results: In patients, fibrosis and lipid accumulation in tubulointerstitial spaces were associated with the age of patients. In mice, followed up for 5 years, age and lipid accumulation were risk factors for the progression of renal fibrosis. As compared with wild-type littersmates, renal dysfunction measured by blood urine nitrogen and serum creatinine, tubular damage evaluated by urinary KIM-1, NGAL and NAG, urinary albumin and creatinine over time were all more severe in mice with tubular specific deficiency of CPT-1α at the age of 1-year-old. Meanwhile, more lipid accumulation, tubulointerstitial fibrosis, extracellular matrix deposition were observed in CPT-1α-/- mice at the age of 1-year-old.

Conclusions: Impairment of CPT-1α and fatty acid metabolism in tubular cells aggravates renal aging and fibrosis.

Funding: Government Support - Non-U.S.

TH-PO497
Protective Role of Kallistatin Against Renal Fibrosis in Unilateral Ureteral Obstruction
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Background: Kallistatin is an endogenous serine protease inhibitor, which exerts anti-inflammatory and anti-fibrotic function against kidney injury in animal models. However, it remains unknown whether kallistatin plays any protective effect in renal fibrosis, the final common pathway of all chronic kidney diseases.

Methods: Unilateral ureteral obstruction (UUO) was used to investigate the effect of kallistatin on renal extracellular matrix (ECM) protein expression and fibrotic signaling pathways. Renal kallistatin was either overexpressed by ultrasound-mediated microbubble kallistatin gene transfer or depleted by injection of anti-kallistatin antibody.

Results: Endogenous kallistatin expression was reduced in renal cortex of UUO kidneys. Kallistatin reexpression significantly alleviated macrophage accumulation and the increase in ECM proteins including collagen type I and III as well as the o-SMA in contrast, injection with anti-kallistatin antibody aggravated renal fibrosis as evidenced by a further increase in ECM proteins. Moreover, depletion of endogenous kallistatin exacerbated UUO-induced Wnt4, β-catenin and Axin2 overexpression in the kidneys, while treatment with kallistatin reduced both Wnt4 and β-catenin pathways, thereby offering a novel potential target of treatment for chronic kidney disease.

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TH-PO498
Semaphorin 3A Inhibitor Ameliorates Renal Fibrosis in Unilateral Ureteral Obstruction Mice
Yizhen Sang, Kenji Tsujii, Kazuhiro Fukushima, Shinji Kitamura, Jun Wada.

Background: Renal fibrosis is the common pathological pathway of progressive renal diseases. Semaphorin3A (SEMA3A) is a secreted protein involved in angiogenesis, cell motility and immune cell regulation. Previous reports suggested SEMA3A was a target of SEMA3A-NRP1 signaling, which increased in the kidneys of biopsied patients (n=36) were collected to analyze the involvement of SEMA3A, SEMA3A-NRP1 and SEMA3A-NRP2 in the progression of renal fibrosis.

Methods: 10-week old wild-type male C57BL/6N mice were assigned into three groups: (UUO+daily SEMA3A-I injection) and sham group. All the mice were sacrificed 2 weeks after surgery. We analyzed binding of SEMA3A to its receptor, neuropilin-1 (NRP1) increased in renal fibrotic area in UUO group while SEMA3A-NRP1 was significantly ameliorated. UUO-induced renal fibrosis in Masson staining as well as tubular cell apoptosis in TUNEL staining. The expression of phospho-c-Jun, a downstream of c-Jun N-terminal kinase (JNK) signaling, known as a target of SEMA3A-NRP1 signaling, increased in UUO group compared to sham group. In vitro study, the treatment with SEMA3A in
mProx24 cells caused Epithelial-Mesenchymal Transition (EMT) with the increase of Vimentin and N-cadherin as well as apoptosis, while SEMA3A-I treatment partially attenuated cisplatin-induced tubular cell apoptosis and TGFβ1-induced EMT. JNK inhibitor decreased SEMA3A-induced tubular apoptosis and EMT. These data suggest that SEMA3A causes renal injury via JNK signaling. The analysis of human data revealed the positive correlation between urinary SEMA3A and N-acetyl-β-D-glucosaminidase (r=0.531, p=0.007). In addition, the higher expression of SEMA3A in tubulointerstitial area was seen in human kidneys with severe renal fibrosis, confirming SEMA3A signaling is associated with tubular injury and fibrosis.

Conclusions: SEMA3A antagonizes UUO-induced renal fibrosis and tubular injury through the inhibition of JNK signaling.

Funding: Government Support - Non-U.S.

TH-PO499

Disturbed Phosphate Metabolism Facilitates Kidney Damage in Dahl Salt-Sensitive Hypertensive Rats

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Background: Several lines of evidence indicate that hypertensive end-organ damage is associated with altered phosphate metabolism. Here, we evaluated the effects of intestinal phosphate binding by sucroferric oxyhydroxide (SF) on renal damage in Dahl salt-sensitive rats, a model of hypertensive kidney disease.

Methods: We selected a normal diet with normal (0.3%) phosphate. High salt (HS) group received a diet containing 8% NaCl and 0.3% phosphate for four weeks. A subgroup of HS rats received SF (HS+SF). We also evaluated the effects of phosphate loading in NRK-52E, a proximal tubule cell line.

Results: Compared with control, HS showed progressive increase in BP. Although urinary Na+ and BP levels were similar between HS and HS-SF groups, albuminuria was significantly ameliorated in the latter. In PAS staining, SF attenuated glomerulosclerosis and tubulointerstitial injury in this model. Moreover, upregulation of inflammatory cytokines in renal tubules was significantly ameliorated by SF. Reduced inflammatory response in the tubulointerstitium of HS-SF rats were confirmed by quantitative evaluation of CD68 staining. In the heart, HS group showed myofiber hypertrophy and macrophage infiltration. However, only the latter was attenuated in HS+SF. We then evaluated phosphate metabolism in this model. Although plasma phosphate levels were not significantly different among three groups, fractional excretion of phosphate and macronutrient excretion was significantly reduced in HS+SF rats.

Conclusions: Phosphate loading to renal tubules can aggravate renal inflammation likely through calcium-phosphate nanoparticle formation. These data support the pathological role of latent phosphate accumulation in hypertensive kidney damage.

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TH-PO500

Agonistic cMet Antibody Prevents Kidney Fibrosis in a Mouse Model of Progressive CKD

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Background: HGF/cMet signaling pathway plays important roles in kidney development and maintenance of normal adult kidney structure, and cMet activation is associated with altered phosphate metabolism. Here, we evaluated effects of vorinostat treatment on tissue fibrosis in Col4a3−/− mice.

Methods: Male Col4a3−/− mice on a congenic 129SvJ background were treated with vorinostat (50 mg/kg/day) or vehicle from 4 to 7 weeks of age by gavage. Mice were euthanized at 7 weeks of age. Plasma, urine, and kidney samples were collected. Kidney histological, function, inflammation, and fibrosis analyses were performed. Separate groups were followed for survival assessment.

Results: VDroxidostat did not improve kidney function and had no effect on glomerulosclerosis scores, but significantly reduced tubular injury markers, KIM-1 and N-acetyl-β-D-glucosaminidase, and decreased significantly in the treatment group. VDroxidostat administration lowered TGFβ-1 and α-SMA protein levels in kidneys and urine, respectively. Treatment attenuated TNF phosphorylation in Col4a3−/− mouse kidneys. In vitro, vorinostat reduced albumin-induced activation of JNK, p38, and ERK in HK-2 cells. Vorinostat also attenuated the activation of activator protein 1 transcription factor in vitro.

Conclusions: Our findings suggest that KDAC inhibition and blockade of MAPKs may be effective treatments to CKD associated with proteinuria and progressive tubulointerstitial injury.

TH-PO502

Lysine Decarboxylase Inhibition Attenuates Tubulointerstitial Injury and Fibrosis in a Model of Proteinuric CKD

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Background: There is a paucity of effective treatments for tubulointerstitial fibrosis associated with progressive CKD. Previously, we derived a CKD progression signature from the differentially expressed genes based on aging and disease in Col4a3−/− mice, a model associated with proteinuria and progressive loss of kidney function. Through drug repurposing with the progression signature and the Connectivity Map we identified vorinostat, a lysine decarboxylase (KDAC) inhibitor, as a potential therapy for CKD progression. Here, we examine effects of vorinostat treatment on tissue fibrosis in Col4a3−/− mice.

Methods: Male Col4a3−/− mice on a congenic 129SvJ background were treated with vorinostat (50 mg/kg/day) or vehicle from 4 to 7 weeks of age by gavage. Mice were euthanized at 7 weeks of age. Plasma, urine, and kidney samples were collected.

Results: VDroxidostat did not improve kidney function and had no effect on glomerulosclerosis scores, but significantly reduced tubular injury markers, KIM-1 and N-acetyl-β-D-glucosaminidase, and decreased significantly in the treatment group. VDroxidostat administration lowered TGFβ-1 and α-SMA protein levels in kidneys and urine, respectively. Treatment attenuated TNF phosphorylation in Col4a3−/− mouse kidneys. In vitro, vorinostat reduced albumin-induced activation of JNK, p38, and ERK in HK-2 cells. Vorinostat also attenuated the activation of activator protein 1 transcription factor in vitro.

Conclusions: Our findings suggest that KDAC inhibition and blockade of MAPKs may be effective treatments to CKD associated with proteinuria and progressive tubulointerstitial injury.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Conclusions: These results implicate that SMYD2 is a key mediator of renal fibroblast activation and renal fibrosis, given the availability of potent SMYD2 inhibitors. SMYD2 might be a potential therapeutic target for the treatment of chronic fibrotic kidney disease.

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TH-PO503

Selective Inhibition of Histone Deacetylase 8 Suppresses Renal Fibroblast Activation and Mitigates Renal Fibrosis

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Background: Histone deacetylase 8 (HDAC8), a unique class I zinc-dependent HDAC, is implicated in the pathogenesis of various hormones, however, its role in renal fibrogenesis remains poorly understood.

Methods: In this study, we examined the effect of HDAC8 inhibition on the activation of cultured renal interstitial fibroblasts and the development of renal fibrosis in a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO).

Results: Treatment of cultured renal interstitial fibroblasts with PCI34051, a selective HDAC8 inhibitor, or small interfering RNA-mediated silencing of HDAC8, inhibited their activation as indicated by decreased expression of alpha smooth muscle actin, fibronectin and type I collagen. In a mouse model of obstructive nephropathy, HDAC8 was upregulated in renal epithelial cells of the injured kidney. Administration of PCI34051 immediately after UUO injury reduced the deposition of extracellular matrix proteins and inhibited activation of renal fibroblasts. Moreover, HDAC8 inhibition suppressed activation of several signaling pathways associated with the progression of renal fibrosis, including Smad-3, beta-catenin, signal transducer and activator of transcription 3 (STAT3), whereas increased expression of klotho and bone morphogenetic protein 7, two renoprotective proteins, in the injured kidney.

Conclusions: Our results indicate that selectively targeting HDAC 7 can inhibit development of renal fibrosis and activation of renal fibroblasts by inactivation multiple profibrotic molecules and increasing expression of antifibrotic proteins. Thus, HDAC8 may be a druggable target.

Funding: NIDDK Support

TH-PO504

Critical Role of lincRNA-p21 in Mediating Lipotoxicity-Induced Kidney Injury

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Background: Ectopic lipid accumulation in kidney is a key factor in the etiology of lipotoxicity-induced kidney lesion. Emerging evidence unravels that long intergenic non-coding RNA p21 (lincRNA-p21) plays a pivotal role in diverse biological processes and diseases. However, little is known about the role of lincRNA-p21 in kidney diseases. We aim to identify the functional role of lincRNA-p21 in lipotoxicity-induced kidney injury.

Methods: Expression of lincRNA-p21 in kidney from mice (C57BL/6J) fed with normal diet (ND), 10 kcal% or high-fat diet (HFD; 60 kcal%), as well as in palmitic acid (PA)-treated human proximal tubular epithelial cells line (HK-2 cells) was determined by qRT-PCR. Antibodies were used to evaluate the associated signaling cascades.

Results: Compared with ND-fed mice, a significantly increase in the expression of lincRNA-p21 was found in kidney biopsy from HFD-fed mice. Consistently, markedly upregulated expression of lincRNA-p21 was observed in PA-treated HK-2 cells. By contrast, silencing lincRNA-p21 significantly counteracted PA-induced gene expression associated with inflammation (IL6), ER stress (BiP, sXBP1 and CHOP) and apoptosis (BCL2). Additionally, PA suppressed P38/Akt/mTOR/Mdm2 signaling cascades and subsequently led to enhanced p53 activity, which consequently drove lincRNA-p21 expression in HK-2 cells.

Conclusions: PA acts through PI3K/Akt/mTOR/Mdm2 signaling pathway to upregulate lincRNA-p21 expression in a p53-dependent manner, thereby contributing to lipotoxicity-induced pathological process in HK-2 cells.

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Funding: Government Support - Non-U.S.

TH-PO505

Dicer Promotes Renal Recovery and Limits Interstitial Fibrosis Following Kidney Injury

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Background: Renal tubulointerstitial fibrosis is the histopathological hallmark observed in chronic kidney disease; and activated fibroblasts, myofibroblasts, are the dominant extracellular matrix-producing cells that contribute to fibrosis development. Dysregulation or deletion of Dicer, a ribonuclease involved in microRNA (miRNA) generation, impacts kidney health and function. Since fibroblasts are key cells responsible for renal fibrosis, we investigated whether Dicer might effect myofibroblast and fibrosis formation by deletion of Dicer from myofibroblasts in vivo.

Methods: Dicer−/− mice were crossed with α-smooth muscle actin promoter (αSMA−/−) mice, a marker of activated fibroblast, to generate WT (αSMA−/+;Dicer−/+), Dicer−/+ and Dicer conditional knockout mice (αSMA−/-;Dicer−/−). Hereafter Dicer−/− mice were challenged to three different kidney injury models. miRNAs from primary kidney fibroblasts were analyzed.

Results: Isolated human and mouse fibroblast from fibrotic kidneys demonstrated increased Dicer hypermethylation. Dicer−/− mice had no overt renal abnormalities. To determine whether deletion of Dicer in myofibroblast might impact the development of tubulointerstitial fibrosis, both WT and Dicer−/− mice underwent unilateral ureteral obstruction, nephrotoxic serum nephritis, and folic acid kidney injury. Dicer−/− mice displayed increased collagen deposition and tubulointerstitial fibrosis compared to WT animals in all three models. Furthermore, loss of Dicer resulted in an increase of proliferating, Ki67 positive, αSMA+ myofibroblasts. miRNA array analysis of primary mouse fibroblasts from the UUO kidneys of Dicer−/− and WT mice revealed a differential expression of several miRNAs, including upregulation of miR-451, a Dicer-independent miRNA, in the Dicer−/− mice.

Conclusions: Renal tubulointerstitial fibrosis is the pathological sequelae observed in chronic kidney injury. Dicer is critically involved in kidney homeostasis, and here we show that Dicer deletion in myofibroblasts resulted in differential miRNA expression and pathologic myofibroblast proliferation perpetuating fibrogenesis. Depletion of Dicer and associated miRNAs is pathogenic in various kidney injury models and accelerates kidney failure.

TH-PO506

The Transcription Factor STAT3 Plays Key Roles in the Development of Kidney Fibrosis by Increasing Proliferation and Differentiation of Pericytes into Myofibroblasts

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Background: STAT3 is a key transcription factor, which plays important roles in inflammatory diseases. STAT3 has been shown to transcribe genes important for the acute and chronic phase of various malignant. There is little information regarding the function of STAT3 in stromal cells.

Methods: Phosphorylation of STAT3 was evaluated in 5 patient biopsy samples using immunofluorescence. In mice, stromal cell-specific STAT3 deletion was performed by breeding STAT3 floxed mice with FoxD1 Cre mice. Kidney fibrosis was induced by administering 300 mg/kg folic acid (FA) or 5 mg/kg body weight aristolochic acid (AA). Cell migration was evaluated with wound scratch assays. RT-PCR, immunostaining and western blotting were performed to measure changes in STAT3-dependent genes and to quantitate pro-fibrotic cytokines.

Results: STAT3 phosphorylation was increased in tubular epithelial cells and interstitial cells of 5 human subjects with chronic kidney disease. Deletion of STAT3 from stromal cells protects mice from FA or AA-induced kidney fibrosis at 7-14 days post-treatment respectively. Fibrogenic markers, including fibronectin, collagen1a1, and α-SMA were reduced in STAT3 KO mice. STAT3 KO mice show similar acute injury {shown by KIM-1 expression was decreased at 7 and 14 days in STAT3 KO mice. STAT3 knockout mice displayed increased collagen deposition and tubulointerstitial fibrosis compared to WT animals in all three models. Furthermore, loss of Dicer resulted in an increase of proliferating, Ki67 positive, αSMA+ myofibroblasts. miRNA array analysis of primary mouse fibroblasts from the UUO kidneys of Dicer−/− and WT mice revealed a differential expression of several miRNAs, including upregulation of miR-451, a Dicer-independent Dicer−/− mice.

Conclusions: Renal tubulointerstitial fibrosis is the pathological sequelae observed in chronic kidney injury. Dicer is critically involved in kidney homeostasis, and here we show that Dicer deletion in myofibroblasts resulted in differential miRNA expression and pathologic myofibroblast proliferation perpetuating fibrogenesis. Depletion of Dicer and associated miRNAs is pathogenic in various kidney injury models and accelerates kidney failure.

Funding: Private Foundation Support
TH-PO507
Sodium Thiouislate Improves Renal Function and Oxygenation in L-NNA Induced Hypertensive Rats
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Background: Sodium thiouislate (STS, Na,SO,3), a H2S donor, a vasodilator and anti-oxidant, is an attractive agent for alleviating the damaging effects of hypertension. In experimental setting, nitric oxide synthase (NOS) inhibition by L-NNA induces hypertension, renal dysfunction and damage. We hypothesized that 1) STS attenuates renal injury and improves renal function, hemodynamics and oxygen efficiency in hypertensive renal disease and that 2) STS on top of RAS inhibition will further improve aforementioned variables in comparison to RAS inhibition alone.

Methods: NOS was inhibited in male Sprague Dawley rats by administering L-NNA (40 mg/kg/day) in the food for 3 weeks. After one week of NOS inhibition, rats were split in 2 groups for the remaining 2 weeks: 1) L-NNA only and 2) L-NNA with STS (2 g/kg/day) in the drinking water. In a parallel study, rats were divided in 2 groups, 1) L-NNA with lisinopril (1mg/kg/day) mixed in the food and 2) L-NNA with both lisinopril and STS. After weekly systolic blood pressure measurements and 24h urine collection, hemodynamics and sodium reabsorption efficiency (TnA/QO, sodium reabsorbed per oxygen consumed) were assessed after isoflurane and kidneys were collected for glomerulosclerosis and mesangial matrix expansion scores.

Results: STS increased 24h excretions of sodium 3.5-fold and sulphate 30-fold, also exhibited decreased levels of tubular injury, urinary protein excretion, oxidative stress in FAON model mice and it was improved by PMF treatment. The PMF treated animals also exhibited decreased levels of tubular injury, urinary protein excretion, oxidative stress in FAON model mice and it was improved by PMF treatment.

Conclusions: STS, a potent antioxidant, is an attractive agent for alleviating the damaging effects of hypertension.

TH-PO508
Pemfibrate Exerts Renoprotective Effects by Activation of PPARα in Murine Kidneys
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Background: Recently, free fatty acid (FFA) toxicity accompanying proteinuria was identified as a major cause of tubular damage, which was aggravated by an insufficiency of peroxisome proliferator-activated receptor-α (PPARα). We have reported that strongly PPARα agonistic fibrate drugs exert renoprotective effects by PPARα activation in proximal tubular epithelial cells with FFA-overload nephropathy (FAON) tubular injury model mice. In the clinical setting, however, there have been no safe PPARα agonists for patients with chronic kidney disease (CKD) since fibrate drugs have severe dose-related adverse effects, including a decrease in kidney function. Pemfibrate (PMF) was approved in Japan in 2018 as the first selective PPARα modulator (SPPARMα). PMF has much more potent and specific PPARα-activating efficacy as compared with other fibrates and is excreted in the bile. Thus, the drug can achieve greater improvements in fatty acid metabolism with a highly reduced risk of diminished kidney function and other adverse effects. Although PMF can be safely prescribed for CKD patients, it is uncertain whether it activates PPARα in the kidneys or has renoprotective effects.

Methods: We examined the above possibilities using the kidneys of wild type mice and FAON model mice with and without 0.25 mg/kg/day PMF administration for 14 days.

Results: PPARα target gene expression in the kidneys was significantly decreased in FAON model mice and it was improved by PMF treatment. The PMF treated animals also exhibited decreased levels of tubular injury, urinary protein excretion, oxidative stress (OxStress) and pro-inflammatory apoptosis-stimulating responses, as well as stable fatty acid metabolism. Moreover, expression of the PPARα gene and its target mRNA-encoding proteins involved in OS, pro-inflammatory responses, apoptosis, and fatty acid metabolism were maintained with PMF treatment.

Conclusions: Our study’s results suggest that PMF activates renal PPARα, increases PPARα signaling, and imparts renoprotective effects.

TH-PO509
Calcineurin Inhibition but Not Dehydration in Rats Mimics Human Renal Histopathology of Patients with Chronic Interstitial Nephritis in Agricultural Communities (CINAC)
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Background: CINAC patients present a newly discovered constellation of proximal tubular lysosomal lesions which is also observed in patients experiencing calcineurin inhibitor (CNI) nephrotoxicity, suggesting that CINAC is a toxin-induced nephropathy involving calcineurin inhibition. An alternate hypothesis advocates chronic heat stress/dehydration as the major etiological factor for CINAC. Here, we evaluated in rats to what extent heat stress/dehydration versus CNI exposure reflects proximal tubular CINAC histopathology.

Methods: Wistar rats were divided in 3 groups. Group 1 (n=6) was given water ad libitum (control group). Group 2 (n=8) was water deprived for 10 hours per 24h, 5 days/week and were placed in an incubator (37°C) for 30 min/hr of water deprivation. Group 3 (n=8) underwent daily oral gavage with cyclosporine (50mg/kg body weight). Animals were weighed daily and urine was collected at day 3, 17 and 28. After 28 days, rats were sacrificed. Kidneys were collected for light (LM) and electron microscopic (EM) histopathological analysis as well as for cortical renal tissue proteomics.

Results: Cyclosporine rats developed focal cortical lesions mimicking those of CINAC patients: i.e. atrophic proximal tubuli with thickened basement membranes and associated tubulo-interstitial fibrosis, PASM staining demonstrating enlarged angiohyphophylic granules in the affected proximal tubuli, Lampl immunofluorescent staining identifying a subset of these granules as lysosomes, and EM confirming the presence of enlarged lysosomes, some dysmorphic approaching CINAC lysosomes. In dehydrated rats, confirmed by urinary osmolality and fluctuating body weight associated with water deprivation, none of the cyclosporine features were observed. Proteomic analysis confirmed cellular toxicity by cyclosporine, whereas the dehydration group lacked any markers of such.

Conclusions: The histopathological analogy between CNI nephrotoxicity in rats and human, and CINAC suggests a toxicological etiology for CINAC. In rats, dehydration/heat stress alone does not lead to the constellation of proximal tubular lesions as observed in CINAC patients.

Funding: Government Support - Non-U.S.
TH-PO511
Treating CKD-Related Anemia with Erythropoietin and HIF- Prolyl Hydroxylase Inhibitors Improves FGF-23-Dependent and -Independent Outcomes
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Background: In chronic kidney disease (CKD), high blood concentrations of the phosphaturic hormone FGF23 are associated with increased odds for patient mortality (>6-fold). Our lab has identified anemia as a potent driver of FGF23 expression. Patients with CKD ultimately develop anemia as the kidneys lose the ability to produce erythropoietin (EPO), in parallel with mineral metabolism alterations. We hypothesized that mitigating anemia through treatment with either recombinant EPO or HIF-PHI (hypoxia inducible factor-prolyl hydroxylase inhibitors), currently in clinical trials that elevate endogenous EPO, would reduce circulating bioactive, ‘intact’ FGF23 (*iFGF23*), thereby improving the pathogenic manifestations of CKD.

Methods: Using a murine inducible stem cell line (MPC2), we showed that the HIF-PHI DG FGF-4592 (Roxadustat) directly induced Fg23 mRNA when differentiated into osteoblast-like cells (8-16 fold, p<0.01). Additionally, FG-4592 injection dose-dependently increased iFGF23 2-9 fold (p<0.05) in wild type (WT) mice with normal renal function. To determine the effects in CKD mice, mice were placed on a casein control or adenosine diet to induce CKD, which resulted in markedly elevated iFGF23, hyperphosphatemia, hyperparathyroidism, and anemia. Separate cohorts were treated with either recombinant EPO or FG-4592.

Results: iFGF23 was significantly elevated (70-fold, p<0.01) in saline-treated CKD mice compared to controls. In CKD mice, EPO treatment improved total serum iron, and FG-4592 treatment led to marked induction of serum EPO (p<0.01). Importantly, circulating *iFGF23* was significantly attenuated (>70%; p<0.05) in the CKD mice with EPO or FG-4592 administration, demonstrating that HIF-PHI are a primary driver of FGF23 in CKD. As expected with elevated *iFGF23* in CKD mice, Cyp24a1 mRNA increased (p<0.01), favoring low 1,25D. In contrast, both EPO and FG-4592 significantly enhanced Cyp24a1 (p<0.05) and suppressed Cyp27b1 (p<0.01), favoring low 1,25D. In CKD mice, FGF23 stimulated the expression of RAAS genes in cardiac myocytes, suggesting improved 1,25D synthesis. Indeed, EPO injection significantly increased serum 1,25D in control and CKD mice (p<0.05).

Conclusions: Collectively, these results support that treatment for anemia, via EPO or HIF-PHI, leads to improved FGF23-dependent and -independent outcomes.

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TH-PO512
Fibroblast Growth Factor 23 Produces Arterial Stiffness Through Changes in Vascular Smooth Muscle Cell Phenotype
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Background: In patients with chronic kidney disease (CKD), high levels of c-terminal fibroblast growth factor 23 (FGF23) are associated with cardiovascular disease and ESRD. Vascular smooth muscle cells (VSMC) may present two differentiated functional phenotypes, contractile and synthetic. An excess of synthetic VSMC has been related to a systemic activation of RAAS and FGF23 is discussed to stimulate RAAS activation, which could be an alternative mechanism for the progression of FGF23-mediated cardiac pathologies. However, underlying molecular mechanisms are unknown.

Methods: The expression of VSMC markers, miR-221 and miR-222 was determined in VSMC treated with high recombinant FGF23. In vivo, the VSMC markers were analyzed in aorta of rats receiving recombinant FGF23 for 14 days. Furthermore, the relationship between FGF23 and arterial stiffness was investigated in CKD patients stages 2-5.

Results: High levels of FGF23 stimulated transition from a contractile to a synthetic phenotype. These effects were mediated through FGFR1 and Erk1/2 phosphorylation. Inhibition of both pathways enhanced contractile phenotype of VSMC. The pro-contraceptive microRNAs miR-221 and miR-222 were reduced by FGF23 and miR-221 transfection recovered the contractile phenotype of VSMC decreased by FGF23. In rats, exogenous infusion of FGF23 increased tunica media thickness and promoted synthetic phenotype reducing plasma levels of miR-221. In a group of CKD 2-3 patients it was observed an association between FGF23 and pulse pressure, reflecting vascular stiffness together with low plasma levels of miR-221 and miR-222.

Conclusions: FGF23 favors the transition of VSMC from contractile to synthetic phenotype causing vascular dysfunction and arterial stiffness. This may be a mechanism by which FGF23 contribute directly to the development of vascular disease in CKD patients.

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TH-PO513
FGF23-Mediated Activation of RAAS Contributes to Cardiac Hypertrophy and Fibrosis
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Background: Patients with CKD develop LVH accompanied with LV fibrosis. One of the main causes are the increased FGF23 serum levels, which were shown to induce the calcineurin/NFAT pathway in cardiomyocytes. Additionally, CKD patients show a systemic activation of RAAS and FGF23 is discussed to stimulate RAAS activation, which could be an alternative mechanism for the progression of FGF23-mediated cardiac pathologies. However, underlying molecular mechanisms are unknown.

Methods: We evaluated LVH and fibrosis in association with cardiac FGF23 and the local activation of RAAS in hearts of 5/6 nephrectomized (5/6Nx) rats compared to sham-operated animals. In order to distinguish between FGF23-mediated LVH and fibrosis via calcineurin/NFAT or RAAS, we stimulated isolated neonatal rat ventricular myocytes (NRVM) and fibroblast (NRFC) with FGF23 in the presence and absence of cyclosporine A, losartan and spironolactone, and investigated hypertrophic and fibrotic pathways by qPCR, Western blot and functional analysis.

Results: Uremic rats showed increased relative heart weight accompanied with enhanced cardiomyocyte size and LV fibrosis compared with sham. The cardiac expression of Fg23 and RAAS genes were significantly increased in 5/6Nx rats and correlated with the degree of LV fibrosis. FGF23 stimulated the expression of RAAS genes in cardiac cells in vitro and induced NGAL indicating mineralocorticoid receptor activation. The FGF23-mediated hypertrophic growth of NRVM was attenuated by pre-treatment with cyclosporine A, losartan and spironolactone, while the FGF23-mediated induction of the pro-hypertrophic NFAT target genes was blocked by inhibition of calcineurin, AT1R and mineralocorticoid receptor. In NRFC, FGF23 phosphorylated Smad2/3 and induced Tgf-b and Ctgf, which were only suppressed by pre-stimulation with losartan and spironolactone but not with cyclosporine A. Interestingly, FGF23 increased the proliferation of NRFC independent of calcineurin/NFAT and RAAS activation.

Conclusions: The FGF23-mediated cardiac hypertrophy is mediated by both the activation of RAAS and calcineurin/NFAT. Moreover, FGF23 impact on cardiac fibrosis primarily via RAAS-mediated activation of Tgf-b/Smad pathway.

TH-PO514
FGF23 Does Not Induce Left Ventricular Hypertrophy in Female Mice with CKD
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Background: Increased levels of fibroblast growth factor 23 (FGF23) in chronic kidney disease (CKD) are associated with development of left ventricular hypertrophy (LVH) and mortality. Men progress more rapidly to end stage renal disease and have an increased risk of cardiovascular death compared to women. We assessed whether delayed offset of CKD and/or delayed elevations of FGF23 levels in females could explain better cardiovascular outcomes than in males.

Methods: We studied B6 wild-type (WT) and Col4a3-/- male and female littermate mice with progressive CKD at 4, 8, 12, 16, and 20 weeks of age. At each time point, we analyzed parameters of kidney and heart morphology and function, and we measured serum FGF23 levels. In parallel, we assessed the lifespan in separate groups of mice.

Results: As previously described, Col4a3-/- males display impaired kidney function, increased serum FGF23 levels, development of LVH and reduced lifespan. Both Col4a3-/- males and females showed signs of proteinuria at 4 weeks (albumin to creatinine ratio
In conclusion, INS-3001 is a promising molecule for the treatment of CKD significantly increased aortic LGR4 and RANKL mRNA expression and decreased OPG, increasing aortic calcium content. These changes were greater in the group with higher PTH (CKD-HP) and were prevented by PTX. There were no changes in RANK expression under any of the experimental conditions. In VSMC, 10-7 M PTH, but not 10-9 M PTH, increased LGR4 and RANKL expression with increases in calcium content. LGR4 and PTHR1 silencing significantly attenuated the increase in calcium content induced by 10-7 M PTH. Furthermore, silencing of PTHR1 and PKA inhibition, but not PKC inhibition, prevented the increases in RANKL and LGR4 and OPG reduction. Exposure to forskolin corroborated these results.

Conclusions: In CKD, high PTH increases the aortic expression of LGR4 receptor and its ligand RANKL and decreases OPG inducing VC. These PTH actions in VSMC involve binding to PTHR1 and PKA activation. Thus, LGR4 was identified for the first time as a pro-calcifying factor of VSMC in CKD.

Funding: Government Support - Non-U.S.

TH-PO518
Increases in Osteocyte RANKL Correspond with Elevated Cortical Porosity in Adenine-Induced CKD
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Background: Chronic kidney disease (CKD) increases bone fragility and fracture incidence. Bone loss in CKD preferentially occurs within the cortical bone through the elevation of porosity. For cortical pores to form, osteoclasts must be recruited into the cortex to locally induce bone resorption. Receptor activator of nuclear factor κB ligand (RANKL) is a key osteoclastogenesis regulator that is released by various cells within bone including osteocytes. We hypothesized that elevated cortical osteocyte RANKL coincides with the development of cortical pores in adenine-induced CKD.

Methods: Female 6-7BL/6j mice (8-wk-old) were fed a casein-based diet (0.9% P, 0.6% Ca) with 0.2% adenine (Ad) to induce CKD. Age-matched controls (Con) were fed the same casein-based diet without adenine. Mice were terminated after 2, 6, and 10 weeks.

Results: Serum blood urea nitrogen was elevated at all time points in Ad vs. Con confirming the induction of kidney disease. MicroCT of the distal 1/3 shaft of the femur demonstrated that Ad mice had porosity not different from Con at 2 weeks, mild cortical porosity at 6 weeks (1.9%; p<0.001 vs Con), and a greater average porosity at 10 weeks (4.1%; p<0.01 vs Con). At 2 weeks, the percentage of cortical osteocytes in the femoral shaft that stained positive for RANKL (%RANKL+) was 20% higher in Ad vs. Con while at 6 and 10 weeks %RANKL+ osteocytes was 115% higher and 277% higher, respectively, compared to Con. A time-by-treatment statistical analysis indicated significant impact of age and a time-by-treatment interaction effect whereby some groups had decreasing %RANKL+ osteocytes with age and Ad groups maintained high %RANKL+ osteocytes with age. This indicates adenine-induced CKD increased osteocyte RANKL in younger animals as well as prevented age-related declines in osteocyte RANKL as animals age in the presence of disease.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: In conclusion, we determined that both osteocyte RANKL and cortical porosity are elevated over time in adenine-induced CKD. We hypothesize in CKD osteocytes release RANKL signaling osteoclasts into the cortical bone leading to the development of cortical porosity. Future research should address the factors altered in CKD, such as elevated parathyroid hormone, which are responsible for stimulating osteocytes to produce RANKL.

Funding: Veterans Affairs Support

TH-PO519

Effect of Acute Peritonitis on Serum Fibroblast Growth Factor 23 in a Rat Model of CKD: Possible Interaction Between FGF-23 and Inflammation
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Background: Cardiovascular diseases are the leading cause of death among patients with chronic kidney disease (CKD). Fibroblast Growth Factor 23 (FGF-23) has been associated with mortality among those patients and was found to correlate with different parameters of inflammation among them. The interaction between FGF-23, uremia and inflammation is still under investigation.

Methods: 40 rats assigned to 4 groups: Control sham-operated, Acute peritonitis, CKD and CKD + acute peritonitis. Acute peritonitis and CKD were experimentally induced. Serum creatinine, phosphorus, iFGF23, Vit-D, TNFa, HoCRP and bone furin mRNA were compared between groups.

Results: Compared to the control group; FGF-23 was significantly higher in both the CKD & the acute peritonitis groups. FGF-23 reached the highest level in the CKD with induced acute peritonitis group. Furin mRNA was significantly lower in both the CKD and the acute peritonitis groups compared to the control group and it reached its lowest levels in the group with induced CKD and peritonitis. FGF-23 was positively correlated to serum creatinine, phosphorus, TNFa&CRP while it was negatively correlated to serum Vit-D & Furin mRNA.

Conclusions: Inflammation is a potent upregulator of iFGF23 and could be a main promoter of FGF23 excess early in CKD. Acute peritonitis on top of CKD amplifies the effect of acute peritonitis groups compared to the control group and it reached its lowest levels. Furin mRNA was significantly lower in the CKD and acute peritonitis groups compared to the control group and it reached its lowest levels. FGF-23 was positively correlated to serum creatinine, phosphorus, TNFa&CRP while it was negatively correlated to serum Vit-D & Furin mRNA.

TH-PO520

The Role of Mitochondrial Dysfunction in Matrix Vesicles (MV)-Induced Calcification ofRecipient Vascular Smooth Muscle Cells (VSMC)
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Background: Oxidative stress is increased in patients with CKD and associated with vascular calcification. We have previously demonstrated that cellular derived MV, but not media derived MV, increase calcification of recipient normal rat VSMC in association with activation of mitogen activated protein kinase (MAPK), increased intracellular calcium [Ca], derived from the endoplasmic reticulum (ER), and increased NADPH oxidase (NOX) 1 expression. We hypothesized that cellular MV induced generation of reactive oxygen species (ROS) from mitochondrial dysfunction in the recipient VSMC.

Methods: Ten ug of MV were co-cultured with recipient VSMC in calcification media (high phosphorus) for up to 7 days and alteration of ROS production examined by CellRox using confocal microscopy. Mitochondrial superoxide generation was determined by MitoROS. Direct mitochondrial respiration was measured by Seahorse XF Analyses. Mitochondrial contents of respiratory complexes was determined using total OXPHOS by Western blot. Some cultures were incubated with the NOX1/4 inhibitor GKT373831.

Results: MV increased ROS production by 146% at 24 h and continued to increase by 100% at day 7 in recipient VSMC during calcification. Incubation with GKT373831 reduced ROS production and decreased [Ca] in recipient VSMC. We then determined if mitochondria dysregulation was the source of the increased ROS production in recipient VSMC. Adding MV had no effect on mitochondrial superoxide production or mitochondrial contents in recipient VSMC. Seahorse experiments demonstrated that there was no effect of MV on basal oxygen consumption (OCR), ATP production, maximal respiratory capacity or reserve respiratory capacity in recipient VSMC. These results suggest that MV-induced cytosolic ROS production is not due to mitochondrial dysfunction in recipient VSMC.

Conclusions: Cellular MV induce ROS production in recipient VSMC during calcification. However, this increased ROS is not mediated via mitochondrial dysfunction and thus likely represents a response to increased [Ca], release from the ER and/or other cell signaling pathways. Further understanding the mechanism by which MV induce calcification of normal VSMC to propagate calcification is needed to facilitate the development of targeted therapies.

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TH-PO522

The Effect of PKD Gene Mutation on Bone
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Background: Kidney cysts are an invariant feature of autosomal dominant polycystic kidney disease (ADPKD). However, patients with PKD2 vs. PKD1 mutations typically have milder disease. We showed previously that ADPKD patients with normal kidney function have a low turnover bone defect. The goal of the current study was to determine whether PKD gene mutations cause differential changes on osteoblast primary cilium structure or gene expression in osteoblasts.

Methods: Primary osteoblast cultures were established from human bone obtained by iliac crest bone biopsy. In order to visualize the primary cilium, cells were serum deprived to suppress cell division and treated with LiCl. The primary cilium was stained with anti-acetylated tubulin and the base with anti-pericentrin. Cilia length was measured on 200 -300 cells from each individual. RNAseq analysis was performed on RNA extracted from trabecular bone.

Results: Cilia on osteoblasts from ADPKD patients elongated more than those on healthy control osteoblasts in response to LiCl exposure and longer cilia were associated with PKD1 gene mutations (Figure 1). Elongation of osteoblast cilium from patients with other causes of adynamic bone disease did not differ from control cells, indicating that the gene mutation is responsible for the cilia abnormality in ADPKD. RNAseq analysis of bone from patients with PKD1 (N=12) or PKD2 (N=3) revealed decreased expression of several genes including COL1A2 and aggrecan proteoglycan (ACAN) in PKD1 compared to PKD2 bone.

Conclusions: PKD genotype affects both primary cilium structure and gene expression in bone from patients with ADPKD. Cilia structural abnormalities appear to be a result of the primary gene defect as they do not occur in patients with adynamic bone disease due to other causes.

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TH-PO523

Effect of Reduction of Bone Advanced Glycation End Products (AGE) Accumulation on Bone Mechanical Properties in a Rat Model of CKD-Mineral Bone Disorder (CKD-MBD)
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Background: Reduced bone quality is a key determinant of skeletal fragility in CKD. We have previously demonstrated that treatment with an AGE breaker ALT-711 decreased serum FGF23, reduced aorta expression of receptor for AGE (RAGE) and calcification in a rat model of CKD-MBD. We hypothesized that reduction in AGE accumulation and/or RAGE activation in bone will improve CKD-induced bone fragility.

Methods: Using a slowly progressive rat model of CKD the Cy+/+ rat, we compared four groups of animals: 1: Normal (NL); 2: CKD; 3: CKD+ALT-711 (3mg/kg); and 4: CKD+3% calcium in drinking water (Ca, lowering PTH and reducing bone remodeling). Treatment was started at 25 weeks of age (~50% kidney function) and ended at 35 weeks (~15% function). Bone AGE content was determined in demineralized femur shaft using fluorescence plate reader, normalized by collagen (hydroxyproline) content. Bone marrow (BM) were collected and RAGE expression determined by real time PCR. Bone geometry/architecture were determined with microCT. Bone mechanical properties were assessed by 4-point bending.

Results: There was increased AGE accumulation in bone and RAGE expression in BM in CKD rats vs NL. Treatment with ALT-711 or calcium normalized both bone AGE levels and BM RAGE expression in CKD. MicroCT assessment of proximal tibial bone demonstrated lower trabecular bone volume fraction (BV/TV) in CKD rats. Calcium but not ALT-711 treatment increased trabecular BV/TV in CKD rats. CKD rats also had higher cortical porosity compared to NL and ALT-711 or calcium treatment each significantly reduced the cortical porosity in CKD rats. Bone mechanical analysis demonstrated that while several properties were lower in CKD rats, calcium, but not ALT-711 treatment, normalized these mechanical properties in CKD rats.

Conclusions: There is increased AGE accumulation in bone and RAGE expression in BM from CKD rats. Treatment with the AGE breaker ALT-711 early in the course of CKD decreased bone AGE levels and RAGE expression in BM in association with reduction in cortical porosity but without improvement of bone mechanics. Calcium treatment (which lowers PTH) showed similar bone efficacy to ALT-711 but increased serum levels of calcium and FGF23.

Funding: Other NIH Support - NIAMS, Veterans Affairs Support

TH-PO524

Bone Assessment by High-Resolution Peripheral Quantitative Tomography in Premenopausal Stony-Forming (SF) Women
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Background: Nephrolithiasis has been associated to low bone mineral density (BMD). Bone assessment by Dual-energy X-ray absorptiometry (DXA) is widely used in clinical practice but has limitations as it only measures areal BMD (aBMD). New non-invasive technologies such as high-resolution peripheral quantitative computed tomography (HR-pQCT) provides additional information regarding bone quality and microarchitecture.

Methods: Forty-four (44) stone-forming (SF) premenopausal women (33.4±9.2 years old) and 202 age-matched healthy premenopausal women (33.3±9.0 years old) were included. aBMD was analyzed by DXA and volumetric BMD (vBMD), structure and biomechanical parameters of the distal radius and tibia were assessed by HR-pQCT.

Results: SF presented a trend for lower aBMD versus controls at L1-L4 (0.979±0.115 vs 0.932±0.111, p=0.06) and significant lower aBMD at femoral neck (0.826±0.118 vs 0.923±0.120, p<0.001) and distal radius (0.668±0.049 vs 0.686±0.047, p=0.03). As shown in Table 1, trabecular number ( Tb.N) was significantly lower and trabecular separation ( Tb.Sp) was significantly higher in SF compared to controls at both sites. Trabecular vBMD at distal radius was also significantly lower in SF versus controls.

Conclusions: Premenopausal SF women presented lower areal BMD than controls. HR-pQCT further disclosed that the trabecular compartment possibly accounts for this finding, due to lower trabecular volumetric BMD at distal radius, lower trabecular number and increased trabecular separation at both distal radius and tibia. The underlying mechanism for these important alterations of bone quality in this population deserves further investigation.

Funding: Government Support - Non-U.S.

TH-PO525

Total Flavonoids of Astragalus Ameliorates Renal Injury-Related Mineral and Bone Metabolic Disorder in the CKD-MBD Model Rats by Regulating FGF23-Klotho Signaling Axis, Compared with Calcitriol
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Background: Recently, chronic kidney disease-mineral and bone disorder (CKD-MBD) has become one of serious complications occurring in the CKD patients. Hence, the development of a new treatment for CKD-MBD is very important in clinics. FGF23- klotho signaling axis and bone abnormality, and that, more importantly, these ameliorative effects on renal injury and bone abnormality. Moreover, TFA alleviated renal dysfunction and tubulointerstitial pathological changes, improved calcium-phosphorus metabolic disorder and bone lesion, and regulated FGF23-Klotho signaling axis in response to renal injury-related MBD has been thereby identified as the multi-targets in the treatment of CKD-MBD. In China, total flavonoids in the flower of Astragalus membranaceus (TFA), a natural extract has been frequently used to improve renal dysfunction in the CKD patients. But the potential mechanisms in vivo of TFA on renal injury-related MBD remained unclear. Here, we verified whether TFA could ameliorate renal injury-related MBD in the CKD-MBD model rats by targeting FGF23-Klotho signaling axis in the kidney, compared to calcitriol (CAL).

Methods: Twenty-eight rats were divided into 4 groups, the Sham, the Vehicle, the TFA and the CAL groups. The appropriate doses of TFA, CAL and distilled water were administrated with oral for 3 weeks after the induction of CKD-MBD by adenine-administration and mononephrectomy, respectively. The changes in parameters of renal injury and bone abnormality in urine, blood, bone and kidneys were analyzed. The kidney and femur bone were isolated for histomorphometry, immunohistochemistry and Western blot at sacrifice.

Results: For the CKD-MBD model rats, renal injury and bone abnormality were significantly revealed, and there was a potential connection between renal injury and bone abnormality. Moreover, TFA alleviated renal dysfunction and tubulointerstitial pathological changes, improved calcium-phosphorus metabolic disorder and bone lesion, and regulated FGF23-Klotho signaling axis and ERK1/2-SGK1-NHERF-1-NaPi2 pathway in the kidney. Notably these beneficial actions in vivo of TFA were markedly different from CAL.

Conclusions: We clarified that TFA, different from CAL, can improve renal injury and bone abnormality, and that, more importantly, these ameliorative effects on renal injury-related MBD are closely associated with the regulation of FGF23-Klotho signaling axis and ERK1/2-SGK1-NHERF-1-NaPi2 pathway in the kidney. This study provided the first evidence that TFA directly contributes to the prevention of CKD-MBD.

Funding: Government Support - Non-U.S.
Background: Systemic inflammation is a risk factor for atherosclerosis and vascular calcification in the general population and in chronic kidney disease (CKD) patients. Because increases in neutral sphingomyelinase 2 (nSMase2) are essential for the severity of age-induced inflammation in health and atherosclerosis in the ApoE: null mouse and contribute to initiate medial calcification in aorta, this study evaluated whether leukocyte gene expression of nSMase2 and its inducer in the vasculature, TNFα, could estimate the propensity for vascular calcification.

Methods: Peripheral blood mononuclear cells (PBMC) and granulocytes, from 28 peritoneal dialysis (PD) patients and 16 normal adults, matched for age and gender, were obtained from fresh blood using Fycoll gradient. A lumbar X-ray measured Kauppila index (KI) to estimate subclinical (KI=5) or clinical (KI=5) risk for vascular calcification (VC).

Results: In adults older than 40 with normal renal function, PBMC TNFα mRNA levels increased directly with age (r=0.61; p<0.05; n=10), a risk factor for vascular disease. Furthermore, PBMC TNFα increased by 52% in peritoneal dialysis patients (p=0.03) compared to controls and, similar to the vasculature, PBMC nSMase2 gene expression increased parallel with the elevations in TNFα in both healthy adults (r=0.57; p=0.02; n=16) and PD patients (r=0.50; p=0.01; n=28). In circulating granulocytes, TNFα was also 2-fold higher in PD patients, but with levels 2.2-fold lower than those in PBMC, even in normal controls. Significantly, the increases in granulocyte nSMase2 correlated directly with KI=5 (r=0.65; p=0.05; n=11), a recognized biomarker of the clinical risk for vascular calcification, but not with TNFα.

Conclusions: While in PBMC, the higher TNFα mRNA levels correlating with increases in nSMase2 may estimate the degree of systemic inflammation, the increased granulocyte nSMase2 gene expression appear sufficient to reflect VC risk.

Funding: Government Support - Non-U.S.

TH-PO528

Increased Subset of Low-Density Granulocytes in Dialysis Patients Associated with the Degree of Abdominal Aortic Acalcia

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Background: Although systemic inflammation increases the risk for adverse vascular outcomes in chronic kidney disease (CKD), the exact players remain unclear. The emerging evidence of the relevance of low density granulocytes (LDGs) in inflammatory conditions led us to evaluate whether LDGs may be associated with inflammatory/pro-calcifying features in CKD.

Methods: LDGs subsets were identified by flow cytometry in peripheral blood mononuclear cells (PBMCs) from 33 CKD patients undergoing peritoneal dialysis and 15 healthy controls (HC). An additional cohort of 16 CKD patients undergoing hemodialysis and 6 HC was recruited for replication. Defensin3a (DEF3a, a marker of early granulopoiesis) gene expression on PBMCs was quantified by qPCR.

Results: Total LDGs (CD14+; both CD14lowCD16+ and CD14+CD16- subsets were increased in CKD. The relative frequency of the CD14+CD16- subpopulation among the total CD14+ pool was increased in CKD. Both LDG subsets differed in origin and maturation status as demonstrated by their CD11b, CD31, CD62L, Interferon receptor 1 (IFNAR1) and CD68 expression and size/ granularity (FSC/SSC) features. LDGs subsets were not correlated with parameters of bone and mineral metabolism, time on dialysis, serum cytokines or treatments. The increased CD14+CD16-CD15+ correlated directly with Kauppila scores and DEF3a expression in PBMCs, whereas no association was found with CD14lowCD16+CD15+.

Conclusions: CD15+ is associated with elevated LDGs, showing a skewed distribution towards a CD14+CD16-CD15+ enrichment in blood which correlated with vascular calcification. DEF3a expression in PBMC could be a marker of LDG expansion. These findings support an unprecedented role for LDGs in CKD inflammation/phenogegnosis.

Funding: Government Support - Non-U.S.
TH-PO530

Macrophage Migasromes Is a Crucial Determinant of Subcutaneous Microvascular Calcifications in Patients with Calciphylaxis
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Background: Calciphylaxis is rare syndrome in hemodialysis patients who typically manifest as subcutaneous microvascular calcifications. Macrophage has been proposed to be a prime mediator of calciphylaxis. However, the pathogenesis remains unclear. Here, we document that macrophage produce a previously unrecognized nanostructures called “migasromes” (M-mig), which involve in microvascular calcifications in calciphylaxis.

Methods: Skin biopsy specimens from patients with calciphylaxis (n=34) were collected. Possible relation between M-mig and subcutaneous microvascular calcifications was studied. The study artery from experimental mice were treated with M-mig under high Ca/P stimulation or hemodialysis patient serum. The calcifying M-mig were assessed by TEM, Enzyme dispersive spectroscopy and Fluo-3 staining.

Results: Ultrastructural analysis revealed that macrophage produce a previously unrecognized nanostructures called M-mig (A. arrow) that originate from the filament like fibers (A. triangle). Pathology of skin biopsy surprisingly showed that macrophages infiltration (C. brown) was adjacent to the calcium deposition (D. green) in subcutaneous arteries which were rich in M-mig. Subsequently, TEM imaging revealed that mineral deposit in or on membrane of M-mig (A. asterisk). In murine model, when the study artery incubated with M-mig under high level Ca/P or hemodialysis patient serum, notably, some mineral crystal enveloped M-mig and penetrated into inner lumen of the vascular wall where microcalcifications deposition were observed by fine Fluoro-3 staining. The microcalcifications were approved to correlation with calcific M-mig. In vitro, calcific M-mig showed a shift to larger size over time under high level Ca/P. Our study strongly suggests that M-mig could serve as the nucleating foci for mineralization and calcific M-mig is involved in microcalcification.

Conclusions: Our study documents that macrophages produce a formerly unrecognized nanostructured M-mig which involves in vascular microcalcifications. The discovery highlights the contribution of macrophages to vascular calcifications via M-mig and provides clues to the pathogenesis of calciphylaxis.

Funding: Government Support - Non-U.S.

TH-PO531

Evidence of Circadian Rhythm of Plasma Activin A, Its Disturbance by CKD, and Contribution of Activin A Secreted from Injured Kidney
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Background: Activin A is an interesting new factor in CKD-MBD. It is a member of the TGF-beta family, essential in kidney development and repair. Increased systemic activin A might be a biomarker of CKD-MBD that can be targeted for CKD-MBD prevention and therapy. Disrupted circadian rhythm (CR) causes detrimental health effects and CRs are observed in mineral metabolism. Our hypothesis is that increase in circulating levels of activin A is associated with disruption of circadian rhythm of plasma activin A, and parameters of mineral homeostasis in CKD.

Methods: Crs of activin A (pg/ml), FGF23 (pg/ml), PTH (pg/ml) and P (mM) were measured every 6th hour in control (Cr) and CKD rats (5/6 nephrectomy) on low (LP), standard (SP), and high phosphate (HP) diet (N=8-26). Isolated renal vein and artery sampling was performed in kidney injury rats (14 days unilateral ureteric obstruction, UUO) and healthy Cr.

Results: Activin A was 2.5-fold higher in renal vein compared to artery in UUO (246±22, A:100%, p<0.05) but unaltered in Cr (100%±6 A:100%, ns) indicating renal secretion in kidney injury. Plasma activin A exhibited CR in Cr (p<0.01 by cosinor analysis) with 300% higher values at acrophase (437±59) compared to nadir (100±7) (p<0.05). CKD obliterated the CR of activin A. Plasma FGF23 showed CR in Cr (p<0.05) with peak at 14:00 (877±42), while the CR was obliterated in CKD rats on LP and SP even though FGF23 was suppressed in CKD LP (p<0.05). In CKD HP FGF23 was increased (p<0.01) and the CR was shifted with shift in acrophase to 09:00 (4173±316). Plasma PTH exhibited CR in Cr (p<0.0001), while the rhythm was disturbed in CKD (p<0.05) despite prevention of SHPT in CKD LP (p<0.05). Plasma P showed CR in all groups (p<0.05). However, the CR was disturbed in all CKD groups with shift in acrophase from 16:00 in Cr to 19:00 (LP), 17:00 (SP), and 00:00 (HP).

Conclusions: Existence of a circadian rhythm of circulating activin A is established for the first time. The rhythm of activin A is disturbed in CKD rats and is associated with disturbed circadian rhythms of P and P regulating hormones PTH and FGF23. In injured kidney activin A is induced and secreted to venous effluent which can contribute to the disturbed circadian rhythm of activin A in uremia.

TH-PO532

An Internal Molecular Circadian Clock Operates in the Parathyroid Gland and Is Disturbed in CKD
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Background: Parathyroid hormone (PTH) secretion exhibits a well-known circadian rhythm (CR) which is disturbed in secondary hyperparathyroidism (SHPT). The mechanism behind the CR of PTH is, however, unknown and not correlated to the CRs of calcium (Ca) and phosphate (P). Furthermore, the parathyroid gland is not controlled by a superior “hypothalamic-pituitary axis”. The possible existence of a molecular circadian clock in the parathyroid cell has not previously been examined.

Methods: Normal male Wistar rats were kept in 12:12 light-dark cycle and fed ad libitum. Parathyroid glands were harvested with 4 hours interval for 24 hours, along with plasma samples for PTH (pg/ml), FGF23 (pg/ml), total Calcium (mM), Urea (mM) and Creatinine (μM). (N=38; 6 per timepoint). Gene expression was examined by qPCR analysis. SHPT was induced by 5:6 nephrectomy and high phosphorus diet for 24 weeks. (N=10 and 16 age-matched controls).

Results: Parathyroid glands showed clear expression of core molecular clock genes: BMAL1, Clock, Per1-3, Cry2 and Rev-Erba. The circadian rhythm was examined by cosinor analysis fitted to a period of 24h and was significant for Bmal1 (p<0.001), Per2 (p<0.0001), Per3 (p<0.0001), Cry1 (p<0.0001), Cry2 (p<0.002) and Rev-Erba (p<0.0001). Significant rhythm was also found for the cell cycle gene Cyclin D1 (p<0.003). In parathyroid glands from uremic rats, downregulation of Clock (1.61±0.83, p<0.041) was found as well as circadian clock output gene CRY2 (1.05±0.24 vs. 2.27±0.34, p=0.047). Also cell cycle gene Cyclin D1 was downregulated in uremic rats (1.20±0.42 vs. 3.56±0.73, p=0.041).

Conclusions: The existence of a parathyroid molecular circadian clock is demonstrated for the first time. The expression of the parathyroid circadian clock genes is disturbed in uremic parathyroid gland, which potentially can contribute to the disturbed circadian rhythm of circulating PTH and to the development of parathyroid hyperplasia in uremia.

TH-PO533

Possible Clinical Relevance of Growth-Hormone Stimulated α-Klotho Upregulation
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Background: An aging suppressor protein, α-Klotho, known as a key factor for calcium-phosphorus homeostasis, is believed to have diverse physiological properties, because its global genetic deletion animal model shows short-stature and multi-organ dysfunction, resulting in early death. Interestingly, recent studies suggest that pituitary function plays an intriguing role, because growth hormone (GH)-producing pituitary adenomas significantly upregulates systemic α-Klotho levels. In end stage kidney disease (ESKD), growth spurt of pediatric patients is disturbed and often GH-resistant, whereas adult bone mineral disorder remains an unsolved clinical entity.

Methods: To elucidate the magnitude of GH/α-Klotho axis on both pituitary and bone-mineral reaction, we performed experiments involving GH administration to wild-type mice and adenine-induced kidney failure mice. GH was intraperitoneally given to 4-week-old male mice (C57BL/6J). We examined α-klotho mRNA expression, quantified by RT-PCR, in the pituitary gland and censored bones of mice with or without kidney damage. Additionally, we performed immunohistochemistry (IHC) analysis of α-Klotho expression, surgically obtained from patients with pituitary adenomas.

Results: Exogenous GH increased α-klotho mRNA levels in the pituitary, and more robustly in censored bones. Strikingly, kidney failure cancelled GH-induced α-klotho expression in the pituitary and trabecular bones. Unexpectedly, GH administration induced modest α-klotho mRNA expression and markedly increased urinary excretion of soluble α-Klotho in wild-type mice, suggesting that GH triggers systemic circulation of α-Klotho in the bloodstream. IHC results indicated that pituitary GH-producing adenomas showed α-Klotho expression more strongly than other (ACTH-producing, TSH-producing, or non-functioning) adenomas.

Conclusions: Established chronic kidney disease causes bone mineral disease, possibly by disrupting GH/α-Klotho axis. GH supplementation alone fails to catch up bone loss in juvenile patients with ESKD partly because of disrupted GH-triggered α-Klotho upregulation. Its stimulation might be a treatment option for patients with refractory bone and mineral disorders in ESKD. Organ-specific activation of GH/α-Klotho pathway might be a therapeutic target for restoring each organ function, leading to ideal organ rejuvenation and function.

Funding: Private Foundation Support
Cinacalcet was a positive calcimimetic control and was tested to rescue grape calcilytic bone mineral metabolism disorders. In addition, elucidation of the heretofore, unexplained mechanism of lethal grape toxicity in dogs which 3) could nutraceutical compounds may influence both human and canine medicine; 2) may provide compounds, we conclude that 1) these mechanisms explain how naturally-derived.

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Many universities and research institutions are conducting studies on the effects of calcimimetic and calcilytic activity of dietary plant polyphenols on bone and mineral metabolism. These studies are being conducted on both human and canine models. In particular, the role of the calcium sensing receptor (CaSR) in regulating calcium homeostasis is being investigated.

Secondary hyperparathyroidism (SHPT) is a common complication of CKD that correlates with morbidity and mortality. In experimental SHPT there is increased PTH secretion, gene expression and parathyroid cell proliferation. The high PTH gene expression is due to increased PTH mRNA stability mediated by the balanced protein-PTH mRNA interaction of AU-rich binding protein 1 (a-RBP) that stabilizes and KSRP (K-homology splicing regulatory protein) that destabilizes PTH mRNA. P1 binds to and sequesters phosphorylated Ser/Thr-Pro motifs in target proteins, including mRNA binding proteins. P1-KSRP interaction leads to degradation of KSRP at Ser181 that then binds to PTH mRNA with higher affinity to induce PTH mRNA decay. In SHPT, P1 isomerase activity is decreased and phosphorylated KSRP fails to bind PTH mRNA, resulting in increased PTH mRNA stability and levels. P1 activity is regulated by phosphorylation at Ser16 and Ser71 that disrupts its interaction with target proteins and catalytic isomerase activity.

We performed proteome and phosphate-proteome analysis of parathyroid glands from normal and adenine high phosphorus induced CKD rats. P1 phosphorylation was demonstrated by immunofluorescence staining. The P1 activator forskolin or P1 inhibitor H89 were added to mouse thyrocalcitonin glands in culture or HEK293 cells transfected with a PTH expression plasmid. Secreted PTH was measured by ELSA and mRNA levels by qRT-PCR.

Results: Phospho-proteome analysis confirmed KSRP hyper-phosphorylation in parathyroids of SHPT rats, that would prevent PTH mRNA-KSRP binding and decay. It also identified that P1 binds to P1 targets and signaling pathways. Phosphorylation of both P1 and P1 targets results in decreased P1 activity. Accordingly, parathyroid extracts from SHPT rats showed increased in vitro phosphorylation activity towards recombinant GST-P1. P1 activation, that leads to P1 Ser16 phosphorylation, increases PTH secretion in parathyroid organ cultures and PTH mRNA in transfected HEK293 cells. P1a inhibition had the opposite effect.

Conclusions: P1 activity is central to the pathways of SHPT by orchestrating PTH mRNA-protein interaction and thus mRNA decay. The resulting increased PTH mRNA stability leads to the high serum PTH levels in SHPT.

TH-P0535

Novel Calcimimetic and Calcilytic Activity of Dietary Plant Polyphenols

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Background: Plant-derived polyphenols have diverse medicinal effects involving multiple signaling pathways. With grapes reportedly improving human bone mass and associated with hypercalcemia in certain dogs, we hypothesized a new mechanism involving grape polyphenols (GSPs). We investigated whether compound(s) in GSPs are calcimimetic, calcilytic, or both.

Methods: In vitro studies performed on MC3T3-E1 cells and HEK293 cells. GSPs were tested for calcimimetic and calcilytic activity using an alkaline phosphatase (ALP) assay and an alkaline phosphatase (ALP) assay, respectively, for calcium supplementation and phosphate supplementation, respectively. In vivo studies performed on male Sprague-Dawley rats fed a normal or high phosphorus diet. The effect of GSPs on bone mineral density (BMD) and serum calcium levels was measured.

Results: GSPs exhibited both calcimimetic and calcilytic activity in vitro and in vivo. The calcimimetic activity was observed at concentrations as low as 10 µM, while the calcilytic activity was observed at concentrations as high as 1000 µM.

Conclusions: GSPs are novel calcimimetic and calcilytic compounds that may have potential for the treatment of osteoporosis and hypercalcemia.

TH-P0537

Dicer and miRNA Deletion Leads to Ectopic Parathyroid Hormone (PTH) Expression

Alia Hassan, Rachel Levin, Justin Silver, Tally Naveh-Many, Hadassah Hebrew University Medical Center Jerusalem, Jerusalem, Israel; 3The Jikei University School of Medicine, Tokyo, Japan.

TH-P0538

Pin1 Isozyme Activity Determines PTH Gene Expression in Uremic Secondary Hyperparathyroidism

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Background: Secondary hyperparathyroidism (SHPT) is a common complication of CKD that correlates with morbidity and mortality. In experimental SHPT there is increased PTH secretion, gene expression and parathyroid cell proliferation. The high PTH gene expression is due to increased PTH mRNA stability mediated by the balanced protein-PTH mRNA interaction of AU-rich binding protein 1 (a-RBP) that stabilizes and KSRP (K-homology splicing regulatory protein) that destabilizes PTH mRNA. P1 binds to and sequesters phosphorylated Ser/Thr-Pro motifs in target proteins, including mRNA binding proteins. P1-KSRP interaction leads to dephosphorylation of KSRP at Ser181 that then binds to PTH mRNA with higher affinity to induce PTH mRNA decay. In SHPT, P1 isomerase activity is decreased and phosphorylated KSRP fails to bind PTH mRNA, resulting in increased PTH mRNA stability and levels. P1 activity is regulated by phosphorylation at Ser16 and Ser71 that disrupts its interaction with target proteins and catalytic isomerase activity.

Methods: We performed proteome and phosphate-proteome analysis of parathyroid glands from normal and adenine high phosphorus induced CKD rats. P1 phosphorylation was demonstrated by immunofluorescence staining. The P1 activator forskolin or P1 inhibitor H89 were added to mouse thyrocalcitonin glands in culture or HEK293 cells transfected with a PTH expression plasmid. Secreted PTH was measured by ELSA and mRNA levels by qRT-PCR.

Results: Phospho-proteome analysis confirmed KSRP hyper-phosphorylation in parathyroids of SHPT rats, that would prevent PTH mRNA-KSRP binding and decay. It also identified that P1 binds to P1 targets and signaling pathways. Phosphorylation of both P1 and P1 targets results in decreased P1 activity. Accordingly, parathyroid extracts from SHPT rats showed increased in vitro phosphorylation activity towards recombinant GST-P1. P1 activation, that leads to P1 Ser16 phosphorylation, increases PTH secretion in parathyroid organ cultures and PTH mRNA in transfected HEK293 cells. P1a inhibition had the opposite effect.

Conclusions: P1 activity is central to the pathways of SHPT by orchestrating PTH mRNA-protein interaction and thus mRNA decay. The resulting increased PTH mRNA stability leads to the high serum PTH levels in SHPT.

Funding: Government Support - Non-U.S.
Bone and Mineral Metabolism: Basic

Thursday/Poster

TH-P0538
Dietary Protein and Branched Chain Amino Acids Protect the Kidney from Phosphate Burden
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Background: Phosphate homeostasis is critically important for the maintenance of health. High phosphate intake has been reported to be harmful to the kidney. Although levels of dietary phosphate intake closely correlate with dietary protein intake, effects of dietary protein on phosphate toxicity remain uncertain.

Methods: Phosphate-induced chronic kidney disease (CKD) model were prepared by feeding a diet containing 2% phosphate to male Wistar rats for 6 weeks. Rats were randomly divided into 3 groups based on concomitant feeding of 12.5%, 25%, or 37.5% casein. Similar models were prepared by feeding ovalbumin instead of casein. We also analyzed the effects of dietary branched chain amino acids (BCAA) on phosphate-induced kidney injury.

Results: Dietary casein suppressed serum levels of creatinine and phosphate, but elevated serum urea nitrogen, in a dose-dependent manner. Dietary casein did not affect levels of food intake nor fecal phosphate. Although dietary casein elevated urinary protein in normal Wistar rats without phosphate burden, dietary casein did not increase urinary protein in phosphate-fed CKD rats. Both real time PCR and histological analyses revealed that dietary casein protected the kidney from phosphate-toxicity-induced toxicity. Dietary casein maintained the mitochondrial integrity in tubular cells, and thereby suppressed oxidative stress. Ovalbumin showed even better renoprotective effects with unchanged serum urea nitrogen and suppressed urinary protein. To investigate underlying mechanisms of renoprotection by dietary proteins, we measured plasma amino acid levels and found that both dietary casein and ovalbumin elevated plasma valine, leucine, and isoleucine.

Conclusion: Dietary casein protects the kidney from phosphate burden. BCAA supplementation may be even better to suppress phosphate toxicity to the kidney.

Funding: Private Foundation Support

TH-P0539
Do You Know What Your Experimental Animals Eat?
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Background: The bioavailability of dietary protein in the rat body in Akp3-/- renal failure model.

-/- could contribute to the development of a new CKD model.

Methods: Dietary casein suppressed serum levels of creatinine and phosphate, but increased urinary protein in normal (NL) littersmates were assigned to 3 diets: autoclaved 0.7% phosphate grain-based diet for 28 wks (AGES), autoclaved diet for 17wks followed by non-autoclaved 0.7% bioavailable phosphate casein-based diet until 28 wks (AGES + Casein), or a non-autoclaved diet for 17wks followed by a non-autoclaved casein-based diet (non-AGES + Casein) until 28 wks. We examined kidney function, plasma biochemistries, and intestinal gene expression (phosphate transporters, the receptor for AGE (RAGE), and NADPH-oxidases). We assessed the effects of diet (CDK vs NL), diet, and the interaction by two-way ANOVA.

Conclusion: Dietary casein protected the kidneys in Akp3-/- mice and indicate that Dicer and miRNA are required for parathyroid differentiation and morphogenesis.

Conclusions: Parathryoid Dicer and miRNA are essential for development, migration, localization and function of the parathyroids.

Funding: Government Support - Non-U.S.

TH-P0540
Intestinal Environmental Control and Renal Protection by Intestinal Alkaline Phosphatase (IAP)
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Background: Hyperphosphatemia is an independent risk factor for mortality, and prevention and correction of it is a major goal of the treatment of chronic kidney disease (CKD). Inorganic phosphate (Pi) balance is maintained by intestinal absorption, renal excretion, and bone accretion. Especially, the regulation of intestinal Pi absorption is an important target for the treatment of hyperphosphatemia. Intestinal alkaline phosphatase (IAP) is a brush border phosphohomomerase that catalyzes the hydrolysis of nonspecific Pi ester bonds at an alkaline pH, and a plasma membrane-bound glycoprotein that dephosphorylates several substrates, including Pi additives. The relationship between IAP and Pi metabolism is not clear. We investigated whether intestinal alkaline phosphate (IAP) was required for the treatment of hyperphosphatemia in CKD.

Methods: We analyzed Pi homeostasis in Akp3 knockout mice (Akp3-/-), and studied the expression of renal failure, and intestinal environment in an Akp3-/- renal failure model.

Results: In humans, rats, and mice, intestinal alkaline phosphatase (IAP, AKP3) is expressed throughout the gastrointestinal tract with the highest expression in the duodenum. Akp3-/- mice have high intestinal Pi-binding protein, which results in reduced growth in the gut. Changes in the extracellular ATP concentration affected Pi transport. In the renal failure model, genetic deletion of Akp3 suppressed abnormal mineral homeostasis, progression of renal failure and inflammation of the intestinal and whole body (whole-body Pi). As a result, Akp3-/- extended the life span (P<0.001). In the Akp3-/- renal failure model, hyperphosphatemia was alleviated by suppression of intestinal Pi absorption via paracellular mechanisms as well as transcellular Pi transport.

Conclusions: Elucidation of the mechanism of suppression of renal disease patients confirmed by Akp3-/- could contribute to the development of a new CKD treatment.

Funding: Government Support - Non-U.S.
**TH-PO542**

**Inhibition of Sodium Phosphate Transporter Npt2a Increases Urinary Phosphate Excretion and Improves Experimental Vascular Calcification in Rats**

**Juergen Klär,1 Anja Giese,1 Alexander Ehrmann,2 Christoph Thiel,1 Bernd Riedl,1 Frank Ettinger,2 Bayer AG, Berlin, Germany; 3Bayer AG, Wuppertal, Germany.**

**Background:** A dysregulated phosphate homeostasis is strongly associated with mortality, cardiovascular events and vascular calcification, particularly in patients suffering from CKD. Inhibition of the tubular sodium phosphate transporter Npt2a provides a novel and unique mechanism to address phosphate homeostasis imbalance.

**Methods:** Npt2a activity was measured in a cell based assay, using a stable CHO cell line with inducible Npt2a expression. Male Wistar rats were used for all experiments. Healthy rats were treated orally with BAY 76, a potent Npt2a inhibitor developed at Bayer AG. Vascular calcification was induced by administration of a pan-FGFR inhibitor (25mg/kg) for 10 days.

**Results:** BAY 76 was identified as potent Npt2a inhibitor, with an IC50 of 2.96 nM on rat human Npt2a, respectively, selective over Npt2b, Npt2c and Pit-1. Single dose treatments of healthy rats resulted in a significant, dose-dependent increase in urinary phosphate excretion within 16h. Multiple dose treatments (3d) significantly reduced plasma phosphate levels from 2.0 mmol/l to 1.6 mmol/l at the highest tested dose. Congruent levels of FGF23 as well as PTH were decreased to 46% and 43% as compared to untreated controls, respectively. In an experimental vascular calcification model, treatment with the Npt2a inhibitor significantly inhibited vascular calcification and normalized plasma phosphate levels in comparison to untreated rats that developed massive vascular calcification and hyperphosphatemia. In the same model 2.2% lanthanum carbonate was demonstrated to be beneficial with respect to vascular calcification.

**Conclusions:** Our results show for the first time that treatment with a Npt2a inhibitor improves vascular calcification by addressing urinary phosphate excretion and phosphate homeostasis in rats. Npt2a inhibition may provide a new therapeutic principle for patients suffering from disbalanced phosphate homeostasis and vascular calcifications, including CKD patients.

**Funding:** Commercial Support - Bayer AG

**TH-PO543**

**High Phosphate-Inducing Valvular Interstitial-Endothelium Cross-Talk Through mir-382/SOD2 Axis in CKD with Valve Injury**

**Liting Wang, Yu-xia Zhang, Si-Jie Chen, Yu Guo, Xiao-chen Wang, Li-Hua Ni, Kaiyin Song, Xiao-liang Zhang, Bi-Cheng Liu, Ri-ning Tang. Institute of Nephrology, ZhongDa Hospital, school of medicine, Southeast University, Nanjing, China.**

**Background:** CKD valve injury is the main cause of CVD among CKD patients, but its underlying mechanisms are still unknown. Previous studies demonstrated valvular interstitial cells (VICs) participate in valve injury to produce excessive quantities of the valvarul ECM. Recent findings suggested valvular interstitial-endothelium crosstalk are closely related to valve homeostasis and injury. Hence, we want to investigate the mechanism of VICs and VECs upon high phosphate (HP) stimulation.

**Methods:** We used c57/b mouse and HP-stimulated VIC as in vivo and in vitro model of CKD, respectively. Tranwell migration were performed to determine VIC could aggravate valve endothelial cell(VEC) EndMT upon HP stimulation by qPCR, WB and immunofluorescence. ELISA were performed to detect the expression of TGFβ-1 in VIC cell supernatant. The expression of key factors involved in EndMT process, such as CD31, VE-cadherin, α-SMA, FSP1 were evaluated by western blotting and immunofluorescence. qRT-PCR was used to measure levels of miR-382 in VEC.

**Results:** TGFβ-1 were significantly increased in VIC upon HP stimulation. Tranwell migration were proved VIC could aggravate VEC endothelial-to-mesenchymal transition (EndMT) upon HP stimulation, with the up-regulation of mesenchymal markers (FSP1 and α-SMA) and stem cell markers (CD44 and CD10) and down-regulation of the endothelial marker (CD31, VE-cadherin), consistent with CKD aortic valve samples. Knockdown of EC miR-382, which was up-regulated by TGFβ1, could attenuate TGFβ1-induced loss of the endothelial marker VE-cadherin and CD31. miR-382 was confirmed by 3'-untranslated region reporter assay to target superoxide dismutase 2 (SOD2) that were downregulated at the protein level by TGFβ1. Knockdown of miR-382 attenuated TGFβ1-induced downregulation of SOD2. Overexpression of SOD2 ameliorated loss of the endothelial marker and CKD aortic leaflets thickening.

**Conclusions:** VIC could secret TGFβ-1 upon HP stimulation, which lead to EndMT through mir-382/SOD2 axis. This could cause CKD aortic leaflets thickening and aggravate valve injury.

**TH-PO544**

**A Crossover Study of Continuous Intake of the Different Phosphorus Bioavailability Meal in Healthy Japanese**

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**Background:** Dietary phosphorus (P) management based on its bioavailability is crucial to prevent and treat the risk of cardiovascular disease and mortality in both general population and chronic kidney disease (CKD) patients. Our previous study has demonstrated that P bioavailability in various independent foods as the relative value of sodium phosphate. However, it remains unclear that P bioavailability in mixed meal. Thus, we conducted the short-term dietary intervention study that ingested mixed meal consisting of different P bioavailability foods.

**Methods:** We conducted an open-label crossover study of 4 different test meals consumed for 5 days by 5 men and 5 women healthy young subjects, aged 20-30 years old. We obtained multiple points of blood and 24 h urine samples at before and after each intervention. Each meal was designed to have the same amount of 1,200 mg/d and only a half of P (600 mg/d) sources varied as test foods: soybean and tofu, pork and ham, milk and process cheese, and sodium P supplement for low, medium, high, and control P bioavailability test foods, respectively.

**Results:** After continuous ingestion of high P bioavailability meal, fasting serum intact fibro blast growth factor 23 (iFGF23) levels increased, accompanied with decrease in serum 1,25-dihydroxyvitamin D levels and urinary P excretion [Figure 1]. Additionally, serum P and iFGF23 levels were lower in low P bioavailability meal compared with other test meals throughout the day. These results indicate consuming higher P bioavailability food results higher increase of iFGF23 which reflect more severe P burden.

**Conclusions:** Habitual ingestion of low P bioavailability food decreases P burden despite equivalent amount of P and may contribute to reduce the risk of disease and mortality in CKD patients.

**Funding:** Private Foundation Support

**TH-PO545**

**Extracellular Matrix Stiffness Modulates Calcification of Vascular Smooth Muscle Cells via Phosphate Uptake**

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**Background:** In patients with chronic kidney disease (CKD), stiffening and calcification of blood vessels are common and predict mortality and adverse cardiovascular events. Our preliminary data suggests that stiffening occurs early in CKD and could be independent of calcification. Stiffness of the extracellular matrix (ECM) has also been shown to influence differentiation of pluripotent stem cells. Thus, we hypothesize that stiffness of the ECM will increase phosphate mediated osteoblastic transformation and calcification of vascular smooth muscle cells.

**Methods:** Human aortic smooth muscle cells (HASMCs) were plated on polyethylene glycol gels of varying stiffness: 8kPa, 50kPa, or plastic (~10,000kPa). Cells were cultured in either control or calcification medium (3.0mM phosphate and 2.7mM calcium).

**Results:** There was a 4-fold increase in calcium in HASMCs plated on 8kPa (243 ± 124 µg/mg of protein) compared to those on 50kPa (549 ± 59 µg/mg of protein, P<0.05) and a 9-fold increase from 50kPa to plastic (8246 ± 1324 µg/mg of protein, P<0.05) (Fig 1). HASMCs on plastic had a near 2-fold increase in ALP activity when cultured in calcification medium (0.58 ± 0.12 vs 0.33 ± 0.05 µU/mg of protein, P<0.05), while cells on 8kPa (0.36 ± 0.02 vs 0.35 ± 0.04 µU/mg of protein, P>0.05) and 50kPa (0.33 ± 0.03 vs 0.39 ± 0.05 µU/mg of protein, P<0.05) showed no appreciable increase in ALP activity. Similar to ALP data, phosphate uptake was increased in cells plated on plastic (2.21-fold increase, P<0.05) but not for the 8kPa and 50kPa gels in calcification media (Fig 2).

**Conclusions:** Our study showed that ECM stiffness increases calcification of HASMC. Osteoblastic transformation was abolished on soft gels. The decrease in osteoblastic transformation appears secondary to downregulation of phosphate uptake. Targeting molecular pathways that mediate stiffness induced upregulation of phosphate uptake might decrease calcification and improve cardiovascular outcomes in CKD.

**Funding:** Other NIH Support - NHLBI, K-808KL130945

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Bone and Mineral Metabolism: Basic

**TH-PO546**

**ASARM Peptide Reverses Hyperphosphatemia; Prevents Calciphylaxis-Like Lesions; and Corrects Renal, Bone, Brain, and Cardiovascular Calcification in a Rat Model of CKD**

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**Background:** Abnormalities in mineral metabolism, bone and vascular calcification occur in Chronic Kidney Disease (CKD-MBD). Cognitive function also declines as the disease progresses. Bone ASARM peptides are strong inhibitors of mineralization and induce hypophosphatemia by inhibiting phosphate uptake from the gut. We hypothesize treatment of CKD-MBD rats with ASARM peptides will reverse hyperphosphatemia, correct mineralization defects and improve mortality.

**Methods:** To test our hypothesis, we used a rat 5/6 Nephrectomy experimental model (NEPHREX) and sham operated rats (SHAM) as controls. Male rats (16 wk, 250 gm) were fed 2% P, 2000 IU Vit D diet to worsen mineral metabolism defects along with a tendency towards a lower bone area which however, was inversely associated with the MC dose and was abolished when the mineralized area over bone area was considered. Similar patterns were observed for the bone formation and mineral apposition rates respectively. No significant effect of MC treatment on the number of osteoclasts was observed.

**Conclusions:** Mortality was limited as only 1 animal died before the study end. MC did not impact renal dysfunction nor did it affect PTH, phosphorus, Ca or FGF-23 levels. Arterial Ca content was assessed as well as area % Von Kossa positivity. Bone status was evaluated by histomorphometric analysis as static and dynamic bone parameters.

**Funding:** NIDDK Support

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**TH-PO547**

**Effect of PARP Inhibition on the Development of Vascular Calcification (VC) in CKD Rats**

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**Background:** A new therapeutic approach for VC consists in the use of molecules directly interfering with the calcification process. Potential candidates for this are Poly ADP Ribose Polymerase (PARP) inhibitors. Through the understanding of PARP/PAR processes that occur in new bone formation, it has recently been discovered that VC is also mediated by PARP/PAR processes that release PAR from dying cells in the vascular wall. We evaluated the effect of the PARP inhibitor minocycline (MC) on the development of VC in a rat model with ademine-induced CKD.

**Methods:** 56 male Wistar CKD rats were randomly assigned to 4 study groups (n=14 each) and treated daily during 6 wks with either tap water (CKD-Veh) or MC at doses of 5, 10 or 50 mg/kg respectively. MC treatment was initiated 1 wk after the start of adenine dosing (0.75% in diet during 4 wks). VC was evaluated by measuring arterial calcium (Ca) content as well as area % Von Kossa positivity. Bone status was evaluated by quantitative histomorphometric analysis of static and dynamic bone parameters.

**Results:** Mortality was limited as only 1 animal died before the study end. MC did not impact renal dysfunction nor did it affect PTH, phosphorus, Ca or FGF-23 levels. Arterial Ca content as well area % Von Kossa positivity, indicated MC treatment to dose dependently decrease calcification in the aorta, carotid and femoral arteries which become significant in the 50 mg/kg group. Compared to CKD-Veh rats MC treatment went along with a tendency towards a lower bone area which however, was inversely associated with the MC dose and was abolished when the mineralized area over bone area was considered. Similar patterns were observed for the bone formation and mineral apposition rates respectively. No significant effect of MC treatment on the number of osteoclasts was observed.

**Conclusions:** MC treatment reduced VC without affecting renal function and associated mineral disturbances, suggesting a direct and local action on the arterial wall. Because the effects on the vasculature reveal that PARP inhibition might be a promising, safe and effective treatment of VC. Further studies are warranted to get a more profound insight in the potential effects of MC on bone.

**Funding:** Commercial Support - Cycle Pharma

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**TH-PO548**

**Inorganic Polyphosphate Amplifies the Macrophage-Inflammatory Response Induced by Lipopolysaccharide**

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**Background:** Recent studies have revealed that inorganic polyphosphate (polyP), a linear polymer of orthophosphate, is involved in various physiological events like blood clotting, inflammation and energy metabolism. Infection, particularly sepsis, is a major cause of death in patients with chronic kidney disease (CKD) and is associated with high levels of plasma polyP. However, the role of phosphate in the induction of an inflammatory response during CKD is largely unknown. In this study, we examined the effect of polyP on LPS-induced macrophage proinflammatory signaling in vitro.

**Methods:** A reaction of THP-1 derived macrophages with LPS (1.0 ng/mL) from Escherichia coli and polyP of various chain lengths (1, 2, 3, 15, 65, 100, 700 mer) and concentrations (1-200 μM, calculated as an orthophosphate monomer) was carried out. The levels of inflammatory cytokines released into the culture medium were measured using ELISA. The expressions of proinflammatory cytokine mRNAs of IL-1β, TNFα and IL-6 and signaling proteins like NF-κβ and MAPK were analyzed by real-time PCR and western blotting, respectively. The effect of polyP on LPS binding to the Toll-like receptor (TLR) 4 on cells and its structure was examined by quartz crystal microbalance (QCM), flow cytometry and fluorescence microscopy visualization, and isothermal titration calorimetry (ITC) and dynamic light scattering spectroscopy (DLS), respectively.

**Results:** PolyP amplified the inflammatory cytokine production induced by LPS (IL-1β, 50 μM PolyP-65: 23.0 ± 2.9 pg/mL; 1 ng/mL LPS: 440.8 ± 45.7 pg/mL; 1 mg/mL LPS + 50 μM polyP-65: 1666.6 ± 162.4 pg/mL, p<0.05) in a dose- and chain length-dependent manner, whereas orthophosphate had no such effect. It also enhanced the expression levels of proinflammatory cytokine mRNAs, LPS-induced macrophage signaling (indicated by an increased expression of NF-κβ, MAPK) and LPS micelle formation. Results of QCM, flow cytometry and fluorescence microscopy showed that polyP bound directly to LPS, enhancing its interaction with TLR4.

**Conclusions:** This study suggests that polyP may be important in promoting an LPS-induced inflammatory response in macrophages and could be a form of phosphate associated with acute inflammation in patients with CKD.
Resveratrol Ameliorates High-Phosphate-Induced VOT and AMC in CKD Through Regulating Wnt/β-catenin Signaling

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Background: Vascular smooth muscle cells (VSMCs) to osteoblast-like cells transdifferentiation (VOT) induced by high-phosphate is a crucial step in the development of arterial medial calcification (AMC) in patients with chronic kidney disease (CKD). Our previous study demonstrated that Wnt/β-catenin signaling played an important role in promoting VOT and calcification in VSMCs induced by high-phosphate. Studies in cancer field have confirmed that resveratrol, a natural polyphenol, could regulate Wnt/β-catenin signaling. However, the potential effect of resveratrol on VOT and AMC through Wnt/β-catenin signaling remains to be elucidated.

Methods: An animal model of chronic renal failure with AMC was established by feeding rats a diet containing 0.75% adenine and 0.9% phosphorus. VOT and AMC in arterial ring was induced by placing isolated thoracic aortic rings from mice in culture medium containing 10 mM β-glycerophosphoric acid (β-GP). VOT and calcification of cultured VSMCs was also induced by 10 mM β-GP. The effect of resveratrol on VOT and/or calcification was observed in the in vivo, ex vivo and in vitro models mentioned above. The regulation of resveratrol on Wnt/β-catenin signaling in VSMCs was also examined.

Results: Resveratrol ameliorated AMC in chronic renal failure rats fed with high-phosphate diet and calcium deposition in arterial rings and VSMCs cultured in a high-phosphate environment. Resveratrol suppressed the induction of Runx2, osteocalcin and osteopontin and restored the expression of SM22α in arterial rings and VSMCs treated with high-phosphate. In vitro, resveratrol inhibited the upregulation of two forms of active β-catenin, diphosphorylated on Ser37/Thr41 and phosphorylated on Ser675 sites, and β-catenin nuclear translocation, stimulated by high-phosphate. Furthermore, porcupine and wntless was induced in VSMCs treated with high-phosphate in a time-dependent manner, which could be inhibited by resveratrol. Resveratrol also inhibited the phosphorylation of LRP6 induced by high-phosphate. However, it seemed that resveratrol couldn’t inhibit the expression of Runx2 induced by Wnt3a.

Conclusions: The results presented in our study suggest that through targeting Wnt/β-catenin signaling, which in turn impeding VOT induced by high-phosphate, resveratrol possesses an effect on retarding AMC in CKD.

Funding: Government Support - Non-U.S.

Increased Basal Tone and Impaired Smooth Muscle Cell Contractility of the Carotid Artery in a CKD Rat Model


Background: Increased arterial stiffness (AS) is linked to aging and accelerated in patients with CKD. Traditionally, CKD has been closely associated with the development of arterial media calcifications (AMC), which together with changes in extracellular matrix composition are typical examples of passive stiffening. AS, on the other hand also has cellular, active components. Endothelial induced relaxation and vascular smooth muscle cell (VSMC) contractility, in response to pressure changes, are crucial to maintain a proper vessel tone. Using a CKD rat model this study aims to unravel the passive and active mechanisms underlying CKD related AS.

Methods: Eight Wistar rats were administered an adenine supplemented/phosphate rich diet for a period of 8 wks to induce CKD-related AMC, and compared to 8 age-matched control rats with normal renal function. Serum creatinine and phosphate were determined to follow up CKD development. AMC was investigated by measuring bulk Ca content in the aorta. AS was evaluated in vivo, using echo evaluation of the abdominal aorta pulse wave velocity (PWV). An in house ex vivo organ bath setup to mimic cyclic stretch, was used to evaluate endothelial and VSMC functionality and to quantify the Peterson’s elastic modulus (Ep, measure of AS).

Results: AS could be concluded from serum creatinine and phosphate levels, severe CKD developed in the adenine fed rats. Significantly higher Ca content in the aorta (p<0.01) of adenine rats confirmed AMC development. After 8 wks, adenine fed animals showed increased AS, both in vivo and ex vivo: significantly higher PWVα (p<0.01) and Ep (p<0.01) compared to controls. Furthermore, adenine rats have increased, pressure dependent, basal tone and diminished VSMC contractility (p<0.01).

Conclusions: The adenine rat model is suited to investigate the progressive character of AS. We observed an interplay between active and passive components. The reduction in VSMC contractility is detrimental for the arterial system to buffer pulsatile flows at higher pressures, further promoting AS. A logical next step would be to include earlier time points to study endothelial contribution and VSMC shift towards a pro-calcifying phenotype. Discovery of early mechanisms underlying AS will contribute to the development of novel AS preventive treatments.

Funding: Government Support - Non-U.S.

The Inhibitory Effect of Zinc Chloride on Phosphate-Induced Calcification via Suppression of HIF1α Expression in Human Vascular Smooth Muscle Cells

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Background: Vascular calcification is a life-threatening pathophysiological abnormality in CKD. It was demonstrated that phosphate (Pi), a main inducer of vascular calcification, enhances oxidative stress and its resultant inflammation, leading to osteochondrogenic differentiation and calcification in cultured vascular smooth muscle cells (VSMCs). Because plasma Zn levels are low in CKD patients and Zn has anti-inflammatory effects, we examined effects of ZnCl2 on Pi-induced inflammation, osteochondrogenic differentiation, and calcification in human VSMCs.

Methods: Human VSMCs were cultured in DMEM plus 10%FCS and 2.0 mM Pi with 0, 0.5, 1, 5, 10, 50, or 100 mM ZnCl2 for 5, 7, or 14 days. The precipitated calcium contents and expression of inflammatory mediators, osteochondrogenic differentiation markers and its inducers, including HIF1α and VEGF, were evaluated.

Results: At 14 days, ZnCl2 inhibited calcification in a concentration-dependent manner, and high concentrations (≥10mM) of ZnCl2 reduced calcification by almost 90% (p<0.01). Moderate to high concentrations (≥5mM) of ZnCl2 suppressed expression of osteochondrogenic differentiation markers (SOX9, MSX2, and RUNX2) and inducers (BMP, PiT1, and MMP2) (p<0.01). Moreover, moderate to high concentrations of ZnCl2 suppressed IL-1b expression at earlier time points (3 and 7 days, p<0.01) and also inhibited expression of HIF1α and VEGF, a downstream gene of HIF1, through the period (p<0.01). Expression of both HIF1α and VEGF positively correlated with IL-1b expression, precipitated Ca content, and expression of BMP2, SOX9, MSX2, RUNX2, PiT1, and MMP2, respectively (p<0.01).

Conclusions: ZnCl2 can directly inhibit Pi-induced inflammation and HIF1α expression, leading to suppression of osteochondrogenic differentiation and calcification in human VSMCs.

Funding: Government Support - Non-U.S.
TH-PO553
Combining Phosphate Binder Therapy with High Vitamin K2 Diet Inhibits Vascular Calcification in an Experimental CKD Animal Model
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Maastricht, Netherlands; 2RWTH University of Aachen, Aachen, Germany; 3RWTH University of Aachen, Aachen, Germany; 4Maastricht University, Maastricht, Netherlands; 5Maastricht University Medical Center, Maastricht, Netherlands; 6Biomedical Engineering, University of Technology, Eindhoven, Netherlands; 7RWTH University Medical Center, Maastricht, Netherlands.

Background: Hyperphosphatemia may contribute to cardiovascular disease and mortality. Therefore, phosphate binders (PB) are widely used, but a proof of risk reduction is lacking. By binding vitamin K PB may offset beneficial effects of phosphate reduction on vascular calcification (VC). Here we tested whether high vitamin K2 supplementation in combination with PB can inhibit VC in an experimental animal model for CKD.

Methods: Description of the model (Figure 1). Blood chemistry was analyzed to verify the CKD model. Aortic arch, abdominal aorta and cartilage was analyzed for calcification using high resolution micro CT scan (in paraffin embedded aortas and formalin fixed tibia’s) and by invasive ucMGP using conformation specific antibodies.

Results: 3/4Nx resulted in increased circulating creatinine (mmol/L) and urea (mmol/L) (>0.01 for both). PB combined with low vitamin K2 diet resulted in significant vascular and cartilage calcification of combination for high vitamin K2 revealed significantly less ectopic calcification. Immunohistochemical staining of tissues for ucMGP revealed that ucMGP was present at sites of vascular calcification, mainly in the low vitamin K2 treated groups, indicating severe vascular vitamin K deficiency (Figure 2).

Conclusions: These experiments demonstrate that PB therapy in CKD cannot prevent VC, but that the combination with high vitamin K2 did. The inhibitory effect on vascular and cartilage calcification of combined phosphate binder with vitamin K2 therapy lies in the synergy of phosphate control and correction of vitamin K deficiency.

Funding: Private Foundation Support

TH-PO554
Evidence for Disordered Acid-Base Balance in Calcium Stone Formers

Background: Normal women (W) have higher urine pH (UpH) than normal men (M). Thus W are predisposed to urine calcium phosphate (CaP) crystallization which occurs at higher UpH, and CaP stones are more common in W. M are more likely to form calcium oxalate (CaOx) stones due to lower UpH. In a General Clinical Research Center study, we investigated whether W CaOx stone formers (SF) and M CaP SF, who are atypical for their sex, have abnormal acid-base balance or renal acidification and if so, what components of acid-base metabolism are responsible for the altered UpH.

Methods: We measured UpH and determinants of acid-base regulation in 25 normal subjects (13 M), 18 CaOx SF (12 M) and 17 CaP SF (9 M). We collected 15 urines and 20 blood samples over a 15 hour day; diet was fixed. Gastrointestinal anion excretion (GIAE) = (Na+ – K+ + Ca2+ + Mg2+ – Cl– + Pi) in urine.

Results: Ammonia (NH3) excretion was higher in CaP SF of both sexes and W CaOx SF vs same sex normal (N) even after adjustment for sulfate and GIAE (Table). Urine citrate (U Cit) and fractional excretion of citrate (FE Cit) were lower than in M CaP SF. Net acid excretion (NAE) was high in all M SF vs normal M. W CaOx SF had lower GIAE than W CaP SF or W N (1.50 ± 0.62 mmol/hr vs 2.48 ± 0.22 or 3.11 ± 0.18 resp, p<0.05). Conclusions: CaP SF of both sexes and women CaOx SF have different but clear disorders of acid-base handling, the former seemingly localized to abnormal renal proximal tubule acidification and the latter to aspects of food anion absorption.

Funding: NIDDK Support

Figure 1

Figure 2

TH-PO555
Regulation of Claudins by Metabolic Acidosis via Calcium-Sensing Receptor in Rat Kidney
Gheun-Ho Kim,1 Chor ho Jo;2 Sua Kim.2 Hanyang University College of Medicine, Seoul, Republic of Korea; 2Hanyang University, Seoul, Republic of Korea.

Background: Metabolic acidosis (MA) may present with nephrocalcinosis and nephro lithiasis because of hypercalcicuria. Most of the calcium reabsorption paracellularly occurs through tight junctions in the proximal tubule (PT) and thick ascending limb (TAL) whereas the distal convoluted tubule and connecting tubule are the major regulatory sites of active calcium transport. However, the regulatory contribution of PT for MA calcium transport in the PT and TAL to hypercalcicuria in MA remains to be elucidated.

Methods: Male Sprague-Dawley rats were randomly divided into four groups to see the effects of calcium-sensing receptor (CaSR) stimulation (using cinacalcet) and inhibition (using NPS-2143) in the presence of MA: controls (n=6), MA-loaded (n=6), MA,Ci-loaded (n=6), and MA,Ci/NPS-2143-cotreated rats (n=6). After seven days’ animal experiment, renal calcium expressions were examined by semiquantitative immunoblotting, qPCR analysis, and immunofluorescence microscopy.

Results: Urinary calcium excretion was insignificantly increased by cinacalcet treatment, and it is significantly elevated by MA,Ci load and reversed by NPS-2143 coadministration. Renal claudin-2 protein/mRNA were not altered by cinacalcet treatment, and they were suppressed by MA,Ci loading and recovered by NPS-2143 coadministration. Claudin-16 protein/mRNA and claudin-19 protein/mRNA were not altered by cinacalcet treatment, and they were suppressed by MA,Ci loading and recovered by NPS-2143 coadministration. Claudin-14 protein/mRNA were upregulated by MA,Ci loading and reversed by NPS-2143 coadministration. The effects of acid loading were confirmed by immunofluorescence microscopy.

Conclusions: In metabolic acidosis, not only claudin-2 in PT but also claudin-16/19 in TAL are downregulated to produce hypercalcicuria. The CaSR in rat kidney appears to have a regulatory role in MA-induced hypercalcicuria.

Funding: Commercial Support - Myoungpoong Medical Co.

TH-PO556
Familial Hypocalciuric Hypercalcaemia (FHH) Induced by Gene Deletion of Transient Receptor Potential Canonical 1 (TRPC1) Channels Is Independent of Gender, Like Ca Sensing Receptor (CaSR) Mutations
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Background: Previously in TRPC1 null males, we reported the mouse phenotypes of FHH, causally related to reduced cell free [Ca] (& hyperparathyroidism, like human FHH induced by haploidal l oss-of-function mutations in the CaSR gene. But haploidal TRPC1 deletion induces only hypercalcemia, no hypocalciuria or hyperparathyroidism. Here we tested the hypothesis that phenotypes in TRPC1 null mutation are gender non-specific, like CaSR mutations.

Methods: In age-matched female mice, we performed classical metabolic balance studies & measured blood & urine Ca & Mg by standard methods. We analyzed creatinine by HPLC & calciotropic hormones by mouse ELISA.

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Results: Similar to null males, 7 mon old TRPC1 null females also exhibited hypocalciuria, whether expressed as mean 24 h urine Ca (9.8 ± 0.3 (SE) vs 16.6 ± 3.4 mg%/d, p<0.003) or as urine Ca:cre ratio (2.0 ± 0.3 vs 3.1 ± 0.1, p<0.02), or as Ca clearance (13 ± 2 vs 22 ± 1 µl/min, p< 0.01). Like null males, TRPC1 null females were also hypercalcemic, whether fasted (9.8 ± 0.3 vs 8.1 ± 0.4 mg%, p<0.005) or fed ad lib (9.6 ± 0.2 vs 8.5 ± 0.2 mg%, p<0.005). Mean fasting serum PTH in TRPC1 null females (690 ± 461 pg/ml) was numerically higher, but shy of statistical significance which we found in null males. But the hypercalcemia in null females failed to suppress PTH, suggesting similar dysregulation in PTH secretion by TRPC1 deficiency like the null males. Indeed, over the same age range, serum PTH in 10.5-10.6 month old females (652 ± 2 ± 484 and 4 ± 42 mg%, p<0.04). In contrast to the disturbed Ca homeostasis, there was no difference between null & wild type females in serum or urine Mg, again, similar to comparable data on Mg metabolism between null & wild type males. Mean fasting serum calcium (353 ± 332 mg%) & calcium (2.1 ± 2.1 mg/ml) were similar between female genotypes, like comparable data between male genotypes.

Conclusions: We conclude that deletion of the gene encoding TRPC1 channels produces the phenotypes of hypercalciuric hypocalcemia in females as in males though hyperparathyroidism is milder. Our data support the current concept that alongside CaSR, by mediating store-operated Ca entry, TRPC1 plays a key role in intracellular Ca homeostasis & in regulating PTH secretion.

Supporting: NIDDK Support, Veterans Affairs Support, Private Foundation Support, Clinical Revenue Support

TH-PO557
Deletion of the Proton Receptor OGR1 in the Osteoclast Impairs Metabolic Acidosis-Mediated Bone Resorption
Nancy S. Krieger,1 Luojing Chen,2 Jennifer Becker,1 Michaela Chan,2 Daniel Mammals,1 Formation in Drosophila Renal Structures Revealing Potential Roles in Subdued, an Anoctamin 4 Homolog, Changes Calcium Oxalate Crystal 8th-PO558
5.3% (OC-cKO) vs 26.6
Bone and Mineral Metabolism: Basic

Funding: NIDDK Support, Private Foundation Support

TH-PO556
Spatial Mapping of Cell Populations in the Human Kidney Papilla Using 3D Tissue Cytometry
Mohammad S. Makki,1 Bhopen S. Shrestha,2 Seth Winfree,3 James Williams,1 Tark K. El-Achkar,1

Background: Kidney stone disease or nephrolithiasis affects 10% of US population with estimated healthcare cost of $14 billion. To date, no remarkable insights have been identified for the initiation and progression of kidney stone disease. A contributing factor to this knowledge gap is a poor understanding of the various cell types comprising the nephron segments and the surrounding interstitium in the papilla. To fill this gap, we developed a novel approach to classify cell types of the papilla based on spatial and morphological features, using a computer-aided fluorescence based imaging system. We then performed a detailed transcriptomic and proteomic analysis of these cell subtypes to understand their functional diversity.

Methods: Papillary biopsies were obtained at the time of percutaneous nephrolithotomy or from patients with nephrolithiasis. Fifty-micron thick sections of papilla were stained with fluorescently labelled DAB (Dolichos Biflorus), PNA (Peanut Agglutinin), and/or AQP1. Large scale 3D imaging was performed using confocal microscopy, followed by 3D tissue cytometry analysis using our software tool Volumetric Tissue Exploration and Analysis (VTEA).

Results: With this strategy, VTEA analysis deconvolved all the cells in the papilla into specific subpopulations, which were directly visualized within the tissue. Various subtypes of AQP1 thin lining dendritic and AQP1 thick lining cells were classified based on the presence of co-labeling with DAB and/or PNA. Collecting ducts and ducts of Bellini, which are easily identified by morphological features, stained predominantly with PNA. AQP1 weak staining cells that did not stain with any lectins were identified as vascular cells of the vasa recta.

Conclusions: Using a straightforward fluorescence based staining strategy, we can distinguish subpopulations of epithelial and vascular cells in the papilla. Implementing this model system can provide significant insight into renal papilla physiology and disease in several conditions and further understanding of the role of the cell subtypes in human papilla.

Supporting: NIDDK Support

TH-PO558
Antibiotics Affect the Intestinal Microbiome and Alter Kidney Stone Formation in Genetic Hypercalciuric Stone-Forming Rats
Joshua M. Stern,1 Nancy S. Krieger,1 John R. Asplin,2 Ignacio Granja,2

Background: There is growing evidence that antibiotic exposure is associated with incident stone disease. The intestinal microbiome (IMB) can rapidly shift in response to outside stimuli such as antibiotics. We utilized genetic hypercalciuric stone-forming (CHS) rats, whose pathophysiology parallels that of human hypercalciuria and who spontaneously form calcium phosphate (CaP) stones, to determine the effect of antibiotics on the intestinal microbiota, urine ion excretion and stone formation.

Methods: 116th generation CHS rats were fed a fixed amount of normal Ca (1.2%) and P (0.65%) diet, housed in metabolic cages and divided into 3 groups (n=10): control (CHS), ciprofloxacin (Cipro, 5 mg/d) or Bactrim (250 mg/d). Urine and fecal pellets were collected at 6, 12, 18 and 24 weeks for analyses. Fresh fecal pellets were stored at -80°C and then prepared for analysis by DNA extraction and amplification of the 16S rRNA V4 region using barcoded primers on Illumina platform. QHME was used for analysis. At 18 wks kidney stone formation was determined by Faxitron analysis and assessed by 3 blinded reviewers.

Results: After 18 wks, urine Ca decreased with Bactrim (CTL=17.3 ± 0.4, Bactrim=12.1 ± 0.4 mg/d, p<0.05) as did urine oxalate (CTL=1 ± 2.2, Bactrim=0.8 ± 0.2 mg/d, p<0.05). CaP supersaturation increased with Bactrim (CTL=6.8 ± 0.4, Bactrim=12.1 ± 0.4 mg/d, p<0.05). Mean fasting serum PTH in TRPC1 OC-cKO (Bone V olume / Total V olume: 0.7 ± 0.001 mm (ctl); Tb. Number: 6.3 ± 0.001 mm (ctl)) and OC surface 26.6 ± 0.2/mm (ctl)) and OC surface staining. Mature OCs grown on cover slips were incubated in neutral CT) and immunohistochemistry. Mesenchymal stem cells (MSC) from femurs of OC-cKO and control (ctl) mice were differentiated to OC. Mature OC were stained by TRAP staining. Mature OCs grown on cover slips were incubated in neutral (pH 7.4) or Met (pH 7.1) medium for 45 min and then stained for NFTAl to define active OGR1. Results: p<0.05. TRAP staining ofibia sections indicated a decrease in OC number / bone surface from OC-cKO (4.6±0.7/mm2 (ctl)) to 7.4±0.2/m (ctl)) and OC surface area / bone surface (13.8±3.5% (OC-cKO) to 26.6±2.2% (ctl)) (ctl). We observed that OC density in the MSC of OC-cKO have less TRAP staining (OC/cKO:10.1±2.0 vs OC/cKO:38.9±9.7 (ctl)) and decreased OC surface area (mm2/mm: 0.05±0.02 (OC-cKO) vs 0.19±0.02 (ctl)). OC-cKO OC in response to Met had decreased nuclear translation of NFTAl, a master transcriptional regulator of OC differentiation and proliferation, compared to ctl (17.6±2.6% (OC-cKO) vs 29.7±3.3% (ctl) (p<0.05) but no difference at pH 7.4.

Conclusions: Our results indicate that OC OGR1 is directly regulated by Met and important in acid-induced bone resorption. Characterization of the direct role of OGR1 in acid-induced bone resorption may assist in understanding bone loss associated with the metabolic acidosis in patients with chronic kidney disease.

Supporting: Private Foundation Support

TH-PO558
Subdued, an Anotcamin 4 Homolog, Changes Calcium Oxalate Crystal Formation in Drosophila Renal Structures Revealing Potential Roles in Mammals
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Background: Anotcamin function as Ca2+ activated C1 channels (CaCC) or as phospholipid scramblases. Cation 6-10.3%, pH 7.4, H2O: 15%, H2O: 5%, R1, in a risk locus for recent calcium oxalate (CaOx) stones harboring an anotcamin (A4) variant. Human stone formers have decreased CaCC function as a CaCC and scramble. Subdued also functions in bacterial defense, so we knocked it down to determine if the knockout changes crystal growth.

Methods: Subdued knockdown (KD) in MT principal cells was used as a MT-promotor and a subdued-RNAi. CaOx crystalization experiments were conducted on ex-vivo MTs by 1h addition of osmotic sodium (NaOs); while prolonging feeding (4d) assays used food

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Underline represents presenting author.
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Background: Cystathionine-gamma-lactamase (CSE), along with cystathionine-beta-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (3-MPST) contribute to the production of the gazotransmitter hydrogen sulfide (H$_2$S) in various tissues. In the kidney, H$_2$S is expressed in the cortex and in the outer stripe of the outer medulla, but its role remains elusive. Recent studies using pharmacological inhibition of CSE, or CSE deficient mice, have suggested a pro-inflammatory role of H$_2$S in various inflammatory mouse models. Moreover, administration of H$_2$S donor worsened the inflammation in these models. Here, we explored the role of CSE in a recently established mouse model of renal calcium oxalate crystallopathy.

Methods: CSE-deficient (Cse$^{-/-}$) mice were obtained from Dr. Ishii (Showa Pharmaceutical University, Tokyo, Japan). Eight-week-old Cse$^{-/-}$ mice were allocated to either 1.5 calcium plus 1.5% hydroxyproline-enriched diet or to control diet for 3 weeks. Mice were kept in metabolic cages for 24 h urine collection before termination of the experiments. Indirect methylene blue method was used to measure H$_2$S producing capacity compared to Cse$^{+/+}$ littersmates. Renal morphology and function were normal at baseline in both genotypes. After three weeks exposure to calcium-hydroxyproline-enriched diet, creatinine and blood urea nitrogen levels, while Cse$^{-/-}$ mice had decreased crystal deposits, lower inflammation and fibrosis, as assessed by morphometry and qPCR. Crystal-adherent proteins were less expressed in Cse$^{-/-}$ mice and in primary culture of proximal tubules exposed to calcium-oxalate crystals. 

Conclusions: CSE deficiency protects from inflammation and fibrosis in a model of renal calcium oxalate crystallopathy function, and preserves renal function. Collectively, our data show that H$_2$S-producing enzymes might be suitable pharmacological targets for calcium-oxalate nephropathy.

**Funding:** NIDDK Support, Private Foundation Support

**TH-PO561**

**Cystathionine-Gamma-Lactamase Deficiency Protects Against Calcium Oxalate Nephropathy**

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Background: Cystathionine-gamma-lactamase (CSE), along with cystathionine-beta-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (3-MPST) contribute to the production of the gazotransmitter hydrogen sulfide (H$_2$S) in various tissues. In the kidney, CSE is expressed in the cortex and in the outer stripe of the outer medulla, but its role remains elusive. Recent studies using pharmacological inhibition of CSE, or CSE deficient mice, have suggested a pro-inflammatory role of H$_2$S in various inflammatory mouse models. Moreover, administration of H$_2$S donor worsened the inflammation in these models. Here, we explored the role of CSE in a recently established mouse model of renal calcium oxalate crystallopathy.

Methods: CSE-deficient (Cse$^{-/-}$) mice were obtained from Dr. Ishii (Showa Pharmaceutical University, Tokyo, Japan). Eight-week-old Cse$^{-/-}$ mice were allocated to either 1.5 calcium plus 1.5% hydroxyproline-enriched diet or to control diet for 3 weeks. Mice were kept in metabolic cages for 24 h urine collection before termination of the experiments. Indirect methylene blue method was used to measure H$_2$S producing capacity compared to Cse$^{+/+}$ littersmates. Renal morphology and function were normal at baseline in both genotypes. After three weeks exposure to calcium-hydroxyproline-enriched diet, creatinine and blood urea nitrogen levels, while Cse$^{-/-}$ mice had decreased crystal deposits, lower inflammation and fibrosis, as assessed by morphometry and qPCR. Crystal-adherent proteins were less expressed in Cse$^{-/-}$ mice and in primary culture of proximal tubules exposed to calcium-oxalate crystals. 

Conclusions: CSE deficiency protects from inflammation and fibrosis in a model of renal calcium oxalate crystallopathy function, and preserves renal function. Collectively, our data show that H$_2$S-producing enzymes might be suitable pharmacological targets for calcium-oxalate nephropathy.

**Funding:** Government Support - Non-U.S.

**TH-PO562**

**Chlorthalidone Plus Potassium Citrate Decreases Calcium Oxalate Stone Formation Better Than Either Agent Alone While Also Improving Bone Quality in Genetic Hypercalciuric Stone-Forming Rats**

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Background: To study human idiopathic hypercalciuria (IH) we developed an animal model, genetic hypercalciuric stone-forming (GHS) rats, whose pathophysiology parallels that found in human IH. All GHS rats spontaneously form calcium oxide crystals when the oxalate precursor, hydroxyproline is added to the diet. Here we tested the hypothesis that CTD and KCit combined would effectively reduce CaOx stone formation and improve bone quality in the GHS rats better than either agent alone.

Methods: 113th generation GHS rats were fed a fixed amount of a normal Ca (1.2%) and P (0.65%) diet with 5% hydroxyproline added, housed in metabolic cages and divided into four groups. Diets were supplemented with KCl (4 mmol/d), as a control, KCit (4 mmol/d), CTD (4-5mg/kg/d), or KCit+CTD. Urine (u) was collected at 6, 12, and 18 wks for analyses and kidney stone formation and bone parameters were determined at 18 weeks.

Results: Compared to the KC control, KCit reduced uCa (KCit=17.2±0.3 mg/dL, KCit=14.4±0.3), resulting in further (CTD=13.0±0.6) and KCit+CTD reduced it even further (KCit+CTD=9.3±0.4). The combination of KCit+CTD decreased uCa compared to all other groups. There were no significant differences in CaOx supersaturation in any group. Compared to KC (stone formation with a range of 0.4-1.5), CTD (2.1±0.1), KCit did not alter stone formation (2.0±0.3), while there was less stone formation in the GHS rats fed with CTD alone (CTD=1.6±0.2). The combination of KCit+CTD (0.8±0.2) resulted in significantly fewer stones than CTD or KCit alone. Vertebral trabecular bone was increased by both CTD (38.5±3.2% vs CTL=26.8±5.1%) and KCit+CTD (34.7±3.4%), p<0.05 for both. Cortical bone area was increased by CTD (7.3±0.3 mm2 vs CTL=6.9±0.2 mm2) but not altered with KCit+CTD or with KCit alone. Mechanical properties of trabecular bone were improved by CTD alone, but not the combination.

Conclusions: Thus in GHS rats, when fed a diet that results solely in CaOx stone formation, the combination of KCit+CTD prevented stone formation better than either agent alone. The improvements in bone quality were principally due to CTD alone; adding KCit provides no additional benefit.

**Funding:** NIDDK Support

**TH-PO563**

**Understanding the Pathogenesis of Human Kidney Stone Disease by Spatially Mapping Its Proteome**

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Background: Nephrolithiasis affects approximately one-in-eleven people in the United States. A detailed hypothesis of the mechanisms of stone disease etiology remains elusive, and thus difficult to treat and prevent. The present study aims to advance the understanding of the pathogenesis of stone disease by determining the pattern of protein organization within the matrix of human kidney stones.

Methods: The approach of this work relies on an innovative technique to perform histological sectioning of calcium oxalate (CaOx) stones following demineralization. Multi-photon imaging and label-free proteomics were used on laser micro-dissected (LMD) specific regions to assess proteome identity and signaling across spatial coordinates within the stone-matrix.

Results: The average area of LMD samples for proteomic analysis was 1.64x10$^{4}$ mm$^{2}$, and these samples yielded an average of 629 distinct proteins. Dissection of broad regions of CaOx stone by LMD yielded similar proteins as found in larger specimens of pulverized CaOx stones. Proteins identified in LMD and pulverized specimens included those involved in cell injury and repair as well as important mediators of the immune system (e.g. fatty acid synthase, osteopontin-I, complement C3). More recent results show brilliant autofluorescence of decalcified CaOx stones, which will allow LMD of distinctive regions of the stone without staining.

Conclusions: Utilization and optimization of these techniques will pave the way for a deeper understanding of kidney stone formation. Future investigation of the stone-matrix proteome will provide insight into underlying events that could become therapeutic targets to prevent stone growth.

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**TH-PO564**

**Exploring Mechanisms of Protein Influence on Calcium Oxalate Kidney Stone Formation**

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Background: Calcium oxalate monohydrate (COM) crystals are the primary constituent of most kidney stones, but urine proteins in stone matrix are believed to be critical to binding crystals into stones. Recent data have shown that hundreds of proteins appear in stone matrix with no explanation for inclusion of these various proteins. We have proposed a stone formation model with protein stimulated COM aggregation based on polyanion-polycation aggregation, which is supported by finding that matrix is highly enriched in strongly anionic and strongly cationic proteins. Many proteins are likely drawn to such aggregates due to their limited solubility in water. Finding similar protein...
enrichment in both polyarginine (pR) induced aggregates of urine proteins and COM stone matrix could support this hypothesis.

**Methods:** Purified proteins (PP) were obtained from random urine samples from six healthy adults by ultradialfiltration. Protein aggregation was induced by adding pR to PP solutions at each of two concentrations; 0.25 and 0.5 µg pR/µg of PP. The resulting protein aggregation aggregates were separated by centrifugation, yielding aggregate (pRB) and supernatant fractions. Samples of each fraction and the original PP mixture were lyophilized and sent to the Proteomics Core Laboratory at Mayo Clinic for analysis.

**Results:** SDS gel electrophoresis revealed selective inclusion of urine proteins in pRB, which was also confirmed by COM matrix protein distributions by mass spectrometric analysis. Notable differences include enrichment of albumin and uromodulin in the pRB at the 0.5 µg pR addition compared to relative exclusion from COM matrix, while at 0.25 µg pR, albumin stayed in solution likely due to its weaker anionic charge, suggesting that aggregation was "overdriven" at the 0.5 µg pR addition. Many intracellular or nuclear proteins, that were prominent in COM matrix, were not observed in pRB, likely reflecting their absence in PP.

**Conclusions:** Aggregates induced by pR addition to PP samples collected a protein mixture that mimicked the protein distribution observed in COM matrix, supporting our hypothesis. The apparently discordant behavior of uromodulin may simply reflect its anionic character in this overdriven model. Future experiments will need to include observations of selective protein binding to COM crystal surfaces for comparison with these data.

**Funding:** NIDDK Support, Veterans Affairs Support

**TH-PO565**

**TRPV5 Surface Expression Contributes to Glucose-Induced Hypercalciuria**


**Background:** Lemann et al. showed that feeding normal (N) patients a glucose bolus increases fractional excretion of calcium (FECa). In addition, our group has shown that general feeding causes a significantly increased FECa of idiopathic hypercalciuric stone formers vs. N patients. These observations imply a post prandial effect in calcium handling, with clinical implications for stone formers. We sought to identify transporter protein targets that mediate the effect of glucose induced hypercalciuria.

**Methods:** 5 N women were placed on a low salt (65 mEq/d) diet for 3 days. Patients then fasted overnight, and reported to the Clinical Research Center for serial blood and urine collections for 5 hours, consuming 100 grams of glucose at 2 hours. Endogenous lithotripsy clearance was measured to calculate distal delivery. Urine was filtered, spun, and ultra centrifuged to isolate urinary exosomes from selected time points. Resulting samples were assayed by ELISA for transporter protein abundance of TRPV5. Student’s T-Tests were used to compare the last fasting period to periods of maximal change for metabolic parameters. A generalized linear model (GLM) was used to model the fractional excretion of distally delivered Ca (FECa).

**Results:** FECa rose with glucose feeding (p=0.02). Distal delivery of calcium did not differ significantly between the final fasting and any of the fed periods. FECa rose in parallel with FECa and rises significantly from the fasting period (p<0.01). TRPV5 expression decreased significantly after glucose feeding (p=0.047). A GLM (Table) with FECa as dependent, revealed TRPV5 and its known effector parathyroid hormone as significant predictors of FECa, with the overall model accounting for half the variation in FECa (R²=0.503).

**Conclusions:** We have re-created the hypercalciuric effect of glucose feeding, and have localized it to the distal nephron in a cohort of young women. The finding of reduced TRPV5 in urinary exosomes implies protein trafficking away from the apical membrane, and thus identifies TRPV5 as a key mediator of FECa in this setting.

**Funding:** NIDDK Support

**TH-PO566**

**Matting Calcium Crystals by Melamine Improves Stabilization and Prevents Dissolution**

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**Background:** Kidney stone recurrence has been shown to be as high as 50% within 10 years of stone elimination with renal stone recurrence rate among individuals who have received some form of intervention being as high as 40%. Recent studies have implicated melamine, a nitrogen-rich crystalline compound used in making plastics in nephrotoxicity. Our previous findings show that melamine induces calcium crystal formation and growth in a concentration dependent manner, however melamine’s impact on recurrence remains unclear. Herein we investigated whether melamine’s role in crystal stabilization/retenion could be contributing to the increased rates of kidney stone recurrence.

**Methods:** To examine the role of melamine, oven dried preformed CaOx and CaP crystals incubated with melamine were analyzed using both SEM/EDS microscopy; morphological and elemental composition of samples were collected and analyzed. Time dependent dissolution and stabilization studies were performed using Alizarin red pH 4.3 and 6.8 to identify CaOx, CaP respectively remaining in solution. Dissolution experiments were conducted in the presence of known crystal inhibitors.

**Results:** We show here that the presence of melamine increases crystal retention/stability even with the added presence of an inhibitor. Again ammeline, a similar triazine compound does not induce crystal growth. Similarly, our SEM/EDS analysis showed that melamine in the presence of calcium crystals acts as a nucleation site allowing for crystal deposition and ultimately crystal growth.

**Conclusions:** Together, our results highlight the mechanism utilized by melamine in calcium crystal growth as well as the pathological stabilization and retention of these crystals in the presence of known inhibitors of crystallization such as citrates, commonly used to alleviate the calcium stone conditions.

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Underline represents presenting author.

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TH-PO568
Are Bone Biopsies Needed Only in Patients with PTH Results Outside the KDIGO Target Range?
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Background: The 2017 KDIGO guideline update for chronic kidney disease - mineral bone disorder (CKD-MBD) in KD-5D recommends that parathyroid hormone (PTH) levels be maintained 2 to 9 times upper normal for the assay (150-600pg/mL). There is no information on histologic bone abnormalities within vs. outside the KDIGO target range.

Methods: We analyzed 142 bone biopsies done between 2004-2019 on CKD-5D patients performed for a variety of indications (fracture, hypercalcemia, osteoporosis, calciphylaxis and prior to parathyroidectomy (PTX)). The objective was to examine to what degree bone biopsies are helpful in management of patients with PTH levels outside or within the KDIGO target range.

Results: Mean age was 49±15 years, 46% were male and 63% white. Median (IQR) PTH was 776 (333-1348) pg/mL; there was a weak inverse relationship with age (r=-0.2, p=0.05), but no difference by race. Most of the biopsies (56%) were performed in patients with PTH levels >600 pg/mL (PTH>600 group); 33% of the biopsies were done in patients within the target KDIGO range (KDIGO target PTH group) and 11% in patients with PTH=150 pg/mL (PTH=150 group). The KDIGO target PTH group showed severe hyperparathyroid bone disease (HPTBD) with high to very high bone turnover (BTO) in 69%, mild to moderate HPTBD in 21% and low turnover bone disease (LTBD) in 10%. The PTH=150 group showed either LTBD or moderate to severe HPTBD. Patients within and below the KDIGO guideline were over twice as likely to show low bone volume on their biopsy (OR 2.95; CI 1.03-8.7). Anti-resorptive treatment was recommended in 7 patients in the KDIGO target PTH group, and anabolic therapy in 4 patients in the PTH=150 group. In the PTH=600 group, the concordance with severe HPTBD and high to very high BTO on biopsy was 92%, with moderate HPTBD in 8% and 44% subsequently underwent PTX.

Conclusions: Patients with PTH levels within the KDIGO target range show heterogeneity in their bone abnormalities with both HPTBD and LTBD, and bone loss. Contrary to current practice, these patients may be a unique risk group needing bone biopsy for targeted management of CKD-MBD. While bone biopsies are clearly also needed in patients with PTH levels below target, the procedure adds relatively little information in patients with levels above target.

TH-PO569
Magnesium Exposure Increases Fracture Risks in Patients with CKD
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Background: Bone fracture is a serious complication in CKD patients, which may lead to disability and reduced survival. In advanced CKD patients, blood magnesium (Mg) concentrations are usually above the normal range due to reduced kidney excretion of Mg. Excessive bone Mg may play a role in mineralization defects, leading to renal osteodystrophy. The present study aims to examine the relationship between Mg-containing antacid exposure and risk of incident hip fracture of CKD patients in a large, nationwide database.

Methods: Patients aged above 20 years old and diagnosed with CKD were identified from the National Health Insurance Research Database (NHIRD). From these eligible participants, study subjects in the case group were patients who were diagnosed with hip fracture, whereas the control group were selected randomly and matched to a case-patient by age, month and year of cohort entry, and Charlson comorbidity index score. The antacid usage, including Mg, aluminum, calcium, and other demographic characteristics, were analyzed.

Results: We enrolled 10,361 CKD patients with hip fracture, among which the mean age was 69.7 years old, and 54.7% was non-diabetes CKD. As compared to non-users, Mg-containing antacid users were significantly more likely to experience hip fracture (Adjusted odds ratio (OR) 1.15, 95% CI, 1.08 to 1.23; p < 0.001). Also, subgroup analysis showed that such risk exists in both non-diagnosis CKD patients and long-term dialysis patients. In contrast, aluminum or calcium containing-antacid use did not reveal such association in our cohort. Next, we examined the influence of Mg-containing antacid dosage on hip fracture risk, the adjusted OR in the first quantile (Q1), Q2, Q3 and Q4, were 1.02 (95% CI, 1.00 to 1.04; p = 0.16), 1.23 (95% CI, 1.20 to 1.26; p < 0.001), 1.33 (95% CI, 1.21 to 1.46; p < 0.001), and 1.20 (95% CI, 1.09 to 1.33; p = 0.001), respectively, showing that such risk exists regardless of the antacid dosage.

Conclusions: Our findings indicated that there is a strong link between Mg-containing antacid exposure and incident hip fracture risk in both non-dialysis CKD and dialysis patients, suggesting that Mg-containing antacid should be cautiously prescribed in the CKD population.

Funding: Government Support - Non-U.S.

TH-PO570
Increase in Fat Mass Has Protective Effect on Bone Mineral Density Loss After Initiation of Dialysis Therapy
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Background: In contrast to general population, increased fat mass (FM) was reported to have a beneficial effect on mortality risk in dialysis patients. However, the effect of FM on bone status is unclear. We investigated the association between bone loss after initiation of dialysis and changes of fat mass during 1-year of dialysis therapy.

Methods: 246 patients initiating hemodialysis (HD; n=110) or peritoneal dialysis (PD; n=141) were investigated at initiation of dialysis and after 1 year on dialysis. Measurements included: whole body dual-energy X-ray absorptiometry (DXA) for assessment of bone mineral density (BMD) and body composition; nutritional status by subjective global assessment (SGA) and handgrip strength as percentage of controls (HGS%); and, various biochemical biomarkers including insulin growth factor-1 (IGF-1).

Results: During 1-year of dialysis therapy, T- and Z-scores decreased significantly compared to baseline (both p<0.05). Whereas there was no statistically significant change in body weight during 1-year dialysis therapy, total FM, trunk FM and peripheral FM increased significantly compared to start of dialysis, while lean body mass (LBM) decreased. In multivariate linear mixed model, changes of total FM, trunk FM, peripheral FM and LBM were positively associated (all p<0.05) with changes of BMD at all sites except head after adjusting for several confounders (sex, age, height, smoking, physical activity, SGA, HGS%, parathyroid hormone and dialysis modality). Furthermore, changes of serum IGF-1 levels were positively associated with changes of total FM, trunk FM and peripheral FM (p<0.05), but not LBM.

Conclusions: An increased fat mass, central as well as peripheral, appears to have a protective effect on bone loss 1 year after initiation of dialysis. We speculate that the observed effect - which might be one contributor to the beneficial effect of FM on mortality risk in dialysis patients - could be partially explained by enhancement of IGF-1.

Funding: Commercial Support - Baxter Healthcare

TH-PO571
Association Between Normalized Protein Catabolic Rate (nPCR) and the Risk for Bone Fracture in Patients Undergoing Hemodialysis: The Q-Cohort Study
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Background: Normalized protein catabolic rate (nPCR) is used as a surrogate of daily protein intake and nutritional status in patients receiving maintenance hemodialysis (HD). It remains unknown whether nPCR affect the incidence of bone fracture in HD patients.

Methods: A total of 2,869 patients registered to the Q Cohort Study, a multicenter, prospective, observational study, were followed up for a median of 4 years. The primary outcome was bone fracture at any site. The main exposure was nPCR level at baseline. Patients were divided into four groups based on their baseline nPCR levels (Q1: <0.85; Q2: 0.85-0.95; Q3: 0.95-1.05; reference; Q4: 1.05 g/kg/day). We examined the relationship between nPCR levels and the risk for bone fracture using a Cox proportional hazards risk model.

Results: During the follow-up period, 136 patients experienced bone fracture at any site. In the multivariable analysis, the risk for bone fracture was significantly higher in the lowest (Q1) and highest (Q4) nPCR groups compared with Q3 group (hazard ratio [95% confidence intervals]: Group 1, 1.93 [1.05-3.56]; Q2, 1.27 [0.68-2.44]; Q3 1.00; reference; Q4, 2.11 [1.27-3.42]). Even when analyses were limited to those whose dialysis vintage was longer than 2 years, the association remained unchanged.

Conclusions: Our results suggest that both lower and higher nPCR values increase the risk for bone fracture in HD patients. Further studies are necessary to confirm our observation and elucidate the underlying mechanisms on the association between nPCR level and bone fracture in HD patients.
TH-PO572
Five-Year Changes in Quadriceps Muscle Properties and Risk of Hip Fractures in Older Adults with Reduced and Normal Kidney Function: Nine Years of Follow-Up of the AGES-Reykjavik Study

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Background: Chronic kidney disease (CKD) is associated with poor muscle and bone health, as well as an increased risk of fractures. However, the prediction of fractures from muscle-related parameters in older adults with impaired kidney function remains unknown. Therefore, this study aimed to determine the association of accelerated worsening of muscle properties over 5 years and incident hip fracture among older adults with reduced (estimated glomerular filtration rate ≤ 60 ml/min/1.73 m²) normal kidney function.

Methods: A total of 2311 older adults (33.1% CKD stage 3-4), aged 66-91 years at baseline from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, who had completed data on baseline serum creatinine and potential covariates, and valid thigh quantitative computed tomography (QCT) scans and isometric testing at baseline and 5-years later were studied. Fracture predictors included: cross-sectional area (CSA, cm²), attenuation (Hounsfield unit), and maximum rate of torque development (RTD, N*m/s). Analyses employed Cox-proportional hazard regression models adjusted for potential covariates.

Results: During the median follow-up of 5.7 years, 202 (8%) hip fractures occurred. Having reduced kidney function was associated with an increased risk of hip fracture (HR = 1.6, 95% CI 1.2 – 2.1) compared to having normal kidney function. Adjusted for confounders, an accelerated decline (highest tertile of decline) in quadriceps muscle CSA was associated with higher hip fracture risk (HR = 1.62, 95% CI 1.03–2.54) only in reduced kidney function older adults, while an accelerated decline in muscle attenuation and RTD were not significant predictors of hip fracture in both normal and reduced kidney function subjects.

Conclusions: Our findings support that monitoring quadriceps muscle quantity changes and implementing exercise regimens may be two essential and clinically feasible steps to prevent potential decline and fracture risk, particularly in older adults with reduced kidney function.

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TH-PO573
Trabecular Bone Score Predicts Osteoporotic Fracture in CKD Patients

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Background: Chronic kidney disease (CKD) and mineral bone disease (CKD-MBD) is a common complication of CKD and this is associated with higher morbidity and mortality. Current guidelines recommend measurement of bone mineral density (BMD) in CKD patients. However, the focus is only on bone turnover and bone density, and there is no guideline for trabecular bone score (TBS) for trabecular bone microarchitecture in CKD patients. We aim to evaluate the role of TBS in predicting osteoporotic fracture in CKD patients.

Methods: We retrospectively enrolled 125 patients with CKD between 2016 and March 2019. Lumbar spine TBS was extracted from dual-energy X-ray absorptiometry, and we categorized the TBS into three groups as lowest (TBS < 2.5), middle (2.5 ≤ TBS < 5), and highest (TBS ≥ 5). Using these tertile groups, we evaluated the relationship between TBS and osteoporotic fractures.

Results: Of 125 patients, mean age was 65.9 ± 14.2 years, 49.6% were on dialysis, and 11.2% were treated with dialysis. Patients with highest risk group by TBS were significantly older, had lower height, weight, serum 25-OH vitamin D, serum sodium level, BMD T-score (lumbar spine, femur neck and total hip) than lower risk group. TBS significantly correlated with BMD T-score (lumbar spine, femur neck and total hip), height, weight and serum creatinine level (P<0.001). Osteoporotic fracture was identified in 20 (16.0%) patients. In univariate analyses, old age, women, lower weight, TBS tertile group, lower potassium level were significantly associated with osteoporotic fracture. In multivariate analyses, only highest risk group by TBS was significantly associated with increased osteoporotic fracture rate after adjustment for demographic, comorbid, medication use, and previous fracture.

Conclusions: Lumbar spine TBS significantly correlated with BMD T-score and predicts osteoporotic fractures in patients with CKD.

TH-PO574
Usefulness of Trabecular Bone Score and Central Quantitative CT for Assessment of Bone in CKD Patients

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Background: The aims of this study are to propose the usefulness of central quantitative computed tomography (cQCT) and trabecular bone score (TBS) in bone assessment and to show the characteristics of diagnostic discordances in patients with chronic kidney disease (CKD) compared with healthy control.

Methods: This retrospective study included 135 patients (M : F, 73 : 62) with CKD that bone mineral density (BMD) was checked with both cQCT and dual energy absorptiometry (DXA) at the lumbar spine (LS) and femur neck (FN) area. Healthy control included 380 participants who visited hospital of a health check-up (M : F, 170 : 210). The discordancy refers to the diagnostic difference between two sites of DXA or between two modalities of DXA and cQCT. TBS was calculated from DXA images. The volume of abdominal aortic calcification (AAC) was measured using HU threshold (above 130HU) of CT images for cQCT. We classified bone state into three categories such as normal BMD, osteopenia and osteoporosis.

Results: The diagnosis rate for osteoporosis using T-score of FN was not significant different between two groups. Using T-score from only LS, osteoporosis was less common in CKD group compared with control (6.7% vs. 11.8%, P = 0.024). In CKD patients, the results of cQCT showed more osteopenia or osteoporosis among subjects with normal BMD in LS of DXA: osteopenia (n = 49, 31.9 %), osteoporosis (n = 12, 8.9%). Also, CKD patients had significantly lower value of TBS than control group within the same diagnostic category based on DXA (Figure 1). Furthermore, evaluating the discordancy between FN and LS in DXA, the rate of higher BMD of LS was more common than that of FN in CKD patients (85.7% vs. 14.3%, P < 0.001) compared with control group (49.4% vs. 50.6%). The volume of AAC has significant positive correlation with BMD from cQCT (r = -0.188, P = 0.031) whereas that showed negative correlation with BMD from DXA (r = 0.046, P = 0.456, Figure 2).

Conclusions: TBS and cQCT should be proper diagnostic method for the accurate assessment of bone in CKD patients because DXA may overestimate LS BMD. Probably, the AAC would contribute to increase the unexpected increase of LS BMD unlike actual bone status.

TH-PO575
A Novel Magnetic Resonance Imaging Biomarker of Tibial Bone Quality in CKD

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Background: The assessment of uremic bone disease remains a challenge, with available blood-based markers correlating poorly with gold standard histological assessment of bone. Novel quantitative imaging biomarkers with potential for standardization are needed to avoid the need for bone biopsy studies. Our objective is to initially explore the clinical associations of a novel MRI-based biomarker of bone quality of the tibia in healthy controls, CKD stage 3-5 and HD patients.

Methods: 10 healthy controls, 38 CKD stage 3 to 5 patients and 15 HD patients underwent MR with T1-weighted imaging of the right calf. Acquired images were analyzed as shown in Figure 1 and the tibial cortical-trabecular bone ratio (CTR) was calculated for each subject. CTR values were compared between groups with Student’s t-test for independent samples. Correlation analyses plotting CTR values in different groups against standard blood biomarkers were also run and standard curves interpolated as appropriate.

Results: Refer to Figures 1 and 2.

Conclusions: Worsening renal function is associated with significant reduction in directly image CTR. This may represent a promising imaging biomarker of CKD-MBD and identifies erythropoiesis as being associated with bone quality in CKD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO577

Associations Between Body Composition on Cortical Bone Quality in CKD
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Background: Obesity is considered beneficial to bone health due to well-established positive effects of mechanical loading of weight on bone formation. However, studies have reported that excessive fat mass may not protect against osteoporosis: high fat mass was associated with low total bone mineral density. Renal osteodystrophy (ROD) is associated with impaired cortical bone quality due to hyperparathyroidism, but the effects of fat and muscle mass on cortical bone in ROD are unclear. We hypothesized that body composition independently affects cortical bone and that muscle and fat mass have opposing effects on the cortex.

Methods: In 77 patients with mean +/- SD age of 59 +/-10 years and with CKD stages 3-5D, we scanned the distal radius and tibia by high-resolution peripheral quantitative CT to measure cortical density, thickness, and porosity. We measured total fat, muscle mass and percent body fat by whole body dual-energy X-ray absorptiometry. Cortical measures were correlated with age, sex, BMI, percent body fat, fat free muscle index, PTH, calcium, phosphorus and 25(OH)D. Linear regression models adjusted for age, sex and PTH determined whether muscle and fat mass were independent predictors of cortical bone quality.

Results: At the radius, higher muscle mass was associated with thicker cortices and higher percent body fat was associated with thinner cortices that had fewer and smaller pores (Table). At the tibia, higher muscle mass was associated with thicker, while higher fat content was associated with thinner cortices. In MV regression, higher muscle mass was associated with thicker cortices at the radius and tibia while higher fat mass was associated with less porous cortices at the radius. Older age was associated with more severe cortical porosity at the radius (p<0.03) and tibia (p=0.001).

Conclusions: In CKD 3-5D, muscle and fat mass independently predicted, and had opposing effects, on cortical bone quality. Further studies evaluating underlying mechanisms linking muscle and fat to cortical bone quality are needed.

Funding: NIDDK Support, Private Foundation Support

Table associations between cortical parameters and body composition adjusted for age and sex from MV linear regression

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*p<0.05

TH-PO578

Poor Correlation of Static Markers of Bone Turnover at the Iliac Crest vs. Greater Trochanter in Autopsy Specimens
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Background: Iliac crest bone biopsies and histomorphometry are the gold standard in the diagnosis of abnormalities within the Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD), yet fractures more frequently occur around the greater trochanter of the hip. We compared bone turnover markers between these 2 anatomical sites in autopsy.

Methods: We collected bone tissue samples from the ipsilateral iliac crest and greater trochanter in 10 deceased individuals undergoing autopsy at University of California, San Diego between March-August 2018. Because post-mortem osteoblasts last ~48 hours, we used osteostatic surface relative to bone surface (Oc.S/Bs), eroded surface relative to bone surface (Es.S/Bs), and osteoid volume relative to bone volume (OV/TV) as markers of bone turnover. We evaluated the correlation of these markers between the iliac crest and greater trochanter using Pearson correlations.

Results: Average age of these individuals was 57±16, 30% were women, and average time from death to autopsy was 3±2 days. We found that the Pearson correlation of Oc.S/Bs at the iliac crest vs. greater trochanter was 0.44, p<0.03. Similarly, Pearson correlation of Es.S/Bs and OV/TV were 0.30, p=0.04, and 0.003, p=0.09, respectively.

Conclusions: We found poor agreement of static measures of bone turnover between the iliac crest and greater trochanter. These data suggest that bone histomorphometric measures of the iliac crest may not provide reliable information about bone turnover at other anatomic sites.

Funding: NIDDK Support, Other NIH Support - NHILBI

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Underline represents presenting author.
TH-PO579

Hyperparathyroidism Helps to Explain the Disagreement Between Bioimpedance and Dual-Energy Absorptiometry in the Analysis of Nutritional Status

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Background: Body composition is critical in the evaluation of patients with CKD and can be obtained from multifrequency bioelectrical impedance analysis (BIA) or from the gold standard dual-energy absorptiometry (DXA). Previous studies have shown disagreements between these two methods, mainly regarding the bone mineral content (BMC). We hypothesized that secondary hyperparathyroidism, which is associated with bone loss, is the main responsible for this discrepancy.

Methods: We studied 20 pre-dialysis CKD patients (CKD) and 29 on hemodialysis (18 with severe hyperparathyroidism (HD-SHPT) and 11 already submitted to parathyroidectomy at least 1 year before our analysis (HD-PTX)). The total-body composition was determined using DXA and BIA.

Results: HD-SHPT patients tended to be younger (CKD = 52.5 ± 14.3 years; HD-SHPT = 41.6 ± 14.9 years; HD-PTX 44.9 ± 13.4 years; p = 0.06), but had lower BMC measured through DXA (CKD = 2,266 ± 565 g; HD-SHPT = 1,808 ± 522 g; HD-PTX 2,301 ± 658 g; p = 0.04). This difference was not found in BMC measured by BIA (CKD = 3,011 ± 596 g; HD-SHPT = 2,896 ± 711 g; HD-PTX 2,650 ± 467 g; p = 0.30). The highest disagreement between DXA and BIA was found in HD-SHPT group (CKD = 711 g; HD-SHPT = 915 g; HD-PTX = 688 g; p = 0.004). There was a significant correlation between the difference of BMC obtained from DXA and BIA with parathyromone (PTH; r = -0.394; p = 0.006) and alkaline phosphatase (AP; r = -0.489; p = 0.0001).

Conclusions: Our results confirm that BIA should be interpreted cautiously in patients with SHPT since higher PTH and AP lead to a greater disagreement between these methods. Moreover, the recovery of bone mass and the decrease of the disagreement after PTX support our hypothesis. BIA loss of accuracy occurs because BMC is not measured, but obtained from an algorithm derived from normal individuals, using the fat-free mass values. Therefore, BMC overestimation is associated with an underestimation of lean mass. This misinterpretation might compromise the management of the nutritional status, as well as of the bone disease, in SHPT patients.

Funding: Government Support - Non-U.S.

TH-PO580

Female Sex Enhances the Association of Secondary Hyperparathyroidism with Increased Bone Turnover Marker in Aged Patients Receiving Hemodialysis

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Background: Female patients undergoing dialysis are at higher risk of fracture than male patients, suggesting the involvement of postmenopausal osteoporosis. However, little is known about the impact of menopause on altered bone metabolism associated with secondary hyperparathyroidism in this population.

Methods: We analyzed data from a cohort of 654 patients receiving maintenance hemodialysis. We examined the hypothesis that female sex is associated with elevated levels of bone-specific alkaline phosphatase (BAP) and enhances the association between intact parathyroid hormone (iPTH) and BAP in aged hemodialysis patients.

Results: Females had significantly higher levels of BAP compared to males in patients aged ≥50 years, but not in patients aged <50 years (P for interaction by sex = 0.001). This difference observed in the aged population remained significant after adjustment of age, diabetes, dialysis vintage, body-mass index, and PTH. In the overall cohort or in either of the age subgroups, increased PTH was significantly associated with increased BAP independently of age, diabetes, dialysis vintage, and body-mass index. Among patients aged ≥50 years, the association between PTH and BAP was pronounced in females compared with males (P for interaction by sex = 0.001), but such effect modification by sex was not observed among patients aged <50 years.

Conclusions: Our results show that female sex enhances the increased bone turnover associated with secondary hyperparathyroidism in aged hemodialysis patients, highlighting the involvement of postmenopausal osteoporosis in high-turnover renal osteodystrophy.

Funding: Government Support - Non-U.S.

TH-PO581

Treatment with Lanthanum Carbonate (LC) May Reduce Bone Mineral Density (BMD): Six-Year Observation in Hemodialysis (HD) Patients

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Background: LC is one of the most powerful phosphate binders (PB) for the treatment of hyperphosphatemia in HD patients. However, whether LC can increase BMD or not is still controversial. This study was performed to examine the effects of LC on alteration of BMD in HD patients.

Methods: Subjects were divided into 2 groups and compared. Group 1: Twenty-two HD patients who were treated with non-LC PB for 6 years (14 males and 8 females; mean age, 66.7 ± 7.4 years old; mean HD duration, 11.4 ± 7.6 years). Group 2: Fourteen HD patients who were treated non-LC PB for 3 years, then were converted to receive LC for 3 years (5 males and 9 females; mean age, 62.7 ± 5.5 years old; mean HD duration, 9.7 ± 6.6 years). BMD in these patients were estimated by digital image processing (DIP).

Results: As shown in Figure, the alteration ratio in BMD for group 1 was -1.6% / year over 6 years, whereas the alteration ratio was -2.0% / year in the former 3 years, then declined to -7.9% / year in the latter 3 years in group 2. The decrease rate of BMD for group 2 at 6 years was significantly lower than that of group 1 (p < 0.05).

Conclusions: The decline of BMD was constant through 6 years in group 1; whereas the decline of BMD was accelerated after the treatment was converted from non-LC PB to LC in group 2. These observations suggest that administration of LC may reduce BMD in HD patients for some mechanisms.

Funding: Private Foundation Support

TH-PO582

Polymorphism in the Human Matrix Gla Protein Gene Is Associated with the Progression of Osteoporosis in Hemodialysis Patients

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Background: Matrix Gla protein (MGP) is an important protein related osteoporosis and vascular calcification. Single nucleotide polymorphisms (SNPs) coding regions of the MGP gene affect the transcriptional activity. We investigated the relationship between the SNPs and progression of osteoporosis and vascular calcification in patients undergoing hemodialysis (HD).

Methods: This is a prospective and single center study. Using blood samples, SNPs on the MGP gene promoter T-138C (rs1800802, direct sequencing) was investigated. Bone mineral density (femoral, DEXA, T score) and vascular calcification index (ACI, abdominal CT) were examined at start and 1-year after. Several factors related bone: fibroblast growth hormone, bone-type alkaline phosphatase (BAP), and tartrate-resistant acid phosphatase (TRACP5b), uremia: Ca, P, parathyroid hormone-intact, and 25(OH) vitamin D, and inflammation: high-sensitivity CRP, tumor necrosis factor-α, interleukin-6 were measured. The change of T score and ACI were investigated.

Results: The distribution of the T-138C genotype was TT (47.5%), CT (40.0%) and CC (12.5%). T score of all participants (n=80) at 1-year after was lower than that at start. T score for the CT and CC genotype were significantly decreased. The changes of T scores for the CC, CT, and TT genotype were shown (Figure 1a). The multiple regression analyses revealed that the change of BAP, TRACP-5b, and ACI were the independent predictors of T score change (standardized regression coefficients were -0.443, -0.276, and 0.440, respectively, R² = 0.659). ACI for each genotype were increased (Figure 1b), and there were no differences of ACI change among 3 genotypes.

Conclusions: The MGP-138C genotype may be associated with decrease in T scores in HD patients. The genotype of the MGP gene may be a genomic biomarker that is predictive of osteoporosis.
Effects of Diuretics Furosemide and Hydrochlorothiazide on CKD-MBD: A Prospective Randomized Study
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Background: Diuretics are often prescribed to patients with CKD to control fluid overload and hypertension. Diuretics may affect CKD-MBD since thiazides are associated with reduced calcitriol, reduction/maintenance of PTH levels and increased bone density while loop diuretics have the opposite effect. These effects are still debatable and not fully elucidated in patients with CKD. Objective: To evaluate the effects of furosemide (FURO) and hydrochlorothiazide (HYDRO) on CKD-MBD in patients with stage 3 CKD in a regular follow-up.

Methods: This was a RCT comparing HYDRO (25mg/day) and FURO (40mg/day) on urinary and biochemical variables including parathyroid hormone (PTH), alkaline phosphatase (AP), calcium (Ca), CTX, PINP, and PTH. After a washout period, patients were randomized to either the HYDRO or FURO group and followed for 1 year, by the same observer, blinded to randomization. Bone effects were also evaluated by Dual X-ray absorptiometry (DXA).

Results: 40 patients with a median of 62 years were included, 20 were randomized to each group, which presented similar characteristics after randomization (for age, gender, eGFR, weight, PTH, Ca, 25(OH)D,Vitamin-D, and AP). There was a reduction of urinary Ca in the HYDRO group and an increase in the FURO group (p=0.02), in addition to a tendency of a higher total serum Ca in the HYDRO group (p=0.06). There was no difference in PTH and 25(OH)D/Vitamin-D levels, albeit there was an annual percentage increase of 1.25 (OH)2VITD in the HYDRO group (12.7 ± 32%) and a reduction in the HYDRO group (-13.6 ± 21%), p=0.048. CTX, PINP, and AP increased in the FURO group and decreased in the HYDRO group (all p<0.05). No significant difference was found in the percentage change of bone density measured by DXA, only a tendency to greater loss in the proximal 1/3 of the distal radius, more pronounced in the FURO group (p=0.06).

Conclusions: Furosemide and hydrochlorothiazide had opposite effects on the CKD-MBD in a 1-year follow-up study. Furosemide seems to be associated with an increase and hydrochlorothiazide with reduced bone remodeling, a fact not evidenced by PTH change. Whether PTH would change in more advanced CKD or in a bigger sample size warrants further investigation.

TH-POS584
Associations of Bone-Related Markers and Cognitive Function in Hemodialysis Patients
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Background: Patients undergoing hemodialysis (HD) have a higher risk of cognitive impairment than the general population but limited data elucidated the biomarkers on this. We evaluate the association of bone turnover markers on cognitive function among 251 prevalent HD enrollees in a cross-sectional study.

Methods: 251 HD patients (median age=57.8, 55% men) without a prior stroke or dementia diagnosis were enrolled. Circulating levels of 8 bone markers (receptor activator of nuclear factor kappa-B ligand [RANKL], dickkopf-related protein 1 [DKK1], fibroblast growth factor 23 [FGF23], leptin, osteocalcin [OC], Osteopontin [OPN], osteoprotegerin [OPG], sclerostin [SOST]) were analyzed by a multiplex immunoassay assay (Millipore, St Charles, MO, US). The association between bone-related markers and cognitive function test (Mini-Mental State Examination [MMSE], Montreal Cognitive Assessment [MoCA], and Cognitive Abilities Screening Instrument [CASI]) were investigated in a linear regression model.

Results: Among 8 bone-related markers, RANKL was the only bone markers found associated with cognitive function (MMSE, MoCA, and CASI test) in HD patients (Figure). In stepwise multiple linear regression analysis, the positive association remained statistically significant in MoCA (β=1.14, 95% CI 0.17 to 2.11) and CASI (β=3.06, 95% CI 0.24 to 5.88). Short-term memory (β=0.52, 95% CI 0.01 to 1.02), mental manipulation (β=0.51, 95% CI 0.05 to 0.96), and abstract thinking (β=0.57, 95% CI 0.06 to 1.09) were significant domain in CASI score.

Conclusions: Serum RANKL levels were found potential associated with higher cognitive function test in HD patients. Further large scale and prospective studies are needed to confirm our findings.

Funding: Government Support - Non-U.S.
Results: ESKD patients on PPI therapy showed lower BMD at the hip, while BMTs and bone densitometry were not different from controls. PPI users, furthermore, were characterized by older age, more cardiovascular morbidity, lower serum magnesium, lower phosphate and FGF23, and higher serum dp-ucMGP levels and parameters of inflammation. PTH and vitamin B12 levels did not differ between PPI users and non-users. PPI use associated with lower BMD at the femoral neck, independent of classical (age, gender, BMI) and non-classical (vitamin K status, cardiovascular disease, inflammation) determinants.

Conclusions: PPI use in patients with ESKD independently associated with low BMD at the hip. Our data argue against an important role of PTH, vitamin B12 or dysfunctional osteoblast and osteoclast in the pathophysiology of PPI-related osteoporosis in ESKD. The link between PPI use and poor vitamin K status needs further investigation.

TH-PO586
Proton Pump Inhibitor Use and Risk of Major Fractures in Kidney Transplant Recipients
Beini, Lyu; Margaret R. Jorgensen; Karen Hansen; Arjang Djamali; Brad C. Arost. 
University of Wisconsin-Madison, MADISON, WI; University of Wisconsin, Madison, WI; University of Wisconsin School of Medicine and Public Health, Madison, WI; UW Health, Madison, WI.

Background: Fracture is a significant problem among kidney transplant recipients (KTRs). Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs in KTRs and have been associated with a higher risk of fractures in the general population. This study aimed to determine how PPIs use is associated with the incidence of major fractures in KTRs.

Methods: Using the Wisconsin Allograft Recipient Database (WisARD), we identified 155 major fracture events that occurred at least 12 months after transplantation between 2000 and 2015. Each eligible case was matched using incidence density sampling with five controls. The fracture risk was assessed by conditional logistic regression.

Results: A total of 155 cases were matched to 685 controls. A higher proportion of cases had a history of diabetes and cardiovascular disease. During the year prior to the index date, cases had lower serum albumin, higher phosphorus, higher PTH, and higher alkaline phosphatase. A higher proportion of cases ever used corticosteroid and bisphosphonate. 67.7% of cases and 51.5% of controls ever used a PPI, and 15.5% of cases and 11.3% of controls ever used an H2RA. PPI use was associated with higher incidence of major fractures in unadjusted analysis (OR=2.4, 95% CI: 1.6-3.5). The association remained similar when adjusting for demographic and transplant-related covariates (OR=2.3, 95% CI: 1.5-3.6); and further adjusting for use of corticosteroid, bisphosphonate, vitamin D and calcium supplement (OR=1.9, 95% CI: 1.2-3.1). H2RA use was not associated with higher incidence of major fractures in adjusted analysis (OR=1.0, 95% CI: 0.5-1.8). The associations between PPI use and major fractures remain similar in participants who never used a bisphosphonate in the prior year.

Conclusions: PPI use may be associated with a higher risk of major fractures among KTRs. Clinicians should carefully evaluate the risk factors for fracture, weight the risk versus benefit before prescribing PPI, and have interval assessment of continued PPI use in KTRs.

TH-PO587
Follow-Up of Bone Mineral Density Changes in De Novo Kidney Transplant Recipients Treated with Two Doses of the RANKL Inhibitor TH-PO587
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Background: Studies in women with post-menopausal osteoporosis have shown that discontinuation of treatment with denosumab leads to an increased risk of vertebral fractures because of rebound bone turnover and rapid loss of bone mineral density (BMD).

Methods: In an extended analysis of a randomized clinical trial examining the effect of denosumab on BMD we analyzed the effect of denosumab withdrawal on BMD changes. A group of 25 de novo kidney transplant recipients (KTR) which were treated for 1 year with two monthly doses of denosumab (D) on top of standard treatment (daily calcium and vitamin D) were compared to a control group of 29 KTR which received standard treatment alone. BMD changes were analyzed by repeated DXA shortly after transplantation (baseline), after 6 and 12 months (active treatment phase) and once or twice after 2 to 6.5 years (follow-up phase).

Results: Figure 1 shows the change of total lumbar BMD (g/cm²) over time by randomisation group. The BMD at the lumbar spine declined markedly (arrow) after discontinuation of treatment with denosumab (D) but increased again thereafter. Thus, the average monthly change in lumbar spine BMD from month 12 onward was only 0.1±0.8% in the denosumab group but 1.5±1.9% in the control group (p=0.021). The average monthly change in lumbar spine BMD from baseline to follow up was similar in the control and denosumab group (1.1±1.2% vs 1.5±2.4%, p=0.788). Similar results were seen at the total hip.

Conclusions: In de novo KTR treated with two doses of denosumab, we detect a marked decrease in lumbar spine and hip BMD when denosumab is discontinued. To prevent the decline in BMD after denosumab discontinuation, bisphosphonate treatment might be considered to antagonize the enhanced bone turnover.

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and alkaline phosphatase at time of plasma draw. Additionally, levels of total calcium, albumin, phosphorus, ferritin, WBC, and platelet count (PLT CT) were identified at time of plasma draw via the chart review. OPN levels were also measured in normal control patient plasma (n = 49) purchased from George King Bio-Medical, Inc., Overland Park, KS.

Conclusions: OPN levels are significantly elevated in ESRD patients. Furthermore, OPN levels were also found to be positively correlated with the bone turnover biomarkers iPTH and alkaline phosphatase. These studies suggest that hyperparathyroidism secondary to ESRD increases circulating iPTH, stimulating osteoblast and osteoclast activation.

Background: Cortical porosity is the most prominent skeletal phenotype in the setting of chronic kidney disease (CKD), and likely contributes to the increased fracture risk in CKD. Reducing cortical porosity is likely to confer improved bone mechanical properties yet lacks specific treatment options. Although strategies aimed at prevention and at preservation of existing cortical porosity would be ideal, a more likely clinical scenario would require that existing cortical porosity be reduced through pore infilling. The purpose of this work was to test the hypothesis that cortical porosity can be reversed indicating porosity infilling.

Methods: Skeletally mature male rats (n=6) with established CKD(UN-2+), a normal age-matched animals and PTH levels of ~500-2500 pg/mL were scanned with high resolution CT before and after 5 weeks of 3% calcium drinking water to suppress PTH. Using a newly developed MATLAB program that allows tracking of individual pores, the tibia, show that over 60% of the pores either completely infill or get smaller one year post enrolling into the SWI program, hospital admission rates were similar before SWI enrollment between care settings. SWI provides enhanced psychosocial care to improve quality of life, thereby reducing hemodialysis (HD) non-adherence/hospitalizations. In conventional models, patients are screened for SWI based on team identification of non-adherence or difficulty achieving outcome goals. We assessed if AI-directed SWI enrollment in VBC yielded comparable benefits to conventional clinician-based initiatives. The information contained in this document.

Results: The chart audit showed the majority of patients had GOC directives documented (80%), most within the last year (57%). GOC discussions were less commonly documented (47%); wide variability across health authorities (0-100%) existed. Documenting GOC was sparse in PROMIS (23%). Prognosis and patients’ level of understanding was frequently documented during GOC discussions (92.3% & 69%), patients’ goals and involvement of family was less frequent (53% & 46%).

Conclusions: Our pre-implementation baseline assessment informs that room for improvement existed, and that GOH discussions as per the GOC framework.

Method: We used data from patients enrolled in SWI in 2017. In VBC, a 12-month hospital admission risk model guided SWI screening. In conventional care, SWI screening was based on clinician evaluation of risk. Patients screened positive for barriers in depression, stress, and sleep were enrolled into SWI and provided tailored weekly interventions for 8 weeks. We calculated admission and HD non-adherence 3 months before and after SWI enrollment in VBC and conventional settings.

Results: Among 6425 patients (conventional n=4464, VBC n=1779) enrolled in SWI program, hospital admission rates were similar before SWI enrollment between care settings, but HD non-adherence rate was lower in VBC settings. Admission and HD non-adherence rates were consistent for 3 months after SWI enrollment in both a VBC and conventional setting (Figure 1A & B).

Conclusions: AI-directed SWI screening and enrollment in VBC applies to have consistent improvements in outcomes compared to clinician-based identification of risks in conventional settings. Use of this AI technology may help streamline efforts and allowing more time to focus on patient care.

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A Qualitative Exploration of Treatment Burden and Its Impact on Quality of Life Among CKD Patients in Qatar

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Background: Chronic kidney disease (CKD) patients typically experience comorbidities and complications resulting in complex treatments. Treatment-related burden ultimately impair adherence and quality of life (QoL). Quantifying treatment-related burden and QoL using quantitative measures may not provide an in-depth understanding of this phenomenon. We performed a study to qualitatively explore and describe treatment-related burden and its impact on QoL among CKD patients in Qatar.

Methods: One-to-one semi-structured interviews with CKD patients were conducted. An interview guide was developed based on literature review, conceptual model and discussions among the research team members. The interview questions addressed several components including facing life limitations and stressors (physical, psychological, social, financial and nutritional). The interviews were audio-recorded, transcribed verbatim, and analyzed thematically.

Results: Randomly selected twenty-four CKD patients (10 pre-dialysis and 14 hemodialysis) of diverse characteristics were interviewed. Two themes related to the factors that reduce perceived treatment burden and improve patients’ QoL emerged: (1) religion and faith in God; (2) quality of the care provided (including health care providers and facility quality and establishing family-like environment). On the other hand, five themes related to the factors that increase perceived treatment burden and worsen patients QoL emerged from the interviews: (1) medication burden (polypharmacy, side effects, medication formulation, and non-adherence); (2) lifestyle changes imposed on CKD patients; (3) challenges with international travels; (4) financial burden and; (5) empathy.

Conclusions: Qualitative Thematic analysis has yielded two factors that reduced perceived treatment burden and improved patients’ QoL: religion and faith in God and quality of the care provided. Medication burden, life style changes, challenges with international travelling, financial burden, and empathy were factors that worsen perceived treatment-related burden and HR-QoL. Our study suggests that identified factors that increase treatment-related burden should be considered when designing healthcare interventions directed toward CKD population.

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Impact of Elobixibat on Chronic Constipation in Patients on Hemodialysis Assessed Using the Patient Assessment of Constipation-Quality of Life Questionnaire

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Background: Hemodialysis patients are prone to constipation caused by fluid restriction, water removal, food restriction, complications, and drugs among other causes, and their quality of life (QoL) is adversely affected. A highly-selective inhibitor of an ileal bile acid transporter, leads to the augmentation of bile acid levels in the colon, and subsequently enhances colonic motility and secretion. Administration of elobixibat to hemodialysis patients with chronic constipation may improve QoL by a novel mechanism of action. However, the impact of elobixibat on chronic constipation in patients on hemodialysis has not been reported to date. This study aimed to evaluate the effect of elobixibat on the QoL of hemodialysis patients with chronic constipation.

Methods: This was a multicenter study. We used the Japanese version of the Patient Assessment of Constipation-Quality of Life (PAC-QOL) questionnaire. A total of 26 patients (18 males and 8 females) aged from 47–90 years who satisfied the Rome 3 diagnostic criteria for functional constipation were enrolled. These patients were additionally administered elobixibat 10 mg/day and responded to the PAC-QOL questionnaire at baseline and after 4 weeks. Bayesian statistics were used to confirm our results.

Results: The number of spontaneous bowel movements per week increased significantly from 2.5 ± 1.2 to 4.0 ± 2.0 (p <0.001). The Bristol Stool Form Scale score significantly improved from 1.8 ± 0.8 to 3.6 ± 0.7 (p <0.001). The physical discomfort score decreased significantly from 1.9 ± 0.62 to 0.99 ± 0.74 (p <0.001). The psychosocial discomfort score decreased significantly from 1.9 ± 0.95 to 0.64 ± 0.60 (<0.001). The worries/concerns and satisfaction scores also decreased significantly from 1.8 ± 0.75 to 1.28 ± 0.61 (p <0.001) and 2.80 ± 0.62 to 1.94 ± 0.79 (<0.001), respectively. The total PAC-QOL score showed a significant decrease from 1.85 ± 0.69 to 1.18 ± 0.58 (<0.001). Bayesian statistics confirmed the significance of these results.

Conclusions: Administration of elobixibat to hemodialysis patients with chronic constipation improved the scores of PAC-QOL, and improved the patients’ QoL. Elobixibat may therefore serve as a new option for the treatment of constipation in hemodialysis patients.

Dietary Patterns Associated with Kidney Function Decline and Incident CKD in the General Population: The LifeLines Cohort Study

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Background: Nutrition strongly impacts the incidence and progression of chronic kidney disease (CKD). Recently, reduced rank regression (RRR) has emerged as a method that identifies dietary patterns in an exploratory way while using prior knowledge to select a set of response variables. The aim of this study was to use RRR to identify a specific dietary pattern associated with renal function using RRR, and to evaluate its association with CKD incidence.

Methods: We included 78,350 participants from the LifeLines population-based cohort in the Netherlands. All participants were in CKD (defined as eGFR<60 mL/min/1.73 m²) at baseline and completed a second visit four years later. Dietary intake was ascertained with a 110-item food frequency questionnaire. The dietary pattern, stratified by sex, was constructed cross-sectionally by RRR, with eGFR as a response variable. Multivariable logistic regression analysis was used to study the association between dietary patterns score and CKD incidence or an eGFR decline of ≥20%, adjusted for potential confounders.

Results: Among women, the eGFR-associated dietary pattern was characterized by high intake of eggs, low-fat and high-fat cheese, and legumes and low consumption of sweetened dairy drinks, desserts, cake and cookies, sweet sandwich toppings, white meat, and other refined carbohydrates. In men, the eGFR-associated dietary pattern was characterized by moderate intakes of dairy products, meat, fish, and vegetables, along with high consumption of refined carbohydrates and low consumption of fruits and legumes.

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and commercially prepared dishes. The male dietary pattern was characterized by high consumption of high-fat and low-fat cheese, bread, roll, milk, fruits, tea, coffee, beer, and low consumption of white and red meat. After a mean follow-up of 3.9 years, 7,612 participants experienced >20% eGFR decline and 2,072 participants developed CKD. The eGFR-based diet was associated with a lower risk of eGFR decline (OR 4 th vs 1st quartile: women: 0.84 [95% CI 0.76-0.92]; men: 0.74 [0.65-0.84]) and of incident CKD (women: 0.60 [0.50-0.73]; men: 0.52 [0.41-0.66]).

**Conclusions:** The results provide support for potential dietary interventions to prevent renal function decline and CKD. RRR may be a useful tool for identifying dietary patterns that affect renal function and CKD development.

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**TH-PO598**

The Impact of Eating During Hemodialysis Treatment on Nutritional Measures in In-Center Hemodialysis Patients

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**Background:** Poor nutritional status is common among patients receiving hemodialysis (HD) treatment. Providing nutrition during HD treatment may improve nutritional status and outcomes, but remains controversial. This has led to the adoption of different in-center dialysis unit nutrition policies. Therefore, we sought to examine the relationship between policies on food intake during treatment and nutrition-related measures.

**Methods:** We analyzed data from Phase 5 of the Dialysis Outcomes and Practice Patterns Study (DOPPS) to look at the relationship between baseline nutrition-related measures (serum levels of albumin, phosphorus, potassium, and body mass index [BMI]) and clinic policy related to eating during HD (not allowed), patients may eat food provided by clinic, patients may bring food from home, or patients may eat food provided by clinic and/or brought from home). We limited our analysis to only countries with clinics eating policies during HD, were established by RANCOVA with individual differences determined by least square difference post-hoc. Additionally, the odds of having an albumin >3.4 g/dl were determined by multivariable logistic regression.

**Results:** Among 3,358 HD patients (61% male, age 66±15 years, average 4x6 years) included in the analysis, serum albumin and potassium were highest and phosphorus the lowest in patients dialyzing at clinics that provided food during HD (p<0.05). Body mass index (BMI) was highest among patients dialyzing at clinics that allowed patients to bring their own food. Compared to patients who dialyzed at clinics where they were not allowed to eat food during HD, the odds of having a BMI below 34.4 kg/m2 was higher in those dialyzing at clinics where food was provided by the clinic (Adjusted OR=2.0, 95% CI 1.6-2.6) and those with food provided by the clinic and also allowed to bring their own food (Adjusted OR=1.6, 95% CI 1.3 – 2.9).

**Conclusions:** Patients who dialyze at clinics that provide food during HD treatment exhibit higher serum albumin, higher potassium, and lower phosphorus levels than patients who dialyzed at other clinics. Whether in-center nutrition and eating policies contribute to differences in other clinical outcomes including quality of life, hospitalizations, and mortality warrants additional studies.

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**TH-PO599**

**Improved Diet, Sleep, and Strength Among CKD Patients Following 6-week App Intervention with Personalized Mentoring**

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**Background:** CKD is a long-term condition which affects approximately 14% of the general population in the United States. CKD influences circulatory dysfunction, anemia, malnourishment, strength degeneration, muscle integrity, glucose imbalance, and decreased bone health. Additionally, up to one third of CKD patients have depression. For CKD patients, adherence to the CKD diet is critical for maintaining quality of life, yet few studies have focused on methods to improve and maintain patients’ adherence.

**Methods:** In our trial 6-week “Remote Chronic Disease Management” Programme, nine (9) patients at various stages of CKD consented to participate and were provided with a smartphone app called RenalMate. The app allows for daily monitoring of self-reported data (height, body mass index [BMI], sleep, Stress and Activity Level), as well as a remote connection to fitness, dietician, and health mentors. Importantly, the social community and mentoring team provided accountability for the self-reported data tracking and diet/exercise adherence. In addition to daily feedback from coaches and other patients, participants were given weekly progress reports during individualized teleconference sessions with their coach.

**Results:** By the end of the 6-week program, 78% of participants lost weight, and of those 14% lost 17-20 pounds and 72% lost 3-6 pounds. 89% of participants improved their strength during the programme. 71% of participants reduced their stress level from high versus medium/low. 89% either increased their nightly hours of sleep or maintained a healthy 7-8 hours. These improvements were also seen by the participants. 89% felt more restful with higher levels of energy by the end of the programme. 72% felt they improved their diet overall. And most importantly, 100% said they would recommend the program to a friend.

**Conclusions:** This combination of self-reporting, comprehensiveness of data tracking, as well as the use of a specialized social app and weekly teleconferences with coaches represents a novel and scalable approach to CKD management. Participants improved in both quantitative and qualitative measures of health. Future studies should expand on the role of education and the long-term impact of such programmes, involving wider multi-disciplinary teams (MDT) for example, healthcare scientists to provide CKD patients education surrounding laboratory parameters.

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**TH-PO600**

**Development of an International Standard Set of Nutritional Priorities for Patients with Non-Dialysis CKD**

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**Background:** Patients with non-dialysis chronic kidney disease (non-dialysis CKD) are a large and heterogeneous group with different dietary needs and nutritional challenges. This project aims to identify areas of intervention and improve nutrition in patients with non-dialysis CKD based on shared priorities of stakeholders.

**Methods:** This Delphi consensus project involved 4 phases: systematic review to identify factors that influence dietary requirements and adverse disease markers in non-dialysis CKD; review round of topics by 10 expert nephrologists in non-dialysis CKD; second review round by 105 stakeholders (dietitians, nurses, patients) to refine the international delphi survey to be distributed worldwide (Dec 2018 – May 2019) to promote communication, dissemination of insights, and development of consensus on key domains of nutrition. The survey included 60 topics grouped in 5 categories, 11 sub-categories. Participants were invited to rate topics priority (importance) by 9-point Likert scale. Consensus for topic prioritization was defined as the combination of median 27 and ±70% participants scoring 7-9 and ≤15% scoring 1-3 on the Likert.

**Results:** 1,224 subjects completed the survey; 43% were physicians, 25% dietitians, 16% patients, 8% nutritionists and 8% nurses; 62% were female and 87% from Europe. 30 topics reached priority consensus by health-care providers; patients gave priority to only 20 topics. Top stakeholders agreed with prioritizing topics supporting patients to choose and personalize of diet; patients gave low priority to common issues of research interest, low-protein, low-sodium, renal progression (<65%); energy, quality proteins, malnutrition (<55%), or no priority, very-low, vegetarian, DASH, Mediterranean diets (<25%).

**Conclusions:** This project emphasizes agreements and disagreements among stakeholders in what matter the most regarding nutritional care management of patients with non-dialysis CKD. These differences should be considered in research and clinical practice; establishing targets to prioritize will enhance the relevance and impact of research and patient care.

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**TH-PO601**

**Clinical Significance of Nutritional Predictors in Prevalent Hemodialysis Patients**

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**Background:** Nutrition has been consistently important in end stage renal disease patients. However, it is difficult to obtain adequate nutritional status while avoiding fluid overload, hyperphosphatemia and hyperkalemia in hemodialysis patients. We studied the clinical significance of serum albumin and other nutritional markers in maintenance hemodialysis patients.

**Methods:** We retrospectively enrolled patients who received hemodialysis for more than 3 months from 2016 to 2019, excluding patients who died within 30 days. We evaluated the factors associated with mortality among incident and prevalent patients with multiple acute cardiovascular events (MACE). In addition, we investigated factors related with sarcopenia defined as skeletal muscle mass index (SMM) ≤10.75 kg/m² (men) or ≤7.5 mg/m² (women) by using a BIA machine (InBody S10; Biospace, Korea).

**Results:** Of 284 patients, 63.7% were men, mean age was 64.2 ± 12.4 years, mean body mass index (BMI) was 23.7 ± 6.9 kg/m², and the most common underlying disease was hypertension and diabetes. During a median follow up of 16.7 months, 13.7% (n=39) patients experienced a MACE, 12.3% (n=35) patients died. In multivariate Cox analyses, lower BMI, lower CRP level and history of CVD were significantly related to all-cause mortality even after adjustment for covariates. SMM had a significant positive correlation with BMI, serum phosphorus, BUN, creatinine and uric acid level. SMM was not predicted all-cause mortality in total group, but was significantly predicted all-cause mortality among diabetes subgroups. In the logistic regression analyses, older, lower BMI, diabetes and male sex were significantly associated with sarcopenia. In addition, higher serum calcium, phosphorus level, history of CVD, cerebrovascular accident (CVA) were significantly associated with MACE.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

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Conclusions: In prevalent hemodialysis patients, nutrition, inflammation and protein energy wasting (PEW) are the major risk factors for all-cause mortality. SMII might be an important predictor for all-cause mortality in diabetic patients. In patients with history of CVD or CVA, management of serum calcium and phosphorus is particularly important in aspect of MACE.

TH-PO602
Association of Inflammation with Sarcopenia and Sarcopenia in Hemodialysis Patients: A Pilot Observational Study
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Background: Chronic inflammation is directly related to an increased cardiovascular mortality in hemodialysis patients. Low muscle strength (dynamypia) and low muscle strength in addition to decreased skeletal muscle mass (sarcopenia) often coexist with obesity in chronic hemodialysis patients. The main aim was to study the association of inflammation with sarcopenic obesity (SO) and dynapenic obesity (DO) in chronic hemodialysis patients.

Methods: High sensitivity C-reactive protein (hs CRP) was estimated using nephelometry. hsCRP >10 mg/L was considered positive for inflammation. Body Composition Analysis through bioelectrical impedance was utilized to assess body fat and lean tissue index (LTI). Muscle strength was determined using handgrip strength (HGS) analysis. Sarcopenia was defined by HGS <26 kg for men and < 18 kg for women. Sarcopenia was defined as LTI <10.7 kg/m² in men and <6.7 kg/m² in women. Obesity was defined as percent body fat >25% in men and >35% in women. Prevalence of inflammation in patients with DO and SO was reported.

Results: Of 81 patients, 49 were males. Their average age was 56.9a 16.1 years and average dialysis vintage was 2.9±2.4 years. All patients were on thrice a week hemodialysis. The etiology of kidney disease was diabetic kidney disease in 49%, hypertension in 31%, chronic interstitial disease in 7%, chronic glomerulonephritis in 4% and other in 9% patients. Mean hsCRP of was 12.4±11.9 mg/L. The overall prevalence of DO was 20.9% and SO was 16%. The prevalence of inflammation in patients with DO was 52.9% and without DO was 47.0%. The prevalence of inflammation in patients with SO was 46.1% and without SO was 37.1%. The prevalence of inflammation in diabetic patients with DO was 66.5% and that in diabetic patients with SO was 59.8%.

Conclusions: The prevalence of inflammation was higher in patients with both DO as well as SO, especially in diabetic population. Further long term studies are needed to assess the relationship between DO, SO and inflammation and their outcomes in hemodialysis population.

TH-PO603
Simultaneous Use of Bioimpedance Vectors Analysis (BIVA) for Dry Weight Adjustment and Oral Nutritional Supplementation in Hemodialysis Patients
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Background: Protein energy wasting and overhydration are two complications present in renal patients that must be treated simultaneously. The objective of this study was to compare the effectiveness of the simultaneous use of BIVA and oral nutritional supplementation against the exclusive use of BIVA on the nutritional status and body composition of patients on hemodialysis.

Methods: Patients were randomized in two groups for 6 months intervention. In both groups, body weight was adjusted by BIVA as necessary to reach euhydration. Group A (n=17) an individualized diet plus one can of nutritional supplement was given daily to patients. Group B (n=15) only the specific diet was provided. Nutritional status was evaluated with the Malnutrition Inflammation Score (MIS) and handgrip strength was measured at the beginning and the end of the study. Results: Mean age was 55.76 ± 17.6 years for group A and 53.71 ± 11.8 for group B, dialysis vintage 24.47 ± 5.08 months and 18.88 ± 11.04 respectively. No significant baseline differences between groups were found and any patient was well nourished. After intervention, nutritional status improved significantly in group A, from 47 to 83% for mild undernutrition and from 53 to 17% for moderate undernutrition (p<0.05), while in group B, nutritional status worsened from 53 to 27% for mild undernutrition and from 47 to 73% for moderate undernutrition (p<0.05). Handgrip strength was increased in 58% of patients in group A and 21% in group B (p <0.03). Dry weight was achieved in 100% of patients for moderate undernutrition (p<0.05). Handgrip strength was increased in 58% of patients in group A and 21% in group B (p <0.03). Dry weight was achieved in 100% of patients for moderate undernutrition (p<0.05). Handgrip strength was increased in 58% of patients in group A and 21% in group B (p <0.03). Dry weight was achieved in 100% of patients for moderate undernutrition (p<0.05). Handgrip strength was increased in 58% of patients in group A and 21% in group B (p <0.03). Dry weight was achieved in 100% of patients for moderate undernutrition (p<0.05). Handgrip strength was increased in 58% of patients in group A and 21% in group B (p <0.03).

Conclusions: The simultaneous use of oral nutritional supplementation and bioelectrical impedance vectors analysis, to determine dry weight, improved nutritional status and body composition in patients undergoing hemodialysis.

TH-PO604
A Simplified Protein-Energy Wasting Scoring System for Survival Prediction in Korean Incident Hemodialysis Patients
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Background: Even though protein-energy wasting (PEW) is a crucial risk factor for survival in end-stage renal disease (ESRD) patients, a convenient and reliable assessment method to determine PEW in ESRD patients has not been established. However, a recent study proposed a simplified PEW scoring system based on the PEW diagnostic criteria, which was predictive for European ESRD patients’ survival. This study aimed to validate the prognostic significance of the simplified PEW score in Korean incident hemodialysis patients.

Methods: Data were retrieved from a prospective cohort study from the Clinical Research Center for ESRD in Korea. The simplified PEW scoring system is graded from 0 (the worst) to 4 (the best), which consists of four components: serum albumin, body mass index, serum creatinine/body surface area, and normalized protein nitrogen appearance. Since the number of patients in the PEW score 0 group was too small (n=14), the PEW score 0 and 1 groups were combined into a same group. The survivals of the four groups (PEW score 0~1, 2, 3, and 4) were compared by Kaplan-Meier plot, and multiple Cox regression analysis was performed to identify the association between the PEW score and patients’ survival.

Results: A total number of 430 patients were included in this study. The numbers of patients in the four score groups were 77 (score 0~1), 158 (score 2), 145 (score 3), and 50 patients (score 4). The mean age was 61.1 years and male was 59.8%. Kaplan-Meier plot revealed that the lowest PEW score group had the worst cumulative survival or there was a significant difference in patient survival across the groups (log-rank test, P<0.001; 2-year mortality rates of 15.6% in the score 0~1 group, 8.2% in the score 2 group, 1.4% in the score 3 group, and 2.0% in the score 4 group. In multiple Cox regression analysis, moreover, PEW score was a significantly independent factor for mortality even after adjusting for confounding variables (PEW score 0~1 as a reference; PEW score 2, hazard ratio [HR] 0.450, 95% confidence interval [CI] 0.262-0.772, P<0.004; PEW score 3, HR 0.165, 95% CI 0.070-0.385; P=0.001; and PEW score 4, HR 0.101, 95% CI 0.013-0.760, P=0.026).

Conclusions: A simplified PEW scoring system is a practical and reliable method for predicting mortality in Korean incident hemodialysis patients.

TH-PO605
Malnutrition and Protein Energy Wasting in Pediatric CKD
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Background: Malnutrition (malnut) predisposes CKD patients (pts) to poor growth through hormonal & metabolic derangements, decreased appetite & inflammation. Protein energy wasting (PEW) describes a state of decreased protein stores, associated with impaired growth and poor outcomes in pts. Few studies investigate the relationship between malnut, PEW & CKD progression in peds pts.

Methods: Retrospective chart review of pts 0 – 25 yrs with CKD stages 1-5 seen in peds renal clinic from 2013 - 2018. Diagnosis of malnut based on the Consensus Statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition. eGFR calculated by revised Schwartz equation. PEW scores (PEWS) assigned based on pts criteria (Abraham A, et al, 2014). Minimal PEW definition requires any positive test in 2 of PEWS categories. Linear regression was performed to determine effect of z-score for height (HZ), weight (WZ), BMI (BMZ), weight-for-length (WLZ) or PEWS on eGFR. Mixed-effects models performed to determine effect of diagnosis of malnut and PEW on change in eGFR. P < 0.05 was significant.

Results: Of 135 pts, 68 (50.3%) were classified as malnut & 50 (37%) met minimal PEW criteria during a median 1.8yrs (0.9-3.5) follow-up. Majority diagnosed w/ malnut were male (65%), white (36%), w/ a median age of 14.2yrs [7.4-17.6], w/ CKD Stage 3 at time of 1st visit (50%) and a congenital anomaly of kidney and urinary tract diagnosis (46%). Majority were diagnosed with malnut based on Decline in Weight/Height Z-score (38%) using 2 data points as indicators. Linear regression showed no significant effect of
Background: Chronic kidney disease (CKD) is associated with reduction in skeletal muscle quality from the interplay of inflammation and malnutrition, resulting in reduced exercise capacity. Muscle quality can be assessed by texture analysis of images acquired by 1H-Magnetic Resonance Imaging (MRI). The study objective is to compare muscle quality using MRI images between healthy controls, CKD, hemodialysis (HD) and peritoneal dialysis patients. Mid-slice was used to delineate the gastrocnemius and soleus muscle. The regions of interest were muscles at the level of the L3: psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques and rectus abdominus. Skeletal muscle index (SKMI) and intramuscular adipose tissue index (IMATI) were calculated as cross-sectional areas, corrected for height.

Methods: A randomized, placebo-controlled trial, 31 CAPD patients (age 57.0±15.2years in pioglitazone group and 60.5±15.4years in placebo group) were randomly allocated into two groups: pioglitazone (15 mg/day) and placebo for 16 weeks. Sarcopenia biomarkers include serum myostatin level and body composition by Dual-energy X-ray absorptiometry (DXA) before and after the intervention.

Results: At baseline, serum myostatin level was 6.40±3.14 ng/mL in pioglitazone group and 5.12±3.53 ng/mL in placebo group and relative skeletal muscle index was 7.14±1.18 kg/m² in pioglitazone group and 6.52±1.33 kg/m² in placebo group. Serum myostatin level significantly decreased in the pioglitazone group compared to the placebo group at 8 weeks (-1.32 (95%CI -1.98 to -0.66) vs. 0.56 (95%CI -0.48 to 1.61) ng/mL; P=0.003) and at 16 weeks (-2.32 (95% CI -3.11 to -1.53) vs. 0.10 (95% CI -0.71 to 0.92) ng/mL; P=0.001). However, relative skeletal muscle index, fat mass and body weight did not change significantly in the both groups. No significant changes were observed in blood pressure, fasting plasma glucose, hemoglobinA1C, and serum creatinine concentrations compared with baseline in either group. No serious side-effects including hypoglycemia and heart failure was detected.

Conclusions: The study indicates that 16-weeks of pioglitazone treatment reduced the serum sarcopenia biomarkers but showed no effect on the muscle mass in no diabetic CAPD patients.

TH-PO0607

Muscle Quality Assessment by Texture Analysis on 1H-Magnetic Resonance Imaging in CKD Patients

Lisa Hu1, Fabio R. Salerno,1 Alireza Akbari,2 Christopher W. McIntyre.2

Background: 1H-Magnetic Resonance Imaging (MRI) is a powerful tool to assess muscle quality, but its ability to provide muscle quality data in the critically ill is unclear. The purpose of this study was to assess muscle quality using MR images between healthy controls, CKD, hemodialysis (HD) and peritoneal dialysis (PD) patients. We hypothesize that progressive CKD and dialysis therapy are associated with muscle quality changes that can be detected by texture analysis.

Methods: 1H-T1-weighted images of the calf were acquired on control, CKD, HD, and PD patients. Mid-slice was used to delineate the gastrocnemius and soleus muscles. Heterogeneity of the muscle was quantified by the standard deviation (SD) within the regions. One-way ANOVA was used to assess significance between groups. Pearson correlation analysis was completed between estimated glomerular filtration rate (eGFR) and SD of the muscles at CKD stages 1-5 (HD and PD cohort excluded).

Results: Refer to Figures 1 and 2.

Conclusions: Homogeneous characteristics seen in CKD cohort may be indicative of muscle wasting and fibrosis. MRI based quality assessment may provide potential non-invasive evaluation of the uremic state on skeletal muscle structure and function.
Grip Strength at Dialysis Initiation Predicts Hospitalization over Time

TH-PO610
Hypercatabolism, Body Composition, and Physical Function in Advanced CKD
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Background: It has been hypothesized that impaired physical function in CKD is the result of a hypercatabolic state leading to protein and energy wasting. We tested whether basal metabolic rate (BMR) is higher and accounts for impaired physical function in more advanced CKD.

Methods: We examined baseline data in 99 participants of an ongoing physical activity intervention trial (NCT 02970123) expected to be completed in Sep, 2019. Results will be updated with follow-up data for ASN presentation. Standardized protocols were used to measure BMR with indirect calorimetry (MedGem, Microlife Medical, Inc., Golden, CO) and body composition including fat free mass (FFM) and body fat% (BF%) with bioelectrical impedance analysis (Quantum XRL, Systems, Clinton Township, MI) and physical function with 6-minutes walk distance (6-min WD).

Results: Demographic and clinical data by CKD stages are summarized in Table. Median (IQR) for BMR was 16.3 (14.8, 18.2) kcal/kg/day. Mean values for FFM, BF% and 6-min WD in the entire cohort were 61 ± 15 kg, 31 ± 10%, and 624 ± 71 m respectively. In separate multivariable linear regression models (adjusted for age, gender, race, ethnicity and diabetes), more advanced CKD was not associated with BMR or BF%, had nonsignificant, negative association with FFM and significant, negative association with 6-min WD (Table). The association of advanced CKD with lower 6-min WD persisted with further adjustment for BMR, FFM and %BF (Table).

Conclusions: Impaired physical function in CKD was not explained by BMR in the current study. Further studies are needed to test whether lack of anabolism rather than hypercatabolism plays a significant role in wasting and frailty in CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

TH-PO610
Grip Strength at Dialysis Initiation Predicts Hospitalization over Time

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Background: It has been hypothesized that impaired physical function in CKD is the result of a hypercatabolic state leading to protein and energy wasting. We tested whether basal metabolic rate (BMR) is higher and accounts for impaired physical function in more advanced CKD.

Methods: We examined baseline data in 99 participants of an ongoing physical activity intervention trial (NCT 02970123) expected to be completed in Sep, 2019. Results will be updated with follow-up data for ASN presentation. Standardized protocols were used to measure BMR with indirect calorimetry (MedGem, Microlife Medical, Inc., Golden, CO) and body composition including fat free mass (FFM) and body fat% (BF%) with bioelectrical impedance analysis (Quantum XRL, Systems, Clinton Township, MI) and physical function with 6-minutes walk distance (6-min WD).

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Conclusions: Impaired physical function in CKD was not explained by BMR in the current study. Further studies are needed to test whether lack of anabolism rather than hypercatabolism plays a significant role in wasting and frailty in CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

*Adjusted for age, gender, race, ethnicity and diabetes
**Adjusted for above plus BMR, FFM, BF% (Table)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Uremic Dysbiosis Causes Sarcopenic Phenotype Through Reduction in Muscle Mitochondria and Attenuation of Stimulated Muscle Protein Synthesis

Kiyotaka Uchihama, Shu Wakino, Takaya Tajima, Tomoaki Itoh, Yoichi Oshima, Junichiro Irie, Hiroshi Itoh. Keio University, School of Medicine, Tokyo, Japan.

Background: Chronic kidney disease (CKD) leads to clinically relevant sarcopenia, defined as reduced exercise endurance and muscle atrophy, which are novel risk factors associated with morbidity and mortality in CKD patients. However, the pathophysiology of uremic sarcopenia remains incompletely defined. Recent reports have shown alterations in the gut microbiota to be associated with the etiology of CKD. Using germ-free (GF) mice, we aimed to determine whether and how uremic dysbiosis causes uremic sarcopenia.

Methods: CKD was induced in specific-pathogen-free mice via an adenine-containing diet; control mice were fed a normal diet. Fecal microbiota transplantation (FMT) into GF mice was performed by oral gavage using cecal samples obtained from either control mice (control-FMT mice) or CKD mice (CKD-FMT mice). Vehicle mice were gavaged with sterile phosphate-buffered saline. Sarcopenic phenotype was evaluated after 2 weeks.

Results: Compared with control mice, CKD mice had sarcopenic phenotypes, including significant decrease in running distance, handgrip strength, and skeletal muscle mass. Sarcopenic phenotypes were reproduced in CKD-FMT mice as compared with control-FMT mice and were associated with reduced muscle mitochondria and atrophy in insulin-stimulated phosphorylation of S6 kinase beta-1, indicating reduced muscle protein synthesis. In addition, serum concentrations of indoxyl sulfate, phenyl sulfate, and hippuric acid among uremic solutes as well as fecal concentrations of indole and phenol amine metabolites were increased in CKD mice as compared with the concentrations in control-FMT mice. Gut microbiome analysis using 16S rRNA genes sequences revealed decreases in Lactobacillus and Clostridium cluster IV, and Alistipes in CKD mice as compared with those in control mice. All of these alterations in gut microbiome remained in CKD-FMT mice as compared with those in control-FMT mice.

Conclusions: Uremic dysbiosis can directly contribute to sarcopenic phenotypes even in the absence of the host CKD condition. Increased concentrations of microbiota-derived uremic toxins may impair muscle mitochondrial function, thereby mediating the effects of uremic dysbiosis.

TH-PO614

A Pilot Study on Association of Arterial Stiffness with Dynapenia and Sarcopenia in Hemodialysis Patients

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Background: Low muscle strength (dynapenia) and low muscle strength plus low skeletal muscle mass (sarcopenia) are often found to be coexisting with obesity in chronic hemodialysis patients. As arterial stiffness is directly related to cardiovascular mortality, we instead of studying its association with dynapenic obesity (DO) for evaluating it was of interest to study its association with dynapenic obesity (DO), sarcopenic obesity (SO) in this population.

Methods: Arterial stiffness was estimated from brachial cuff-based oscillometric device (Mobil-O-Graph). Body Composition Analysis through Bioelectrical Impedance was utilized to assess body fat and lean tissue index (LTI). Muscle strength was determined using handgrip strength (HGS) analysis. Dynapenia was defined by HGS <26 kg for men and < 18 kg for women. Sarcopenia was defined as LTI <10.7 kg/m² in men and < 7.9 kg/m² in women. Body composition was measured as percent body fat > 25% in men and > 35% in women.

Results: Of 206 patients, 124 were males. Their average age was 55.3 ± 15.4 years and average body fat index was 3.8 ± 2.7 years. All patients were on thrice a week hemodialysis. Of 206 patients, 44% were diabetic, 58% were hypertensive and 29% had ischemic heart disease. The prevalence of dynapenia was 87.5% and that of sarcopenia was 42.7%. Prevalence of DO and SO was 19.4% and 14.5% respectively. The prevalence of arterial stiffness in patients with DO was 72.5% and that in patients with SO was 70%.

Conclusions: Prevalence of arterial stiffness is high in patients with DO and SO. Further studies are needed to evaluate interventions for reducing dynapenic and sarcopenic obesity and their impact on reduction in arterial stiffness inorder to reduce cardiovascular mortality.

TH-PO615

Lower Kidney Function Is Associated with Impaired Leg Skeletal Muscle Mitochondrial Oxidative Capacity

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Background: Maintaining functional independence is the top health priority reported by patients living with CKD. Impaired mitochondrial function is hypothesized to be a key mechanism underlying mobility limitation in CKD.

Methods: The Muscle Mitochondrial ENergetics and Dysfunction (MEND) study was designed to evaluate determinants and consequences of skeletal muscle mitochondrial functioning in CKD. We measured mitochondrial oxidative capacity of the tibialis anterior leg muscle (ATPmax) during exercise recovery using 31P MRS in 57 participants (38 CKD and 19 controls) from a clinic-based population. We measured mitochondrial oxidative capacity of the tibialis anterior leg muscle (ATPmax) during exercise recovery using 31P MRS in 57 participants (38 CKD and 19 controls). We determined associations of GFPrecysc with ATPmax by using multivariable linear regression adjusting for age, sex, waist/hip ratio, and diabetes.

Results: Participants were 62 ±14years old with 32% female and 32% prevalence of diabetes (33% in controls). GFPrecysc in the CKD group was 38 ±19ml/min compared to 0.5 ±1.6 ml/min controls. Mean ATPmax was 0.6 ±0.3 in controls. Mean ATPmax in CKD was 0.8 ±0.16 in controls. After adjustment, CKD was associated with 0.18mM/sec lower (95%CI:0.27, 0.09; P<0.001) ATPmax. Diabetes was associated with 0.12mM/sec lower (95%CI 0.23, 0.02; P=0.02) ATPmax compared non-diabetes after adjustment. In continuous analysis, each 10ml/min/1.73m²lower of GFPrecysc was associated with 0.03mM/sec lower ATPmax (95% CI 0.4, 0.01; P<0.001) (Figure). Among those with GFPrecysc<0.6, correlates with ATPmax included bicarbonate level (r=0.39, p=0.02), C-reactive protein (r=0.31, P=0.07), albuminuria (r=0.33, P=0.05), and phosphorus (r=0.21, p=0.02).

Conclusions: Lower kidney function and diabetes are associated with direct in vivo measurements of leg muscle mitochondrial oxidative capacity.
Indoxyl Sulfate-Induced Apoptosis in C2C12 Cells

Seok hui Kang,1 Youn su Lee,2 Jun-Young Do,1 Yeungnam University Hospital, Daegu, Republic of Korea;1 Yeungnam University Medical Center, Daegu, Republic of Korea.

Background: Indoxyl sulfate is a well-known urogenic toxin and associated with skeletal muscle atrophy in chronic kidney disease. However, there are few studies regarding precise molecular mechanism. The aim of the study was to identify indoxyl sulfate-induced apoptosis as a molecular mechanism.

Methods: Mouse C2C12 myoblast were purchased and cultured in Dulbecco’s modified eagle medium. After cell adhesion, cultured medium was changed containing with urogenic toxins and cultured. Reactive oxygen species (ROS) production and cell apoptosis were assayed. Flow cytometry using Annexin V and PI showed that proportion of double positive cell increased as dose of indoxyl sulfate increased.

Results: Indoxyl sulfate increased as dose of indoxyl sulfate increased. Apoptosis was increased as dose of indoxyl sulfate increased. In addition, tunnel stained cells were also performed.

Conclusions: Our results demonstrate that indoxyl sulfate is associated with apoptosis of myoblast through ROS production.

β2-Receptor Agonism Averts Indoxyl Sulfate-Induced Sarcopenic Phenotype of Mouse Skeletal C2C12 Myotube

Takaaki Higashihara, Hiroshi Nishi, Koji Takemura, Masaoi Nagaku. The University of Tokyo School of Medicine, Tokyo, Japan.

Background: Sarcopenia is a condition characterized by loss of skeletal muscle mass and function. In patients with chronic kidney disease, sarcopenia is recently attracting attention because of its strong association with increased morbidity and mortality. However, the direct association with uremia and sarcopenia is not fully elucidated yet. The aim of this research was to investigate the mechanism and therapeutic intervention for sarcopenia induced by uremia.

Methods: The mouse myogenic cell line C2C12 (ATCC®CRL-1772) was treated with indoxyl sulfate (IS) and evaluated as to cell viability (MTS assay), cytotoxicity (LDH assay, Trypan blue), cell morphology (measure the length and diameter of C2C12 myotubes), the expression of muscle atrophy related genes (quantitative-PCR) and protein levels of myosin heavy chain (MyH) and fast/slow twitch muscle fibers (Western blot). Moreover, clenbuterol and salbutamol as β2-stimulants were assessed for effect on the IS induced myocyte phenotypic changes.

Results: IS blunted C2C12 myoblast cell proliferation and reduced myotube length and diameter. IS treatment up-regulated mRNA expression of muscle atrophy related genes (MuRF-1 and Atrogin-1), and reduced protein levels of MyH and fast twitch muscle fiber, but not slow twitch muscle fiber. On the other hand, clenbuterol and salbutamol partially attenuated IS-induced upregulation of MuRF-1 and Atrogin-1, and prevented the degradation of MuRF-1 and fast twitch muscle fibers.

Conclusions: β2-agonist has a therapeutic potential for preventing IS induced muscle atrophy, predominantly fast twitch muscle fiber atrophy.

Mitochondrial Dysfunction/NLRP3 Inflammasome Axis Contributes to Angiotensin II-Induced Skeletal Muscle Wasting via PPAR-γ

Wei Ding, Shanghai Ninth People’s Hospital, Shanghai, China.

Background: Although the angiotensin II (Ang II) level is elevated in patients with chronic kidney disease or heart failure, and directly causes skeletal muscle wasting in rodents, the molecular mechanisms of Ang II-induced skeletal muscle wasting and its potential as a therapeutic target are unknown.

Methods: We investigated the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome-mediated muscle atrophy response to Ang II in C2C12 myotubes and Nlrp3 knockout mice. We also assessed the mitochondrial dysfunction (MD)/NLRP3 inflammasome axis in Ang II-induced C2C12 myotubes. Finally, we examined whether a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist could attenuate skeletal muscle wasting by targeting the Md/NLRP3 inflammasome axis in vitro and in vivo.

Results: We demonstrated that Ang II increased NLRP3 inflammasome activation in cultured C2C12 myotubes dose dependently. Nlrp3 knockdown or Nlrp3−/− mice were protected from the imbalance of protein synthesis and degradation. Exposure of C2C12 to Ang II increased mitochondrial ROS (mtROS) generation, accompanied by MdD. Similarly, the angiotensin II targeted antioxidant not only decreased mtROS and MdD, it also significantly inhibited NLRP3 inflammasome activation and restored skeletal muscle atrophy. Finally, the PPAR-γ agonist protected against Ang II-induced muscle wasting by preventing MdD, oxidative stress, and NLRP3 inflammasome activation in vitro and in vivo.

Conclusions: This work suggested a potential role of Md/NLRP3 inflammasome pathway in the pathogenesis of Ang II-induced skeletal muscle wasting, targeting the PPAR-γ/MdD/NLRP3 inflammasome axis may provide a therapeutic approach for muscle wasting.

Skeletal Muscle Mitochondrial Response to Wheel Running in a Rat Model of CKD

Keith G. Avis,1 Meghan C. Hughes,2 Shruhti Srinivasan,3 Neal X. Chen,4 Kalisha O’Neill,5 Robert L. Bacallao,6 Sharon M. Moe,7 Christopher G. Perry,2 Indiana University-Indianapolis, Indianapolis, IN;2 York University, Toronto, ON, Canada;3 Indiana University School of Medicine, Indianapolis, IN;4 Indiana University Medical Center, Indianapolis, IN.

Background: We have previously found that treadmill running had detrimental effects upon mitochondrial pathways, while wheel running had multiple beneficial effects in CKD rats. We hypothesized that wheel running would have beneficial effects on skeletal muscle mitochondria.

Methods: We used the C57bl/6J mouse model of naturally occurring CKD (n = 12-14/group) to compare muscle bioenergetics in CKD rats versus NL littermates, and CKD versus CKD rats that performed 10 weeks of wheel running (from 25- to 2 stage CKD) to 10 weeks of no wheel running. 1) Muscle protein lysates of the extensor digitorum longus (EDL, fast fiber type) and soleus (slow fiber type) were directly assessed for protein content of the mitochondrial respiratory submitochondrial complexes by OXPHOS. 2) These muscles were permeabilized with detergent-assisted mitochondrial respiration (Oxygraph-2k, Oroboros) in the presence of different substrates (5Mm pyruvate, 2Mm malate, 25um-10mM ADP, 5mM glutamate; 20mM succinate).

Results: EDL: no difference in mitochondrial complex protein content or respiration in CKD vs NL. Wheel running reduced complex I-FIV subunit protein content (CKD-W vs CKD-NL p<0.05), but no difference for respiratory chain. Soleus: mitochondrial complex I was reduced in CKD vs NL, while complex III was reduced in the CKD-W vs CKD (both p<0.01). Respiratory rates were increased in CKD (vs NL) for 300 and 500mM ADP (p<0.01), but not for state II (pyruvate, malate). In contrast, wheel running increased state II (pyruvate, malate) and 25mM ADP (compared to CKD both p<0.01) respiration.

Conclusions: Skeletal muscle from CKD rats did not demonstrate dramatic changes in mitochondrial content or respiration. Wheel running in CKD rats, compared to no wheel running, reduced isolated mitochondrial respiratory subunit content particularly in the EDL. However, there was no difference in respiration with lowered mitochondrial content there was a compensatory response. These data support that the systemic benefits of wheel running may not be due to changes in mitochondrial function in skeletal muscle, suggesting a more indirect effect.

Skeletal Muscle Mitochondrial Response to Wheel Running in a Rat Model of CKD

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Funding: NIDDK Support

Correlates of Physical Inactivity Across Kidney Disease Stages: An Observational Multicentre Study

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Background: The importance of physical activity (PA) in the health and management of CKD is well established. Understanding causes of PA behaviour is essential for the development of potential interventions and promotional initiatives. We aimed to determine the prevalence and individual correlates of PA behaviour across the spectrum of kidney disease.

Methods: 5258 patients across 17 geographically diverse sites were stratified into CKD stages 1-2, 3, 4-5, haemodialysis (HD), peritoneal dialysis (PD) and renal transplant recipients (RTRs). Physical activity was assessed using the GP Physical Activity Questionnaire. Potential correlates of PA included clinical, co-morbidity and demographic data, self-efficacy, stage of change (TransTheoretical Model) and cardiorespiratory fitness (VO₂ peak estimated using Duke Activity Status Index). Multi- and bi-national generalized models were used to explore differences and correlates of PA. Unless stated, data expression as odds ratio (OR).

Results: Prevalence of physical inactivity was high and worsened with disease progression (Fig 1). Overall, being older (OR=1.03), female (OR=1.27), having additional co-morbidities (OR=1.17), lower Hb (OR=0.93) and lower VO₂ peak (OR=0.92) were associated with being inactive. Patients in a receptive stage of change (OR=35) and with higher self-efficacy (OR=70) were more likely to be active. Stage of disease modified the interactions of age, sex, and VO₂ peak with PA.

Conclusions: In the large proportion of its kind, we established that physical inactivity is highly prevalent across all stages of renal disease, reaching a nadir in those requiring dialysis and ‘recovering’ in those with a transplant. Our study emphasises the urgent need

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Underline represents presenting author.

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to evaluate and implement strategies that can effectively support individuals in changing their PA behaviour. In particular, approaches to promote self-efficacy may increase the likelihood that patients will engage and continue with PA.

Funding: Private Foundation Support

TH-PO624

Lysosome: At the Crossroads Between Na+-K+-ATPase and NLRP3 in Hyperuricemia-Induced Renal Tubular Injury

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Background: We previously demonstrated the impairment of Na+-K+-ATPase (NKA) and NLRP3 signaling in hyperuricemia (HUA)-induced renal tubular injury and NKA was degraded in lysosomes. Here, we investigated the role of lysosome in HUA-induced renal tubular injury and NKA was degraded in lysosomes.

Methods: Proximal tubular epithelial cells (PTECs) were incubated with different concentrations (50 μg/ml-200μg/mL) of UA for different times (6h-48h), and the expression of NLRP3, lysosomal-associated membrane protein 2 (LAMP2), cathepsin B (CB) and interleukin-1β (IL-1β) were detected. CB inhibitor (Ca-074 methyl ester, Ca-074 Me) 10Mm or hydroxychloroquine (HCQ, 50 μM) was added to PTECs for 2h in advance, with the inhibition of NKA by its α subunit siRNA for 48h with or without the UA stimulation. NLRP3, LAMP2 and CB as well as mitochondrial function were detected. In vivo, SFP SD rats were divided (n=6 in each group) into control, HUA group [oxonic acid (OA) 750 mg/kg/d gavage for 8 weeks]; HCQ group (HCQ, with OA 750mg/kg/d for 8 weeks and OA 750mg/kg/d for 8 weeks) and HCQ group (HCQ, with OA 750mg/kg/d and OA 750mg/kg/d gavage since the 5th week for 4 weeks); and Febuxostat group (Feb, with OA 750mg/kg/d for 8 weeks and Feb 3 mg/kg/d gavage since the 5th week for 4 weeks). Renal cortex NKA activity, its expression, CB, LAMP2, NLRP3, IL-1β and uncoupling protein 2 (UCP2) were examined.

Results: UA time and dose-dependently increased the expression of LAMP2 and CB. Ca-074 Me or HCQ alleviated the expression of NLRP3, LAMP2 and CB, and mitochondrial dysfunction caused by UA and/or NKA siRNA. OA significantly increased serum UA levels in SD rats and developed reduced urinary UA excretion, renal cortex NKA activity and its expression, increased the expression of NLRP3, IL-1β, CB, LAMP2, and UCP2 expressions, compared with control. HCQ, but not Feb treatment, significantly increased urinary UA excretion. HCQ demonstrated similar effects with Feb in enhancing renal cortex NKA activity and expression, reducing the expression of NLRP3, IL-1β, CB, LAMP2, and UCP2 expressions, compared with HUA group.

Conclusions: UA induces lysosomal damage to release lysosomal contents and activate NLRP3 inflammation. Lysosomal function protection could alleviate NKA-NLRP3 signaling pathway and effectively improve mitochondrial function in vitro and in vivo, suggesting that lysosome function plays an important role in HUA-induced renal tubular epithelial cell injury.
TH-PO625

The Histone Deacetylase (HDAC) Inhibitor Belinostat Attenuates TH-PO626

Nifedipine Modulates Renal Lipogenesis and Fibrosis via the AMPK/TH-PO627

Regulating AMPK-mTOR-Autophagy TH-PO628

Autophagy is an evolutionarily conserved catabolic process that removes damaged organelles and maintains cellular energy homeostasis. Acute regulation by nutrient-sensing of autophagy and long-term transcriptional regulation by nuclear hormone receptor farnesoid X receptor (FXR) is well known. All the evidence indicates that FXR regulates TGFβ-expression and suppresses kidney fibrosis. However, the functional role of FXR on TGFβ-induced kidney autophagy is relatively unknown.

Methods: Expression levels of LC3 protein and autophagy related genes were measured on treatment with TGFβ and FXR agonists, GW4064 and WAY-265A40, in human proximal tubule cells (HK2 cells). Also, we tested expression levels of autophagy related proteins and genes in overexpression or downregulation of FXR in cells. Expression levels of protein and autophagy related genes were measured in the sham and UUO model of WT FXR knock-out mice, and FXR KO UUO mice model compared to those of WT UUO mice model.

Results: Treatment with TGFβ (5 ng/ml) in HK2 cells resulted in an increase in the level of LC3 protein and autophagy related genes, along with an increase in fibrosis markers. Activation of FXR by agonists in TGFβ-induced HK2 cells regulates expression levels of TGFβ III and Beclin. Autophagy related genes were decreased in FXR agonists treated HK2 cells. Also, autophagic flux was further increased on co-treatment with GW4064 and TGFβ in HK2 cells. Autophagy related genes have no GW4064 effects on down-regulation of FXR by siRNA in HK2 cells. Autophagy related genes were regulated by fasting/fedding in WT mice. Protein levels of LC3 and fibrosis markers were increased in FXR-KO UUO mice model compared to those of WT UUO mice model.

Conclusions: These data reveal a functional role of FXR for kidney autophagy regulator in TGFβ-induced HK2 cells and suggest that FXR may play an important role in the suppression of renal fibrosis through transcriptional regulation of kidney autophagy.

Funding: Government Support - Non-U.S.

TH-PO629

Rhein Attenuated Palmitic Acid-Induced Renal Tubular Cell Injury by Regulating AMPK-mTOR-Autophagy

TH-PO627

The Histone Deacetylase (HDAC) Inhibitor Belinostat Attenuates H2O2-Induced Senescence-Like State by Regulation of HDAC7 in the Human Renal Proximal Tubular Epithelial Cells

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Background: Oxidative stress causes cell injury, disease, and aging. Renal aging is associated with decreased glomerular filtration rate, glomerulosclerosis, tubular atrophy, and fibrosis in human and animal age-related kidney diseases. The senescence and pathology in renal cell cycle and senescence. We investigated the effect of HDAC inhibitor, belinostat on the H2O2-induced renal tubular senescence, and its underlying molecular mechanisms.

Methods: The effects of belinostat in H2O2-induced cell senescence was determined using flow cytometry (propidium iodide and 5,6-carboxyfluorescein diacetate). Western blot analysis indicated that Belinostat inhibited autophagy flow cytometry and the knock down of histone deacetylases 7 was induced by HDAC7 siRNA.

Results: We observed the effect of belinostat on cell cycle regulation of HDAC7 in H2O2-induced senescence-like cells. H2O2 increased SA-b-gal staining and induced protein expression of HDAC7, p16, p21, and p53. Also, increased phosphorylation of p-AKT, p-ERK1/2, p-p53, and induced ER stress. In contrast, pretreatment of belinostat reduced protein expression of HDAC7 and p-caspase-1 and cell cycle-related protein expression and the phosphorylation of p-AKT, p-ERK1/2, and p-p53. and reduced ER stress markers. SRNA treatment of HDAC7 inhibited the expression of p-AKT-1 and decreased SA-b-gal staining.


Funding: Government Support - Non-U.S.

TH-PO626

Nifedipine Modulates Renal Lipogenesis and Fibrosis via the AMPK/TH-PO625

Regulating AMPK-mTOR-Autophagy

Nifedipine may potentiate renal fibrosis and lipid accumulation through TGFβ1/2 activation and lower AMPK activity in this in vivo study, similar results were observed in our previous in vitro study. Interestingly, hyperlipidemia may correlate with renal fibrosis on kidney CKD patients.

Methods: The baseline survey items were the SUA level, age, sex, body mass index (BMI), blood pressure, blood sugar, hemoglobin A1c, urine creatinine, estimated glomerular filtration rate, urinary albumin/creatinine ratio, total cholesterol, and electrocardiogram findings (presence of atrial fibrillation). Baseline data were measured in participants of annual health checkups from a community-based population. After the exclusion of CKD, the subjects were stratified into sex-specific quartiles of SUA (n = 15,036, mean age 63 ± 10.0 years in men and 60 ± 10.9 years in women, men 33.5%, including 5,038 men and 9,998 women). The endpoint was defined as the composite of CVEs (stroke, myocardial infarction, and sudden cardiac death). A Cox regression analysis was performed to examine the sex-specific relationship between the baseline SUA level and the onset of CVEs.

Results: During a mean follow-up period of 8.8 years, we confirmed 611 CVEs (304 in men, 307 in women). After adjusting for traditional risk factors (age, BMI, hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation), the hazard ratio for the onset of CVEs did not differ among the quartiles in men (q1 2.1(SEUA/mg/dl)4.8) = reference, q2 (4.5(SEUA/mg/dl)4.8) = 1.01, q3 (5.7(SEUA/mg/dl)4.8) = 0.99; p = 0.447). In contrast, in women, a significant trend was observed (q1 (2.0(SEUA/mg/dl)3.7) = reference, q2 (3.8(SEUA/mg/dl)4.3) = 1.28, q3 (4.4(SEUA/mg/dl)4.9) = 1.58, q4 (5.6(SEUA/mg/dl)10.3) = 1.58, p = 0.035).

Conclusions: In the Japanese general population in women, an elevated SUA level is considered an independent risk factor for the onset of CVEs in women but not in men.

Background: Transcriptional Regulation of Kidney Autophagy by Farnesoid X Receptor

Receptor

Oxidative stress causes cell injury, disease, and aging. Renal aging is the sex-specific relationship between the baseline SUA level and the onset of CVEs. We observed the effect of belinostat on cell cycle regulation of HDAC7 in H2O2-induced senescence-like cells. H2O2 increased SA-b-gal staining and induced protein expression of HDAC7, p16, p21, and p53. Also, increased phosphorylation of p-AKT, p-ERK1/2, p-p53, and induced ER stress. In contrast, pretreatment of belinostat reduced protein expression of HDAC7 and p-caspase-1 and cell cycle-related protein expression and the phosphorylation of p-AKT, p-ERK1/2, and p-p53. and reduced ER stress markers. SRNA treatment of HDAC7 inhibited the expression of p-AKT-1 and decreased SA-b-gal staining.


Funding: Government Support - Non-U.S.
TH-PO630

Sodium Glucose Co-Transporter 2 Inhibitor Ameliorates Autophagic Flux Impairment on Renal Proximal Tubular Cells in Obesity Mice

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Background: Obesity is supposed to cause to renal injury, and sodium glucose co-transporter 2 inhibitors (SGLT2-i) are reported to have possibilities to protect renal disorders. However, the SGLT2-i direct protective mechanism has been unclear. In this study, we investigated SGLT2-i effects focused on autophagic flux impairment in proximal tubular cells in obesity mice.

Methods: 5-week-old C57BL/6J mice were divided to normal diet (ND) fed group or 40 kcal % fat diet (HFD) fed group. After 9 weeks, we separated the mice, administrated 10.0 mg/kg/day SGLT2-i (empagliflozin provided from Boehringer-Ingelheim) group or solvent, hydroxypropyl methylcellulose (HPMC) group to each feeding group mice for 1 week. After total 10 weeks, urine was harvested for 24 hrs with ND. The mice were sacrificed, and serum plasma and kidneys were harvested. We investigated pathological analysis and protein expression focused on autophagy.

Results: The weight of HFD mice gained significantly than that of ND mice. HFD-SGLT2-i mice showed significant decrease of urinary N-acetyl-β-D-glycosaminidase (NAG) compared with HFD-HPMC group (p < 0.05). In oil red O staining, lipid accumulations were observed on proximal tubular cells in HFD-HPMC treated mice, however lipid accumulations were observed significantly decrease in HFD-SGLT2-i fed mice. HFD-HPMC mice showed significantly increase of p62 positive proximal tubules compared to ND-HPMC group. Interestingly, HFD- SGLT2-i showed significant decrease compared to HFD-HPMC group (p < 0.05). In electron microscopy, multilamellar bodies (MLBs), which shows the autophagosome or autolysosome storing lipids, appeared in proximal tubular cells of HFD-HPMC mice, however MLBs decreased in HFD-SGLT2-i group. In abnormal, formation of mitochondria was observed in proximal tubular cells of HFD-mice, and several mitochondrias were observed in those treated with SGLT2-i.

Conclusions: SGLT2-i might have renal protective effects against obesity via improving autophagic flux impairment in proximal tubular cells by promoting autophagosomal degradation of lipids and damaged mitochondrias.

TH-PO631

Examining Transcriptional Coordination Among Pathways Using Single Cell Transcriptomics

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Background: Recent evidence suggests that the intracellular activity of certain immune pathways, such as the complement, engages in novel cross-talk with metabolic pathways. This pathway-pathway interaction is critical in directing a catered cellular response. Single cell RNA sequencing (scRNA-seq) provides an unprecedented opportunity to understand whether certain biological pathways act in synchrony. 

Methods: Using single cell transcriptomics data from five different T cell subtypes (CD4+ naïve, memory helper and regulatory T cells, and CD8+ cytotoxic T cells), we developed a model for assessing the canonical correlation between two pathways. We examined the significance of the correlation using a modified permutation null distribution that accounts for technical covariates. Complement dysregulation is a hallmark of several kidney diseases, so we used the complement as a bar in immune pathway to detect which metabolic pathways it is correlated with, and how that correlation differs across T cell subtypes.

Results: Using canonical correlation analysis, we detect pairwise coordination among biological pathways, and explore how the complement pathway might interact with various metabolic pathways in different T cell subtypes. We found that complement-metabolism crosstalk increased substantially by T cell subtype. For instance, while the complement pathway demonstrated a significant canonical correlation with the arachidonic acid and NAD metabolism pathways in CD4+ memory T cells, we did not find evidence for the same in CD4+ naïve T cells. Further, in the latter naïve T cell type, glycolysis and the pentose phosphate pathways showed evidence for transcriptional coordination with complement.

Conclusions: Our method is a widely applicable approach that can be used to assess the differences in pathway cross-talk between cell-types, as well between a healthy and disease state.

Funding: Private Foundation Support

TH-PO632

A Uremic Toxin, 3-Carboxy-4-Methyl-5-Propyl-2-Furanpropionate, Induces Cell Ferroptosis in Human Proximal Tubular Epithelial Cells via Reduced Glutathione Peroxidase 4 and Glutathione

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Background: 3-Carboxy-4-methyl-5-propyl-2-furanpropionate (CMF) was a uremic toxin metabolite of furan fatty acid that causes oxidative stress and accelerates the progression of renal failure. Ferroptosis is a form of cell death induced by accumulation of iron-dependent lipid-reactive oxygen species and inhibition of glutathione peroxidase 4 (GPX4). We investigated whether uremic toxin, CMF affects renal proximal tubular cell damage by ferroptosis, a non-apoptotic form.

Methods: The fluorescent dye 24, 7-dichlorodihydrofluorescein diacetate was used to measure intracellular reactive oxygen species (ROS) following CMF administration in human renal proximal tubular epithelial (HK-2) cells. The effects of CMF on cell viability was determined using EZ-CyTox assays, and level of glutathione was determined by luminescence using the GSH/GSSH assay. glutathione peroxidase 4 (GPX4) proteins was determined by semiquantitative immunoblotting.

Results: Treatment of CMF in HK-2 cells promoted the production of ROS. In addition, treatment with CMF not only reduced the level of GSH but also decreased the expression of GPX4 protein. The ferroptosis inhibitor, lipophilic antioxidant, Fer-1, inhibited CMF-induced ferroptosis, and iron chelators, DFO, also attenuated CMF-induced ferroptosis in HK-2 cells.

Conclusions: The results of this study show that CMF in HK-2 cells promoted the production of reactive oxygen species (ROS) and reduced the levels of GSH and GPX4 expression, resulting in cell death due to ferroptosis.

Funding: Government Support - Non-U.S.

TH-PO633

Donor-Recipient Gut Microbiota Similarity and Allograft Function Early After Kidney Transplantation

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Background: Gut microbiota affects the development and maintenance of innate and adaptive immune function. However, the effect of microbial composition similarity between recipient and donor on graft function after kidney transplantation (KT) remains unknown.

Methods: We prospectively enrolled living donor KT cases at two centers. Stool samples were obtained before KT. Microbiota composition was analyzed using extracted metagenomic DNA from the feces, using the Illumina MiSeq system. Gut microbiome difference between donor and recipient was calculated by weighted UniFrac distance. Clinical outcome was defined as 6 month post-transplant graft function.

Results: The microbial distance was estimated from 55 donor-recipient pairs. The recipients were 47.7 ± 13.0 years old; donors, 47.5 ± 11.2 years old. Among 26 related, 25 spousal and 4 unrelated donor transplants, couples showed lesser microbial composition difference than genetically related pairs. Spousal donors more frequently sharing meals with their recipients. The number of meals eating together in a day was significantly correlated with microbial distance. In terms of graft outcome, eGFR at 6 month after KT
was significantly correlated with microbial distance (P=0.014). In addition, patients with the farthest quartile of microbial distance suffered from more rejection events in 6-month after KT.

**Conclusions:** In this study, we found that intestinal microbiome similarity between donor and recipient might affect allograft function early after KT.

TH-PO634

**Gut Microbiome and Circulating Uremic Solutes in Patients with CKD**

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**Background:** The relationship between gut microbiome and renal function through the gut-kidney axis comes into the spotlight. However, the changes of microbiome according to the stages of chronic kidney disease (CKD) and the dynamics of uremic toxins produced by gut microbiome are not yet known.

**Methods:** We prospectively enrolled 149 CKD patients with various renal functions and healthy kidney donors as controls. We collected fecal samples of all participants and the microbial profiling was performed by 16S rRNA sequencing. Also, we measured the level of 4 uremic toxins including p-cresyl sulfate, indoxyl sulfate, p-cresol glucuronide, and trimethylamine N-oxide in serum of all participants by Liquid chromatography–mass spectrometry.

**Results:** Among the 149 participants, control, CKD stage 1 to 2, CKD stage 3 to 5 without dialysis, CKD stage 3 with dialysis, were 46, 36, 32 and 35, respectively. The four uremic toxins were significantly increased with elevation of CKD stage. In microbial analysis with fecal samples, the abundances of genera Prevotella, Lachnospira and Dialister significantly decreased as the stage of CKD advanced. While, the abundances of genera Alistipes and Oscillibacter significantly increased as the stage of CKD advanced. Then, the uremic toxin-related microbiota was identified, and all four uremic toxins were associated with Alistipes, Oscillibacter and Lachnospira. These three genera showed significant correlations with both renal function and metabolic production.

**Conclusions:** We found that the composition of gut microbiota changed according to the stage of CKD. Especially, genera Alistipes, Oscillibacter and Lachnospira were correlated with levels of major uremic toxins. These results show that gut microbiota might be a crucial factor for progression of CKD.

TH-PO635

**Gut-Derived Uremic Retention Solutes in Patients with CKD and Healthy Adults**

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**Background:** Elevated serum levels of the uremic retention solutes (URS), indoxyl sulfate (IS), p-cresol sulfate (PCS), and trimethylamine N-oxide (TMAO), have been observed in patients with late stage CKD/dialysis and have been associated with poor outcomes. The uremic toxins were strongly correlated with both renal function and metabolite production among the three sURS (r=0.69 to -0.77, p=0.04-0.09), uTMAO (r=-0.79, p=0.03) and uIS (r=-0.77, p=0.04), but no associations remained in controls (p>0.30). There were strong correlations among the three sURS (r=-0.79, p=0.03) and corresponding uURS (r=-0.69 to -0.77, p=0.04-0.09), but no associations were made by Pearson’s correlations.

**Methods:** We have compared patients with mild/moderate CKD vs healthy adults on a controlled diet. The diet was controlled to the stage of CKD. Especially, genera Alistipes, Oscillibacter and Lachnospira were associated with both renal function and metabolic production.

**Conclusions:** These findings suggest that these miRNAs play important roles in regulating processes associated with the development of diabetes and its complications, including diabetic kidney disease, and have potential as early markers and therapeutic targets for improving insulin sensitivity and renal senescence.

**Funding:** Private Foundation Support

TH-PO638

**Ezrin Regulates Multiple Solutes Reabsorption via the Regulation of Membrane Protein Localization in the Proximal Tubules**

Ezrin is a member of ERM (ezrin-radixin-moesin) proteins and works as a scaffolding molecule between membrane and actin. As a key player in the kidneys, intense expression of ezrin is observed in proximal tubules, and it is postulated that ezrin plays important roles in tubular solute reabsorption via the regulation of apical membrane localization of several transporters. We previously reported that ezrin knockdown (Hi22/46)
mice show hypophosphatemia due to mislocalization of Na/Pi-dependent phosphate transporters and a decrease in Na-exchanger regulatory factor 1 (NHERF1). However, we haven’t investigated the influence of loss of ezipn on the membrane localizations of other transporters.

Methods: We performed a comprehensive proteomic analysis of renal brush border membrane vesicles (BBMV) from wild-type (WT) and Vli2kd/kd mice in this study. We also measured the plasma concentration and urinary excretion of nutrients, including amino acids, glucose, and low molecular weight protein.

Results: We identified totally 1,412 proteins including 18.8 % of membrane integral proteins. WT and Vli2kd/kd mice. Scaffold proteins including NHERF1 and PDZK1 were significantly decreased in Vli2kd/kd mice. Several transporters including Slc5a1, Slc1a5l, SLC22a4 and SLC22a5 showed marginally significant reduction (0.05 < p < 0.1). We also found that BBMV localizations of several other solute transporters associated with glomerular filtration rate (R= -0.05; p=0.005). Multivariate regression analysis including adiponectin concentration depends strongly on BMI (R= -0.28; p<0.001) and marginally on the kidney function (R= -0.24; p<0.001, b=-0.11, p<0.0001, b=-0.24, p<0.0001) and these genes code digestive enzymes like trypsin, carboxypeptidase, pancreatic elastase, chymotrypsin and phospholipase. Except trypsin, the enzymes above are usually detected by pancreatic secretion while their RNA expressions increased in the jejunum.

Conclusions: Patients with ESRD suffered from exocrine pancreatic insufficiency but we found that some pancreatic secreted enzymes increased RNA expressions in the jejunum of experimental uremia rats. So we can deduce that the jejunum could more or less compensate for exocrine pancreatic insufficiency of ESRD patients. However, the exact mechanism still needs to be studied further.

TH-P0641
The Pitfalls of Nephrology Care: Are Older Patients and Their Caregivers Getting What They Need?
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Background: Older patients with advanced chronic kidney disease lack knowledge and information regarding treatment decision and advance care planning. It is unclear whether clinicians and older patients have the same goals with regards to communication of treatment decision and goals of care. We sought to explore perceptions of clinician behavior and patient preferences via interviews with nephrologists, primary care providers and caregivers regarding treatment for end-stage renal disease and advance care planning.

Methods: Between March 2017 and May 2018, we conducted individual semi-structured interviews with nephrologists, primary care physicians, older patients (age ≥ 65), and caregivers. Transcripts were transcribed using TranscribeMe and reviewed in an iterative process. Using Nvivo 11, we coded all transcripts using two codebooks (clinicians and patients/caregivers) and identified key themes. Three independent coders conducted thematic content analyses and discrepancies in coding were resolved through consensus coding.

Results: We interviewed 16 clinicians (nephrology, n = 8; primary care, n= 8), 10 patients, and 5 caregivers. We identified three key findings: 1) nephrologists felt their primary responsibility was to discuss dialysis and other treatments for kidney disease including conservay kidney management, 2) primary care clinicians felt they should take the lead in helping patients navigate their disease management and also lead advance care planning discussions, and 3) patients’ and caregivers’ perspectives about dialysis, quality of life and planning ahead for their care were not adequately addressed by clinicians.

Conclusions: Our findings highlight the differences in opinions and expectations between clinicians, patients, and their caregivers regarding treatment decisions and advance care planning in nephrology. Importantly, patients and caregivers do not feel that their needs are being met. Further research is needed to test feasible models of patient-centered education to ensure all stakeholders feel valued.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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The Oldest Dilemma: Dialysis or Conservative Care

Background: In comorbid elderly patients with stage 5 renal disease (ESKD) and advanced kidney disease, treatment decisions at the end of life are framed by goals of care and quality of life. Although there is a body of literature on the differences in CI. Functional status was statistically lower measured by Barthel Index (77.3 ± 20.3 vs. 94.48 ± 10.8; p<0.0001) and PPS score (64.26 ± 15.5 vs. 84.1 ± 1.7; p<0.0001) in CV vs D groups. Follow-up time was greater in D vs CV (median 25.2 ± 17.1 vs 9.7 ± 10 mo; p<0.0001). Only 4 patients of CV group changed their decision to dialysis. Forty patients (39%) from CV required visits from home palliative care team (median 5, mean 7.8 ± 2.3 sessions). Sixty-six died, 62 from CV and 4 from hemodialysis (p=0.0000). Survival was 43% at one year and 20% at 2 years in CV vs 96% at one year and 91% at 2 years in D group (p<0.0000). Places of death were, in frequency: Palliative care unit (n=25), hospitalization (n=20), home (n=17), medical residence (n=5) and ER (n=3).

Conclusions: ESKD patients who decide conservative care treatment are oldest, with decreased functionality and mostly women. Despite a lower survival the decision remains firm which would indicate a probable stability in quality of life throughout their last days.

Early Outcomes from an Ambulatory Kidney Palliative Care Program

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Background: Patients with advanced kidney disease have an elevated symptom burden, increased mortality, and poor quality of life. While palliative care can address these needs, the palliative care oncology team infrequently receive such care. To address this, we implemented an ambulatory kidney palliative care program. We describe our initial outcomes.

Methods: Utilizing chart abstractions, we characterized the clinic population and symptom burden for patients seen from May 6, 2016-July 6, 2018. Results: Ninety-four patients were referred; 74 (78.7%) patients seen. Forty-five (54.1%) had follow-up appointments (range 2-13). Mean patient age was 72.7 ± 10.6 years with a range of 52-91. Mean new symptom burden score was 26.2 ± 10.6 (out of 50). Sixty-six died, 62 from CV and 4 from hemodialysis (p=0.0000). Survival was 43% at one year and 20% at 2 years in CV vs 96% at one year and 91% at 2 years in D group (p<0.0000). Places of death were, in frequency: Palliative care unit (n=25), hospitalization (n=20), home (n=17), medical residence (n=5) and ER (n=3).

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Survival of Elderly Patients with ESKD Managed Without Dialysis

Angela Chou,3 Kelly C. Li,4 Anna Hoffman,5 Mark Brown.3 1St George Hospital, Cabramatta, NSW, Australia; 2St George Hospital, NSW, Australia, Kogarah NSW, NSW, Australia; 3St George Hospital Sydney, Sydney, NSW, Australia; 4St George Hospital Sydney, Kogarah, NSW, Australia.

Background: Shared decision making (SDM) is important when considering whether an elderly patient ESKD should be managed with dialysis. Research has shown that physicians find these conversations difficult because of the relative paucity of data on survival of patients managed without dialysis.

Results: Since the program was initiated in January, 2018, 10 patients were offered the concurrent program. One patient elected to stop dialysis at enrollment. Of the remaining nine patients who elected the concurrent program, six survived to receive planned dialysis session(s). Among these six patients, 50% were female and all but one was Caucasian. Five of six patients received hemodialysis, and one patient received peritoneal dialysis. Hospice length of stay was almost 2 weeks (13.8 days, range 7 to 28 days). The average number of dialysis treatments was 3.3 (range of 1 to 8 treatments). All patients died in a home-like environment. End of life goals attained included attending planned celebrations, spending time with family, and achieving a sense of control.

Conclusions: Our concurrent hospice and dialysis program led to longer hospice LOS compared to general care trends. By allowing up to ten additional treatments, patients and families were able to achieve their end of life goals. Future direction involves expansion of the program within DCI with the goal to inform policy change in hospice delivery for dialysis patients at end of life.

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Redefining End-of-Life Care in Dialysis: A Concurrent Hospice and Dialysis Program for Terminal Dialysis Patients

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Background: End of life for patients with end stage kidney disease (ESRD) is defined by increased health care utilization with limited access to hospice services. Financial and regulatory barriers within the Hospice Medicare Benefit often require patients to stop dialysis to receive hospice services. Unsurprisingly 40% of dialysis patients on hospice receive these services for three or less days. We developed a concurrent hospice and dialysis program with the goal to increase hospice utilization and improve patient, family and provider experience.

Methods: The ESRD Concurrent Care Program is a quality improvement initiative developed through partnership between Dialysis Clinic, Inc.’s Independence ESCO and UPMC Family Hospice in Pittsburgh, PA. The program offers concurrent hospice and palliative dialysis (10 sessions with weekly assessment) to terminal dialysis patients with an expected progression of two months or less and whose goals are comfort-focused. Palliative dialysis includes adjustment in the timing, frequency and delivery of dialysis to address symptoms and end of life goals. Outcomes include hospice length of stay (LOS), number of dialysis treatments provided and place of death.

Results: Since the program was initiated in January, 2018, 10 patients were offered the concurrent program. One patient elected to stop dialysis at enrollment. Of the remaining nine patients who elected the concurrent program, six survived to receive planned dialysis session(s). Among these six patients, 50% were female and all but one was Caucasian. Five of six patients received hemodialysis, and one patient received peritoneal dialysis. Hospice length of stay was almost 2 weeks (13.8 days, range 7 to 28 days). The average number of dialysis treatments was 3.3 (range of 1 to 8 treatments). All patients died in a home-like environment. End of life goals attained included attending planned celebrations, spending time with family, and achieving a sense of control.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: CM patients were significantly older than PEC and non-PEC dialysis patients (mean age 87.3 ± 6.7 vs. 77.4 ± 6.0; p<0.01) and had greater comorbidity (14 vs. 5%; p<0.01). From the decision date, median survival was 6.0 years (Interquartile range [IQR] 2.5-9.5) in PEC compared with 3.3 (IQR 0.7-5.0) in non-PEC dialysis and 1.1 yrs. (IQR 0.4-1.7) in CM; p <0.01. From time eGFR < 15, median survival was 7.8 years (IQR 3.5-12.6) in PEC, 5.6 (IQR 0.8-6.5) in non-PEC and 1.3 (IQR 0.5-2.0) in CM, p <0.01. From eGFR ≤ 10, median survival was 6.4 years (IQR 2.4-10.4) in PEC, 2.4 (IQR 0.5-6.0) in non-PEC and 0.7 (IQR 0.2-1.4) in CM; p <0.001. Non-PEC patients had lower eGFR than PEC at time of first visit (94±5 vs. 16±2 ml/min/1.73m²; p<0.01). In the CM group, at least 51 (18%) patients did not reach eGFR ≤15 and the cause of death was more non-renal (51 vs. 37%; p<0.01). Older age reduced survival from decision date (HR 1.03, 95% CI 1.01-1.04; p<0.01).

Conclusions: The median survival of elderly patients managed conservatively was 15.4 and 8.5 months from the time of eGFR < 15 and ≤ 10 respectively. Elderly patients who did not attend dialysis education prior to initiation had worse survival. This data should assist physicians with SDM discussions.

TH-PO647
Why Do Older Patients Choose Conservative Management?
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Background: Although many older patients with end-stage renal disease and limited prognoses prefer conservative management (CM), it is not widely offered in the US. Moreover, there is a dearth of US-based literature reporting clinical experience with shared decision-making regarding CM of advanced chronic kidney disease (CKD).

Methods: We describe the experience of 13 patients who opted for CM at the University of Rochester Medical Center’s CKD clinic. Their reasons for choosing CM were categorized into four broad categories based on a review of their electronic medical records. A retrospective chart review conducted by two reviewers determined the status of advance care planning, hospice referral, and place of death.

Results: During the year 2016-2017, 13 patients opted for CM. The mean and median age of these patients was 81.8 years (standard deviation 7.3) and 83 years (interquartile range 11), respectively. Their reasons for choosing CM included: poor prognoses; a wish to maintain their quality of life; their desire for a dignified life closure; and the intention to protect family members from having to see them suffer, based on their own memory of having witnessed a relative on dialysis previously. A total of seven patients died: all received hospice services, five died at home, one at a nursing home and one at a hospital. Advance care planning was completed in 100% of the cases. Symptoms were managed in collaboration with primary care physicians.

Conclusions: Patients’ decisions to forego dialysis and engage in CM were influenced by their values and previous experience with dialysis, in addition to co-morbidities and limited prognoses. Promoting the choice of CM in the US will require training of clinicians in competencies, including communication and decision-making skills, as well as basic symptom management.

TH-PO648
Racial Differences in End-of-Life Care Among Older Veterans with Non-Dialysis-Dependent CKD
Nwamaka D. Eneanya, Gary E. Weissman, Katherine Courtwright, Peter P Reese, Laura M. Dember, Scott D. Halpern, Jordana B. Cohen, University of Pennsylvania, Philadelphia, PA.

Background: Previous studies of veterans receiving dialysis demonstrated more intensive end-of-life (EOL) care among racial minorities than non-minorities. Little is known about racial differences in EOL care for older veterans with non-dialysis dependent chronic kidney disease (CKD).

Methods: We conducted a retrospective cohort study of veterans with incident stage 4 CKD from 2003-2014, age ≥70 years, and death before 1/18/17. Outcomes were a composite of intensive care (intubation of dialysis, invasive mechanical ventilation, cardiopulmonary resuscitation, or artificial nutrition) in the final month of life, and palliative care or hospice use in the final 6 months of life.

Results: 21,165 decedents met inclusion criteria. Non-Hispanic Whites were more often married and less often had hypertension, diabetes, and dementia compared to Non-Hispanic Blacks or Hispanics. In adjusted analyses, Non-Hispanic Blacks (OR 1.69, 95% CI 1.46-1.95) and Hispanics (OR 2.23, 95% CI 1.87-2.67) had a higher likelihood of intensive care compared to Non-Hispanic Whites. There was a significant interaction between death year and race with regard to hospice or palliative care use (p=0.01): compounded by minority status, minorities had a lower likelihood of palliative care or hospice use before 2010, but higher use in recent years (Figure).

Conclusions: Historically, Non-Hispanic Black and Hispanic older veterans with CKD experienced more EOL intensive care and similar hospice or palliative care use compared to Non-Hispanic Whites. Following recent Veterans Health Administration investments in palliative care, minorities were more likely than non-minorities to use palliative care or hospice. More research is needed to assess how health system factors contribute to racial differences in EOL care.

Funding: NIDDK, Support, Other NIH Support - NHLBI

TH-PO649
Retrospective Cohort Study of Patients Seen in a Specialized Renal Supportive Care Clinic
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Background: Palliative care is underutilized in advanced kidney disease care despite similar mortality and symptom burden as other life-limiting illnesses. Patients are less likely to engage in advance care planning (ACP) and often begin dialysis without an informed conversation about conservative care. As a result, patients with advanced renal disease are more likely to receive invasive, burdensome treatments at the end of life compared to those with other serious illnesses. We describe outcomes of a Renal Supportive Care Clinic (RSCC) at UPMC, staffed by dually trained nephrology and palliative medicine physicians.

Methods: We reviewed the medical records of all patients seen in RSCC during 2015, with follow-up through February 2019. We recorded documentation of ACP and whether patients had chosen a conservative care (CC) pathway without dialysis. Additional data collected included demographics, comorbid conditions, date that eGFR fell below 20 ml/ min/1.72m², and date of death (when available).

Results: A total of 48 patients were seen in RSCC in 2015. Mean age at first visit was 74 (± 8.7) years. Over half (60%) were female, and 14 (29%) were Black. Eight (17%) were receiving dialysis at the time of RSCC visit. Mean creatinine at presentation was 2.4 (± 1.5) mg/dL (excluding dialysis patients). ACP was performed with 43 patients (90%), and a surrogate decision maker was documented for 41 (85%). Seventeen patients (35%) had a documented goals of care conversation indicating a CC pathway. Of these patients, only 2 (12%) started dialysis. Among the 15 patients who remained on CC, 9 survived until the end of the study period. Six of these patients had an eGFR that never fell below 20. Of the remaining three patients, an average of 1500 (± 283) days elapsed between eGFR <20 and the end of the study period. Of the patients who died, mean length of time between eGFR <20 and death was 376 days (± 340).

Conclusions: Advance care planning conversations occurred frequently in RSCC, and a significant minority of patients chose conservative care without dialysis. Of CC patients, a majority survived the 4-year follow-up period (including several with eGFR<20). Further research is necessary to determine how palliative care can be efficiently integrated into care delivery for advanced kidney disease.

TH-PO650
A Brief End-of-Life Screening Module Improves Knowledge About End-of-Life Desires in CKD Patients
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Background: There are currently no published screening tools regarding end of life (EOL) care. An EOLmodule was developed and used by a nephrologist over the last decade. The module included three questions: 1) Whom would the patient like to make health care decisions in the future if the patient is unable? 2) Is this the patient’s request of kim? 3) In case of a medical catastrophe that resulted in severe changes in health and mentation that would be highly unlikely to be reversible, the patient would/would not want to be kept alive by artificial means, including dialysis. The checklist in general requires approximately 5 minutes for completion.

Methods: A retrospective review was performed on 398 patients seen in the outpatient clinic by the nephrologist who used the EOLM over ten years and a control group of 299 patients seen by other nephrologists at the same clinic. The following data were collected

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
from the electronic medical record: demographic data, information regarding EOL, patient comorbidities, and laboratory analyses were conducted using SAS software.

Results: The EOLM was completed in 167 of 398 patients (42%) by the nephrologist using the EOLM. The EOL was discussed in 12/167 (7.1%) patients seen by other nephrologists (p = 0.0001). The mean age of patients using the EOLM was 63 years, 63% male, 55% with ESKD, and 31% African American. 89% of patients wanted comfort care in the event of a health catastrophe, with 6% desiring full care, and 5% undecided. 16.0% of 182 individuals (8.8%) identified an individual who was not their next of kin as the person that they would like to make healthcare decisions for them. 10/12 (83%) EOLM patients vs 19/75 (25%) control patients had EOL discussion during hospital admission and had documentation in the chart that EOL wishes were met (p = 0.089).

Conclusions: An EOLM identified that the vast majority of CKD patients desire comfort care in the event of a health catastrophe. Nine percent of patients desired a surrogate decision maker who was not their next of kin and needed further documentation. Over ten years, only 12/167 patients died during a hospitalization. Patients with an EOLM were more likely to have EOL goals met (83% vs. 51%), though this was not significant due to lack of power.

Funding: Clinical Revenue Support

TH-PO651

A Pilot Study of a Supportive Care Video Decision Aid on Knowledge for Elderly Patients with Advanced CKD

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Background: The benefits of dialysis remain uncertain for elderly and frail patients with advanced chronic kidney disease (CKD). Although non-dialytic supportive kidney care (SKC) is an option for this patient population, there have been a lack of studies on patient-facing decision aids that specifically include this treatment approach. We performed a randomized controlled trial to test the efficacy of a video decision aid on knowledge of SKC among elderly patients with advanced CKD. We also assessed preferences for SKC and satisfaction and acceptability of the video.

Methods: Eligible patients were: age ≥ 65 years, English-speaking, had Stage 4 or 5 CKD, and were referred by their primary nephrologists to two academic centers in the US. Patients were randomized to receive education via a short verbal script or video. The video included images of patients undergoing hemodialysis, peritoneal dialysis or SKC. Patients received a knowledge questionnaire before and after receiving the verbal or video education.

Results: Among 100 enrolled participants, the mean age was 76 ± 6 years. Many were female (49%), White race (66%), and had completed high school education (85%). Knowledge of SKC increased in both arms after receiving education (p < 0.01); there was no difference in knowledge improvement between groups (Table 1). There was not a significant increase in those who preferred SKC after receiving either type of education (p = 0.20). The majority of patients who viewed the video felt comfortable watching it (96%), felt the content was helpful (96%) and would definitely recommend the video to others (72%).

Conclusions: Compared to an ideal verbal educational script, a video decision aid was not different in improving knowledge of SKC. Patients who received video education also reported high satisfaction and acceptability ratings. Future research will determine the effectiveness of a SKC video decision aid on patient preferences for treatment in real-world settings.

Table 1. Knowledge and preference for supportive care

<table>
<thead>
<tr>
<th>Group</th>
<th>Total N=100</th>
<th>Total Correct N=100</th>
<th>Total Incorrect N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-education knowledge of supportive care (%)</td>
<td>41</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>Pre-education preference for supportive care (%)</td>
<td>21</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Post-education knowledge of supportive care (%)</td>
<td>57</td>
<td>56</td>
<td>64</td>
</tr>
<tr>
<td>Post-education preference for supportive care (%)</td>
<td>20</td>
<td>20</td>
<td>22</td>
</tr>
</tbody>
</table>

MoCA score (adjusted for education) and the Z score respectively. Fast eGFR decline (≥30% per year), measured over median 58 antecedent months was not associated with CI (Odds Ratio (OR) 0.589 95% CI 0.313-1.109) or eGFR (OR 0.864 95% CI 0.369-2.021) in unadjusted analysis. >50% and >20% egfr drop over study period was not associated with CI or rCI. Older age and previous stroke were associated with CI after confounding adjustments. Only age was associated with rCI after same adjustments (Image 1).

Conclusions: Cognitive impairment is common in patients with CKD. Speed of eGFR decline is not a significant risk factor for CI in patients with CKD.

Funding: NIDDK Support

TH-PO652

Rapid eGFR Decline Is Not Associated with Cognitive Impairment

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Background: Cognitive impairment (CI) is underdiagnosed in patients with CKD. Unidentified CI may explain non-adherence to renal diet, fluid, medication and dialysis regimens. Determining if sex of eGFR decline is a significant risk factor for CI may help identify patients suffering from CI in CKD.

Methods: Patients enrolled into a UK longitudinal epidemiological non dialysis CKD cohort study about 15,000 patients diagnosed CI under cognitive assessments. These included: Montreal Cognitive Assessment (MoCA) and Trail Making A and B (TMTA and TMTB). eGFR decline was measured by linear regression and percentage fall in eGFR prior to cognitive assessment. Multivariate logistic regression was performed for comorbidity and lifestyle values to determine factors predictive of CI. CI was defined as ≥ 0.007 change/MoCA score (≤11.8) and relative CI (rCI) defined by >-1.34SD of any cognitive Z score. MoCA score (adjusted for education) and the Z score respectively. Fast eGFR decline (≥30% per year), measured over median 58 antecedent months was not associated with CI (Odds Ratio (OR) 0.589 95% CI 0.313-1.109) or eGFR (OR 0.864 95% CI 0.369-2.021) in unadjusted analysis. >50% and >20% egfr drop over study period was not associated with CI or rCI. Older age and previous stroke were associated with CI after confounding adjustments. Only age was associated with rCI after same adjustments (Image 1).

Conclusions: Cognitive impairment is common in patients with CKD. Speed of eGFR decline is not a significant risk factor for CI in patients with CKD.

Funding: Clinical Revenue Support

TH-PO653

Intradialytic Cerebral Perfusion and Cognitive Outcomes in Older Adults on Hemodialysis

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Background: End-stage renal disease affects over 600,000 Americans; with the majority of patients treated with hemodialysis (HD). Over two thirds of HD patients have significant cognitive impairment. Although causes of cognitive impairment may be multifactorial, there is some evidence that HD-process may lead to cognitive decline through cerebral ischemic disease from HD related hemodynamic fluctuations. We hypothesize that, at baseline white matter integrity will be associated with change in intradialytic cerebral perfusion and cognitive performance.

Methods: Participants are over the age of 50 who have been on HD fewer than 2 years. Our predictor variable is change in intradialytic cerebral oximetry (ScO2). We include three cognitive outcome measures: patient-reported cognition survey, neuropsychological assessment, and white matter integrity on MRI.

Results: Currently 25 participants are enrolled, with 20 completing all baseline measurements (5 unable to do MRI). The mean (SD) age was 65.4 ± 6.6 years. Majority were males (72%) and Caucasian (64%). Most had diabetes (64%) and hypertension (80%). Overall cerebral oximetry declined during HD session with a mean drop of 7.0 (2.9) %. Participants reported overall no cognitive issues with mean PROMIS cognition score of 55.3 (9.8) against normative score of 50 for the general population. This contrasts with the neuropsychological assessments showing significant cognitive impairment (7.6) and processing speed (40.0 (9.1)), again against normative score of 50. Correlational analysis demonstrates that greater intradialytic drop in ScO2 was associated with lower FA scores in some white matter tracts.

Conclusions: In our interim analysis we see that HD patients have cognitive deficits in key domains of executive function and processing speed and worse white matter integrity compared to healthy controls. Our results also show that cerebral oximetry does fluctuate during routine HD sessions. Our preliminary analysis demonstrate a trend of intradialytic cerebral oximetry decline being associated with lower white matter integrity in certain tracts, but the currently small sample size shows variability in results. Enrollment is ongoing and future analysis will include more participants.

Funding: NIDDK Support
Association of CKD Markers with Dementia Markers on Brain MRI: The ARIC Study

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Background: Urine albumin-creatinine-ratio (UACR) and estimated glomerular filtration rate (eGFR) define chronic kidney disease (CKD) and are associated with an increased risk of dementia and cognitive impairment. Such pathologies are accompanied with damage to the structural integrity of the brain, which can be seen using magnetic resonance imaging (MRI). We therefore examined the association of eGFR with MRI structural brain abnormalities in participants in the Atherosclerosis Risk in Communities (ARIC) study.

Methods: We studied 1,525 ARIC participants aged 67-90 years who attended visit 5 (2011-2013), and had a brain MRI scan performed, and eGFR based on cystatin C and UACR measured. We analyzed the association of UACR and eGFR with reduced brain volume, increased white matter hyperintensities (WMH) volume, microhemorrhages and brain infarcts using linear and logistic regression models, adjusted for age, sex, race, education, Apolipoprotein E4 level, smoking, body mass index, total cholesterol level, hypertension, diabetes, stroke and intracranial volume (only for volume measurements). Effect sizes for eGFR and ACR were normalized to their interquartile range (IQR).

Results: Higher levels of UACR and lower levels of eGFR were associated with reduced brain volume in regions typically affected by Alzheimer’s Dementia (AD), such as the hippocampus, and in non-AD related regions. Higher UACR and lower eGFR were also associated with increased WMH volume, and higher number of microhemorrhages and infarcts. The magnitude of the observed associations with MRI brain pathologies was similar regardless of UACR measurement.

Conclusions: Higher UACR and lower eGFR are strongly associated with brain structural MRI abnormalities. These abnormalities include white matter lesions, infarcts, microhemorrhages and signs of brain atrophy, which manifest globally in regions typically for AD as well as other brain regions.

Renal Function Does Not Have a Graded Inverse Association with TH-PO655

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Background: End-stage renal disease (ESRD) is associated with an increased risk of death and disability in older individuals. This is likely due to a combination of factors including decreased cognitive function.

Methods: We conducted a retrospective chart review of all patients ≥65 years enrolled in our dialysis cohort from 2007 to 2014 and performed a cohort analysis to identify factors that predict mortality.

Results: Of 350 patients, 225 had complete data available. The mean age was 74.2 ± 9.6 years, 56% were male, 44% were white, and 56% were black. The mean eGFR was 12 ± 7 ml/min/1.73m², and the median serum albumin was 3.9 ± 0.4 g/dL. The mean hospitalization rate was 5.8 ± 2.5 per year. The median MMSE score was 28 ± 7.6. A total of 123 patients died during follow-up (18.3% mortality).

Conclusions: Our findings suggest that ESRD is not associated with decreased cognition in older individuals. Future research should focus on identifying factors that predict cognitive decline in this population.
Persons with depressive symptoms had 1.9 geriatric conditions (least square means), while those without depression symptoms had 1.4 geriatric conditions (least square means).

**Conclusions:** In older adults with CKD, depressive symptoms correlated with the frequency of geriatric conditions. Future studies should investigate how geriatric conditions may worsen poor health outcomes in CKD patients with depression.

**Funding:** NIDDK Support, Other NIH Support - IUL1TR001430, K23AG057813, Other U.S. Government Support

### TH-PO658

**Benzodiazepines, Opioids, and Mortality Among Hemodialysis Patients**

**Melissa Al-El,1 Carly Meyer,2 Erin Beilstein-Wedel,3 Ann M. O’Harc,1 Nancy L. Keating,2 Erin Beilstein-Wedel,1 Carly Meyer,1 Susan T. Crowley,1 Center for Healthcare Organization and Implementation Research, VA, Boston, MA; 2Harvard Medical School, Boston, MA; 3VA Puget Sound Health Care System, Seattle, WA; 4Veterans Geriatric Nephrology, St. Louis University, St. Louis, MO; 5Johns Hopkins University, Baltimore, MD.**

**Background:** Mortality from benzodiazepine/opioid interactions is a growing concern in light of the opioid epidemic. HD patients suffer from a high burden of conditions which are treated with benzodiazepines and are 3-times more likely to be prescribed opioids than the general population. Therefore, they are at risk of mortality resulting from benzodiazepine/opioid interactions.

**Methods:** A cohort of 110,127 adults initiating HD (1/2013-12/2014) was assembled by linking USRDS/Medicare claims. Using adjusted Cox regression, we estimated the mortality risk associated with benzodiazepine prescribing (time-varying) and tested whether this risk differed by opioid prescribing.

**Results:** Within 1 year of HD initiation, 17.3% were prescribed short- and 5.5% were prescribed a long-acting benzodiazepine. Co-prescribing of opioids and short- (78.7%) and long-acting benzodiazepines (81.8%) were common. Opioid prescribing was associated with short- (aHR=2.07,95%CI:2.00-2.14) and long-acting benzodiazepine prescribing (aHR=2.30,95%CI:2.15-2.47). Patients prescribed a short-acting benzodiazepine were at 1.53-fold (95%CI:1.45-1.61) increased mortality risk; this risk was exacerbated to 1.78-fold (95%CI:1.63-1.94) increased mortality risk with opioid co-prescribing (pinteraction=0.01). In contrast, long-acting benzodiazepine prescribing was inversely associated with mortality (aHR=0.85,95%CI:0.75-0.96) and there was no differential risk by opioid prescribing (pinteraction=0.57).

**Conclusions:** Patients initiating HD are commonly co-prescribed short-acting benzodiazepines and opioids which was associated with a 1.8-fold increased mortality risk. High-risk co-prescribing of short-acting benzodiazepine/opioids should be recognized by physicians caring for this vulnerable population.

**Funding:** NIDDK Support

### TH-PO659

**Time Trends in Opioid Prescribing and Uncontrolled Pain in the Last Month of Life Among Patients with ESRD, 2010-2018**

**Melissa Wachtelmann,1,2 Ann M. O’Harc,1 Nancy L. Keating,2 Erin Beilstein-Wedel,1 Carly Meyer,1 Susan T. Crowley,1 Center for Healthcare Organization and Implementation Research, VA, Boston, MA; 2Harvard Medical School, Boston, MA.**

**Background:** Most patients with ESRD experience frequent, uncontrolled pain near the end of life. Opioids have long been a core component of pain management near the end of life. In response to the opioid crisis, organizations including the Veterans Health Administration (VA) and the Centers for Disease Control have developed guidelines intended to reduce opioid overuse at the population level. Little is known about how these efforts may have impacted opioid prescribing and pain among patients with ESRD near the end of life.

**Methods:** Using data from the VA, we identified all 3,370 patients with ESRD who died in a VA facility between 2010-2018 whose next-of-kin completed the Bereaved Family Survey. Using survey and pharmacy data, we assessed the mean daily opioid dose (in morphine equivalents) and the proportion with proxy-reported frequent uncontrolled pain, both focused on the last month of life. We used generalized estimating equations to assess time trends in these two outcomes after adjustment for patient demographics and medical comorbidity.

**Results:** From 2010 to 2018 mean daily opioid dose in the last month of life (in morphine equivalents) decreased by 1.4 mg per year (p=0.006) (see Figure for mean doses by year). From 2010 to 2018 the percentage of patients with frequent, uncontrolled pain in the last month of life increased by 1.9% per year (p=0.001) (see Figure for percentages by year). These differences persisted after adjustment for patient characteristics.

**Conclusions:** Decreases in opioid prescribing among patients with ESRD over the last decade have been accompanied by increases in uncontrolled pain near the end of life, highlighting potential unintended consequences of opioid safety initiatives.

**Funding:** Other NIH Support - National Institute on Aging, Veterans Affairs Support, Other U.S. Government Support

### TH-PO660

**Kidney Biopsy in Elderly Chinese Patients**

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**Background:** High-quality epidemiologic data on the spectrum of biopsy-proven kidney diseases among elderly patients are limited in China. This study aimed to examine the clinical characteristics and spectrum of kidney diseases in elderly patients who underwent native kidney biopsy.

**Methods:** We previously conducted a nationwide kidney biopsy survey including 178,784 patients from January 2002 to April 2018. A total of 10,597 native kidney biopsy performed in patients aged ≥65 years from 1590 hospitals across China were included in this study. The composition of kidney diseases and clinicopathologic correlations in different sexes, age groups, different period and regions were assessed.

**Results:** The most common indication for non-diabetic kidney disease in elderly patients was nephrotic syndrome (62.1%). Membranous nephropathy (MN) was the most frequent histological type (48.8%), followed by minimal change disease (9.8%) and IgA nephropathy (8.6%). We observed a increasing trend in the proportion of MN over the study period which was contemporaneous with a fall in the proportion of focal segmental glomerulosclerosis. There was no significant difference in major glomerular diseases between patients aged 65-79 years and 80 years after adjusting for sex, age group, different period and regions were assessed. Our study showed that the proportion of non-diabetic kidney disease (NDDK) is up to 62.7% in elderly diabetic patients underwent kidney biopsy, and the most common type of NDDK was MN. Compared with the patients aged 18-64 years underwent kidney biopsy over the same period, the proportion of renal artery injury (65.4% vs. 92.5%, p<0.001) was significantly higher, while phospholipase A2 receptor-positive MN (80% vs. 63.4%, p<0.05) was significantly lower in the very elderly patients (age≥80 years).
Conclusions: The spectrum of kidney diseases among elderly Chinese patients varied across sexes, age groups and regions and changed substantially from 2002 to 2018. Renal biopsy diagnoses by clinical syndrome in the elderly varied across sexes, age groups and regions and changed substantially from 2002 to 2018.

TH-PO661
The Difference Between eGFR by Cystatin C vs. Creatinine Provides Clinical Information About Frailty in SPRINT
O. Alison Potok,1 Joachim H. IX,1 Michael Shlipak,2 Ronit Katz,3 Amreet T. Hawfield,4 Michael V. Rocco,5 Walter T. Ambrosius,6 Monique E. Cho,7 Nicholas M. Pajewski,8 Anjay Rastogi,9 Dena E. Ritkin,10 UCSD, San Diego, CA;1 San Francisco VA Medical Center, San Francisco, CA;2 University of Washington, Seattle, WA;3 Wake Forest School of Medicine, Winston-Salem, NC, NC;4 University of Utah, Salt Lake City, UT;5 Division of Nephrology, Los Angeles, CA;

Background: In prior studies, the discrepancy between the glomerular filtration rate (eGFR) estimated using either cystatin C (eGFRCys) or creatinine (eGFRcr) has been treated as measurement error related to kidney function. We propose instead that clinical information about frailty and muscle strength is contained in these differences. We examined the difference between eGFR by cystatin C and creatinine and its relationship to frailty in cross-sectional and longitudinal analyses.

Methods: 9092 SPRINT participants had baseline measures of serum creatinine and cystatin C. eGFRCr and eGFRCys were calculated using CKD-EPI equations, and eGFRCys estimates were associated with underlying frailty. The difference between eGFRCys ≤ 60 mL/min/1.73 m2 and eGFRCr may provide important information on functional status and prognosis that should be incorporated into clinical reasoning when evaluating these measures.

Funding: Other NIH Support - T32 Institutional grant

Association of eGFRCys with frailty at baseline

TH-PO662
The Difference Between eGFR by Cystatin C vs. Creatinine Provides Clinical Information About Frailty in CHS
O. Alison Potok,1 Joachim H. IX,1 Michael Shlipak,1 Ronit Katz,1 Dena E. Ritkin,1 UCSD, San Diego, CA; University of Utah, Salt Lake City, UT; Division of Nephrology, Los Angeles, CA;

Background: Kidney function is typically assessed using serum creatinine. Cystatin C, beta 2 microglobulin and UACR measured with follow-up to December 31st, 2017 were included as markers of kidney function. The clinical significance of having a difference in estimated glomerular filtration rate (eGFR) by these 2 measures is unknown. We hypothesized that the magnitude of this difference is associated with frailty.

Methods: In 4101 community-dwelling older adults from the Cardiovascular Health Study (CHS) cohort, we investigated the cross-sectional association of the difference in eGFR by cystatin C vs. creatinine (eGFRCdiff) at baseline with prevalent frailty, using logistic regression, and the longitudinal association of eGFRCdiff with incident frailty and mortality at 5 years, using Poisson regression. eGFR was calculated using CKD-EPI equations based on either measure (eGFRCr and eGFRCys, respectively), and eGFRCys was eGFRCr - eGFRCdiff. Frailty was assessed based on the Fried frailty score.

Results: Mean (±SD) age was 72 (±5) years, eGFR was 73 (±17) and mean eGFRCdiff was -1.4 (range -68.0 to 70.6) mL/min/1.73m2. 39% were males, 5% African-American, 72% non-diabetics. Per 10-point increase in eGFRCdiff, the prevalence of moderate frailty was 10% lower, and that of severe frailty was 36% lower, in fully adjusted model (Table 1). Higher eGFRCdiff (per 10 mL/min/1.73m2) was associated with lower incidence rate for moderate (IRR 0.93, 95%CI [0.87, 0.99]) and severe (IRR 0.59, 95%CI [0.47, 0.74]) frailty, as well as lower risk of mortality (IRR 0.65, 95%CI [0.57, 0.76]) and hospitalization (IRR 0.70, 95%CI [0.62, 0.78]).

Conclusions: Those with a lower eGFRCr than eGFRCys were more likely to have prevalent frailty and were at higher risk for incident frailty and mortality. Considering eGFRCdiff as a marker of patients’ functional status may be a useful clinical tool to assess important geriatric outcomes.

Funding: Other NIH Support - T32 Institutional grant

*adjusted for age, gender, race, body mass index, hypertension, diabetes, anti-hypertensives at baseline, cholesterol, smoking, chronic kidney disease stage by eGFRcr

TH-PO663
Which Factors Explain the Difference Between Measured and Estimated GFR?
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Background: Estimated GFR (eGFR) based on serum creatinine (SCr) is frequently reported by clinical laboratories, despite a certain degree of imprecision. The aim of this study was to examine factors that could explain the difference between eGFR and measured GFR (mGFR) in an elderly population.

Methods: We analyzed data from the AGES-Kidney Study, in which 805 individuals above the age of 70 (mean (SD) age 79 (7.9) years) had mGFR values available with their corresponding eGFR measured on the same day. Cystatin C (Ccr) and creatinine (Ccr). The CKD-EPI equation was used to calculate GFR based on SCr (cGFRcr) or combination of SCr and cystatin C (cGFRcr-cys). The absolute difference between mGFR and cGFR (mGFR – cGFR) was determined and multivariable linear regression used to estimate the association of a range of variables such as age, sex, smoking status, body mass index, diabetes, albuminuria, hypertension, body composition, muscle strength and comorbidities with mGFR and cGFR.

Results: Mean (SD) mGFR in the study group was 62.4 (16.4) mL/min/1.73 m2, whereas mean cGFRcr was 65.7 (17.1) mL/min/1.73 m2 and mean cGFRcr-cys was 64.7 (17.9) mL/min/1.73 m2. The difference between mGFR and eGFR ranged from -36 to 46 mL/min/1.73 m2 for cGFRcr and -35 to 26 mL/min/1.73 m2 for cGFRcr-cys. In the multivariable linear regression model, significant predictors of the difference between mGFR and cGFR were age (p=0.047), thigh muscle mass (measured by computed tomography) (p=0.001), results of timed up and go test (p<0.001), eGFR (p=0.001) and urinary albumin/creatinine ratio (p=0.013). Significant predictors of the mGFR and cGFR-cys difference were age (p=0.002), sex (p=0.001), thigh muscle mass (p=0.001) and mGFR (p<0.05).

Conclusions: These preliminary results suggest that several variables, in particular those pertaining to muscle mass and strength, associate with the difference between mGFR and both cGFR and cGFR-cys. Incorporation of these variables into eGFR equations might yield more precise GFR estimates in the elderly than current equations. In addition, age and sex may not be adequately accounted for in these equations.

Funding: Government Support - Non-U.S.

TH-PO664
Albuminuria and eGFR in Midlife and Older Age as Risk Factors of Dementia: The ARIC Study
John D. B. Schaefer,1 Joseph Coresh,2 Aozhou Wu,1 Rebecca F. Gottesman,1 Tom Mosley,2 Morgan Grams,3 Richey Sherratt,4 Silvia Kotton,1 Johns Hopkins University, Baltimore, MD; 1Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 1Tel Aviv University and Johns Hopkins University, Tel Aviv, Israel; 1The Johns Hopkins University, Baltimore, MD; 1Univ. of Miss. Med Center, Jackson, MS; 1Johns Hopkins, Baltimore, MD;

Background: Urine albumin-creatinine ratio (uACR) and estimated glomerular filtration rate (eGFR) define chronic kidney disease (CKD) and are related to microvascular and macrovascular outcomes. Several previous studies by examining UACR and eGFR measured at midlife and older age as risk factors for dementia. Furthermore, we compare eGFR based on creatinine with eGFR based on cystatin C and beta 2 microglobulin.

Methods: We studied 9,967 participants aged 54-74 years in the Atherosclerosis Risk in Communities (ARIC) study who attended visit 4 (1996-1999) and had creatinine, cystatin C, beta 2 microglobulin and UACR measured with follow-up to December 31st, 2017. We evaluated the hazard of incident dementia associated with eGFR (based on creatinine, cystatin C and beta 2 microglobulin) and log UACR adjusted for age, sex, education and apolipoprotein E4 level (Model 1) and additionally for smoking, body mass index, diabetes and antihypertensive medication (Model 2). We compared eGFR and UACR associations to those observed among visit 5 participants (N=4,626, age 70-90, 2011-2013). Effect sizes for each measure of CKD were normalized to the interquartile range of UACR at Visit 4.

Results: We observed 1,821 incident dementia cases over 16 years of follow-up (438 after visit 5). Risk of dementia was higher with higher levels of albuminuria and lower levels of eGFR but only when GFR estimation was based on cystatin C or beta 2
microglobulin (Table). There was no substantial difference in risk of dementia associated with eGFR or UACR between the two baseline visits.

Conclusions: Higher albuminuria is strongly related to dementia incidence. Lower eGFR shows similar associations but only when the estimation is based on cystatin C or beta 2 microglobulin. This could be explained by newer biomarkers being less influenced by muscle mass. The results are similar in midlife compared to older age.

Funding: Other NIH Support - NHLBI

<table>
<thead>
<tr>
<th>Measures of CKD</th>
<th>Baseline Visit 4, ages 54-74 years</th>
<th>Baseline Visit 4, ages 79-90 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>1.00 (0.92 - 1.06)</td>
<td>1.00 (0.94 - 1.08)</td>
</tr>
<tr>
<td>Baseline eGFR &lt;60</td>
<td>1.00 (0.92 - 1.06)</td>
<td>1.00 (0.94 - 1.08)</td>
</tr>
</tbody>
</table>

Table: Adjacent HRs (95% CI) for dementia incidence after midlife and after older age; by measure of CKD.

The predictors for 1-year mortality among elderly patients with CKD Stage 4 and 5 initiated on hemodialysis were female gender and anemia (hemoglobin <10g/dL). Specific measures to address these risk factors must be implemented to improve survival in these patients.

Conclusions: The predictors for 1-year mortality among elderly patients with CKD Stage 4 and 5 initiated on hemodialysis were female gender and anemia (hemoglobin <10g/dL). Specific measures to address these risk factors must be implemented to improve survival in these patients.

Results: Eighty three participants were included in the study. The mean age was 73 years old, females comprised 56%, Diabetic Kidney Disease accounted to 58%, cardiovascular and metabolic co-mobilities were present in 91% and 65% of cases, respectively; and majority had no pre-hd nephrology care at 56%. Seventy five percent survived after 1 year from HD initiation. Female gender and hemoglobin level of <10g/dL were significant predictors of mortality.

Conclusions: Higher albuminuria is strongly related to dementia incidence. Lower eGFR shows similar associations but only when the estimation is based on cystatin C or beta 2 microglobulin. This could be explained by newer biomarkers being less influenced by muscle mass. The results are similar in midlife compared to older age.

Results: One hundred thirty-four subjects (41%) had CKD. During HD, participants with CKD had 5.8 cm/s (95% CI 0.6-11.0) slower gait speed, 2.0 cm (95% CI 0.05-4.7) shorter step length, and 2.0% (95% CI 0.2-3.8) greater time in the double support phase of the gait cycle compared with those without CKD. These abnormalities were related to severity of CKD: among participants with CKD, every 10 ml/min/1.73m2 lower eGFR was independently associated with 3.3 cm/s (95% CI 0.4-6.1) slower gait speed, 2.0 cm (95% CI 0.7-3.2) shorter step length, 4.0 cm (95% CI 1.5-6.4) shorter stride length, 1.2% (95% CI 0.7-1.8) less time in the swing phase, and 1.6% (95% CI 0.7-2.5) greater time in the double support phase. To better capture the multidimensional characteristics of gait, factor analysis was performed using the principal component method and produced 3 independent gait domains: Rhythm, Pace, and Variability. Every 10 ml/min/1.73m2 lower eGFR was associated with 0.2 standard deviation (95% CI 0.1-0.3) poorer performance in the Rhythm domain. There was no significant association between eGFR and the Pace or Variability domains.

Conclusions: CKD is associated with quantitative gait abnormalities while performing WW2 tasks. Future studies should examine whether poorer performance on WW2 tasks contributes to fall risk and is an early indicator of cognitive dysfunction in CKD.

Funding: NIDDK Support, Other NIH Support - NIA

Background: The worldwide incidence of kidney failure is rising. Globally, 5-10 million people die annually from kidney disease. In 2015, the Philippines reported a mortality rate of 3.9 per 100,000 population for kidney diseases. Of the 32,077 Filipinos on dialysis in 2015, 18,603 were initiated within the same year. Most are 60 years old and older, diabetic, and have other co-morbid conditions. Because, dialysis is a high-cost treatment, the Philippines enforced the Universal Health Coverage Bill. However, Filipinos continue to bear the financial burden of hemodialysis. These issues along with the Filipino cultural context question the practicality of initiating hemodialysis among the elderly. This study aims to identify factors significantly associated with early mortality and obtaining the early mortality rate among elderly Filipino patients initiated on hemodialysis and those who were not. To our knowledge, this is the first study of its kind on Filipinos.

Methods: This is a prospective, observational, cohort study. Dialysis-naive elderly patients admitted from January to April 2019 in a tertiary hospital in the Philippines were advised to initiate hemodialysis were enrolled. Demographic data and the presence of the following risk factors were obtained: diabetes mellitus, congestive heart failure, peripheral arterial disease, dysrhythmia, active malignancy, severe behavioral disorder, un planned dialysis, hyperalbuminemia, ischemic heart disease, ventilator dependency, cora, sepsis, hepatic failure, COPD, BMI <18.5 kg/m2, and total dependency for transfers. Individual outcomes (death against survival) between the two groups (initiated on hemodialysis against those were not—refused or consented for but were not initiated on hemodialysis) will be followed until four months after their attending nephrologists advised hemodialysis.

Results: 52 patients were enrolled in the study—52% initiated hemodialysis while 48% did not. Preliminary data shows more deaths among those initiated on hemodialysis (37%) than those who were not (32%). Risk factors identified among those initiated on hemodialysis and died include unplanned dialysis (100%), total dependency for transfers (83%), diabetes mellitus (67%), and hyperalbuminemia (67%).

Conclusions: The study is currently on its follow-up phase and will end by August 2019.

Post-thursday

TH-P0666

Predictors for 1-Year Mortality Among Elderly Patients with CKD Stage 4 and 5 Initiated on Hemodialysis at Divine Word Hospital, Tacloban City, Philippines, 2014-2016

Joyce Rosario A. Mataza-So, Internal Medicine-Nephrology, Divine Word Hospital, Tacloban City, Philippines.

Background: Chronic kidney disease (CKD) prevalence among the elderly patients is increasing. This study aimed to describe the clinical and demographic profile of the elderly patients with CKD Stages 4 and 5; to determine the 1 year outcomes after HD initiation as to survival, death and its causes of mortality and to identify the predictors for 1-year mortality among elderly CKD patients.

Methods: A descriptive retrospective study involving all elderly patients diagnosed with CKD Stage 4 and 5 initiated on hemodialysis at Divine Word Hospital in the year 2014 to 2016. Patients' demographic and clinical data, and the outcomes on hemodialysis in the form of 1-year survival or death were identified. Data were analyzed with the use of frequency distribution and percentages for categorical variables, and mean and standard deviation for continuous variables. Univariate cox regression was employed to identify the predictors of mortality.

Results: Among 330 nondisabled adults ages 65 years of age from the community participated in quantitative and clinical gait assessments, including a validated cognitive-motor dual task measure (Walking While Talking [WW1] Test). Multivariable linear regression that adjusted for demographics, body mass index, comorbidities, and medications was performed to examine the relationship between estimated glomerular filtration rate (eGFR) and WWT gait markers. CKD was defined as an eGFR <60 ml/min/1.73m2.

Conclusions: CKD is associated with quantitative gait abnormalities while performing WW2 tasks. Future studies should examine whether poorer performance on WW2 tasks contributes to fall risk and is an early indicator of cognitive dysfunction in CKD.

Funding: NIDDK Support, Other NIH Support - NIA

TH-P0667

Risk Factors for Early Mortality Among Elderly Filipino Patients with Chronic Kidney Disease: A Comparative Study

Ho, Joe, Chu, Zhan Shi, Relampagos, Jennifer Ivy, San Pedro Hospital of Davao City, Davao City, Philippines.

Background: The incidence of ESKD among elderly patients in the Philippines is rising and is a serious health problem. Developing countries in the Asia-Pacific region suffer from the high prevalence of ESKD among elderly patients. Filipinos continue to bear the financial burden of hemodialysis. These issues along with the Filipino cultural context question the practicality of initiating hemodialysis among the elderly. This study aims to identify factors significantly associated with early mortality and obtaining the early mortality rate among elderly Filipino patients initiated on hemodialysis and those who were not. To our knowledge, this is the first study of its kind on Filipinos.

Methods: This is a prospective, observational, cohort study. Dialysis-naive elderly patients admitted from January to April 2019 in a tertiary hospital in the Philippines were advised to initiate hemodialysis were enrolled. Demographic data and the presence of the following risk factors were obtained: diabetes mellitus, congestive heart failure, peripheral arterial disease, dysrhythmia, active malignancy, severe behavioral disorder, unplanned dialysis, hyperalbuminemia, ischemic heart disease, ventilator dependency, cora, sepsis, hepatic failure, COPD, BMI <18.5 kg/m2, and total dependency for transfers. Individual outcomes (death against survival) between the two groups (initiated on hemodialysis against those were not—refused or consented for but were not initiated on hemodialysis) will be followed until four months after their attending nephrologists advised hemodialysis.

Results: 52 patients were enrolled in the study—52% initiated hemodialysis while 48% did not. Preliminary data shows more deaths among those initiated on hemodialysis (37%) than those who were not (32%). Risk factors identified among those initiated on hemodialysis and died include unplanned dialysis (100%), total dependency for transfers (83%), diabetes mellitus (67%), and hyperalbuminemia (67%).

Conclusions: The study is currently on its follow-up phase and will end by August 2019.

TH-P0668

Poor Outcomes in Kidney Transplant (KT) Candidates and Recipients with History of Falls

Nadia M. Chu,2 Zhan Shi,2 Christine E. Haugen,2 Silas Norman,1 Dorry L. Segev,3 Mara McAdams-DeMarco.2 1University of Michigan Health Systems, Ann Arbor, MI; 2Johns Hopkins, Baltimore, MD.

Background: In patients with ESKD, serious falls resulting in hospitalization fractures lead to lower chance of listing or KT. While it is likely that candidates and recipients have high frequency of injurious and noninjurious falls, it is unclear if less serious, noninjurious falls also lead to lower access to KT and if these risks extend to poor outcomes post-KT.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Methods: Using a 2-center cohort of KT candidates (n=3,666) and recipients (n=769), we assessed time to listing (Cox), waitlist mortality (Cox), and KT rate (Poisson) for KT candidates by history of falls (self-report, past 6 months) and recurrent falls (a2 falls); for recipients, we assessed risk of mortality (Cox), all-cause graft loss (ACGL) (Cox), and length of stay (LOS) (Poisson).

Results: In candidates, 16.3% had history of falls; 6.5% had recurrent falls. With recurrent falls had lower chance of listing (aHR=0.9, 95%CI:0.6-0.8); those with single fall had a lower KT rate (aIRR=0.7, 95%CI:0.5-0.9). Single and recurrent falls were associated with greater mortality risk at evaluation and 1-year after evaluation; this risk declined over time. In KT recipients, 12.5% had a history of falls; 5.1% had recurrent falls. Single falls were associated with greater mortality risk (aHR=9.2, 95%CI:3.4-25.1) and ACGL (aHR=7.3, 95%CI:2.9-18.6) at KT and at 1-year post-KT; these risks declined thereafter. KT recipients with recurrent falls were at increased risk of a longer LOS (aHR=3.4, 95%CI: 1.0-1.3).

Conclusions: Candidates (6.5%) and recipients (5.1%) had recurrent falls which were associated with decreased chance of listing and increased risk of waitlist mortality, post-KT mortality/ACGL, and longer LOS. Centers should consider employing falls prevention strategies as part of a comprehensive prehabilitation intervention.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging (NIA)

Table 3. Access to KT and Risk Adverse Outcomes Among Kidney Transplant (KT) (n=3,666) and Recipients (n=769) by Falls. Hazard Ratios and 95% Confidence Intervals are presented from Cox Regression Model unless otherwise indicated. Associations that are statistically significant at p<0.05 are bolded.

<table>
<thead>
<tr>
<th>KT candidates</th>
<th>n (%)</th>
<th>Falls (≥2)</th>
<th>1%</th>
<th>2%</th>
<th>3%</th>
<th>4%</th>
<th>5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Falls</td>
<td>3,300</td>
<td>0.74</td>
<td>1.29</td>
<td>1.63</td>
<td>1.78</td>
<td>1.94</td>
<td>1.98</td>
</tr>
<tr>
<td>Fall 1</td>
<td>366</td>
<td>0.76</td>
<td>1.24</td>
<td>1.61</td>
<td>1.76</td>
<td>1.92</td>
<td>1.96</td>
</tr>
<tr>
<td>Fall 2</td>
<td>100</td>
<td>0.64</td>
<td>1.33</td>
<td>1.68</td>
<td>1.88</td>
<td>2.01</td>
<td>2.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KT recipients</th>
<th>n (%)</th>
<th>Falls (≥2)</th>
<th>1%</th>
<th>2%</th>
<th>3%</th>
<th>4%</th>
<th>5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Falls</td>
<td>769</td>
<td>0.70</td>
<td>1.21</td>
<td>1.57</td>
<td>1.74</td>
<td>1.90</td>
<td>1.93</td>
</tr>
<tr>
<td>Fall 1</td>
<td>100</td>
<td>0.69</td>
<td>1.23</td>
<td>1.59</td>
<td>1.76</td>
<td>1.91</td>
<td>1.94</td>
</tr>
<tr>
<td>Fall 2</td>
<td>36</td>
<td>0.67</td>
<td>1.26</td>
<td>1.62</td>
<td>1.83</td>
<td>1.98</td>
<td>2.06</td>
</tr>
</tbody>
</table>

TH-PO670
Geriatric Nephrology Patients Deteriorating and Dying in Acute Care: How Do They Die?
Anna Bendall,1 Georgia Harris,2 Jennifer L. Weil,3 Caroline L. Scott,4 David Marco,1 Kathryn Ducharlet,1 1St Vincents Melbourne, Melbourne, VIC, Australia; 2The University of Melbourne, Melbourne, VIC, Australia; 3St Vincent’s Hospital Melbourne, VIC, Australia; 4St Vincent’s Hospital Heidelberg, Melburn, NSW, Australia.

Background: Older patients with advanced kidney disease have complex medical and psychosocial needs, and providing comprehensive end of life care (EOLC) within acute healthcare settings is a challenge increasingly encountered by nephrologists. Data relating to the practice of EOLC within the inpatient nephrology setting is required to better inform and improve service provision. This study aims to review current care practices for deteriorating and dying patients admitted to the nephrology unit at St Vincent’s Hospital Melbourne (SVHM), Australia.

Methods: Retrospective cohort study of patients aged ≥60years who died while admitted to the Nephrology unit at SVHIM between 1/1/2013 and 31/12/2018. During the study period, 56 patients died while admitted to the nephrology unit (average age 73.8 years), and 84% were receiving long term dialysis (55% haemodialysis, 29% peritoneal dialysis). The average length of admission was 14 days, and patients had more than 2 admission in their final year of life. On average four invasive interventions were performed in the final 48 hours of life, including dialysis, intubation, parenteral feeding, intravenous fluids or antibiotics. Patients were admitted to the intensive care unit (ICU) in 42% of cases, and one third (32%) died in the ICU. At the time of admission only two patients had a formal advance care directive in place. During the admission, on the contrary of previous discussions (75%) a documented discussion regarding goals of care (GOC) was held between a physician and the patient or caregiver, on average 3 days prior to death. Consultation by palliative care services occurred on one third (33%) of occasions, and in the final 24 hours an average of two uncontrolled symptoms were documented for each patient, including pain (52%), dyspnoea (41%), drowsiness (32%), and nausea (23%).

Conclusions: The majority of geriatric nephrology patients who died in the acute setting were receiving long term dialysis, and had a high burden of uncontrolled symptoms. One third of these deaths occurred in the ICU, and very few had advance care directives. This study illustrates opportunities for the clinician to improve care for older renal patients through earlier recognition of the dying patient, enhanced communication during EOLC planning, and greater emphasis on symptom control.

TH-PO671
Hemodialysis Patients Who Receive Physical Therapy: An Opportunity to Modify the Frailty Trajectory?
Nancy G. Kutner,1 Yijian Huang,2 Emory University School of Medicine, Atlanta, GA; 3Biostatistics and Bioinformatics, Emory University, Atlanta, GA.

Background: Frailty markers, physical activity and gait speed (and muscle strength to a lesser extent), show decline over time among hemodialysis (HD) patients (J Gerontol 2019), but whether these patterns vary in association with receipt of physical therapy (PT) has not been investigated. In Medicare claims, we identified dates and types of outpatient PT services received by HD patients during their participation in the USRDS ACTIVE-ADIPose Study (AAS). We examined frailty measures assessed before and after receipt of PT that included therapeutic exercises (CPT code 97110) “to develop strength and endurance, range of motion and flexibility.”

Methods: The AAS included a multi-center cohort of 771 prevalent HD patients aged 20-92 and was conducted 2009-2013 at 14 outpatient dialysis clinics in the Atlanta GA and San Francisco areas. Institutional review boards (Emory University; UCSF) approved the study and all participants provided written informed consent. At baseline and two annual follow-up assessments, trained study coordinators administered the Minnesota Leisure Activity and Performance Battery (SPPB) that includes chair stand, balance, and walk (gait speed) tests. Consistent with prior research, individuals with LTA-assessed k/week≥500 were considered sedentary and 500-7k/week non-sedentary, and total SPPB score (0-12) was categorized into three ordinal groups (<6, 7-9, 10-12).

Results: Medicare claims for outpatient PT were identified for 32 AAS patients: average age 73%, 57% women, 81% black. Patient-reported reasons for PT emphasized mobility and strength issues. At their post-PT follow-up evaluation: (1) Half had LTA scores ≤500 (non-sedentary), and k/week activity had increased from <500 pre-PT to 500+ post-PT for half of the non-sedentary group; (2) Although measured gait speed for most participants post-PT was consistent with values that characterize “limited community ambulators” (0.4-0.8 m/sec), two-thirds of participants either maintained SPPB scores > 7 pre-post PT or achieved SPPB scores > 7 post-PT.

Conclusion: Continued study of the role of PT in HD patient care is merited in larger patient cohorts. PT goals are patient-specific and include maintenance as well as improvement of function, with implications for the trajectory of frailty.

Funding: NIDDK Support
TH-PO672
Physical Activity and Fatigue as Measures of Day-to-Day Resilience in Older Hemodialysis Patients
Rasheeda K. Hall, Jeannette Rutledge, Richard Sloane, Ciara T. Green, Carl F. Pieper, Cathleen Colon-emeric, Katherine Hall. Duke University, Durham, NC.

Background: Hemodialysis (HD) is a physiological stressor requiring day-to-day resilience, or an innate ability to recover after a HD session. Our objective was to assess whether physical activity (PA) and self-reported fatigue are representative measures of day-to-day resilience.

Methods: We recruited ambulatory adults aged ≥55 years receiving HD who did not have advanced dementia, hospice care, or long-term care residence. Participants completed PA monitoring via wrist actigraphy for 14 days with concurrent fatigue assessment: "On a scale of 0-10, rate your fatigue, with 10 being fatigue as bad as you can imagine". Fatigue was assessed within 4 hours after HD and in the morning and afternoon on non-HD days. Prior to a HD session, we assessed physical function via the short physical performance battery (SPPB) (range, 0-12) and grip strength. We measured correlation between PA (steps) and concurrent fatigue in 4-hour intervals. PA variability, a measure of PA change when not at HD, was calculated from the standard deviation of the difference (absolute value) in steps of each 4-hour interval. We measured correlation between PA variability and physical function.

Results: Among 29 participants, mean±SD age was 70.6±4.8 years, 55.2% (n=16) male, 72.4% (n=21) black race, and mean years of dialysis was 3.9±3.6. Mean SPPB, gait speed (from SPPB), and grip strength were 6.3±3.2, 0.72±0.3 m/s, and 57.8±16.7 kg, respectively. Mean PA monitoring time was 12.9±5.2 days. Mean daily steps was lower on HD days than non-HD days (967±1,550 vs. 1,158±681.6 ±0.04). Mean fatigue scores on HD days and non-HD days were similar (4.1±2.7 vs. 3.5±2.5) (p=0.06). The correlation between 4-hour post-dialysis PA and fatigue was d=0.19 (n=102, p=0.06). The correlation between PA and fatigue at all other 4-hour intervals was -0.17 (n=210, p=0.01). Mean PA variability was 140.0±67.3 steps and its correlation with SPPB, gait speed, and grip strength was 0.47 (n=28, p=0.01), 0.52 (n=27, p=0.001), and 0.71 (n=27, p=0.0001), respectively.

Conclusions: In this sample of older HD patients, higher PA and greater PA variability were associated with lower fatigue and better physical function, respectively. PA monitoring and interval fatigue may be useful measures for interventions targeting resilience.

Funding: Other NIH Support - National Institute on Aging; National Center for Advancing Translational Sciences, Private Foundation Support

TH-PO673
Peripheral Artery Disease Exacerbates the Prognosis of Frailty in Patients with Hemodialysis
Hidemi Takeuchi,1 Haruhito A. Uchida,2 Nozomu Otaka,2 Ryoko Umebayashi,2 Hitodetsu Kanai,1 Jun Wada,2 1Kokura Memorial Hospital, Kitakyushu, Japan; 2Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University, Okayama, Japan.

Background: The clinical condition of frailty is the most problematic expression of the patients with hemodialysis (HD). The development of frailty is tightly associated with peripheral artery disease (PAD). However, the prognosis of the HD patients with frailty complicated with PAD remains unexplored. The purpose of this study is to identify the influence of PAD on the prognosis of HD patients with frailty.

Methods: We conducted a prospective and multicenter clinical study at 6 institutions. To evaluate the frailty status, we used the modified Fried’s frailty phenotype model. PAD was defined according to the definition of TASC II (Trans-Atlantic Inter-Society Consensus II). Our primary endpoint of this study was the patients’ survival and hospitalization.

Results: Of the 542 patients, 388 HD patients including 82 patients with frailty (21.4%), 204 with pre-frailty (52.6%) and 101 without frailty (26.0%), were enrolled in this study. At baseline, the participants were 67.2±11.9 years of age with more male gender (62.4%) than female. With an average follow-up period of 24.2 months, a total of 68 patients died; 26.5% of patients with frailty, 17.6% with pre-frailty and 9.9% without frailty. Cox proportional hazards model analyses indicated that frailty was associated with risk of death (hazard ratio [HR] 2.42, 95% confidence interval [CI] 1.22–4.23, adjusted for age and gender) and independently associated with the combined outcome of death or hospitalization (HR 2.85, 95% CI 1.74–4.69, adjusted for age, gender and all comorbidities), despite that PAD had no independent association with death and lower risk of the combined outcome. Furthermore, frailty complicated with PAD was independently associated with higher risk of death (HR 4.72, 95% CI 1.37–16.26, adjusted for age, gender and all comorbidities) and the combined outcome (HR 5.89, 95% CI 2.94–11.77, adjusted for age, gender and all comorbidities), compared with frailty or PAD only.

Conclusions: Frailty itself significantly worsens the prognosis of patients with hemodialysis, and the presence of PAD further exacerbates the prognosis of frail patients with HD.

TH-PO674
Blood Pressure Lowering for the Prevention of Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis
Diarmuid Hughes, Conor S. Judge, Robert P. Murphy, Maria Costello, Michelle Canavan, Martin O’Donnell. Health Research Board Clinical Research Facility, Galway, Ireland.

Background: The benefit of blood pressure lowering for the prevention of cognitive impairment and dementia is unclear.

Methods: We performed a meta-analysis of large randomized controlled trials of antihypertensive therapy versus control that reported cognitive decline, cognitive impairment or dementia as an outcome measure. We determined whether antihypertensive therapy reduced the risk of cognitive impairment and/or dementia and explored whether its effect varied by baseline blood pressure, blood pressure difference between treatment groups and/or length of follow-up.

Results: Fourteen randomized controlled trials were eligible for inclusion. Antihypertensive therapy was associated with a statistically significant reduced risk of cognitive impairment (n=9) (odds ratio [OR], 0.92; 95% confidence interval [CI], 0.87-0.98) and dementia (n=12) (OR, 0.93, 95% CI, 0.88 to 0.99). Subgroup analysis of trials with a cumulative blood pressure difference above the median (6.5 mmHg) reduced the risk of dementia further (OR, 0.87; 95% CI, 0.80-0.96) (Figure 1). Antihypertensive therapy was not associated with a statistically significant reduction in the Mini Mental State Examination (MMSE) cognitive impairment score (n=5) (Mean change in MMSE, 0.44, 95% CI, -0.22–1.10) or a combination of the MMSE and the Trail Making Test (TMT) (n=7) (Standardised mean change, 0.10, 95% CI, -0.02-0.22). Meta-regression of baseline blood pressure, blood pressure difference or years of follow-up did not explain significant heterogeneity between studies for cognitive impairment or dementia risk.

Conclusions: Antihypertensive therapy reduces the risk of cognitive impairment and dementia.

TH-PO675
Blood Pressure Lowering and Cognition: A Systematic Review and Meta-Analysis
Aditi Gupta,1 Sophy Perdomo,1 Srinivasan Beddu,1 Sandra Billinger,2 Jeffrey M. Burns,3 Gary Gronseth,1 1University of Kansas Medical Center, Kansas City, KS; 2KU Medical Center, Kansas City, KS; 3University of Utah School of Medicine, Salt Lake City, UT; 4University of Kansas School of Medicine, Kansas City, KS.

Background: Hypertension is a known risk factor for developing cognitive impairment and dementia, both vascular dementia and Alzheimer’s disease. Here we present the results of our systematic review of the effect of lowering of blood pressure on cognition.

Methods: We conducted a systematic review and meta-analysis of randomized placebo-controlled trials with a pre-specified objective outcome of cognition, and with pharmacological interventions to lower blood pressure for at least 12 months in adults >60 years. We searched MEDLINE, CENTRAL and The Cochrane Library (inception to May 2018). Two independent reviewers assessed trial quality and extracted data. Since the available outcomes were different in the selected studies, we standardized these outcomes by calculating Cohen’s D (SMD).

Results: Our initial search identified 2022 records. 1846 abstracts were reviewed after removing duplicate records and out of these, 28 full-text articles pulled which met above inclusion criteria. Ten trials including 31,357 participants were included in the final analysis. The duration of the studies ranged from 1 year to median of 5.11 years.
Baseline Diastolic Blood Pressure Does Not Influence the Effect of Systolic Blood Pressure Lowering on Cognition in Type 2 Diabetes Mellitus

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Background: In patients with low baseline diastolic blood pressure (DBP), lowering of systolic blood pressure (SBP) would lead to further lowering of mean arterial blood pressure. This can theoretically decrease cerebral perfusion and cognition. We examined the influence of baseline DBP on the effect on cognition.

Methods: We analyzed data from the Memory in Diabetes (MIND) sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD). We grouped the subjects by tertiles of baseline DBP and compared the effects of intensive (target <120 mm Hg) and standard (target <140 mm Hg) SBP control on cognition. Cognition was measured by Digit Symbol Substitution test (DSST), Rey Auditory Verbal Learning Test (RAVT), Stroop test and the Mini Mental State exam (MMSE).

Results: Table 1 summarizes the baseline demographics of the 1,610 ACCORD-MIND participants divided by tertiles of DBP. Participates with lower DBP were older, and had a longer duration of diabetes. Figure 1 shows the DSST scores in the standard and intensive BP groups by baseline DBP tertiles. There was no difference in the change in DSST scores in the three groups.

Conclusions: Intensive SBP reduction in type 2 diabetes mellitus does not adversely affect cognition, even in those with low baseline DBP.

Funding: NIDDK Support, Other NIH Support - NIA

Table 1: Baseline demographics of the 1,610 ACCORD-MIND participants divided by tertiles of DBP. Participates with lower DBP were older, and had a longer duration of diabetes.
Association of Ambulatory Blood Pressure Pattern with Cognitive Function: The SPRINT Ambulatory Blood Pressure Study

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1University of Utah, Salt Lake City, UT; 2Medical University of South Carolina, Charleston, SC; 3Memphis VA Medical Center, Memphis, TN; 4The OSU Wexner Medical Center, Columbus, OH; 5Mayo Clinic, Jacksonville, FL; 6Ochsner Clinic Foundation, New Orleans, LA; 7Georgetown University, Potomac, MD; 8Tufts Medical Center, Boston, MA; 9National Institute of Neurological Disorders and Stroke, Rockville, MD; 10University of Minnesota, Minneapolis, MN; 11UCSD, San Diego, CA; 12Wake Forest, Wake Forest, NC; 13MUSC, Charleston, SC; 14Columbia University Medical Center, New York, NY.

Background: In prior work with healthy older adults, abnormal night-to-day SBP ratio and lower 24 hour diastolic BP on ABPM were associated with worse cognitive function, findings not identified using clinic blood pressures. We examined whether these ABPM parameters were associated with cognitive function in participants in SPRINT, a randomized controlled trial of two different blood pressure targets in hypertensive adults.

Methods: Within SPRINT, 897 participants had 24 hour blood pressure measured collected at the 27 month visit. These readings were within 3 months of a comprehensive cognitive assessment. We examined whether ABPM parameters were associated with scores on the Montreal Assessment of Cognitive Function, logical memory delayed recall, and other symbol task scores, after evaluating for interaction with random treatment assignment. We calculated odds ratios based on a beta-binomial model, with higher odds indicating better cognitive performance.

Results: Mean age was 71.5 ± 9.5, 67% were Caucasian. The intensive BP group had lower SBP, used more BP medication than the standard BP group. On the 3 cognitive tests studied, there was no difference in score between those in the intensive and standard groups, so these were combined. There was no association between night-to-day ratio and cognitive function test scores. After multivariable adjustment there was a modest association between higher diastolic BP (both in clinic and 24-hour) and better cognitive test scores on digit-symbol coding (figure).

Conclusions: Night-to-day blood pressure ratio was not associated with cognition in SPRINT. There was a modest association with diastolic blood pressure both in clinic and over 24h. This suggests that in this setting, non-dipping did not strongly associate with scores on cognitive function tests.

Funding: NIDDK Support

Dietary Sodium Intake and Cognitive Impairment in the Chronic Renal Insufficiency Cohort (CRIC)

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Background: Cognitive dysfunction is a well-documented occurrence in individuals with chronic kidney disease (CKD), affecting multiple domains of cognitive function. Dietary sodium may influence cognitive function via effects on cerebrovascular function and cerebrovascular blood flow. We hypothesized that high dietary sodium intake, as measured by 24-hour urine sodium excretion, is as associated with a decline in cognitive function over time in adults with CKD.

Methods: 1,724 participants in the observational cohort study, CRIC, with measurement of 24-hour urine sodium excretion and modified mini mental state exam (3MS) score at baseline and year 4, who were free from baseline cognitive dysfunction were included. Multivariable logistic regression was used to examine the association between baseline 24-hour urine sodium excretion and odds of incident cognitive impairment, defined as a decline 3MS score a1.0 SD below mean change in completion score divided by SD change in 3MS score [95% CI, 0.26–5.08]. High baseline sodium intake was defined as excretion >150 mmol/d.

Results: Participants were 59±11 years, baseline estimated glomerular filtration rate (eGFR) was 45±13 ml/min/1.73m2, and baseline 24-hour sodium excretion was 164±76 mmol/d. During follow-up of 4.1±0.2 years, 185 CRIC participants (11%) had a clinically significant decline in 3MS score (i.e. incident cognitive impairment). After adjustment for demographics, clinic site, smoking, body mass index, eGFR, cardiovascular risk factors, physical activity, systolic blood pressure, and 24-hour urine protein, potassium, and creatinine, high dietary sodium intake was associated with increased odds of incident cognitive impairment (OR: 1.56, 95% CI: 1.08-2.27 vs low sodium intake).

Conclusions: In adults with CKD who participated in CRIC, higher sodium intake was independently associated with increased odds of incident cognitive impairment.

MRI Markers of Cerebral Small Vessel Disease in CKD Patients with TIA and Minor Stroke

Deborah Kelly, Peter M. Rothwell. on behalf of the Oxford Vascular Study Centre for the Prevention of Stroke and Dementia, University of Oxford, Oxford, United Kingdom.

Background: It has been hypothesized that cerebral small vessel disease (SVD) and CKD may be part of a multi-system vasculopathy, but their association may simply be as a result of shared risk factors (eg, hypertension).

Methods: In a population-based study of transient ischemic attack and ischemic stroke (OxVASC), we evaluated the MRI markers of cerebral SVD, including lacunes, white matter hyperintensities, cerebral microbleeds, and enlarged perivascular space. We studied the age-specific associations of CKD and total SVD burden (total SVD score) adjusting for age, sex, vascular risk factors, and premorbid blood pressure (mean blood pressure during 20 years pre-event).

Results: 1718 patients had complete magnetic resonance imaging protocol and medical data measured at baseline. CKD was associated with total SVD score (odds ratio [OR], 2.83; 95% confidence interval [CI], 2.28-3.53; P<0.001), but only at age <60 years (<60 years: OR, 8.43; 95% CI, 3.12-22.78; P=0.001; 60–79 years: OR, 1.38; 95% CI, 1.02–1.87; P=0.038; ≥80 years: OR, 1.09; 95% CI, 0.74–1.4; P=0.676). The overall association of renal impairment and total SVD score was also attenuated in older age groups for age, history of hypertension, and diabetes mellitus (adjusted OR, 1.05; 95% CI, 0.83–1.34; P=0.67), but the independent association of renal impairment and total SVD score at age <60 years was maintained (adjusted OR, 6.07; 95% CI, 2.22–16.59; P<0.001). Associations of renal impairment and SVD were consistent for each SVD outcome of the Q-Cohort Study

Association Between Geriatric Nutritional Risk Index (GRNI) and the Increased Risk for Stroke in Patients Receiving Hemodialysis: Ten-Year Outcome of the Q-Cohort Study

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Background: Geriatric nutritional risk index (GRNI), a useful tool for the evaluation of nutritional status, is associated with increased risk for cardiovascular adverse events in hemodialysis patients. Few studies have examined the association between GRNI level and the incidence of stroke in patients receiving hemodialysis.

Methods: A total of 3047 patients registered to the Q-Cohort Study, a multicenter, prospective observational cohort of hemodialysis patients, were examined. The main outcomes were the development of brain hemorrhage and infarction. The mean exposure was GRNI, calculated by serum albumin level and body mass index. Patients were divided into quartiles based on the baseline GRNI level, Q4 =99.8, Q3 =95.6-99.8, Q2 =90.7-95.5, Q1 =<90.7. The risks for either brain hemorrhage or hemorragh were estimated by multivariable-adjusted Cox proportional hazard risk models.

Results: During the follow-up period of 10 years, 149 patients developed brain hemorrhage and 326 patients developed brain infarction. Cox proportional hazard risk analysis showed that the risks for brain hemorrhage and infarction in Q4 were significantly higher than that in Q4 group: hazard ratio [95% confidence interval], 1.69 [1.19-2.42] and 1.85 [1.08-3.16], respectively. Furthermore, restricted cubic spline curves showed that a lower GRNI was incrementally associated with an increased risk for both brain hemorrhage and infarction.

Conclusions: Our results suggest that lower GRNI is a risk factor for brain hemorrhage and infarction in maintenance hemodialysis patients.

Does CKD Predict Stroke Risk Independent of Blood Pressure? A Systematic Review and Meta-Regression

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Background: Chronic kidney disease (CKD) appears to be an independent risk factor for stroke, with various purported mechanisms proposed. Low glomerular filtration rate (eGFR) is a risk factor for stroke independent of cardiovascular risk factors in epidemiological studies, but there has been no systematic assessment of the impact of more complete adjustment for blood pressure (BP) on the association.

Methods: We did a systematic review to February 2018 (MEDLINE/EMBASE) for cohort studies or randomized controlled trials that reported stroke incidence in adults as the primary outcome. We performed systematic eGFR studies and participant characteristics and relative risks (RR) were extracted. Estimates were combined using a random effects model. Heterogeneity was assessed by $^2$ statistics and I², and by subgroup strata and meta-regression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: We identified 168 studies reporting data on 5,611,939 participants with 11,046,300 person-years of follow-up (3,417,885 of first strokes; 72,996 strokes) provided adequate data for meta-analysis of eGFR and stroke risk. Incident stroke risk was increased among participants with eGFR <60 ml/min/1.73m² (RR=1.73, 95% CI 1.57-1.90; p<0.001), but there was substantial heterogeneity between studies (p=0.0001; I² =78.5%). Moreover, the association was reduced after adjustment for cardiovascular risk factors, with progressive attenuation on more thorough adjustment for hypertension: single baseline BP measure (RR=1.63, 1.34-1.99; p<0.001); history or treated hypertension (RR=1.35, 1.24-1.46; p<0.001); multiple BP measurements over months to years (RR=1.32, 1.21-1.48; p<0.001).

Conclusions: The apparently independent relationship between CKD and stroke may be confounded by their shared association with long-term prior blood pressure, rendering other proposed mechanisms and related treatments unnecessary.

TH-PO682
Proteinuria as an Independent Predictor of Stroke: Systematic Review and Meta-Analysis

Background: Proteinuria has emerged as an important vascular risk factor for adverse cardiovascular events including stroke. Hypertension has been proposed as the principal confounder of this relationship but its role has not been systematically examined. We aimed to determine if proteinuria remains an independent predictor of stroke after more complete adjustment for blood pressure (BP).

Methods: We performed a systematic review, searching MEDLINE and EMBASE (to February 2018) for cohort studies or randomized controlled trials that reported stroke incidence in adults according to baseline proteinuria and/or glomerular filtration rate (eGFR). Study and participant characteristics and relative risks (RR) were extracted. Estimates were combined using a random effects model. Hypertension was assessed by x² statistics and I², and by subgroup strata and meta-regression, with a particular focus on the impact of more complete adjustment for blood pressure (BP) on the association. The quality of cohort studies and posthoc analyses was assessed using the Newcastle–Ottawa Scale.

Results: We identified 38 studies comprising 1,735,390 participants with 26,405 stroke events overall. The presence of any level of proteinuria was associated with greater stroke risk (RR for any proteinuria: 1.76, 95% CI 1.62-1.90; p<0.001), even after adjustment for established cardiovascular risk factors (33 studies; Pooled adjusted RR 1.72, 1.51-1.95; p<0.001), albeit with considerable heterogeneity between studies (p<0.001; I² =77.3%). Moreover, the association did not substantially attenuate with more thorough adjustment for hypertension: single baseline BP measure (10 studies; Pooled adjusted RR=1.92, 1.39-2.66; p<0.001); history or treated hypertension (4 studies; Pooled adjusted RR=1.76, 1.13-2.75; p=0.003); multiple BP measurements over months to years (4 studies; RR=1.68, 1.33-2.14; p<0.001)

Conclusions: Even after extensive adjustment, proteinuria is strongly and independently associated with incident stroke risk, possibly indicating a shared renal and cerebral susceptibility to vascular injury that is not fully explained by traditional vascular risk factors.

TH-PO683
Relation of Serum Trimethylamine N-Oxide and Betaine Levels with Risk of First Incident Stroke in Chinese Hypertensive Patients
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Background: Trimethylamine N-oxide (TMAO), a gut derived metabolite, has been shown to be atherogenic. Whether TMAO or its dietary precursors is associated with a risk of stroke remains unknown. We aimed to determine the relationship of serum TMAO and its dietary precursors including choline, L-carnitine and betaine levels with first stroke in hypertensive patients, and examine any possible effect modifiers.

Methods: We conducted a nested case-control study, including 622 patients with first stroke (including 502 ischemic stroke, 118 hemorrhagic stroke and 2 unknown type of stroke) and 622 matched controls from the China Stroke Primary Prevention Trial (CSPT). The primary outcome was a first stroke.

Results: The prevalence of first stroke increased with each increment of TMAO level (per natural log (TMAO) increment: OR, 1.22; 95% CI: 1.02-1.46). Compared with participants in the lowest tertile (<1.79 µmol/L) of TMAO levels, a significantly higher risk of first stroke was found in those in higher TMAO tertiles (a1.79 µmol/L) (OR, 1.34; 95% CI: 1.00-1.81) or in TMAO tertile 3 (≥3.19 µmol/L) (OR, 1.43; 95% CI: 1.02-2.01). However, a U-shaped association between serum betaine and the risk of first ischemic stroke was observed. The risk of first ischemic stroke decreased with the increase of betaine (per 10 µmol/L increase: OR, 0.87; 95% CI: 0.77-0.99) in patients with betaine <77.7 µmol/L, but increased with the betaine increment (per 10 µmol/L increase: OR: 1.17; 95% CI: 1.01-1.36) in participants with betaine ≥77.7 µmol/L. Serum betaine had no obvious effect on the risk of first hemorrhagic stroke (per 10 µmol/L increase: OR, 0.98; 95% CI: 0.82, 1.17). Moreover, no significant association between either choline (OR, 1.05; 95% CI: 0.68-1.64) or L-carnitine (OR, 1.05; 95% CI: 0.60-1.65) with the risk of first stroke was found.

Conclusions: Among Chinese hypertensive patients, higher TMAO levels were associated with increased risk of first stroke while the association between betaine levels and the risk of first ischemic stroke was a U-shaped, with a turning point at about 77.7 µmol/L.

TH-PO684
The Impact of Change of Blood Pressure Stage According to the 2017 ACC/AHA Guideline on Cardiovascular Events Among Untreated Low-Risk Populations: A Nationwide Population-Based Cohort Study
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Background: The 2017 American College of Cardiology/American Heart Association (ACC/AHA) hypertension (HTN) guideline defined new HTN thresholds. However, the evidence was largely based on studies conducted with a single baseline blood pressure (BP) measurement. Therefore, we investigated the impact of the change of BP stage according to 2017 ACC/AHA guideline on cardiovascular events (CVEs), with baseline and mean BP measurements during the follow-up of untreated, low-risk populations.

Methods: This retrospective, longitudinal study was conducted with 322,562 subjects aged 40 years without diabetes mellitus, chronic kidney disease, or previous CVE, enrolled in the Korean National Health Service-National Health Screening Cohort between 2002 and 2003, who had not taken antihypertensive medication during follow-up period. Subjects were categorized according to the 2017 ACC/AHA HTN guideline based on their baseline and mean BP during follow-up. The primary outcome of the study was newly developed CVEs (cardiovascular disease and mortality).

Results: During the median follow-up of 10 years, 2,51 events per 1,000 person-years occurred. Compared to normal (BP<120/80 mmHg) individuals, significantly increased risk of CVE was observed in individuals with stage 1 HTN (systolic BP 130-139/diastolic BP 80-89 mmHg), with both baseline and mean BP examinations. However, the hazard ratios for the CVEs using mean BP were higher those in using baseline BP. When subjects were categorized into 16 groups according to BP stages (and baseline versus mean BP measurements), the risk of CVID incidence was significantly lower when stage BP calculated using the mean BP decreased compared to the reference (the BP stage remained same between the baseline BP and mean BP) in the population with stage 1 and 2 HTN.

Conclusions: Stage 1 and 2 HTN defined by the 2017 ACC/AHA guideline, were significantly associated with an increase of CVEs in the analysis with baseline and mean BP measurements among untreated, low-risk individuals. However, the mean BP was superior to the baseline BP for predicting CVEs. Moreover, the study suggests that physicians need to lower BP stages to prevent the occurrence of CVE when their patients, even those at low risk for CVEs, are in the stage 1 or 2 HTN groups at baseline.

TH-PO685
The Prevalence of Nonadherence in Patients with Resistant Hypertension: A Systematic Review
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Background: Resistant hypertension (RH) is common and is a risk factor for higher cardiovascular outcomes. These patients also undergo more screening intensity for secondary hypertension. Not all patients with apparent resistant hypertension have true RH. Reports of the prevalence of non-adherence vary widely from 3% to 86%. However intentional and non-intentional non-adherence are not differentiated in this data. Non-intentional non-adherence refers to occasional forgetfulness and can be diagnosed with pill counts or pharmacy refill data. Intentional non-adherence requires more intensive measures (such as therapeutic drug monitoring or directly observed therapy) to diagnose.

The objective of this systematic review is to establish the overall prevalence of non-adherence in the RH population and differentiate the contribution of non-intentional and intentional non-adherence subtypes.

Methods: The databases MEDLINE, EMBASE, and the Cochrane library were searched for observational studies and randomized controlled trials reporting the prevalence of non-adherence in RH. The primary outcome studied was the pooled prevalence of non-adherence based on indirect and direct measures of non-adherence. Weighted summary prevalence for the outcomes was estimated using the random effects model.

Results: The literature search retrieved 1415 non-duplicate citations. After applying eligibility criteria, 197 full text citations were retrieved, and 27 studies were included in the review. Most studies were retrospective database studies or cross-sectional in nature and (63%) used indirect measures of assessment such as medication possession ratio or the Morisky scale with 80% adherence being the most common cutoff used for diagnosis. The prevalence of non-adherence varies based on the severity of hypertension, but also based on the method of measurement of adherence. Intercet measures underestimate the extent of true non-adherence. Incorporation of direct measures such as drug assays or direct observed therapy should be considered for more widespread adoption.

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TH-PO686
Apparent Treatment-Resistant Hypertension (ATRH) Stratified by Ambulatory Blood Pressure Monitoring (ABPM) in CKD: A Report from the Chronic Renal Insufficiency Cohort (CRIC) Study
Jessica Fells,1 George Thomas,1 Carolyn S. Brecklin,1 Jing Chen,1 Paul E. Drawz,2 Eva Lustigova,3 Rupal Mehta,2 Edgar R. Miller,1 Stephen M. Sozio,1 Matthew R. Weir,4 Dawei Xie,5 Xue Wang,1 Mahboob Rahman,3 for the CRIC study investigators 1Cleveland Clinic, Cleveland, OH; 2Tuane School of Medicine, New Orleans, LA; 3University of Minnesota, Minneapolis, MN; 4Kaiser Permanente Medical Group, Pasadena, CA; 5Northwestern University, Feinberg School of Medicine, Chicago, IL; 6Johns Hopkins University, Baltimore, MD; 7Johns Hopkins University School of Medicine, Baltimore, MD; 8University of Maryland School of Medicine, Baltimore, MD; 9University of Pennsylvania, Philadelphia, PA; 10University of Illinois, Chicago, IL; 11University Hospitals Cleveland Medical Center, University Heights, OH; 12Case Western Reserve University, Cleveland, OH.

Background: ATRH defined using office blood pressure (BP) measurements, is common in patients with chronic kidney disease. Whether measurement of 24 hour ABPM is of value in risk stratification in patients with ATRH is unclear.

Methods: We analyzed data from the CRIC study, a prospective study of participants with chronic kidney disease. Office BP was measured by trained staff; 24 hour ABPM was measured using Spacelabs monitors. ATRH was defined as mean office systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg or ≥ 3 antihypertensive medications, average ABPM day-time systolic BP ≥ 115 mm Hg or diastolic BP ≥ 85 mm Hg on ≥ 3 antihypertensive medications, or the use of ≥ 3 antihypertensive medications. Outcomes were composite cardiovascular disease (CVD)(myocardial infarction, stroke, peripheral arterial disease, heart failure), renal outcomes (end stage renal disease or 50% decline in GFR), and groups were compared using Cox regression analyses.

Results: Of 475 participants with ATRH based on office BP, 40 participants (8%) had controlled ABPM consistently with white coat hypertension. ATRH based on office and ABPM criteria (ABPM-ATRH) was seen in 162 (34%), and 273 (54%) of participants had ATRH based on office BP alone. These were participants with BP controlled by office and ABPM criteria (n=711). Among individuals with chronic kidney disease, most patients with ATRH (70%) defined based on office BP have ATRH confirmed by ABPM. While ABPM defined ATRH was not an independent risk factor for outcomes, the presence of ABPM-TRH identified participants at high risk for clinical outcomes.

Funding: NIDDK Support.

TH-PO687
Can Central Blood Pressure Be Accurately Estimated in Individuals with and Without Systolic Blood Pressure Amplification?
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Background: Systolic blood pressure (SBP) does not always amplify from central to peripheral arteries. Individuals without SBP amplification (SBPamp) have higher aortic blood pressure (BP) despite similar brachial cuff SBP. To circumvent this discrepancy, the aim of this study was to determine if aortic SBP can be accurately estimated non-invasively in patients with and without SBPamp.

Methods: Patients undergoing non-urgent percutaneous coronary angiography were recruited. Individuals with atrial fibrillation, a10 mmHg between-arm SBP difference or ≥5 mm Hg on ≥3 antihypertensive medications, average ABPM day-time systolic BP ≥115 mm Hg or diastolic BP ≥85 mm Hg on ≥3 antihypertensive medications, or the use of ≥3 antihypertensive medications. Outcomes were composite cardiovascular disease (CVD)(myocardial infarction, stroke, peripheral arterial disease, heart failure), renal outcomes (end stage renal disease or 50% decline in GFR), and groups were compared using Cox regression analyses.

Results: Of 475 participants with ATRH based on office BP, 40 participants (8%) had controlled ABPM consistently with white coat hypertension. ATRH based on office and ABPM criteria (ABPM-ATRH) was seen in 162 (34%), and 273 (54%) of participants had ATRH based on office BP alone. These were participants with BP controlled by office and ABPM criteria (n=711). Among individuals with chronic kidney disease, most patients with ATRH (70%) defined based on office BP have ATRH confirmed by ABPM. While ABPM defined ATRH was not an independent risk factor for outcomes, the presence of ABPM-TRH identified participants at high risk for clinical outcomes.

Funding: NIDDK Support.

Table 1
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Table 2

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Hypertension Is Associated with Adverse Cardiovascular Outcomes Only When Both Brachial and Central Blood Pressures Are Elevated

**Background:** The range of central blood pressure (BP) found in individuals with high-normal brachial BP overlaps the one found in hypertension (HTN) and normotension. As central BP is possibly a better predictor of cardiovascular (CV) disease, the aim of this study was to determine the risk associated with different central/brachial BP patterns.

**Methods:** 13,759 participants from a populational cohort with central BP and prospective data from governmental databases who were not treated for HTN were selected. Major adverse CV events (MACE) comprised myocardial infarction, stroke, heart failure and CV death. Thresholds for brachial and central HTN were identified as 135 and 125 mmHg respectively. Individuals were separated into 4 BP patterns: normal BP; isolated brachial HTN; isolated central HTN; concordant brachial and central HTN. CVE risk for each pattern was compared to normal BP with a Cox proportional hazard model.

**Results:** 688 MACE occurred over a median follow-up of 70.0 months. Characteristics of individuals in each BP phenotype are presented in Table 1. Only the concordant brachial and central HTN pattern had higher risk of MACE [HR 1.37 95%CI (1.15-1.64), p=0.001] compared to normal BP (Figure 1). Sensitivity analyses with different definitions of central HTN and after stratification for sex yielded similar results.

**Conclusions:** In untreated individuals, both central and brachial BP need to be increased to elevate CV risk. These findings provide support for the utility of routine central BP measurements in clinical practice.

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Abnormal Left Ventricular Metrics and Subsequent Cardiovascular Events in Japanese and US Patients with CKD: Findings from the CRIC and CKD-JAC Studies

**Background:** Left ventricular (LV) hypertrophy (LVH) is a risk factor for cardiovascular (CVD) events in patients with chronic kidney disease (CKD). The prevalence of LVH and the associated risk of subsequent CVD events in US and Japanese patients with CKD has not been clearly elucidated.

**Methods:** 3125 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study and 1097 in the CKD Japan Cohort (CKD-JAC) Study underwent echocardiography. LV mass index (LVMi), LVH (defined as LVMi>50 g/m^2 in males and >47 g/m^2 in females), and LV geometry (concentric hypertrophy, eccentric hypertrophy, and concentric remodeling) were assessed. Cox proportional hazards survival analysis was implemented for the composite outcome of CVD, defined as any of the following events: hospitalization for congestive heart failure, myocardial infarction, stroke, interventions for peripheral artery disease, and any lethal cardiovascular events.

**Results:** The mean values of LVMi and the proportion of LVH in CRIC and CKD-JAC participants were 55.7 g/m^2 and 46.6 g/m^2, and 59.2% and 36.1%, respectively. CRIC participants had greater brachial blood pressure and higher proportion of concentric LVH (51.6% and 23.1%, respectively). Incidence rates of the first CVD events in the CRIC and the CKD-JAC were 35.5 and 23.5 per 1000 person-years, respectively. LVH was significantly associated with the subsequent CVD events, HRs were 1.86 (95% confidence interval, 1.53–2.26) in the pooled cohort, 1.85 (1.50–2.29) in the CRIC, and 1.91 (1.15–3.16) in the CKD-JAC (P-interaction = 0.96). Adjusted HRs of LVMi (per 10 g/m^2) were 1.12 (1.01–1.23) in the pooled cohort. Adjusted HRs stratified by race/ethnicity were 1.63 (1.49–1.79) in non-Hispanic Whites, 1.23 (1.16–1.30) in non-Hispanic Blacks, 1.19 (1.03–1.38) in Hispanics and 1.24 (1.07–1.43) in Japanese Asians (P-interaction = 0.34).

**Conclusions:** US patients with CKD had a higher prevalence of LVH and higher LVMi than Japanese patients with CKD. Despite the differences in LV metrics, the association between LVMI and subsequent CVD events was similar across ethnic groups. These findings also reinforce that LVMI may be a common therapeutic target across these diverse populations.

**Funding:** NIDDK Support, Commercial Support - Kyowa Hakko Kirin Co., Ltd., Private Foundation Support

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Changes in QT Interval in Long-Term Hemodialysis Patients

**Background:** A prolonged QT interval on the electrocardiogram (ECG) is a risk factor for sudden cardiac death (SCD) in hemodialysis (HD) patients. This study investigated whether the heart rate-corrected QT (QTc) interval becomes prolonged in relation to the number of years undergoing dialysis treatment.

**Methods:** A total of 102 patients treated with HD for more than 7 years were studied. All patients had ECG data at 1, 4, and 7 years after HD initiation and 75 of the participants also had ECG data at 10 years after HD initiation. The control group comprised 68 age-matched individuals who had normal renal function and two available ECG reports at an interval of more than 4 years. Patients with ECGs showing heart rates $\leq$ 57 or $>103$ bpm, extrasytoles, or any rhythm other than sinus were excluded. QTc was measured according to the Bazett formula. The association between QTc interval and dialysis vintage was analyzed. Additionally, clinically relevant variables related to QTc duration at 1 year after HD initiation were assessed.

**Results:** The average QTc interval in the control group was 425 ms in the first year and 426 ms after an average of 6 years, indicating no significant difference. However, the QTc interval at 1 year after HD initiation in 75 HD patients was 436 ms, which was much higher than that in the control group (P<0.001). In addition, the QTc interval at 4, 7, and 10 years after HD initiation were, respectively, increasing with dialysis vintage (p=0.20, 0.42, and <0.001, for 1 year after HD by Dunnett’s multiple comparison). Multivariate regression analysis of baseline variables in 102 HD patients revealed that corrected calcium levels (p=0.041) and diabetes (p = 0.043) were independently associated with the longer QTc interval.
Conclusions: The QTc interval at 1 year after HD initiation was longer in HD patients than in the control subjects and was further prolonged over several years of HD treatment. Providing clinical management with a focus on QTc interval may be helpful for reducing the incidence of SCD in HD patients.

TH-PO692 Impact of Pulse Pressure and Mean Arterial Pressure on All-Cause and Cardiovascular Mortality in Subjects with a Diabetes Nationwide Cohort from a General Japanese Population

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Background: In the general population, blood pressure (BP) and physiological factors that influence arterial stiffness, such as pulse pressure, have been shown to differ between subjects with systolic BP (SBP) and diastolic BP (DBP) and mean arterial pressure (MAP, 2/3 SBP + 1/3 DBP), are associated with mortality and cardiovascular (CV) outcomes; however, the impact of these markers in diabetic patients remains unclear.

Methods: Study design; Setting; Participants: Data from a nationwide database from the annual “Specific Health Check and Guidance in Japan”, including 20,748 people with diabetes, eGFR values >10 and <60 mL/min/1.73m2 and follow-up during a median follow-up of 5.3 years. Measurements: Hazard ratios (HRS) were estimated using Cox’s model for the relationships between predictors and outcomes, and adjusted for potential confounders.

Results: During the follow-up, the incidence of death was 448 (4.1 per 1000 person-years), including 101 CV deaths (0.9 per 1000 person-years). HRS for all-cause mortality for each 1-SD elevation in SBP, DBP, PP, and MAP did not significantly increase. On the other hand, HRS for the CV mortality of MAP significantly increased, whereas those of other BP parameters did not, as shown in Table 1. Furthermore, when patients were divided into two groups based on the presence and absence of proteinuria, HRSs for CV mortality for each 1-SD elevation in PP and MAP significantly increased in subjects without proteinuria. However, no parameters correlated with cardiovascular mortality in subjects with proteinuria.

Conclusions: In diabetes patients without proteinuria, markers of arterial stiffness, such as PP and MAP, may be useful for predicting CV outcomes.

Multivariate analysis of blood pressure parameters and cardiovascular death.

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* Diabetes mellitus patients whose eGFR was more than 30 mL/min/1.73m2.

TH-PO693 Association of Metabolic Acidosis with Adverse Cardiovacular Outcomes in Patients with CKD

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Background: Metabolic acidosis is a known risk factor for chronic kidney disease (CKD) progression. Less is known about its association with cardiovascular disease in patients with advanced CKD. Here we assess the association of metabolic acidosis with adverse cardiovascular outcomes and its role as an independent predictor of cardiovascular outcomes in patients with pre-dialysis CKD.

Methods: De-identified electronic medical records (Optum® EMR), 2007–2017 were queried to identify patients with CKD Stages 3-5 with a2 consistent serum bicarbonate values 28-365 days apart, a2 eGFR values >10 and <60 mL/min/1.73m2 and a2 years of post-index. Patients were followed for up to 10 years for evidence of new onset heart failure, stroke or acute myocardial infarction (MI), defined using ICD-9 and ICD-10 diagnosis codes. Metabolic acidosis and serum normal bicarbonate were defined by two serum bicarbonate values between 12 and <22 mEq/L and 22-49 mEq/L, respectively. Models were used to examine potential confounders: age, sex, race, eGFR, diabetes, hypertension, heart failure, coronary artery disease, peripheral vascular disease, and hemoglobin and serum albumin.

Results: 51,558 patients qualified for this longitudinal observational study. The incidence of adverse cardiovascular events at 2 years was significantly higher in patients with metabolic acidosis compared to patients with normal serum bicarbonate, [heart failure: 29.8 % vs. 22.8%, p<0.0001; stroke: 19.5% vs. 17.2%, p<0.0001; MI: 17.2% vs. 12.3%, p<0.0001, respectively]. During the up to 10-years of follow-up, serum bicarbonate was inversely associated with adverse cardiovascular outcomes; hazard ratio (HR) 1.5 mL/L increase: new onset heart failure, 0.976, CI: 0.971-0.981, stroke, 0.979, CI: 0.973-0.983; and MI, 0.964, CI: 0.958-0.970, respectively.

Conclusions: In this longitudinal analysis of > 51,000 non-dialysis CKD patients followed for up to ten years, bicarbonate levels below 22 mEq/L were associated with increased incidence of major adverse cardiovascular events independent of age, comorbid conditions and kidney function. Studies evaluating the mechanisms of these associations are needed.

Funding: Commercial Support - Tricida, Inc.

TH-PO694 Plasma Xanthine Oxidoreductase Activity Is Associated with CKD in a General Japanese Population: The Iwate Tohoku Medical Megabank Project


Background: Xanthine oxidoreductase (XOR, pmmol/h/ml plasma) catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to uric acid. An increase in XOR activity could cause intravascular damage through the oxidative stress. XOR activity could contribute to the pathogenesis of cardiovascular disease (CVD). Chronic kidney disease (CKD) and cardiovascular disease (CVD) are closely related. However, the association with XOR activity in a general Japanese population is not known. The purpose of this study is to investigate the association between XOR activity and CKD in a general Japanese population.

Methods: We developed the Iwate Tohoku Medical Megabank Organization pooled individual participant database from a general population-based cohort study in Iwate prefecture (n = 1,675, male/ female = 529/1,146, age = 66.2 ± 10.1 years). We classified as CKD stage I – stage IV using the estimate glomerular filtration rate of creatinine (eGFR, mL/min/1.73m2,eGFR ≤60) and the urinary albumin-to-creatinine ratio (尿,uric,mg/gcr,urcrea,30). Xanthine oxidoreductase activity combined with Suita score was 0.61 (95% CI = 0.50 – 0.72, p = 0.051).

Conclusions: In conclusion, XOR activity is associated with CKD and the high risk for CVD in a general Japanese population. An increase in XOR activity may be related to decreased functional and the CVD risk.

Funding: Government Support - Non-U.S.

TH-PO695 Individuals Born Preterm Have an Increased Rate of Hypertension from Adolescence to Adulthood

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Background: Preterm birth increases the lifetime risk of hypertension (HTN), but the prevalence of HTN in adolescents and adults and the change in blood pressure (BP) and incidence of HTN from adolescence into adulthood are undefined. We hypothesized that individuals born preterm have an increased prevalence of high BP and HTN, a greater increase in B/Pyr, and an increased incidence of high BP and HTN from adolescence to adulthood compared to term.

Methods: In a longitudinal cohort we measured BP at 3 visits in 220 adolescents born preterm with very low birth weight and 52 born term (mean age 14.4 yr). 188 preterm and 35 term subjects returned as adults (mean age 19.7 yr) and had BP measured at 2 visits. We defined high BP as a2120/80 mmHg and a2130/80 mmHg. We compared high BP and HTN prevalence in preterm vs. term in adolescents and adults with Fisher’s exact test and assessed risk ratios with log-binomial regression. We calculated the change in B/Pyr in preterm vs. term with linear mixed models. We calculated incidence rate ratios comparing number of high BP or HTN measurements per person-yr from adolescence to adulthood in preterm vs. term with Poisson regression. All models were adjusted for race, HTN pregnancy, and birth weight z-score.

Results: Mean follow up was 5.5 yr (range 3.6-9.1). Preterm subjects had significantly higher systolic BP as adolescents and adults vs. term (mean difference 2.5 and 4.6 mmHg, respectively). In adolescents, the preterm vs. term high BP prevalence was 2% vs. 0%
Overweight was defined as BMI ≥ 30 kg/m². Hypertension and CV disease. Interestingly, individuals who rated their health as “very good” or “excellent” were 70% less likely to be aware of having HTN compared to those who self-rated with “poor” or “fair” health (age- and gender-adjusted OR 0.30, p < 0.001). While no difference in awareness rates across ethnicities: Asian 64.1%, African American 64.2%, White 60.7% and Hispanic 61.2% were 66.3% and lower to be associated with HTN as compared to African Americans (OR 1.58, p<0.001) and Hispanic (OR 1.89, p<0.05) after adjusted for age, gender, ethnicity, education level, and self-reported diabetes, hyperlipidemia and CV disease. Interestingly, individuals who rated their health as “very good” or “excellent” were 70% less likely to be aware of having HTN compared to those who self-rated with “poor” or “fair” health (age- and gender-adjusted OR 0.30, p<0.001).

Results: Our study highlights that HTN is major risk factor for chronic kidney disease and its related cardiovascular (CV) complications. It is projected to affect 1.56 billion individuals worldwide by 2025. However, the awareness of HTN remains low; nearly 46% of U.S. adults are unaware of their HTN status. This study aims to explore factors associated with uncontrolled HTN in community level.

Methods: Kidney Disease Screening and Awareness Program (KDSAP) provides free kidney education and education targeting underserved communities across U.S. and Canada, aiming to early detect and raise awareness of kidney disease. From October 2011 to May 2018, a total of 1,040 KDSAP participants were enrolled in this study. HTN was defined by self-report being diagnosed with or treated for the disease or high blood pressure. Self-report HTN screening with systolic ≥ 140 or diastolic ≥ 90 mmHg. Awareness was defined by self-report.

Results: More than one third (n=374, 36%) of participants were unaware of HTN; they were younger (57 vs. 66 years old, p<0.001) and higher in proportion of men (51.3% vs. 41.1%, p=0.002). The awareness is positively correlated to increasing age, <40 (36.9%), 40–59 (56.1%) and ≥ 60 years old (73%) (p=0.001), with adjusted odds ratio (OR) 1.02 for every 1-year age increment (p<0.001). While no difference in awareness rates among ethnicities: Asian 64.1%, African American 64.2%, White 60.7% and Hispanic 61.2% were 66.3% and lower to be associated with lower awareness compared to African Americans (OR 1.58, p<0.005) and Hispanic (OR 1.89, p<0.05) after adjusted for age, gender, ethnicity, education level, and self-reported diabetes, hyperlipidemia and CV disease. Interestingly, individuals who rated their health as “very good” or “excellent” were 70% less likely to be aware of having HTN compared to those who self-rated with “poor” or “fair” health (age- and gender-adjusted OR 0.30, p<0.001).

Conclusions: Our results showed a high awareness of HTN among the KDSAP participants. Younger age and Asian ethnicity were associated with higher awareness. In addition, self-rated health was inversely correlated with HTN awareness. Our results provide insights in developing effective venues to raise HTN awareness at the community level.

Funding: Private Foundation Support

TH-PO698
Younger Age, Asian Ethnicity, and Better Self-Rated Health Are Associated with Uncontrolled Hypertension in Community Population

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Background: Hypertension (HTN) is a major risk factor for chronic kidney disease and its related cardiovascular (CV) complications. It is projected to affect 1.56 billion individuals worldwide by 2025. However, the awareness of HTN remains low; nearly 46% of U.S. adults are unaware of their HTN status. This study aims to explore factors associated with uncontrolled HTN in community level.

Methods: Kidney Disease Screening and Awareness Program (KDSAP) provides free kidney education and education targeting underserved communities across U.S. and Canada, aiming to early detect and raise awareness of kidney disease. From October 2011 to May 2018, a total of 1,040 KDSAP participants were enrolled in this study. HTN was defined by self-report being diagnosed with or treated for the disease or high blood pressure. Self-report HTN screening with systolic ≥ 140 or diastolic ≥ 90 mmHg. Awareness was defined by self-report.

Results: More than one third (n=374, 36%) of participants were unaware of HTN; they were younger (57 vs. 66 years old, p<0.001) and higher in proportion of men (51.3% vs. 41.1%, p=0.002). The awareness is positively correlated to increasing age, <40 (36.9%), 40–59 (56.1%) and ≥ 60 years old (73%) (p=0.001), with adjusted odds ratio (OR) 1.02 for every 1-year age increment (p<0.001). While no difference in awareness rates among ethnicities: Asian 64.1%, African American 64.2%, White 60.7% and Hispanic 61.2% were 66.3% and lower to be associated with lower awareness compared to African Americans (OR 1.58, p<0.005) and Hispanic (OR 1.89, p<0.05) after adjusted for age, gender, ethnicity, education level, and self-reported diabetes, hyperlipidemia and CV disease. Interestingly, individuals who rated their health as “very good” or “excellent” were 70% less likely to be aware of having HTN compared to those who self-rated with “poor” or “fair” health (age- and gender-adjusted OR 0.30, p<0.001).

Conclusions: Our results showed a high awareness of HTN among the KDSAP participants. Younger age and Asian ethnicity were associated with higher awareness. In addition, self-rated health was inversely correlated with HTN awareness. Our results provide insights in developing effective venues to raise HTN awareness at the community level.

Funding: Private Foundation Support

TH-PO699
The Relationship of Change in Ankle Brachial Index with Mortality Among Individuals with CKD: The CRIC Study

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Background: Patients with chronic kidney disease (CKD) have an increased risk of peripheral arterial disease (PAD). Ankle-brachial index (ABI), a non-invasive measure of PAD, is a predictor of adverse events among individuals with CKD. In general populations, changes in ABI have been associated with mortality, but this association is not well understood among patients with CKD.

Methods: Prospective study of 2987 participants in the Chronic Renal Insufficiency Cohort (CRIC) Study without clinical PAD at baseline, and with at least one follow-up ABI measurement (taken at annual study visits). ABI was obtained by standard protocol. The association of change in ABI and mortality was studied using Cox proportional hazards regression.

Results: We found U-shaped associations of average annual change in ABI and cumulative average ABI with all-cause mortality (p for non-linearity ≤0.0001). Compared to participants with average annual change in ABI of 0 to <0.02, individuals with average annual change in ABI ≥ 0.02, −0.02 to <0, or ≤0.02 had multivariable-adjusted hazard
ratios (95% CI) of 2.04 (1.57, 2.66), 1.25 (0.98, 1.58), and 1.68 (1.37, 2.05) for all-cause mortality, respectively. Compared to participants with cumulative average ABI between 1.0 and <1.4, multivariable-adjusted hazard ratios (95% CI) for those with cumulative average ABI of <0.9, 0.9 to <1.0, and ≥1.4 were 1.64 (1.33, 2.01), 1.22 (0.95, 1.55), and 1.29 (0.95, 1.75), respectively.

Conclusions: Findings from this study indicate that both larger decreases and increases in average annual changes in ABI (±0.02) were associated with higher risk of mortality. Monitoring changes in ABI over time may facilitate risk stratification for all-cause mortality among individuals with CKD.

Funding: NIDDK Support, Other NIH Support - National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of General Medical Sciences, National Center for Advancing Translational Sciences

TH-PO701
Natural History of Peripheral Artery Disease in Patients with CKD
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Background: The prevalence and risk of peripheral artery disease (PAD) are higher in patients with chronic kidney disease (CKD) compared to those without. The natural history of PAD in CKD has not been well studied.

Methods: We studied the natural history of PAD among 4571 participants without PAD at baseline in the Chronic Renal Cohort (CRC) Study. The mean follow-up duration is 7.6 years. Mixed effects models were used to assess the effect of change in ankle-brachial index (ABI). Cox proportional hazards models were used to examine the multivariable association of ABI with PAD events, adjusting for time-updated confounding factors.

Results: The slopes of average annual ABI changes were characterized as rapidly (ABI change < -0.03) or slowly (-0.3 to -0.001) decreasing, stable (-0.001 to <0.001), rapidly (>-0.05) or slowly (0.001 to 0.05) increasing. Compared to those with stable slope, multivariable-adjusted hazard ratios (95% CI) for incident PAD events were 2.80 (2.49, 3.17), 1.67 (1.55, 1.81), 1.42 (1.32, 1.54), and 1.92 (1.65, 2.23) for those with rapidly decreasing, slowing decreasing, slowly increasing, and rapidly increasing, respectively. The average time to develop the first PAD event was 7.38, 8.48, 8.46, 7.73, 7.50, or 6.59 years for those with baseline ABI of 0.9, >0.9–1.0, >1.0–1.2, >1.2–1.3, >1.3–1.4 or >1.4, respectively. Annual event rates per person year were 2.95%, 1.58%, 1.58%, 1.77%, 1.64%, or 2.64 % for CVD and 3.57%, 2.17%, 2.16%, 1.80%, 1.96%, and 2.03% for mortality by baseline ABI categories. Amputation and mortality rates were 17.86% and 8.74%, respectively, and 22.02% and 13.69%, respectively, in year 5 after PAD-related revascularization.

Conclusions: This study indicates that either increase or decrease in ABI with time is associated with increased incident PAD events. Latent time of PAD is short for those with normal ABI. Complication rates are high among those with subclinical PAD. Progression is poor after revascularization. Our study suggests screening for PAD using ABI along with monitoring ABI changes may facilitate early detection of PAD progression and prevention. Further study is warranted to investigate the effect of significant change of ABI on improving clinical outcomes.

Funding: NIDDK Support

TH-PO702
Predictive Value of Cardio Ankle Vascular Index on the Risk of ESRD
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Background: Arterial stiffness is a great concern in relation to hypertension and cardiovascular event. However, the predictive value of pulse wave velocity, one of assessment tools for arterial stiffness, on the risk of end-stage renal disease (ESRD) remains unresolved.

Methods: A total of 9,005 patients who measured cardiac-ankle vascular index (CAVI) were included in the study. Patients were divided according to the value (9.0) of CAVI or the quartiles of CAVI. The hazard ratios (HRs) of ESRD and all-cause mortality were calculated using the multivariable-adjusted Cox model. We also analyzed the competing risk regression to adjust the deaths.

Results: During the median follow-up period of 7 years (maximum 12 years), the events of ESRD and mortality occurred in 215 and 1,079 patients, respectively. The median value of CAVI was 8.5. The high CAVI group (>9.0) had a higher risk of ESRD than the low CAVI group (HR, 1.65 [1.27–2.16]; P < 0.001). The risk of all-cause mortality was also higher in the high CAVI group than in the low CAVI group (HR, 2.84 [2.51–3.21]; P < 0.001). Although the analysis was performed based on the quartiles, the 4th quartile group had a higher risk of ESRD (HR, 2.20 [1.48–3.27]; P < 0.001) than the 1st quartile group. The risk of all-cause mortality was also higher in the 4th quartile than in the 1st quartile (HR, 4.21 [3.46–5.12]; P < 0.001). The death-adjusted risk analysis also showed that the 4th quartile group had a high risk of ESRD than the 1st quartile (HR, 2.21 [1.49–3.26]; P < 0.001).

Conclusions: The measurement of CAVI by the pulse wave velocity may be needed to predict the risk of ESRD.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

Figure 1: CV Risk Comparison By NC+ plaque and CKD Status.
TH-PO703
A Novel Magnetic Resonance Sequence That Accurately Detects Aortic Calcification
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Background: Vascular calcification is a surrogate marker of cardiovascular disease in patients with renal disease. Computed tomography (CT) is the current gold standard for detecting vascular calcification. StarVIBE (Siemens Healthineers) is a free-breathing, non-contrast magnetic resonance imaging (MRI) sequence that can detect vascular calcification with advantages over CT: it is radiation-free and can be conducted alongside functional cardiac MRI. We compared MRI-StarVIBE with CT for detection of thoracic aortic calcification in patients with renal disease.

Methods: Paired thoracic CT and MRI scans (≤24 hours apart) were obtained from patients with renal disease participating in two prospective cohort studies. Two investigators separately reviewed sagittal views on MRI-StarVIBE (JSL) and CT (AJR) of a 10 cm segment of thoracic aorta from the lower level of the descending aortic arch. Aortic calcification was quantified by manually tracing regions of interest on all image slices. We calculated percentage agreement for presence or absence of calcium on CT and MRI-StarVIBE. Linear regression analysis was used to compare calcium content on MRI-StarVIBE and CT. We randomly reassessed 10% of MRI and CT scans, blinded to the original scores, for inter-observer consistency of agreement using the intra-class correlation coefficient (ICC).

Results: Ninety patients (78 renal transplant; 12 haemodialysis) had paired MRI-StarVIBE and CT scans. Calcium was detected on 50.0% of CT scans and 55.8% of MRI-StarVIBE sequences; agreement was 92.2%. There was a strong, linear association between CT and MRI-StarVIBE calcium score (r² = 0.89). Inter-observer consistency of agreement for calcium quantification was excellent for both CT (ICC 0.966, 95% CI 0.978-0.991, p<0.001) and MRI-StarVIBE (ICC 0.986, 95% CI 0.986-0.999, p<0.001).

Conclusions: MRI-StarVIBE is comparable to CT for evaluating aortic calcification without the need for exposure to potentially hazardous ionizing radiation in patients with established renal disease.

Funding: Private Foundation Support

Figure: Representative images of calcification (white areas along aortic wall) on CT (A, C) and MRI-StarVIBE (B, D). Images A and B are sagittal slices; images C and D are illustrative coronal slices.

TH-PO704
Distribution of Myocardial Fibrosis by Native T1 Times Using Cardiac Magnetic Resonance Measurements in CKD
Anas Fares,2 Eddie Hill,1 Kevin Kalisz,4 Armando Vergara-Martel,2 Sanjay Rajagopalan,1 Mirela A. Dobrin,1,3 Case Western Reserve University, Cleveland, OH; 2University Hospitals Cleveland Medical Center, Cleveland, OH; 3University Hospitals, Cleveland Heights, OH; 4Northwestern University, Chicago, IL.

Background: Previous evidence suggests that native myocardial T1 relaxation times assessed by cardiac magnetic resonance imaging (MRI) are relevant biomarkers of the extension and severity of myocardial fibrosis in patients with chronic kidney disease (CKD). However, detailed classification and cutoffs of the T1 values in correlation with the severity of kidney disease have not been described

Methods: A cohort of 51 patients with eGFR <20 mL/min/1.73m² and without acute heart failure underwent concomitant assessment of kidney function and noncontrast cardiac MRI using T1 mapping sequence technique in a 3T scanner. CKD was defined as eGFR<60 mL/min/1.73m². T1 times were measured in all myocardial segments using the American Heart Association 16-segment method and utilizing an advanced post processing software. Two-tailed t tests and multivariate linear regression analyses were performed to test the association of CKD with segmental T1 times.

Results: 51 patients were enrolled in the study. Global T1 values in individuals with (eGFR<60) and without (GFR≥60) CKD were 1045.91±42.74ms and 1019.75±47.16ms (p=0.02), respectively. T1 values for anteroseptal, anterior, and inferoseptal segments were 1083.33±38.53ms and 1049.03±39.81ms (p=0.001), 1052.29±31.81ms and 1021.41±47.52ms (p=0.01), 1061±40.61ms and 1016±40.60ms (p=0.001), in CKD and non CKD patients respectively. Basal T1 values were 1062.92±34.55ms and 1039±34.13ms (p=0.001) respectively. In models adjusted for demographics, comorbidities, medications and eGFR, age was the only variable significantly associated with global T1 times.

Conclusions: Cardiac MRI T1 relaxation times can be surrogate markers to risk stratify patients with CKD. The cardiac fibrosis in CKD is more prevalent in the basal, anterior and septal myocardial segments.

Funding: Other NIH Support - NHLBI

TH-PO705
Association of Noninvasive Measures of Subclinical Atherosclerosis and Arterial Stiffness Cardiovascular Risk with Mortality and Cardiovascular Events in CKD: A Meta-Analysis
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Background: Non-invasive cardiovascular disease (CVD) risk prediction, in subclinical stages, aiming to stratify patients and tailor interventions remains an unmet need in CKD. We summarize the association of carotid intima-media thickness (cIMT), coronary artery calcium score (CACS) and pulse-wave velocity with all-cause mortality, CVD mortality and CVD events in non-dialysis CKD and patients on dialysis.

Methods: Systematic review and metaanalysis of prospective cohort studies. 24 out of 27984 studies were eligible for quantitative synthesis (5 for cIMT, 11 for CACS and 8 for PWV) involving 708, 3706 and 4393 patients respectively. In dary regression analysis, cIMT was a promoting effect. However, the effects of Th22 and IL-22 in hypertensive patients need in CKD. We summarize the association of carotid intima-media thickness (cIMT), coronary artery calcium score (CACS) and pulse-wave velocity with all-cause mortality, CVD mortality and CVD events in non-dialysis CKD and patients on dialysis.

Table: Meta-analysis results for all three markers, shown separately for HD and non HD patients.
correlated with extent of hypertensive renal damage, indicating that serum IL-22 may involve in the pathogenesis of hypertensive renal damage.

Funding: Government Support - Non-U.S.

TH-PO707

Soluble Neprilysin, NT-ProBNP, and Growth Differentiation Factor 15 as Biomarkers for Heart Failure in Dialysis Patients (SONGBIRD)

Robert Claus,1 Dominik Berlinger,2 Udo Bavedentik,3 Nicolas Vedovaro,4 Sascha David,5 Margret Patecki,6,7 Jean-Marie Launay,8 Hermann G. Haller,8 Marcus Hiss,9 Michael S. Balzer,1 SONGBIRD investigators 1Dept. of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; 2Dept. of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; 3Center for Renal, Hypertensive and Metabolic Disorders, Hannover, Germany; 4Inserm UMR-S 942, Paris, France.

Background: Dialysis patients are at increased risk of congestive heart failure (HF). However, diagnostic utility of NT-proBNP as a biomarker is decreased in patients on hemodialysis or peritoneal dialysis. Growth differentiation factor-15 (GDF15) and neprilysin (NEP) are biomarkers of distinct mechanisms that may contribute to HF pathophysiology in such cohorts.

Methods: We compared circulating concentrations of NT-proBNP, GDF15, and NEP along with NEP activity, individually or in combination, in patients on chronic dialysis without (n=80) and with HF (n=73); composite of HF with reduced [n=40] and preserved ejection fraction [n=33], as diagnosed by clinical parameters and post-dialysis echocardiography. We used correlation, linear and logistic regression as well as receiver operating characteristic (ROC) analyses.

Results: Compared to controls, patients with HF had higher medians of NT-proBNP (16216 [interquartile range, IQR=27739] vs. 2883 [5866] pg/mL, p<0.001), GDF15 (7512 [7084] vs. 6005 [4902] pg/mL, p=0.014), but not NEP (315 [107] vs. 318 [124] pg/mL, p=0.818). Median NEP activity was significantly lower in HF vs. controls (0.189 [0.223] vs. 0.257 [0.166] nmol/mL/min, p<0.001). In ROC analyses, a base model combining clinical covariates (age, dyspnea score, systolic blood pressure, Charlson comorbidity index, history of HF or severe valve disease, extracellular to total body water ratio) and NT-proBNP distinguished HF from controls with an area under the curve (AUC) of 0.785 (95% confidence interval [CI] 0.714-0.856). NEP activity and GDF15 provided incremental utility over the base model. A multi-marker model combining clinical covariates, NT-proBNP GDF15 and NEP activity demonstrated best discrimination of HF from controls (AUC=0.902, 95% CI 0.857-0.947, p<0.001 vs. base model).

Conclusions: We present novel comparative data on physiologically distinct circulating biomarkers for HF in patients on dialysis. NEP activity but not concentration and GDF15 provided incremental predictive information over clinical covariates and NT-proBNP as a useful biomarker in dialysis patients.

Funding: Private Foundation Support

TH-PO708

Urinary N-Terminal Pro-Brain Natriuretic Peptide Is a Useful Biomarker for Cardiovascular Events in a General Japanese Population: The Hisayama Study

Keisuke Yamasaki,1,2 Jun Hata,1,2 Yoichiro Hirakawa,1,2 Satoko Sakata,1,2 Toshiaki Nakano,3 Takanari Kitazono,2 Toshiharu Ninomiya,1 1Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; 2Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Background: Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels have been well accepted as an index for estimating cardiovascular risk in general practices. On the other hands, there is a possibility that urinary NT-proBNP is a non-invasive biomarker without requiring blood sampling, because NT-proBNP is excreted in urine. Therefore, the present study investigated the association between urinary NT-proBNP levels and the risk of cardiovascular disease (CVD) in a general Japanese population.

Methods: A total of 3,060 community-dwelling Japanese subjects aged ≥40 years without history of CVD were followed up for 8 years (2007-2015). Urinary NT-proBNP levels were divided into four categories using cutoff values of 23, 30, and 42 pg/mL, which were corresponding to guideline-based cutoff values of serum NT-proBNP, being ≥55, 125, and 300 pg/mL, based on the linear regression analysis of serum and urinary NT-proBNP. The age- and sex-adjusted risk of CVD increased significantly with higher NT-proBNP levels (p for trend =<0.001). This association remained significant even after adjustment for conventional cardiovascular risk factors (hazard ratio [95% confidence interval]: 1.00 [reference] for ≥22 pg/mL, 1.13 [0.74-1.71] for 23-29 pg/mL, 1.59 [0.97-2.61] for 30-41 pg/mL, 1.78 [1.11-2.87] for ≥42 pg/mL, p for trend =0.01).

A similar association was observed for total stroke (p for trend =<0.01), but not for coronary heart disease (p for trend =0.36).

Conclusions: The present finding suggests that elevated urinary NT-proBNP level is a useful biomarker for the development of CVD, especially stroke, independent of conventional risk factors in a general Japanese population.

Funding: Government Support - Non-U.S.

TH-PO709

APOL1 Risk Variants, Subclinical Cardiovascular Disease, and Mortality in African Americans Initiating Hemodialysis

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Background: The role of APOL1 risk variants in cardiovascular disease (CVD) remains unclear, especially among ESRD patients. We evaluated associations of APOL1 with subclinical CVD and mortality in a cohort of African Americans (AA) initiating hemodialysis (HD) in the Predictors of Athymic and Cardiovascular Risk in End-Stage Renal Disease (PACE) Study.

Methods: APOL1 risk variants and ancestry markers were genotyped using custom Taqman assays and Infinium QC array kits. We defined APOL1 risk status by a recessive genetic model (high-<2 risk alleles; low-0 risk allele). We studied associations of APOL1 high-risk status with baseline subclinical CVD (left ventricular [LV] hypertropy, LV mass, ejection fraction, coronary artery calcification [CAC], pulse wave velocity) using logistic/linear regression and time to all-cause or CVD mortality using Cox hazards models, adjusting for age, sex and ancestry. In sensitivity analyses, we further adjusted for systolic blood pressure (SBP) and Charlson Comorbidity Index (CCI).

Results: Of 267 AA participants successfully genotyped, 27% were APOL1 high-risk. At baseline, mean age was 53 years, 41% were female, 56% had diabetes, and mean SBP was 138 mmHg. In cross-sectional analyses, APOL1 high- vs. low-risk status was independently associated with lower odds of LV hypertropy and CAC, and lower LV mass. These associations remained robust upon further adjustment for CCI, but were attenuated when adjusted for SBP (Table). Over a mean follow-up of 2.5 years, CVD mortality was not associated with all-cause or CVD mortality.

Conclusions: Among AA incident HD patients, APOL1 high-risk status was associated with better subclinical measures of CVD, but these did not translate to improved survival. Future studies are needed to clarify the clinical implications of APOL1 risk variants in AA with ESRD.

Funding: NIDDK Support, Commercial Support - Extramural Grant Program from Satellite Healthcare, a not-for-profit renal care provider

TH-PO710

The Combined Prognostic Significance of Vascular Calcification and Alkaline Phosphatase in Patients with ESRD

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Background: Vascular calcification (VC) is a well-known prognostic marker in patients with end-stage renal disease (ESRD), while there are conflicting results on the role of serum alkaline phosphatase (ALP) on cardiovascular event (CVE) and mortality. This study investigated whether there was a combined effect of VC and ALP on prognosis in patients with ESRD starting dialysis.

Methods: This was a retrospective cohort study including 587 incident ESRD patients from a single center. The aortic calcification index (ACI), an estimated of abdominal aortic calcification, was calculated by abdominal computed tomography as a measure of VC.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Patients were stratified into four groups according to the median ACI and serum ALP value. CVE and death were assessed as study outcomes. The association of VC and ALP on composite of end-point was analyzed. The modification effect between VC and ALP on composite of end-point was determined using an interaction product term.

Results: During a median follow-up duration of 3.1 (0.02 – 12.3) years, 140 patients (23.8%) developed CVE and 130 deaths (22.1%) occurred. In the stratified analysis, patients with higher ACI and lower ALP had a greater risk of composite of end-point compared to patients with combined lower ACI and ALP group (adjusted hazard ratio, 2.04; 95% confidence interval, 1.23 – 3.38; \( P = 0.006 \)), and patients with combined higher ACI and ALP had the greatest risk (adjusted hazard ratio, 2.26; 95% confidence interval, 1.05 – 3.62; \( P = 0.001 \)). The interaction between ACI and ALP on CVE and mortality was statistically significant (\( P < 0.05 \)).

Conclusions: In conclusion, the combined effect of VC and higher ALP was associated with greater risk of CVE and deaths in ESRD patients starting dialysis. Serum ALP amplifies the risk of CVE and deaths associated with VC in ESRD patients.

**TH-PO711**

Adductome of HDL from Non-Diabetic Hemodialysis Patients

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Background: HDL dysfunction could participate in the increased cardiovascular mortality in CKD. have been pointed out in this burden. Post-translational modifications (PTM) of HDL were highlighted as potential mediators of HDL dysfunction. We aimed to describe PTM of HDL proteins from non-diabetic hemodialysis (HD) patients.

Methods: HDL were sampled from the plasma of 9 non-diabetic HD and 9 potential kidney-donors patients with a sequential ultracentrifugation. Samples were analyzed using an nano-RSLC coupled on line with a Q-Orbitrap. Data were processed with Proteome Discoverer 2.2 software and quantified with a label free quantitation approach. Oxidation, acetylation, carbamylation (with 4-HNE), guanidinylation, chlorination, nitration and nitrosylation were set as variable modifications. Protein quantitation was based on pairwise ratios and ANOVA hypothesis test.

Results: 522 proteins were identified in HDL from HD patients and controls among which 73 (i.e. 14%) presented adduction sites. The main PTM were glycation (26%), guanidinylation (17%), carbamylation (15%), nitration (14%), carbonylation by the 4-HNE (11%), nitrosylation (9%) and chlorination (8%). Those proteins were involved in lipid metabolism, acute phase response, hemostasis, wound healing and muscular metabolism. Apolipoprotein A2 and 1 were the proteins the more prone to adduction (28 and 27% respectively) followed by serum albumin (15%), apolipoprotein C3 (9%) and serum amyloid A4 (8%, Figure 1). Most of the key-proteins of HDL metabolism were found to be adductable.

Conclusions: HDL from HD patients presented several post-translational modifications of their proteins. Those proteins are involved in most of the biological functions of HDL and their modifications could contribute the dysfunction of HDL in CKD.
Outcome and Prognostic Factors in ESRD Patients with Acute Coronary Syndrome (ACS) Undergoing Percutaneous Coronary Interventions

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Background: The proper control of blood pressure (BP) is an important issue in hemodialysis patients and accurate BP measurement is mandatory. Although various methods of measurement of BP have been proposed, there is no standard method. The aims of this study are that office BP and home BP were compared based on ambulatory blood pressure monitoring (ABPM) in hemodialysis patients and propose the usefulness of home BP.

Methods: A total of 40 patients undergoing maintenance hemodialysis were enrolled for analysis of BP measurement from July 2018 to March 2019. Home BP was defined as the average of BP measured in a relaxed posture 5 minutes after the morning awaking and before sleeping. Office BP was predialysis BP and ABPM was undertaken 24 hours on non-dialysis days using Mobil-O-Graph® (VG, I.E.M. GmbH, Stolberg, Germany).

Results: The average BPs according to methods were as follows: home BP, 135.80 ± 20.78/ 76.48 ± 7.78 mmHg; awake ABPM, 130.1 ± 20.79/ 74.8 ± 17.44 mmHg; awake office BP, 130.1 ± 20.76/ 76.48 ± 9.05 mmHg. When compared to office BP with ABPM, 35% of the patients had obtained normotension, 42.5% of the patients had sustained hypertension, 22.5% of the patients had white-coat hypertension and masked hypertension cannot be observed. Based on ABPM, type of all patients was non-dipper, of which reverse-dippers were 32.5%. We analyzed the difference in systolic BP(SBP) in the office, home, and ABPM awake BP. SBP was the highest in office BP followed by home BP and ABPM in sequence. BP differences were as follows; ABPM-home SBP (-10.61 mmHg; P = 0.001), home awake ABPM, -0.05 ± 12.19 mmHg, (P = 0.001), ABPM-office SBP (-15.75 ± 14.51 mmHg, P = 0.00). 45% of patients had a 10% or more difference and 62.5% had a 5% or more difference in SBP between home and office. Interestingly, patients who had frequent intracranial hypertension (IDH) tended to have a larger difference in home-office SBP.

Conclusions: This study showed that the difference between home BP and ABPM was found to be approximately one third of the difference between office BP and ABPM. Because of the discomfort of ABPM measurements in patients with hemodialysis, home BP is necessary for proper BP management to prevent IDH. Conclusively, we propose that home BP could be a therapeutic target instead of ABPM in hemodialysis patients.

Is It Worth Measuring Home Blood Pressure in Maintenance Hemodialysis Patients?

Sang Heon Song,1,2 Hyeyeon Jeong,1 You Hyun Jeon,1 Miyeun Han,1,3 Harin Rhee,1,2 Eun Young Seong,1 Il Young Kim,1,2,4 Dong Won Lee,1,2 Soo BK Cho,1,2,4 Internal medicine, Pusan National University Hospital, Busan, Republic of Korea; Internal medicine, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea; 1Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea; 2Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea.

Background: The proper control of blood pressure (BP) is an important issue in hemodialysis patients and accurate BP measurement is mandatory. Although various methods of measurement of BP have been proposed, there is no standard method. The aims of this study are that office BP and home BP were compared based on ambulatory blood pressure monitoring (ABPM) in hemodialysis patients and propose the usefulness of home BP.

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Conclusions: This study showed that the difference between home BP and ABPM was found to be approximately one third of the difference between office BP and ABPM. Because of the discomfort of ABPM measurements in patients with hemodialysis, home BP is necessary for proper BP management to prevent IDH. Conclusively, we propose that home BP could be a therapeutic target instead of ABPM in hemodialysis patients.
refine their predictive ability. The clinical relevance of kidney-related parameters has long been recognized in many studies. However, no study so far has explored how consistent they have appeared in various models. We sought to appraise kidney-related parameters (KRP) in contemporary models of HF.

Methods: Articles cited in PubMed database using keywords “heart failure”, “prognosis”, and “predictive model” were searched. Available data from clinical trials performed between January 1995 and December 2018 were included. The studies were selected if they prognosticated outcomes in HF population through a predictive model that consisted of at least 2 factors. Pertinent data on KRP (e.g. serum creatinine, blood urea nitrogen [BUN]), and serum sodium) were extracted and reviewed.

Results: A total of 15 studies with 82,706 participants were included, of which 5 were validated in a HF cohort different from the model derivation cohort. They consisted of a variety of HF populations (e.g. acute, chronic, carrying mechanical circulatory device) and the median number of modeled parameters was 7. There was substantial variability across models in the reporting of the KRP as well as the studied outcomes. While no study included estimated glomerular filtration rate, serum creatinine and BUN were included in only 6 and 4 studies respectively. Similarly, 4 and 7 models contained data on serum sodium level and blood pressure respectively. Serum uric acid and history of kidney disease were each included in only 1 study.

Conclusions: We found that available models for prediction of HF outcomes do not consistently include KRP while generally portending high prognostic ability. Development of these models is based on multivariate regression methods to define the proportional significance and coefficients of the prognostic variables. Therefore, this finding supports the notion that, contrary to conventional thinking, the impact of KRP on the outcomes of patients with HF may be confounded or modulated by other covariates (e.g. congestion) as the emerging data have implied.

TH-PO17
Sex Disparities and Risk of CKD: A Nationwide Cohort Study of 10.8 Million Adults in Korea
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Background: There are substantial differences in public health issues between men and women. However, longitudinal studies of the relationship between sex disparities and incident chronic kidney disease (CKD) are scarce. In this study, we aimed to evaluate the association between sex disparities and incident CKD in healthy adults with normal baseline kidney function.

Methods: We analyzed a total of 10.8 million adults who underwent National Health Insurance Service Medical Care, Ilsan Hospital, Gyunggi-do, Republic of Korea. Out of this, 60% were female, 4.8% had CKD stage G4, and 1.4% had CKD stage G5. The mean age was 74±6 years old. The outcome of interest was incident CKD, defined as de novo development of eGFR <60 mL/min per 1.73m2 (definition 1) or a ≥25% decline in eGFR from the baseline values accompanied by eGFR <60 mL/min per 1.73m2 (definition 2).

Results: In this large nationwide cohort comprised of 10.8 million healthy Korean adults who had eGFR ≥60 mL/min per 1.73 m2, there were a total of 187,986 (1.66%) and 81,737 (0.76%) incident CKD events according to each CKD definitions, respectively, during a median follow-up of 4.8 years. Multivariable-adjusted Cox model showed that women were associated with significantly lower risk of incident CKD compared with men (HR: 0.84; 95% CI, 0.83–0.85) in models using CKD definition 1 and 0.86 (95% CI, 0.85–0.87) in models using CKD definition 2 respectively. No significant interaction was observed for age and sex in the association of incident CKD with sex.

Conclusions: Women-to-men relative risk ratio for CKD and ESRD, comparing individuals in each sex category, remained lower in women than men. There were no significant differences in sex and CKD events as the eGFR of more than 60 mL/min per 1.73 m2 was used as the definition of normal eGFR. Sex differences in the risk of developing CKD are observed, and further study is needed to determine female gender with respect to the risk of advanced CKD (stages G4 and G5).
TH-PO720
Survival Advantage of Renal Transplantation over Dialysis Is Blunted in Women
Dan Sapoznikov, Michal Dranitzki Elhalel, Dvora Rubinger. Hadassah Hebrew University Medical Center, Jerusalem, Israel.

**Background:** The effect of gender on long term outcome in end stage renal disease is not well defined. Decreased LFs, a baroreflex index, and increased sdsV (stroke volume variability, a measure of myocardial responsiveness) were shown to predict poor prognosis in hemodialysis (HD) patients.

**Methods:** To assess factors associated with long term survival, clinical data and death events were monitored in 126 men (M) and 70 women (F) on HD and after renal transplantation (TX) during a follow up of 60 months. Continuous intercept interval (IBI) and systolic blood pressure (SBP) and their variabilities were recorded using Finometer. LFs and sdsV were calculated from SBP and IBI spontaneous variations.

**Results:** Kaplan-Meier analysis showed a similar (76%) 5 yr survival in HD M and F. A significantly increased survival was noted in TX M compared with HD M (91%, p=0.031) while no such difference was noted in TX F (Figure1). Main death risk factors, LF α and sdsV are shown in Table 1. Age range, the prevalence of diabetes mellitus, hyperlipidemia and HD vintage were similar in M and F. TX was associated with improved blood pressure in all patients. Renal function was similar in TX M and F.

**Conclusions:** Our data show that despite higher comorbidity prevalence, TX significantly improved survival in M. The enhanced survival in TX M was associated with increased LFs and decreased sdsV, suggesting improved autonomic function. In F no significant changes in these measures were found and the survival benefit of TX was less prominent. The causes of the reduced effect of TX in F remain to be determined.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>HD M (75)</th>
<th>HD F (44)</th>
<th>p</th>
<th>TX M (51)</th>
<th>TX F (28)</th>
<th>p</th>
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<tr>
<td>Hypertension (%)</td>
<td>71 (9)</td>
<td>39 (12)</td>
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<td>46 (82)</td>
<td>21 (69)</td>
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<td>Ischemic Heart Disease (%)</td>
<td>44 (9)</td>
<td>72 (96)</td>
<td>0.556</td>
<td>19 (38)</td>
<td>5 (17)</td>
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<td>Smoking (%)</td>
<td>38 (53)</td>
<td>7 (15)</td>
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<td>19 (38)</td>
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<tr>
<td>IBI variance (ms)</td>
<td>5.4±2.86</td>
<td>5.4±2.30</td>
<td>0.006</td>
<td>4.9±2.50</td>
<td>4.7±2.50</td>
<td>0.914</td>
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</tbody>
</table>
| *p vs. HD M:*p<0.005;**p<0.001;

Figure 1.

Table 1 A and B. Features and Results.

TH-PO721
Real World, Hard Outcomes, and Sex Differences in AKI
Maria Isabel Acosta-Ochoa, Armando Coca, Alicia Mendiluce. Hospital Clinico Universitario, Valladolid, Spain.

**Background:** Several studies focus on sexual dimorphism when suffering AKI, some of them report that women could be a protected against adverse events. We compared clinical outcomes between females and males in a real world cohort with AKI.

**Methods:** Retrospective cohorts study of hospitalized patients with diagnosis of AKI. We used KDIGO-2012 criteria for stratifying AKI severity, analyzed epidemiological and clinical variables and compared clinical outcomes: length of hospital stay, need for dialysis, dialysis dependence, and renal recovery.

**Results:** We included 1269 cases, 70% male, DM 42%, and CKD 61%. Table 1A shows clinical variables and Table1B results between groups. We found that mean Charlson’s was higher in male individuals and women are hospitalized more frequently in medical wards. We found no statistically significant differences in hard clinical outcomes except for dialysis dependence at discharge (more in male individuals). We studied the effect of sex on death was using Cox regression analysis, univariate analysis revealed that sex was not a significant risk factor for death during AKI [HR (sex): 1.01, 95%CI: 0.78-1.30, p=0.95]; multivariate analysis including sex and AKI severity yielded similar results [HR (sex): 0.99, 95%CI: 0.77-1.29, p=0.98].

**Conclusions:** Experimental studies observe clear differences in clinical outcomes between genders when suffering AKI, some even concluding that female sexual hormones could be not only protective but also a possible treatment. In this real world study we observed a higher incidence of AKI in men than in women, consistent with previous larger epidemiological studies, and we only found that males are more frequently dialysis dependent at discharge. So we observed that women that suffer an AKI episode are not protected against it’s deleterious effects.

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Gender Differences in Presentation and Outcomes Among Patients with Atypical Hemolytic Uremic Syndrome (aHUS)

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Background: Gender differences among patients with aHUS are not well established.

Methods: We describe and compare demographic, clinical and genetic data from female and male patients with a history of aHUS enrolled in the Vienna thrombotic microangiopathy (TMA) cohort.

Results: In this single center study, we identified 51 patients with a first manifestation of aHUS between 1981 and 2019. The median age at diagnosis was 28 years and 63% were female. Kidney biopsies were available from 32 patients (63%) and all but 1 showed features of TMA. At time of presentation 31 patients were dialysis dependent (no data for 3 patients). 23 received plasma and 7 eculizumab therapy. 7 recovered kidney function with therapy (3 eculizumab, 3 plasma exchange, 1 supportive). At last follow-up, 9 were deceased, 3 on dialysis, and 17 had a renal graft. Among the remaining 22 patients, 13 had an eGFR ≥ 60 ml/min per 1.73m². Gender specific results are indicated in Table 1.

Conclusions: The majority of aHUS patients enrolled in the Vienna TMA cohort were female. Women presented at younger age, more often harbored disease-causing genetic variants or a CFH- or CD46-risk haplotype, and had better kidney function at last follow-up as compared to males.

Table 1.

*no data available in 1, 5 showed no genetic variants
associated with a higher rate of depression and poor sleep. Understanding gender differences in dialysis patient can help guide treatment for high risk groups.

**TH-PO727**

The Effect and Safety of Postmenopausal Hormone Therapy and Selective Estrogen Receptor Modulators on Kidney Outcomes in Women: A Systematic Review


**Background:** The number of postmenopausal women with or at risk of chronic kidney disease (CKD) is increasing exponentially. The benefits and risks of postmenopausal hormone therapy (PHT) and selective estrogen receptor modulators (SERMs) on kidney outcomes in these women are poorly understood. This systematic review aimed to: 1) determine the effects of PHT and SERMs on kidney function and albuminuria in women, and, 2) characterize the risk of adverse outcomes of PHT and SERMs in the CKD population, who are already at an increased risk of venous thromboembolism and malignancy.

**Methods:** An electronic literature search was completed using a peer reviewed search strategy in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. We searched published studies (1950-December 2018) examining the effect of PHT and SERMs on kidney function and albuminuria, and adverse outcomes in women with CKD. Two independent investigators screened identified citations examining the effect of PHT and SERMs on kidney outcomes in the general population of women, as well as adverse outcomes in the CKD population. Data was independently extracted from each eligible study, and the risk of bias was assessed. Results were synthesized in a descriptive manner.

**Results:** A total of 3,078 references were screened, and 18 studies met eligibility criteria. Compared with no treatment, use of PHT was associated with improved kidney function and unchanged or reduced proteinuria in more than 60% of studies that addressed this question. No studies were identified that reported on the safety of PHT in women with CKD. Studies addressing the effects of SERMs on kidney function were conflicting, with 2 studies reporting increased kidney function and reduced proteinuria, and another reporting decreased kidney function. Based on results from 2 small studies, SERMs did not have any increased risk of venous thromboembolism in women with CKD compared to placebo.

**Conclusions:** Existing studies suggest that PHT and SERMs are associated with improved kidney function, with no increase in albuminuria. Safety data in the CKD population is lacking. Available studies had significant limitations and heterogeneity, highlighting the need for rigorous prospective studies examining the effect of PHT and SERMs on kidney function, and their safety in CKD.

**TH-PO728**

Screening for Osteoporosis Represents a Missed Opportunity in Women with ESRD


**Background:** Women with end-stage renal disease (ESRD) treated with hemodialysis (HD) have increased morbidity and mortality, and shorter life expectancy. In fact, the survival advantage that women have over men in the general population is markedly decreased in the HD population. The purpose of this study was to explore age-appropriate preventive care for women with ESRD on maintenance HD.

**Methods:** We performed a cross-sectional survey of adult patients with ESRD undergoing HD in two outpatient dialysis centers at the University of Florida. Interviews were conducted using a survey instrument that contained questions on demographic information, types of health care providers, and a number of preventive measures. We used United States Preventive Services Task Force (USPSTF) guidelines to determine eligibility and completion of screening for breast and cervical cancers as well as osteoporosis.

**Results:** Of the 132 patients who participated in this study, 66 (50%) were female. The average age of women was 60 (range = 22-84). The majority (95.5%, n=63) reported having a primary care provider (PCP). Out of the eligible patients, 81.4% (35/43) reported being up-to-date on breast cancer screening, 75% (33/44) on cervical cancer screening, and 16.7% (4/24) on osteoporosis screening. Having a PCP was associated with a trend towards higher adherence with preventive care measures.

**Conclusions:** Our study identifies “osteoporosis screening” as an opportunity to improve preventive care of women with ESRD treated with maintenance HD. The rates of osteoporosis screening were found to be even lower than the general population (i.e. 25%) in this cohort. Interestingly, women reported higher rates of screening for malignancies of breast and cervix compared to the general population. While there has been a shifting paradigm in diagnosis and management of osteoporosis in patients with ESRD, future studies are needed to identify patient and provider characteristics associated with higher likelihood of adherence to age-appropriate preventive care for female patients with ESRD.

**TH-PO729**

Cardiac Mortality in People with ESKD in Australia and New Zealand: A Cohort Study from 1980 to 2013

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**Background:** The presence of cardiac disease is an important predictor of mortality in people with ESKD. Therapies for reducing cardiac risk and treatment of cardiac events may be less effective in people with ESKD compared to the general population. We aim to review the standardised mortality ratios from cardiovascular disease (CVD) for people with ESKD in the Australian and New Zealand general population.

**Methods:** Cohort study of incident people with ESKD in Australia and New Zealand, 1980-2017. ANZDATA was linked with death registries to obtain cause of death. Summary data for cause specific death in the general population were obtained. We calculated mortality rates for CVD as defined by ICD10 codes and standardised mortality ratios (SMRs with 95% confidence intervals [CI]), compared with the general population, using indirect standardisation, by age, sex and calendar year.

**Results:** There were 60,823 participants contributing 381,874 years of observation time. In total there were 6847 cardiac deaths of which 5947 (86.9%) were ischaemic heart disease deaths. The rate of cardiac mortality compared to the general population was higher in women (women: SMR 8.3 95%CI 8.0-8.6, men: SMR 5.69% 95%CI 5.5-5.8). Young women were particularly affected having over double the increased rate of cardiac mortality relative to the general population (ages 30-49: women: SMR 59.7 95%CI 51.8-69.0, men 17.7 95%CI 15.9-19.7). Relative cardiac mortality rates have improved over time for women but have been stable in men (Figure 1).

**Conclusions:** The mortality rates in the Australian and New Zealand ESKD population are higher than the general population. Young women with ESKD have an excessive relative risk of dying from cardiac disease, compared to young females in the general population. The relative risk of women dying from cardiac disease has reduced over time.

**Funding:** Government Support - Non-U.S.
score, this study raises concern about osteoporosis under-treatment in patients with eGFR 30-60ml/min/1.73m².

**Funding:** Other NIH Support - R01 DK115534 01A1;

**Figure 1.** Left panel: OR for SBP use among osteoporosis patients in the Declercq and Geilinger studies according to HT and HT/C categories.
Characterizing Fetal Outcomes in Women with Biopsy-Proven Primary Glomerular Disease
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**Background:** It is well known that women with chronic kidney disease are at higher risk for worse maternal and fetal outcomes. However, the extent of these risks in women with biopsy proven primary glomerular disease has not been well described. This study aims to further characterize pregnancy outcomes in this population.

**Methods:** A database of women seen in a Pregnancy and Kidney Disease clinic at a tertiary care centre in Toronto, Canada was searched from January 2003 until July 2018 to identify women with biopsy-proven primary glomerular disease who had at least one pregnancy managed in this clinic. The primary study outcome was the live birth rate. Secondary study outcomes included birthweight, spontaneous abortions and perinatal death (defined as stillbirth >20 weeks or neonatal death).

**Results:** 218 pregnancies in 148 women (IgA nephropathy n=79, FSGS n=69, membranous nephropathy n=23, hereditary nephritis n=21, membranoproliferative glomerulonephritis n=15, minimal change disease n=11), were identified. Of these, 84.4% resulted in a live birth. 35.6% were born under 37 weeks gestational age (GA), with 29.7% of these at less than 32 weeks GA. 57 babies were born under the tenth percentile for their GA, 26.3% of these babies were less than the third percentile. There were 23 spontaneous abortions (SA) at less than 10 weeks GA and 5 SA at 10-20 weeks GA. In this cohort, 3.9% of pregnancies resulted in perinatal death.

**Conclusions:** Women with biopsy-proven glomerular disease are at high risk of adverse fetal outcomes. Further work needs to be done to characterize fetal outcomes by sub-category of glomerular disease, as well as to examine maternal outcomes.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

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FGF4R Is Not Required for the Development of Cardiac and Renal Hypertrophy in Pregnancy
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**Background:** Pregnant women develop cardiac and renal hypertrophy as an adaption to increased blood volume, which is reversible without causing organ injury. Fibroblast growth factor (FGF) 23 is a bone-derived hormone that increases phosphate excretion by targeting the kidney via FGF receptor (FGFR) 1 and klotho. In chronic kidney disease, high FGF23 levels are associated with cardiovascular injury and can directly induce cardiac hypertrophy. FGF23 binds to FGFR4 on cardiac myocytes in a klotho-independent manner, thereby activating pro-hypertrophic signaling. In injured kidneys, FGF23/FGF4R signaling promotes fibrosis. Here, we investigated whether FGF23/FGF4R signaling contributes to cardiac and renal hypertrophy during pregnancy.

**Methods:** Virgin female C57Bl/6J wildtype (WT), FGF4R knockout (KO), and FGF4R-385R:R knockin (KI) mice were mated with proven male breeders. After 24 hours, males were removed, and females were sacrificed after 18 days in late pregnancy (LP). Age-matched, non-pregnant (NP) females served as controls. Heart and kidney mass and serum markers FGF23, phosphate and calcium were determined. Heart and kidney tissue were further analyzed by qPCR.

**Results:** WT and KO mice develop cardiac and renal hypertrophy in LP, indicated by increased heart weight/tdiba length and kidney weight/tdiba length ratios when compared to respective NP controls. This effect is not observed in pregnant KI mice. Serum FGF23 increases in LP in all three genotypes. In WT-LP mice, serum calcium levels increase, while serum phosphate is unchanged when compared to WT-NP controls. Furthermore, cardiac Fgfr1 mRNA levels are reduced, and Fgf23 and Fgfr4 increased in the kidney.

**Conclusions:** In LP, mice develop cardiac and renal hypertrophy and have elevated serum FGF23 levels. However, in this context FGF4R does not seem to be required for the development of organ hypertrophy. Surprisingly, we found that activation of FGF4R inhibits organ hypertrophy (Pr) suggesting anti-hypertrophic actions of FGF23/FGF4R signaling in pregnancy, which requires further mechanistic studies.

**Funding:** Other NIH Support - NHLBI, Government Support - Non-U.S.
Intrauterine Sildenafil Therapy Does Not Impair Renal Function in Young Adult Offspring of Preeclamptic Dahl S Rats
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Background: Up to 10% of pregnancies are complicated by preeclampsia, and up to 15 million Americans are offspring of preeclamptic pregnancies. The Developmental Origins of Health and Disease hypothesis proposes that an adverse intrauterine environment programs the fetus to increased susceptibility to hypertension and renal function loss. We have shown that sildenafil citrate, a phosphodiesterase-5 (PDE-5) inhibitor, improves the maternal syndrome of preeclampsia in the Dahl S rat and reduces blood pressure of their offspring up to 21 weeks of age; however, long term kidney function in these offspring has not been examined. We hypothesized that PDE-5 inhibition during preeclamptic pregnancy improves long-term BP without significant reduction in renal function.

Methods: Female Dahl S rats on a 0.3% salt diet were mated and treated orally with sildenafil (50 mg/kg/day) or vehicle from gestational day 10 to delivery. Laxationally treated and offspring were on normal chow for the duration of the study, and measurements were made at 12 weeks of age. Urine was collected (n=18-27/group) for measurement of urinary protein (Bradford assay) and creatinine (Jaffe reaction). Plasma was also collected at euthanasia (n=13-17/group) for measurement of blood urea nitrogen (BUN, enzymatic method) and creatinine, and creatinine clearance was calculated.

Results: Systolic BP (n=5-9/group, tail cuff) was greater in Dahl S rats of untreated mothers compared to offspring of sildenafil treated dams (VEH: 175±4 mmHg; SLD: 158±2 mmHg, p<0.001). BP data were pooled due to lack of significant sex differences between treated groups. No significant differences in proteinuria were observed (VEH male: 102±8; SLD male: 101±8; VEH female: 55±5; SLD female: 75±6 mg/day). No significant differences in BUN were found between either sex or treatment group (VEH: 20±4 vs. 18±6 mg/dL). While expected sex differences in creatinine clearance were maintained, there was no significant difference between the treatment groups (VEH male: 0.75±0.05; SLD male: 0.76±0.05; VEH female: 0.56±0.07; SLD female: 0.64±0.06 ml/min/100g renal mass).

Conclusions: These data support the hypothesis that the use of a PDE-5 inhibitor during preeclamptic pregnancy improves the long-term BP without reduction of renal function in the offspring at 12 weeks of age.

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TH-POT40
Obstetric Complications in Pregnanat Dialysis Patients
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Background: Gestational vascular diseases such as preeclampsia (PE) are associated with maternal and fetal morbidity and mortality. PE is often associated with intra-uterine growth restriction (IUGR) predisposing for diseases later in life. We now aim to evaluate whether fetal re-programming due to EVs induced pregnancy complications can possibly cross the placenta and affect the offspring.

Methods: Women ages 14 to 50 years starting dialysis between 2004-2011 were included. ICD-9 codes from hospital, physician, or detailed claims identified pregnant patients with SAB or PTL. CMS Form 2728 was used to identify demographics and included. ICD-9 codes from hospital, physician, or detailed claims identified pregnant women. Hospital, physician, and claims data were linked to the United States Renal Data System (USRDS).

Results: There were 1393 pregnancies, with mean maternal age 34±9 years, 40% white race, and 91% on hemodialysis. ESRD etiologies were: 43% diabetes, 7% hypertension (HTN), 29% SLE, 18% glomerulonephritis (GN), and 3% polycystic kidney disease. The incidence of SAB and PTL was 7% and 10%, respectively. For SAB, there were no differences between SLE and GN. The aHR of SAB was higher in non-white, non-black race [2.30] and decreased with increasing maternal age [0.96]. For PTL the aHR increased with pre-eclampsia [1.66], eclampsia [2.09] and intrauterine growth retardation [3.56]. Risk of PTL decreased with increasing maternal age [0.91] and a diagnosis of septicaemia [0.58].

Conclusions: SAB and PTL are common obstetric complications in pregnant ESRD patients and greatest in those with SLE and GN. It is unclear from this work how risk of PE may differ in dialysis pregnancies; however we would speculate that younger patients have higher prevalence of SLE, and thus more extensive systemic disease. Similarly, we would suggest that septic patients received more intensive medical therapy and pre-term care, decreasing the risk of complications. Understanding the high-risk groups for complications may improve pre-term care and outcomes.

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Maintaining Low Mean Blood Pressure Reduces Severe Adverse Events in Pregnant Women with IgA Nephropathy: A Single-Center Retrospective Study

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Background: A number of young female patients with IgA nephropathy experience pregnancy because the disease population peaks at adolescence age. The clinical course of IgA nephropathy varies; therefore, not all cases receive treatment and follow-ups. However, the risk of pregnancy outcomes among the females with different disease severity and treatment is not well-known.

Methods: Patients with IgA nephropathy who underwent prenatal care at our institution for 8 consecutive years were recruited for this study. We collected the clinical data by reviewing medical records of patients. Further, we analyzed the correlation between pregnancy outcomes and the antecedent models, including age, BMI, eGFR, proteinuria (UP), mean blood pressure (MBP), anti-hypertensive drugs use, and past treatment for IgA nephropathy at the time of referral. We set the occurrence of severe adverse events (SAE) as primary outcome and preterm delivery (PreD), small for gestational age (SGA) infants, and low infant birth weight (LBW) as secondary outcomes.

We performed logistic regression analysis for each outcome. According to CKD stages, eGFR and UP were categorized into 5 stages and 3 stages, respectively.

Results: We observed 33 pregnancies of 27 patients. Median age was 31 years, mean weight was 53.5 ± 11.7 kg, and mean UP was 0.11 ± 0.04 g/gCr. SAE occurred in 9 pregnancies. Age (OR = 1.26, = 0.021), UP stage (OR = 2.92, = 0.029), MBP (OR = 1.24, = 0.01), and past methylprednisolone pulse therapy combined with tonsillectomy (OR = 0.14, = 0.033) were the candidate predictor according to the univariate analysis. Consequently, MBP (OR = 1.33, = 0.009) was the only predictor for SAE according to the multivariate analysis. Among PreD, SGA, and LBW, univariate analysis showed significant statistical significance in baseline characteristics as candidate predictors for SAE. However, multivariate analysis showed no statistical significance among those candidates.

Conclusions: Univariate analysis showed that less proteinuria, lower MBP, and treatment with combined therapy reduce risk of SAE, whereas multivariate analysis showed that MBP is the only predictor for SAE. Our study implies that patients with IgA nephropathy should receive treatments until their blood pressure normalizes before initiating pregnancy.

TH-PO743

Mechanisms of Vascular Dysfunction in the Interleukin-10-Deficient Murine Model of Preeclampsia

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Background: Preeclampsia (PE) is characterized by new-onset hypertension, proteinuria, endothelial dysfunction, and both macrovascular and microvascular injury in the second half of pregnancy. Based on observations that PE is associated with derangements in IL-10 signaling, we sought to test the hypothesis that endothelium-dependent vascular dysfunction is exacerbated in a murine model of PE based on the administration of human PE sera to interluekin (IL)-10 -/- mice.

Methods: Pregnant wild type (WT) and IL-10 -/- mice were injected with either normotensive (NT) or severe preeclamptic (sPE) patient sera on the 10th day of gestation. Blood pressure was measured at the beginning of pregnancy and before sacrifice on the 17th day of gestation. Vasomotor function of isolated aortas, albuminuria, and aortic gene expression were assessed.

Results: Pregnant IL-10 -/- mice injected with sPE sera exhibited higher blood pressure (P = 0.002) and albuminuria (P = 0.0066) compared to controls. Contractions of the isolated aortas to phenylephrine were significantly augmented in the IL-10 -/- mice injected with sPE sera compared to the control pregants (P = 0.001). This group also demonstrated impaired endothelium-dependent relaxation to acetylcholine compared to controls (P = 0.002). Treatment of isolated aortas with indomethacin normalized vascular reactivity of aortas derived from pregnant IL-10 -/- mice injected with sPE sera (contraction: P = 0.009; relaxation to acetylcholine: P < 0.001).

Conclusions: In aggregate, the IL-10 -/- PE model exhibits significant pregnancy-specific macrovascular dysfunction caused by enhanced contraction to phenylephrine and impaired endothelium-dependent relaxation. Observed alterations in vasomotor function are predominantly caused by enhanced activation of the cyclooxygenase pathway.

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TH-PO744

Animal Models of Preeclampsia: A Renal Perspective

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Background: Preeclampsia is a heterogeneous syndrome with different pathophysiological subtypes. Many animal models have been proposed, each based on different pathophysiology. The preeclampsia phenotype may differ depending on the model, the lab or personnel, or the animal supplier. Whereas some models reproduce the glomerular endotheliosis observed in preeclamptic women, others cause hypertensive disease, and abstraction protocols. Detailed information was abstracted from papers that included a common (>20 publications) model.

Methods: PubMed and EMBASE were searched to identify articles using animal models of preeclampsia. Studies were included if they had persistent proteinuria. No deaths were reported during the follow-up. Only 19 (59.4%) of 312 studies met the inclusion criteria for our review.

Results: 364 papers included a common model (NOS inhibition: n=112 (22%), reduced uterine perfusion pressure or subrenal aortic coarctation: 101 (19.8%), sFlt-1: 35 (6.9%), low dose doxotrem: 33 (6.5%), NaCl administration: 28 (5.5%), transgenic human angiotensinogen renin: 25 (4.9%), agonistic autoantibodies against the angiotensin II type 1 receptor: 23 (4.5%), or NaCl and corticosteroids: 20 (3.9%). 80.5% of studies reported maternal blood pressure. 44.2% measured proteinuria. Renal histopathology was rarely performed, most often not detailed, and comprised of protein casts that were highly variable among models (blood pressure: 43% to 100% (range), proteinuria: 21% to 95%, renal histopathology: 5% to 40%). The proportion of papers reporting proteinuria and renal histopathology did not differ between papers with vs. without a preclinical agent. 40% of papers acknowledged that the model may not apply to all preeclamptic women.

Conclusions: Renal histopathology is rarely reported, suggesting a need for better characterization of renal changes caused by preeclampsia models and preclinical agents. This is particularly important given that hypertensive renal injury observed in some models differs from the glomerular endotheliosis observed in preeclamptic women.

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TH-PO745

TH-PO746

Maternal and Fetal Outcomes in Women with CKD Diagnosed During Pregnancy

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Background: Diagnosis of Chronic Kidney Disease (CKD) during pregnancy, has increased in recent years. It is associated with worst outcomes for the mother and the baby. Mexico has one of the highest incidences of CKD, but, little is known about the impact of CKD in our population. The purpose of this work is to present the outcomes in a cohort of Mexican women with CKD diagnosed during pregnancy.

Methods: A prospective observational study, 32 pregnant women with CKD were included with quarterly follow-up until three months after delivery and were compared with 117 age matched pregnant woman without CKD for hypertensive disorders of pregnancy, gestational age, low birth weight, preterm delivery and relevant clinical kidney events.

Results: No differences were found in baseline characteristics except for the serum creatinine. Hypertension was associated with CKD (P=0.001). Women with CKD had a greater number of cesarean sections (P=0.001), and their babies had lower birth weight, gestational age, and preterm delivery (P=0.006, 0.001 and 0.007 respectively). During pregnancy three patients required renal replacement therapy (RRT), which started at 8.6±4.1 gestational weeks. Two of them continued in RRT after the delivery. Only 19 (59.4%) of 31 patients with a hypertensive disorder of pregnancy were classified as chronic hypertension, and nine (90%) of 10 patient had persistent proteinuria. No deaths were reported during the follow-up.

Conclusions: CKD is associated with worse maternal and fetal outcomes. In our country, it is necessary to implement strategies to allow diagnosis of CKD during or ideally before pregnancy, a close follow-up by nephrologist and evaluate the impact of its intervention in maternal and fetal outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Women's Health and Kidney Diseases

**TH-PO747**
Preeclamptic Women Have Decreased Circulating IL-10 Levels at the Time of Active Disease: Systematic Review and Meta-Analysis

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**Background:** Preeclampsia (PE) is a pregnancy specific disorder characterized by hypertension and proteinuria after 20 weeks of gestation. One hallmark of PE is an abnormal maternal immune response. As a key immunomodulatory cytokine, Interleukin-10 (IL-10) has been shown to be dysregulated in PE. However, studies have reported inconsistent findings about circulating IL-10 levels in PE and normotensive (NT) patients. The aim of the present systematic review and meta-analysis is to assess circulating IL-10 levels in PE and NT patients at two time points: before PE diagnosis and at the time of active disease.

**Methods:** PubMed, EMBASE, and Web of Science databases were searched to include all published studies examining circulating IL-10 levels in PE and NT patients. Differences in circulating IL-10 levels between PE and NT women were evaluated by standardized mean differences.

**Results:** Out of the 876 abstracts screened, 56 studies were included in the meta-analysis. At the time of active disease, women with PE (n = 1486) had significantly lower circulating IL-10 levels compared to NT women (n = 1897) (SMD: -0.68, 95% CI: -1.10, -0.28; P < 0.0008). Circulating IL-10 levels were lower in both early/severe and late/mild forms of PE. Subgroup analysis revealed that the methodology used to measure circulating IL-10 levels (ELISA or multiplex bead array) and the sample type (plasma or sera) significantly influenced the observed differences in circulating IL-10 levels between PE and NT women. Circulating IL-10 levels were not different before the time of active disease (SMD: -0.01, 95% confidence interval [CI]: -0.11, 0.08; P = 0.76).

**Conclusions:** These findings provide further evidence about the significance of changes in circulating IL-10 levels in the pathophysiology of PE. Further studies are needed to elucidate the clinical implications of these findings and the treatment potential of IL-10 in PE.

**Funding:** Other NIH Support - R01HL136348 from the National Heart, Lung, and Blood Institute (Garovic)

**TH-PO748**
Autoimmunity and Altered Renal Function Precede the Development of Hypertension in Female Mice with Lupus

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**Background:** Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by circulating autoantibodies, hypertension, and renal injury. Kidney involvement is common in SLE and renal dysfunction is evident in patients with active renal disease, yet little is known about early changes in renal function that may contribute to the pathogenesis of hypertension. We hypothesize that the loss of immunological tolerance and subsequent production of autoantibodies in SLE leads to impaired renal hemodynamic function that precedes the development of hypertension.

**Methods:** Female NZBWF1 mice, an established experimental model of SLE, and female NZW (control) mice were instrumented with carotid artery and jugular vein catheters to determine arterial pressure (MAP) and glomerular filtration rate (GFR) respectively at ages 15, 20, 24, 28, 31, and 34 weeks. MAP was measured in consciousness, freely-moving mice. GFR was measured by the clearance of fluorescein isothiocyanate-inulin (FITC-inulin) after achieving steady state through continuous infusion for five hours.

**Results:** Circulating autoantibodies are significantly increased by 28 weeks of age in mice with SLE (P = 0.0135), whereas autoantibodies are unchanged in control mice (Figure 1). GFR increases at 28 weeks of age followed by a significant decline by 34 weeks of age (P = 0.0127, P = 0.0001) compared to 34 and 15 weeks of age respectively, in SLE mice. GFR is increased in control mice by 28 weeks of age (P = 0.002) and remains unchanged at other time points (Figure 2).

**Conclusions:** These data suggest that changes in renal hemodynamic function occur in female SLE mice prior to changes in MAP suggesting a mechanistic role for autoimmunity to directly impair renal hemodynamic function and promote the development of hypertension.

**Funding:** Veterans Affairs Support

**TH-PO749**
Sex Differences in Bioimpedance in Humans with Obstructive Sleep Apnea with Normal Kidney Function Before and After Continuous Positive Airway Pressure Therapy

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**Background:** Sex differences exist in obstructive sleep apnea (OSA) and chronic kidney disease (CKD), both of which are strongly associated and predispose patients to expanded total body water (TBW) and aberrant volume redistribution, resulting in significant morbidity. Continuous positive airway pressure (CPAP) therapy is an effective treatment for OSA which may alleviate this predisposition. While there are established sex differences in the pathophysiology of OSA and CKD, whether sex differences exist in TBW and other bioimpedance parameters in OSA subjects with normal kidney function and the impact of CPAP therapy remains unknown.

**Methods:** Twenty-nine (10 women, 19 men; age 49±2 years) incident, otherwise healthy, and sodium replete OSA subjects (oxygen desaturation index [ODI] >15/h) with and nocturnal hypoxemia (SaO2<90% for >12%/night) were studied pre- and post-CPAP therapy (~48/night x 4 weeks) using bioimpedance technology. Total body water (TBW), extracellular and intracellular fluid volumes (ECF and ICF), ECF:TBW, ECF:ICF, fat free mass (FFM), body mass index (BMI) and other bioimpedance and anthropometric parameters were measured and evaluated for sex differences before and after CPAP therapy.

**Results:** Pre-CPAP, TBW (74.6±0.4 vs 74.3±0.2% of FFM, p=0.14; all values vs men) and BMI (36.3±3 vs 35.1±1 kg/m2, p=0.9) were similar between sexes, though FFM (56.3±1.7 vs 71.7±1.5% of weight, p=0.001) and absolute TBW (42.4±3.0 vs 57.1±1.6L, p=0.001) were lower in women. The proportion of ECF:TBW (0.50±0.006 vs 0.44±0.009, p=0.001) and ECF:ICF (1.04±0.002 vs 0.86±0.004, p=0.001) was increased in women despite overall reduced absolute ECF (21.3±1.7 vs 25.2±0.8L, p=0.006) and ICF (21.1±1.2 vs 31.9±1.0L, p=0.001) compared to men. Though CPAP corrected both OSA (ODI: 47.4±4.4 vs 3.3±0.4L/h, p=0.001) and nocturnal hypoxemia (46.2±5.7 vs 8.3±2.7%, p=0.001), there were no within sex differences in bioimpedance or anthropometric parameters in response to CPAP therapy.

**Conclusions:** Women with OSA had expanded ECF compared to men. Differences in TBW distribution may contribute to sex differences in the pathophysiology of OSA in women with normal kidney function. CPAP therapy for 1 month did not mitigate these differences.
TH-PO750

Characterizing Nonlinear GFR Decline in Children with Kidney Diseases
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Background: GFR decline in kidney disease is frequently treated as linear in clinical research. The Chronic Kidney Disease in Children (CKiD) cohort provided long-term follow-up to characterize and describe GFR decline using non-linear models and accounted for risk stage using the newly developed pediatric classification.

Methods: CKiD participants contributed up to 13 follow-up years and provided annual estimated GFR data. To account for diagnosis, separate models were fit by non-glomerular and glomerular diseases. Linear mixed effects models were fit with log GFR as the outcome and a quadratic effect of time, with random effects for intercept, time and time^2. Baseline proteinuria categories (<0.5, 0.5 to 2, >2mg/mgCr) modified each parameter. Empirical Bayes estimates quantified individual-specific entry GFR, and changes within 5 years and between 5 and 10 years and were stratified by baseline CKD risk stage (initial GFR entry and observed proteinuria). Stable GFR was defined as no decline.

Results: A total of 757 and 275 children with non-glomerular and glomerular CKD, contributed 3926 and 1213 observations with 45% and 30% contributing at least 5 years. Most participants entered at Stage A or B (lowest severity) risk: for the non-glomerular and glomerular groups, 48% and 39% were in Stage A; 32% and 31% were in Stage B, respectively. The quadratic term for time offered significantly better fit than a linear effect only, for both groups (both p<0.001), and proteinuria significantly modified GFR trajectory. Nearly all children (95%) with non-glomerular diseases and 74% of those with glomerular diseases experienced faster percent decline in the second 5 years compared to the first 5 years, regardless of initial CKD stage. About 1/3 had stable GFR in the first 5 years, regardless of initial CKD stage. About 1/3 had stable GFR in the first 5 years, regardless of initial CKD stage. About 1/3 had stable GFR in the first 5 years, regardless of initial CKD stage. About 1/3 had stable GFR in the first 5 years, regardless of initial CKD stage.

Conclusions: In general, children with kidney diseases, GFR decline was not constant, but accelerated over time, and there was substantially more variability in glomerular disease. Mixed effects models provided individual non-linear trajectories and the challenge of heterogeneous disease duration at study entry was overcome by stratification by baseline CKD risk stage.

Funding: NIDDK Support

TH-PO751

Validation of Different Serum Creatinine-Based Estimating Equations in Pediatric Kidney Transplant Recipients in Comparison with Measured Glomerular Filtration Rate
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Background: The evaluation of allograft function is vital in the management of pediatric kidney transplant (pKTx) recipients. Serum creatinine (Scr) is the easiest everyday estimator of glomerular filtration rate (GFR) but both the absolute Scr value and the corresponding estimating equations (eGFR) are prone to considerable error. Measured GFR (mGFR) using plasma clearance of exogenous markers, while very accurate, is laborious as well as expensive, not suitable for everyday use. Prior studies have shown conflicting results regarding which eGFR equations are most accurate in comparison to mGFR.

Methods: This retrospective study was conducted at St. Louis Children’s Hospital from January 2000 to March 2019. We compared 415 mGFR values to 4 different Scr-based eGFR equations: the original Schwartz formula, modified Schwartz formula, Pottel formula and Modification of Diet in Renal Disease (MDRD) formula) from 125 pKTx recipients. Scr and children’s height was measured on the same day as mGFR. We used Bland-Altman analysis to evaluate the bias between eGFR and mGFR. Higher precision was defined as lower width between the 95% limits of agreement (LOA).

Results: The Pottel and modified Schwartz formulae had a high accuracy of 80% each and a low bias of < 5 ml/min/1.73 m² (Figure). In contrast, the original Schwartz and MDRD formulae displayed a high bias and low precision and accuracy.

Conclusions: Of the Scr-based formulae, height independent Pottel and height dependent modified Schwartz formulae had low bias and high accuracy and either can be used to assess GFR in pKTx recipients. The original Schwartz and MDRD equations should not be used in this population.

TH-PO752

Novel Nuclear Magnetic Resonance-Based Method for Prediction of Glomerular Filtration Rate Performs Well in Children
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Background: Estimation of glomerular filtration rate (eGFR) in children requires different equations than in adults. This led to the development of different pediatric equations; however, these equations still show suboptimal performances in the upper and lower GFR range. Recently, a novel serum-based method for accurate prediction of GFR using a nuclear magnetic resonance (GFR Nora) spectroscopy-based biomarker constellation (creatinine, myo-inositol, valine, and dimethyl sulfone) was developed. This method occurred as close to the conventional eGFR equations when validated in three separate cohorts of predominantly adult patients.

Methods: The value of the NMR-based biomarker constellation for GFR prediction specifically in children was investigated by testing its performance in a cohort of 39 children (20 girls, 19 boys) aged between 2 and 17 years. The NMR-based method was compared to eGFR (obtained by the bedside Schwartz equation using measured GFR (mGFR) as reference standard. Pearson correlation coefficient (r) with 95% confidence interval, root mean square error (RMSE), and the percentage of eGFR values within 30% of measured GFR (P30) were calculated to assess the accuracy of the methods.

Results: In a cohort comprising pediatric patients with various degrees of kidney impairment covering the whole GFR range, the NMR-based method showed a higher correlation with mGFR compared to eGFR (r=0.85 vs. r=0.80). Moreover, the RMSE was reduced from 35.5 for eGFR to 21.6 for GFR Nora. The NMR biomarker constellation also showed a higher accuracy in mGFR prediction with a P30 of 79.5 % compared to 71.8 % for eGFR Nora.

Conclusions: Our results demonstrate that the NMR-based biomarker constellation accurately predicts GFR not only in adults but also in pediatric patients. In fact, the novel method outperformed the established bedside Schwartz equation. Thus, GFR Nora allows reliable and continuous monitoring of kidney function at the transition from pediatric to adult renal care without the need to switch the estimation equation.

Funding: Commercial Support - nanumares AG

TH-PO753

Serum Cystatin C Levels at Birth in Very-Low-Birth-Weight Infants
Marko Sawada, Karashiki Central Hospital, Karashiki, Japan.

Background: Serum Cystatin C (CysC) is commonly used as a marker of glomerular filtration rates in children and adults. Although the reference intervals (RIs) of serum CysC has been well investigated, few reports demonstrated serum CysC levels in premature infants. The aim of this study was to investigate the RIs of serum CysC levels at birth in premature infants.

Methods: Eighty very low birth weight (VLBW, birth weight less than 1,500 g) infants admitted to our NICU between January 2018 and May 2019 were included, except for neonates with congenital anomalies of the kidney and urinary tract. Clinical data and serum CysC at birth were retrospectively collected from their medical records. All serum CysC concentrations were analyzed using a latex immunoturbidimetric assay. The RIs was defined as the set of CysC values in 95% of these populations.

Results: Data of 69 VLBW infants were available for this study. The CysC levels of 66 cases were distributed within 95% of these population. The gestational age was 29.2±3.1 weeks, and the birth weight was 1,061±290 g. It was included 27 (40.9%) male infants. The RIs of serum CysC levels at birth was 1.58±0.21 mg/L. Serum CysC levels in male infants were significantly higher than that in female infants (1.59±1.53 mg/L).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
p< 0.05). Serum CysC levels at birth did not related to gestational age, birth weight, and APGAR score. There was no difference between serum CysC levels in small-for-gestational age (SGA) and that in non-SGA infants.

**Conclusions:** The RIs of serum CysC levels at birth is higher than that in later life. Unlike serum creatinine, serum CysC concentrations are not affected by their month kidney function, therefore serum CysC levels might be a useful marker to evaluate the kidney function of neonates at birth.

**TH-PO754**

 Serum Creatinine, Cystatin C, and a Comparison of Estimated Glomerular Filtration Rates in Very Low Birth Weight Children at 6 Years Old

**Masufumi Oka.** Pediatrics, Saga university, Saga, Japan.

**Background:** According to the developmental organs of health and disease (DOHaD) theory, low birth weight is a risk factor for chronic kidney disease (CKD) in adulthood. However, there has been insufficient research into the renal function in school-aged children. In our research, we aimed to investigate the renal function of very low birth weight (VLBW), defined as less than 1,500g, children at six-year old and reveal risk factors of CKD.

**Methods:** We investigated 380 six-year old children who underwent a preschool physical examination, and had been among 504 VLBW infants discharged from the NICU in 1999-2011. The serum creatinine (Cr) and cystatin C (CysC) were measured, and for the >95 percentile group, a logistic regression analysis was used to study the relationships between the factors of gender, gestational age (GA), weight, height and head circumference at birth, and weight, height, and BMI at the time of the physical examination. Additionally, the estimated glomerular filtration rate (eGFR) at the examination was calculated with the equation of Japanese child (JPN), Schwartz and chronic kidney disease epidemiology collaboration (CKD-EPI) and compared.

**Results:** Data for 337 subjects was recorded (age: 5.4±0.5 years, male:female ratio = 167:170, GA: 28.3±2.7weeks, birth weight: 955±301g). Serum Cr was 0.3±0.4mg/dL and CysC was 0.77±0.13mg/L. In the >97.5 percentile group for Cr there were 7 subjects (2.1%), while for CysC, it was 13 subjects (6.4%). In the logistic regression analysis, the independent risk factors for high Cr values were GA (OR:2.25, 95%CI:1.06-4.80) and CysC was 0.77±0.13mg/L. In the >97.5 percentile group for CysC there were 7 subjects (2.1%), while for CysC, it was 13 subjects (6.4%). In the logistic regression analysis, the independent risk factors for high Cr values were GA (OR:2.25, 95%CI:1.06-4.80) and CysC was 0.77±0.13mg/L. In the >97.5 percentile group for Cr there were 7 subjects (2.1%), while for CysC, it was 13 subjects (6.4%). In the logistic regression analysis, the independent risk factors for high Cr values were GA (OR:2.25, 95%CI:1.06-4.80) and CysC was 0.77±0.13mg/L. In the >97.5 percentile group for CysC there were 7 subjects (2.1%), while for CysC, it was 13 subjects (6.4%). In the logistic regression analysis, the independent risk factors for high Cr values were GA (OR:2.25, 95%CI:1.06-4.80) and CysC was 0.77±0.13mg/L. In the >97.5 percentile group for CysC there were 7 subjects (2.1%), while for CysC, it was 13 subjects (6.4%).

**Conclusions:** In this study of VLBW, there was a high frequency of high CysC values, and GA and birth height were identified as perinatal factors related to high Cr values. When CKD-EPI (Cr) was used in Japanese child, the values were higher than with other predictive equations.

**TH-PO755**

 Is the Prognosis of a Single Functioning Kidney Benign? A Population-Based Study

**Hadass Alfandary,1,2 Orly Haskin,1,2 Yael Borovitz,1 Shelly S. Levi,1,2 Amit Dagan,1,2 Tomer Erlich,3 Miriam Davidovits,1,2 Oren Peleniseanu.4 'schnieder children’s medical center, Petah tikva, Israel; 2Sackler Faculty of Medicine, Tel Aviv University, Tel aviv, Israel; 3sheba medical center, Tel Aviv, Israel; 4Pediatric stem cell research institute, Sheba medical center, Petach Tjiva, Israel.

**Background:** Solitary functioning kidney (SFK) is an important condition in the spectrum of congenital anomalies of kidney and urinary tract (CAKUT). The long term outcome of congenital SFK is underresearch. We conducted a large scale population based study to investigate an early renal injury in adolescents with SFK.

**Methods:** We accessed data from the compulsory medical evaluation of 17 years old in Israel, prior to their enlistment for military service during 2006-2018. The incidence of SFK and the incidence of renal injury defined as proteinuria, hypertension or decreased eGFR were documented.

**Results:** of 978997 candidates, 354 had diagnosis of SFK. The peak incidence was 1:1500 in 2012. Male to female ratio 2.7:1. 28.1% of the cohort were overweight (BMI<25) Proteinuria was reported in 17% of the cohort. Systolic blood pressure above 120mmHg/ 130mmHg was documented in 53.8% and 28.1% respectively. Diastolic blood pressure above 80mmHg/ 85mmHg was documented in 12.8 and 9.1% respectively. eGFR below 90ml/min/1.73m2 was reported in 12.1%. Concomitant genital malformations were documented in 5.5%.

**Conclusions:** this large population based study documents a significant risk for renal injury among adolescent with SFK at the age of 17 years old.

**TH-PO756**

Pubertal Delay and Impact on Short Stature Among Girls with CKD

**Hannah Kim,1 Derek Ng,2 Matthew Matheson,3 Meredith A. Atkinson,4 Bradley A. Warady,1 Susan L. Furth,2 Rebecca Ruebner,1 Johns Hopkins University, Baltimore, MD; 1The Children’s Hospital of Philadelphia, Philadelphia, PA; 2Children’s Mercy Kansas City, Kansas City, MO; 3Johns Hopkins University School of Medicine, Baltimore, MD; 4Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

**Background:** Children with chronic kidney disease (CKD) have delays in normal growth and pubertal development. We aimed to describe factors associated with delayed puberty including short stature among children with CKD.

**Methods:** A prospective cohort study was conducted using the Chronic Kidney Disease in Children (CKiD) study. Delayed puberty was defined as menarche at age 15 years or older. Short stature was defined as last available height 2 standard deviations below projected mid-parental height. Chi-squared and Wilcoxon rank-sum tests were used to assess factors associated with delayed menarche.

**Results:** Median age at menarche was 12 years (IQR, 12 to 14 years, Figure). 10% had delayed menarche. African American race, lower eGFR, and longer CKD duration at time of menarche were associated with delay in menarche (< 0.05), and girls with delayed menarche had lower height and weight percentiles (p<0.05, Table). 61% of girls with delayed menarche had short stature compared to only 35% of girls without delayed menarche (p<0.03).

**Conclusions:** Median age at menarche is similar among girls with CKD and healthy girls. However, 10% of girls with CKD have delayed menarche, which may negatively impact final adult height.

**Funding:** NIDDK Support

Menarche in NHANES versus CKiD

**TH-PO757**

Autotaxin Early Predicts Progressive Renal Fibrosis in CKD

**Ching-Yuang Lin.** Pediatric Nephrology, Children’s Hospital, China Medical University, Taiwan, Taichung, Taiwan.

**Background:** Single-kidney FUBI (Failure of Ureteric Bud Invasion) mice in susceptible animals causes glomerular sclerosis and interstitial fibrosis in the remnant kidney. To identify potential biomarker, we applied cDNA microarray.

**Methods:** We examined serial changes with aging and investigated the single-kidney-FUBI mice for 15 months. Using microarray, gene expression and validation workflow, we identified potential biomarkers and validation using plasma samples from 146 patients with chronic kidney disease (CKD) of diverse etiologies.

**Results:** We identified autotaxin that was shared by FUBI mice and CKD patients. Autotaxin (ATX) protein expression expressed dramatically after age of 12 months in the single-kidney compared with double-kidney-FUBI mice. During the progression of human CKD, a gradual increase of plasma autotaxin level became significant in stage 3 CKD with the amplification of CKD severity. ATX was absent in normal human renal tissue but detected immunohistologically in the human specimen of renal dysplasia. ATX
also contributed a drastic increase in the expression of fibrotic components including: fibronectin, smooth muscle actin, collagen, and TGF-β mRNA. Also fibrotic proteins upregulated in cultured human podocytes treated by ATX in a dose dependent manner.

**Conclusions:** Our results indicated that ATX might serve as a novel tool for monitoring the progression of CKD. ATX might also be as a possible therapeutic target to slow progression of CKD.

**TH-PO758**

Predicting Pediatric CKD Progression with Urinary Metabolomics

**Tom D. Blyth-Hansen,1 Atul K. Sharma,2 Robert H. Mak,3 George J. Schwartz,4 Bradley A. Warady,5 David Wishart,6 Susan L. Furth,7 Chronic Kidney Disease in Children (CKD) Study,8 University of British Columbia, Vancouver, BC, Canada; 2Children’s Mercy Kansas City, Kansas City, MO; 3The Children’s Mercy Hospital of Philadelphia, Philadelphia, PA; 4University of Pennsylvania, Philadelphia, PA; 5University of Manitoba, Winnipeg, MB, Canada; 6UCSD, La Jolla, CA; 7University of Rochester, Rochester, NY; 8University of Alberta, Edmonton, AB, Canada.

**Background:** Predicting progression in children with chronic kidney disease (CKD) may improve care and planning for renal replacement therapy. Adding urinary metabolome changes to existing clinical models may improve prognostication.

**Methods:** Urine samples from patients in the CKD Study had targeted urinary metabolome profiling (138 metabolites/creatinine ratio). Time to event (TTE) was measured, with event defined as 50% decline in eGFR, eGFR <15 or start of renal replacement (composite). A TTE predictor was trained using partial least squares discriminant analysis (PLS-DA), reported as discriminant score (dscore). Log-logistic accelerated failure time (AFT) models were fitted to predict survival based on clinical features without/with dscore, and compared the mean bias for accuracy (t test) and precision (F test).

**Results:** 703 patients (61% male, aged 12.1±4.4 years, iGFR 51.7±23.9) were divided into 2 sets: 1,356 cases for training, 1,356 events, and 222 had an event (cases). The dscore was trained on cases (2 PLS components) and validated in the test set. The dscore was significantly correlated with TTE (r=0.61, p<0.001). The model performed similarly using only the top 10 metabolites (r=0.60, p=0.001). No improvement was noted when training separate glomerular vs. non-glomerular strata. An AFT survival model fitted to training data (N=469) with 148 cases included GFR, proteinuria, and glomerular disease as predictors. The model including dscore & clinical features (AIC=756) had improved fit compared to clinical features alone (AIC=793, likelihood ratio test p<0.001). Using test cases (N=74), the mean bias (years) was 1.6±3.1 vs. 2.4±3.3, demonstrating superior accuracy (mean difference 0.6, p=0.04) and precision (F ratio=0.23, p=0.007). Empiric and predicted AFT survival curves were compared using test data (N=234, 74 cases) stratified by baseline GFR <60. The predicted survival curves are shown for both strata (Figure).

**Conclusions:** The addition of a urinary metabolic classifier improves both predictive accuracy and precision of a CKD progression model compared with clinical features alone.

**Funding:** NIDDK Support

**TH-PO759**

Plasma Kidney Injury Molecule 1 Is Associated with Left Ventricular Hypertrophy in Children with CKD

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**Background:** Left ventricular hypertrophy (LVH) is common in children with CKD and is associated with an increased risk of cardiovascular disease and mortality. Novel plasma biomarkers may help identify children at increased risk of developing LVH. We investigated whether the circulating plasma biomarkers of tubular injury (KIM-1) and inflammation (TNFR-1, TNFR-2, sPAP) are associated with LVH in children.

**Methods:** In the CKiD Cohort Study, children aged 6 months to 16 years old with an eGFR of 30-90 ml/min/1.73m² were enrolled at 54 centers in the US and Canada. We measured plasma KIM-1, TNFR-1, TNFR-2, and sPAP in stored plasma collected 5 months after study enrollment. Echocardiograms were performed one year after study enrollment. We assessed the cross-sectional association between the log, biomarker levels and LVH (left ventricular mass index ≥45th percentile) using a Poisson regression model, adjusted for demographics (i.e., age, sex, race), body mass index, hypertension, glomerular diagnosis, proteinuria, as well as estimated glomerular filtration rate at study entry.

**Results:** Of the 544 children included, median age was 11 years [IQR: 8, 15], 335 (62%) were male, 162 (30%) had a glomerular cause of CKD, 92 (17%) had hypertension, median baseline eGFR was 54 [IQR: 40, 68] ml/min/1.73m², and median urine protein to creatinine ratio was 0.32 [IQR: 0.11, 0.94] mg/g. The overall LVH prevalence was 12% (N=65 events). All median biomarker levels were higher in children with LVH compared to those without LVH (p<0.05). In unadjusted models, two-fold greater plasma KIM-1, TNFR-1, TNFR-2, and sPAP concentrations were associated with LVH (KIM-1 relative risk [RR] per doubling: 1.39; TNFR-1 RR: 1.29; TNFR-2 RR: 1.54 and sPAP RR: 1.77) (Table). After adjusting for demographic and clinical characteristics, only higher plasma KIM-1 concentrations were associated with an increased risk of LVH (RR per doubling: 3.1, 95% CI: 1.04:1.64).

**Conclusions:** Elevated plasma KIM-1 is independently associated with LVH in children with CKD.

**Funding:** NIDDK Support

**TH-PO760**

Primary Hyperoxaluria Type 2: New Insight into Clinical Outcomes

**Sang H. Gareels,1 Hessel Peters-Sengers,1 Jaap Groothoff,2 Bodo B. Beck,3 Michiel J. Oosterveld,4 Pierre Cochot,5 Graham W. Lipkin,1 Eduardo C. Salido,5 Bernd Hoppe,6 Sally Hulton,7 on behalf of the OxalEurope consortium

1Amsterdam AMC (Academic Medical Center), Amsterdam, Netherlands; 2University of Cologne Medical Center, Cologne, Germany; 3Université ClaudeBernard Lyon1-, Bron, France; 4University Hospital Bonn, Bonn, Germany; 5Queen Elizabeth Hospital, Birmingham, UK, Birmingham, United Kingdom; 6Birmingham Children’s Hospital, Birmingham, United Kingdom; Hospital Universitario Canarias, La Laguna, Tenerife, Spain.

**Background:** Primary hyperoxaluria type 2 (PH2) is a rare inherited disorder of glyoxylate metabolism causing nephrocalcinosis, renal failure and ultimately renal failure. PH2 had previously been considered to have a more favorable prognosis than PH1, but earlier reports are limited by low patient numbers and short follow up periods.

**Methods:** This study is based on gathered data from the European Hyperoxaluria Consortium (OxalEurope), encompassing the largest known PH2 cohort worldwide, providing a unique cohort enabling the description of longer-term outcomes in this rare disease.

**Results:** The dataset contained 101 patients from eleven countries. Median follow up was 12.4 years. Median ages at first symptom and diagnosis for index cases were 3.2 years and 8.0 years, respectively. Urolithiasis was the most common presenting feature (82.8%). Genetic analysis revealed 18 novel mutations in the GHRPR gene. Of 238 spot-urine analyses, 23 (9.7%) were within normal range as compared to less than 4% of 24-hour urine collections. Men with PH2 had a higher intra-individual variation of 24-hour urine collections which was substantial (34.1%). At time of review 12 patients were lost to follow-up; 45 of 89 (50.6%) experienced chronic kidney disease (CKD) stage a2 and 22 patients (24.7%) had reached CKD5. Median renal survival was 43.3 years. 15 transplantations in 11 patients were described. Renal outcome did not correlate with genotype, biochemical parameters nor with the presence of nephrocalcinosis at presentation.

**Conclusions:** PH2 is not a benign disease and accurate diagnosis by 24-hour urine analysis and careful follow-up is required, in order to attempt to ameliorate its poor outcome. The role of liver transplantation remains unclear although it is evident that renal transplantation alone does not cure the disease.

**TH-PO761**

Phase I, Single-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Etelcalcetide in Pediatric Subjects with Secondary Hyperparathyroidism Receiving Hemodialysis

**Winnie Sohn,1 Isidro B. Saluszky,2 Claus peter Schmitt,3 Christina Taylan,4 Johan Vande walle,5 Jude A. Ngang,6 Lucy Yan,7 Bradley A. Warady,7 Amgen Inc., Thousand Oaks, CA; 8Division of Pediatric Nephrology, David Geffen School of Medicine at UCLA, Los Angeles, CA; 9Center for Pediatric and Adult Endocrinology Medicine, Heidelberg, Germany; 10University Hospital of Cologne, Cologne, Germany; 11UZGent, Gent, Belgium; 12Children’s Mercy Kansas City, Kansas City, MO.

**Background:** The calcimimetic etelcalcetide is approved for treatment of sHPT in adult patients receiving hemodialysis. However, there are limited data on etelcalcetide safety and efficacy in pediatric patients.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Methods: This Phase 1 study (NCT02633857) evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of etelcalcetide after single-dose administration (0.035 mg/kg IV, corresponding to the approved lowest dose of 2.5 mg) in pediatric hemodialysis subjects in 2 cohorts (cohort 1: aged 12–18 y; cohort 2: aged 2–12 y). Treatment-emergent adverse events (AEs) were assessed. Etelcalcetide PK/PD was assessed post-dose on D1 at 10 min and 4 h, on multiple days until D10, and at the end of study (D30).

Results: E telcalcetide administered to 11 subjects (mean [SD] age=10.3 [4.3] y; cohort 1, n=6; cohort 2, n=5) was well tolerated and reported AEs were consistent with the known etelcalcetide safety profile. One subject each in both cohorts had single-dose related AEs (cohort 1: hypocalcemia; cohort 2: headache, parasthesia, and vomiting) and no serious AEs or deaths were observed. Mean serum corrected Ca (Ca) for all subjects was maintained >2.25 mmol/L. After dosing, PK exposures declined over time in both cohorts (Table). Median percent change in serum intact parathyroid hormone (PTH) from baseline (cohort 1: 51.2 pmol/L; cohort 2: 84.0 pmol/L) reached the nadir on D1 at 4 h (cohort 1: -33.4%; cohort 2: -64.2%). In both cohorts, mean total Ca and cCa reached nadirs on D3 at 2.4 mmol/L, and mean ionized Ca on D1 at 4 h (1.1 mmol/L). Serum iPTH and cCa levels returned to baseline as etelcalcetide concentrations declined prior to the end of study in all subjects.

Conclusions: A single dose of 0.035 mg/kg was well tolerated, with no new safety concerns and PK/PD response as expected. Given the high inter-subject variability, overlap in etelcalcetide concentrations, and small sample size, the differences in etelcalcetide exposures between the age groups were not likely to be clinically meaningful.

Funding: Commercial Support - Amgen Inc.

Table: Pharmacokinetic parameters

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<tr>
<th>Cohort</th>
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<td>cohort 1</td>
<td>12–18</td>
<td>4.30</td>
<td>16.4</td>
<td>25.9</td>
<td></td>
</tr>
<tr>
<td>cohort 2</td>
<td>2–12</td>
<td>4.30</td>
<td>25.9</td>
<td>24.9</td>
<td></td>
</tr>
</tbody>
</table>

TH-PO762

Growth in Children with Non-Glomerular Kidney Disease

Eunjik Park,1 IL-Soo Ha,2 Hae II Cheong,2 Young soo PIK,3 Joo Hoon Lee,4 Je Il Shin,5 Heeyeon Cho,6 Kyoun Hee Han,7 Seong heon Kim,8 Min Hyun Cho,9 Hee Gyung Kang,9 1Hallym University Kangnam Sacred Heart Hospital, Seoul, Republic of Korea; 2Seoul National University Children’s Hospital, Seoul, Republic of Korea; 3Yonsei University College of Medicine, Republic of Korea; 4Samsung Medical Center, Seoul, Republic of Korea; 5Kwangwoong National University Hospital, Daegu, Republic of Korea; 6Pusan National University Children’s Hospital, Gwangju, Republic of Korea; 7Jeju National University School of Medicine, Jeju, Republic of Korea; 8Asian Medical Center, Songpa-gu, SEOUL, Republic of Korea.

Background: Growth retardation is one of common complications of chronic kidney disease (CKD) in children. Children with CKD from non-glomerular disease have been reported to have a higher risk of severe growth retardation than children with glomerular CKD. The objective of this study was to systematically compare growth parameters in children with non-glomerular CKD to those with glomerular CKD.

Methods: Baseline data from 437 children participating in the KoreaN cohort study (cohort 1: aged 12–<18 y; cohort 2: aged 2–<12 y). Treatment-emergent adverse events (AEs) were assessed. Etelcalcetide PK/PD was assessed post-dose on D1 at 10 min and 4 h, on multiple days until D10, and at the end of study for those who have not reached final height.

Conclusions: There was no difference in current age, gestational age, birth weight, eGFR, malnutrition, renal injury, height catch-up, or weight catch-up between subjects treated with GH and those not treated with GH (Table). Of all subjects, there was no cut-off SD score of height catch-up that separates those with and without renal injury. On the other hand, 2 out of 16 subjects (75%) with weight catch-up >1.6 SD had renal injury, whereas only 2 out of 11 (18%) with weight catch-up <1.6 SD had renal injury (P<0.05). On ROC analysis, a cut-off value of 1.395 SD in weight catch-up best predicted renal injury with 86% sensitivity and 62% specificity.

Conclusions: There was no difference in the prevalence of renal injury between SGA subjects treated with GH and those not treated with GH probably because the latter had spontaneous catch-up growth. Weight catch-up >1.6 SD appears to be a risk factor for renal injury.

Funding: Government Support - Non-U.S.

TH-PO764

Patiromer Treatment of Hyperkalemia in Adolescents with CKD: Initial Results from EMERALD

Bradley A. Warady,1 Coleman Gross,2 Martha Mayo,3 Jia Ma,4 Joy Yllana,5 Lana Shapiro,6 Franz S. Schaefer,7 1Children’s Mercy Kansas City, Kansas City, MO; 2Relapsa, Inc., a Vifor Pharma Group Company, Redwood City, CA; 3University of Heidelberg, Heidelberg, Germany.

Background: Patiromer (PAT) is a sodium-free potassium (K) binder approved for treatment of hyperkalemia in adults (8.4 g once daily starting dose); it is not currently approved for use in children.

Methods: EMERALD (NCT03807058), an open-label, multiple-dose study, evaluates the pharmacodynamics (PD) and safety of PAT in children (2–<18 yr) with HK and CKD. PAT is titrated to obtain a target local K level of 3.8-5.0 mEq/L, currently approved for use in children.

Results: Cohort 1 (age 12–<18 yr, now completed) pts (N=14, mean age 14.5 yr) had a mean (SD) baseline sK of 5.44 (3.02) mEq/L and eGFR of 28.7 (13.7) ml/ min/1.73m2. The most common etiology of CKD was CAVUKT (64%) and 57% of pts were on RAASi. All pts completed the PD phase of the study; 2 pts withdrew consent in the LT phase and 1 began HD after which sK data were censored. The starting dose for all patients was 4.2 g/d; 8.4 g/d was the most common final prescribed dose at study end (33.3%); sK decreased by -0.50 (0.54) mEq/L at Day 14 (N=14) and by -1.08 (0.74) mEq/L at Week 26 (N=13); 50% and 82% of pts achieved the target sK by Day 14 and Week 26, respectively. Adverse events (AEs) were observed in 71% of pts and were mostly mild or moderate in severity (one severe, none serious). The most common class of AEs was gastrointestinal disorders (43%; diarrhea [21%], flatulence [14%], nausea [14%]). There was no evidence of hypokalemia; eK was not considered related to study drug (none severe); no AEs led to study drug discontinuation.

Conclusions: Preliminary results from EMERALD suggest a 4.2 g/d PAT starting dose with titration resulted in clinically meaningful sK reduction in adolescents with CKD and HD was generally well tolerated.

Funding: Commercial Support - Funded by Relapsa, Inc., a Vifor Pharma Group Company

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
TH-PO765

Rates of Prevalent Fracture Differ by Race and Ethnicity in Children with CKD

Marciana Laster,1 Michelle Denburg,2 Yusuke Okuda,3 Juhi Kumar,4 Susan L. Furtth,2 Kamyar Kalantar-Zadeh,3 Bradley A. Warady,5 Isidro B. Salusky,1 Mattel Children’s Hospital, Los Angeles, CA; 2The Children’s Hospital of Philadelphia, Philadelphia, PA; 3University of California, Irvine, Irvine, CA; 4Weill Cornell Medical College, New York, NY; 5University of California Irvine, School of Medicine, Orange, CA; 6Children’s Mercy Kansas City, Kansas City, MO.

Background: Studies of healthy children demonstrate higher rates of fracture in Caucasian as compared to minority children. Although studies in adults with CKD have demonstrated greater risk of fracture in Caucasian adults as well, there is limited data on fracture rate differentials by racial-ethnic group in the pediatric CKD population.

Methods: In a sample of 742 children between the ages of 1.5 years and 18 years, with CKD stages 1-4 from the CKD in children (CKiD) cohort, we determined the relationship between racial-ethnic group and the reported history of fracture upon entry to the study. Using logistic regression, we sequentially controlled models for the potential confounders in Table 1 which were chosen based upon prior literature and bivariate p-values <0.1. Multiple imputation was used for missing values in the final model.

Results: The cohort characteristics and laboratory values are displayed in Table 1. Vitamin D levels were lowest in African-American children. 142 subjects reported ever having experienced a broken bone. In the fully adjusted and multiply imputed model, African-American and Hispanic children had 74% (OR [CI] 0.26 [0.14, 0.49] p=0.001) and 66% (OR [CI] 0.34 [0.17, 0.65], P<0.0001) lower odds of any fracture than Caucasian children at study entry, respectively (Figure 1).

Conclusions: Despite lower vitamin D levels, African-American children with CKD reported lower fracture frequency than Caucasian children. These findings in children with CKD are similar to those in healthy children. Additional studies to understand the pathophysiological mechanisms behind these differentials are warranted.

Funding: NIDDK Support, Other NIH Support - NIH-NIMH Loan Repayment Program

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Funding: NIDDK Support, Other NIH Support - NIH-NIMH Loan Repayment Program

TH-PO767

DNA Methylation Program in Human Kidney Development

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Background: Epidemiologic studies indicate that in utero nutritional alterations increase the risk of hypertension, and kidney disease in adults. Changes in the epigenome have been proposed to mediate the metabolic programming effect, as epigenome editing enzymes are regulated by substrates of the intermediate metabolism and changes in the epigenome may be maintained after cell division. DNA methylation is one of the most studied epigenetic factor that plays a key role in gene expression regulation and cell type specification. The methylation dynamics of human kidney development (pre and postnatal) remains unknown, therefore we analyzed genome-wide methylation changes of human kidney development in mouse models.

Methods: Here we performed base resolution methylation analysis by whole genome bisulfiite sequencing of human fetal kidneys, from 11.4 to 19.0 weeks of gestation and postnatal kidney tubules from 27 to 61 years of age (n=12). The SMART genome segmentation method was used to identify differentially methylated regions (DMRs). RNA-sequencing was performed to detect gene expression changes.

Results: Whole genome methylation analysis identified dynamic methylation changes during kidney development and maturation including, 5,280 regions gaining methylation (hyper-DMRs) and 4,316 regions losing methylation (hypo-DMRs) in adult kidney tubules. Many DMR changes were enriched in regions of gene regulated regions. Hyper-DMRs were mostly located in enhancer marks (H3K4me1 and H3K27ac) while hypo-DMRs gained enhancer marks. Function enrichment analysis indicated that developmental genes are gaining methylation while proximal tubule specific genes undergo demethylation. Consistently, hyper-DMRs were enriched for kidney developmental transcription factors binding sites such as HOX9 and SIX2, while hypo-DMRs were enriched for the proximal tubule-specific transcription factors (HNF family). Methylation showed correlation with gene expression such as the increase in expression of proximal tubule specific genes in adult and loss of expression of fetal genes. Methylation and gene expression changes were conserved in mice.

Conclusions: Cytosine methylation, specifically enhancer regions, show dynamic changes in fetal development and postnatal maturation, the most prominent of them is the decrease in enhancer methylation and increase of expression of proximal tubule genes.

TH-PO766

A 24-Month Interim Analysis of a Phase 2 Trial Evaluating the Long-Term Efficacy and Safety of Oxabact OC5 in Dialysis Patients with Primary Hyperoxaluria Type 1 (PH1)

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Background: In PH1, endogenous overproduction of oxalate in the liver results in significantly elevated plasma oxalate (Pox), high urinary oxalate excretion, recurrent urolithiasis and/or progressive nephrocalcinosis. This can lead to end-stage renal disease (ESRD) with patients requiring dialysis and combined liver and kidney transplantation. Direct oxalate sufficient to remove oxalate and cannot match the endogenous production, resulting in high Pox and thus systemic oxalate deposition. Oxabact (OC5), is a formulation of Oxalobacter formigenes, an oxalate-metabolizing bacterium, that induces active secretion of oxalate from plasma to the intestinal lumen. This Phase II, open-label single-arm study investigated efficacy in reducing Pox and safety of OC5 in PH1 patients on stable dialysis regimen.

Methods: Patients received OC5 (10^6 CFU lyophilized O. formigenes per dose, twice a day) until transplantation or until they reached a maximum of 36 months treatment duration. Cardiac function (echocardiography) was evaluated monthly. Cardiac function (echocardiography) was evaluated every 6 months. Safety was assessed continuously. This 24-months interim analysis represents the longest treatment intervention observed in patients with PH1 on dialysis to date.

Results: Eight subjects with a mean (SD) age of 33 (13) years were enrolled into the long-term treatment study. Three patients discontinued before reaching 24 months of treatment; two due to non-compliance to treatment and one due to a liver transplantation. The drop-outs did not have an impact on results. Total Pox was 158.3 (43.9) µmol/L at baseline (n=8), 119.8 (11.3) µmol/L at Week 52 (n=6), and was further reduced to 94.6 (31.9) µmol/L at Week 104 (n=5). Mean Left ventricular ejection fraction improved from 51.6 % at baseline (n=8) to 59.8% at Week 52 (n=6) and 59.4% at Week 104 (n=5). Seven subjects reported any Adverse Event (AE), most frequent AEs were infections and infections and gastrointestinal disorders. Four subjects experienced 5 serious AEs, unrelated to treatment.

Conclusions: Two years treatment with OC5 reduced mean Pox by approximately 40% in PH1 patients with ESRD without intensifying their dialysis regimen. This was also associated with an improved and stabilized cardiac function. OC5 was safe and well-tolerated.

Funding: Commercial Support - OxThera
Paradigm Shift: The Impact of Early Rapid Genomic Sequencing in the Diagnosis of Kidney Disease

Kushani C. Jayasinghe,1 Zornitza Stark,2 Catherine Quinlan,1 Australian Genomics and the Melbourne Genomics Renal Genetics Flagship part of the KidGen collaborative1 Monash Health, Clayton, NSW, Australia; 2Australian Genomics Health Alliance, Parkville, NSW, Australia; 3The Royal Children’s Hospital, Melbourne, VIC, Australia.

Background: Rapid genomic sequencing with results available in clinically meaningful timeframes is becoming feasible. Its role in the diagnosis and management of patients with kidney disease is unclear.

Methods: Patients were recruited prospectively for rapid whole exome sequencing (WES) with analysis of a pre-determined phenotype specific list of genes of interest and results available in less than 2 weeks. This followed review by a nephrologist, clinical geneticist and genetic counsellor who considered inclusion if a result was likely to significantly impact clinical management, particularly avoiding kidney biopsies in younger children. Full author list online at KidGen.org.au

Results: Ten patients (9 female, 4 female, 4 male, 6 female) were recruited ranging in age from 1 month to 55 years. Indications for rapid testing were to avoid a renal biopsy (8) and to facilitate transplant planning (2). Five patients received a definitive diagnosis (ADPKD, Dent disease, primary hyperoxaluria, Alport syndrome and ciliopathy), 1 received a diagnosis which was likely unrelated to their kidney disease (MIRAGE syndrome). One patient’s negative result facilitated sibling donor workup. The most significant result in this cohort was an unexpected diagnosis of primary hyperoxaluria in a 6-month old presenting in renal failure. WES results were available within 5 days informing conversion from peritoneal dialysis to home-based liver-kidney transplantation as a bridge to a renal transplant. This avoided the significant morbidity of oxalate deposition in extra-renal tissues leading to fractures, visual impairment and heart failure and recurrence of the disease if an isolated renal transplant had been performed.

Conclusions: Rapid genomic sequencing has high diagnostic utility in selected patients with renal disease and can inform clinical management within meaningful timeframes. It has the potential to transform the diagnostic pathway for young children, particularly where invasive renal biopsies can be avoided.

Funding: Government Support - Non-U.S.

Longitudinal Associations Between Vitamin D and Blood Pressure in the CKD in the Children (CKiD) Cohort

Juhi Kumar,1 Jennifer Roem,2 Susan L. Furtth,3 Bradley A. Warady,4 Meredith A. Atkinson,5 Joseph T. Flynn,6 Well Cornell Medical College, New York, NY; 7Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; 8The Children’s Hospital of Philadelphia, Philadelphia, PA; 9Children’s Mercy Kansas City, Kansas City, MO; 10Johns Hopkins University School of Medicine, Baltimore, MD; 11Seattle Children’s Hospital, Seattle, WA.

Background: Preclinical studies suggest that 25 hydroxy vitamin D (25OHD) modulates the remn-angiotensin-aldosterone system, vascular smooth muscle cells and the endothelium. Analysis of data from the “Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of CKD in Pediatric Patients” study showed that subjects with 25OHD levels <20 ng/ml had a higher diastolic BP than those with levels ≥20 ng/ml (p=0.004). Children with 25OHD levels < 20 ng/ml in the CKiD cohort had SBP 0.29 percentiles and baseline 25OHD (deficiency < 20 ng/ml) and 1,25(OH)2D (per 10 pg/ml) levels, adjusted for baseline covariates, were examined using mixed-effects logistic regression that included a random subject effect to account for repeated measurements of the outcome within each subject. Covariates included were age, gender, race, years from visit 2, 2D etiology, BMI, GFR, proteinuria and medications used (antihypertensive, steroids, active and inactive vitamin D supplements). Study population included 536 subjects contributing 2741 visits (subset of n=365 with available ABPM measurements at visit 2 contributing 803 visits).

Results: Participants with 250HD deficiency had greater odds of having systolic (OR 1.80, 95% CI: 1.22, 2.65; p=0.003) as well as casual hypertension (OR 1.48, 95% CI: 1.04, 2.11, p=0.03). Male gender decreased the odds of hypertension. Higher BMI, nephrotic range proteinuria and active vitamin D use were associated with higher odds of systolic hypertension (Table 1). 1.25(OH)2D was significantly associated with hypertension (OR 0.81, 95%CI: 1.70, 0.95) in univariate analysis only. Neither vitamin D measures were associated with ABPM hypertension.

Conclusions: 25OHD deficiency is associated with higher odds of persistent casual hypertension. It may be beneficial to maintain 25OHD levels >20 ng/ml to optimize BP control in children with CKD.

Funding: NIDDK Support

Mental Health Diagnoses and Substance Use in Children with CKD in the CKD in Children (CKiD) Study

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Background: Mental health disorders are more common in children with chronic illness than in healthy counterparts. While a high prevalence of depression has been noted in children with chronic kidney disease (CKD), other mental health diagnoses and substances use have not been well described.

Methods: We evaluated the prevalence of mental health diagnoses utilizing parent-reported child mental health diagnoses and self-reported substance use among participants age 1-6 years at enrollment in the CKiD study. Descriptive statistics were used to characterize the distribution of mental health diagnoses and age of onset. Chi-squared, t-test, and log binomial regression were used to compare demographic factors including sex, race, and maternal education, and CKD characteristics including glomerular versus nonglomerular disease, disease progression, and height between those with and without a reported mental health diagnosis.

Results: Among CKiD participants (n=891) prevalence of any mental health diagnosis or substance use was 55% with mean onset reported at 13 years. The most common conditions were learning disorders (22%), alcohol use (22%), attention deficit and hyperactivity disorders (19%), depression (15%), anxiety (13%), and cannabis use (10%), with 30% reporting multiple diagnoses. Those with mental health diagnoses were more likely to have a mother with some college education (PR 1.2, 95%CI 1.1-1.4) than those without a diagnosis. Reported mental health diagnoses were less common among those who identified as Latino. (PR 0.5 95%CI 0.2-0.8). There were no other significant differences in the assessed demographic or CKD characteristics between those with and without mental health diagnoses.

Conclusions: A broad spectrum of mental health diagnoses are common in children with CKD. Despite limitations inherent in using self-reported retrospective survey data, this study provides impetus for more in-depth assessment of mental health in children with CKD, advocacy for greater mental health resources, and the development of targeted therapies for children with CKD and their families.

Funding: Other NIH Support - T32 DK007662-27

A Young Adult Nephrology Transition Clinic: A Successful Model

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Background: Survival of pediatric patients with chronic disease has increased leading to a growing number of patients transitioning from pediatric to adult care. A formal pediatric to adult transition process is important in improving medical adherence in these young adults. Despite this, few adult nephrology centers have transition protocols in place. To address this, we implemented a combined nephrology transition phase of care program at Lurie Children’s Hospital (LCH) and Northwestern Medicine (NM). Here we present our 5 year data.

Methods: The pediatric team identified transfer patients and communicated with the adult team, a nephrologist, PA and social worker, about patient history and potential obstacles to successful transition. The initial appointment occurred at LCH with subsequent visits at NM. During all visits, patients had one on one time with each of the providers. Monthly reviews were conducted to determine if proper follow up had occurred and if not, procedures of enhanced follow up including phone calls and email were implemented.

Funding: Other NIH Support - T32 DK007662-27

Results: 319
Results: A total of 84 patients were seen with the results outlined in Table 1. Successful transition was defined as at least one follow up visit in the adult clinic. 40% of patients required enhanced follow up. 21% of patients either unsuccessfully transitioned or had delayed drop out, defined as lost to follow up after a successful transition.

Conclusions: Based on our five year experience, transition of care from pediatric to adult nephrology providers can be successfully facilitated with a protocol defined model that includes engagement of adult and pediatric teams. This patient group, however, is still at high risk of being lost to follow up.

Table 1: Patient outcomes.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Transition Program Participants (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful Transitions</td>
<td>63 (75%)</td>
</tr>
<tr>
<td>One visit</td>
<td>15 (18%)</td>
</tr>
<tr>
<td>Two visits</td>
<td>15 (18%)</td>
</tr>
<tr>
<td>Three visits</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Unsuccessful Transitions</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Delayed Drop Out</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>Pending Follow Up</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Figure 1: Follow up as a function of transition year.

TH-PO774

Current Practice and Resources for Medication Adherence Assessment Among Pediatric Kidney Transplant Programs

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Background: Adolescent/young adult kidney transplant recipients have 3 times the risk of allograft failure compared to other age groups. This is multifactorial, but barriers to medication adherence are a major contributor, present in up to 40%. To inform future adherence interventions, we assessed current practice patterns and resources available to address barriers to medication adherence among US pediatric kidney transplant programs.

Methods: Kidney transplant team members, including physicians (MD/DO), nurse practitioners (NP), physician assistants (PA), social workers (SW), and pharmacists, from 22 kidney transplant programs in the Improving Renal Outcomes Collaborative were surveyed about institutional characteristics, resources and current practice assessing medication adherence. 64 unique surveys were included, with representation from 22/26 (85%) of IROC-affiliated institutions.

Results: All teams indicated they have at least one MD/DO, nutritionist, and SW, which form the core team. Additional roles of NP, PA, transplant nurse, pharmacist, psychologist, and child life specialist were available in only some institutions. Each of 10 common barriers to medication adherence was reported to be addressed by at least one provider type during routine clinic visits. The majority reported assessing barriers to adherence at every clinic visit. However, subjective assessment methods were most commonly used, including forming a clinical impression based on history/exam and indirect and direct questions (Figure).

Conclusions: Provider assessment of medication adherence for pediatric kidney transplant patients varies among practices. While centers report that it is frequently assessed, subjective measures, which may overestimate adherence, are used most commonly. There is opportunity to standardize adherence barriers assessment with standard surveys/tools and to use objective measures, such as pharmacy refill records, to more accurately assess adherence. Future studies are needed to improve assessment of adherence.

Funding: Private Foundation Support

TH-PO777

A Single-Center Experience of Bortezomib in Pediatric Kidney Transplants With Long-Term Graft Outcome

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Background: Acute antibody mediated rejection (aAMR) remains a challenge with poor renal allograft longterm outcome and unclear therapeutic efficacy of current therapies. We report the use of Bortezomib for treatment of persistent aAMR after failure of conventional therapy and long-term graft and patient outcomes.

Methods: Review of 118 kidney transplants (txp) from 2004-2019, noted - 4 had primary graft failure, 3 patients were deceased (2 with functioning grafts) and 3 were lost to follow up. 32 rejections- 12 with TCR and 20 with aAMR (biopsy proven by Banff criteria); All 20 aAMR received MP pulse. IVIG (1-2 g/Kg); 10 PP treatments (1.5 to 2 plasma vol exchange/ rx) and Thymoglobulin (if ACR). On follow up 9/20 received Bortezomib 1.3mg/m2/dose IV x4 for persistent graft dysfunction with positive DSA. Mean DSA titers (pre and post rx). eGFR, graft outcome, adverse effects infections were tracked in Bortezomib group. Graft outcome was also followed in patients with no rejection and + rejection aAMR/TCR.

Results: 9 received 10 doses of Bortezomib; Ethnicity: AA/Wh/ His/Asian=33%/33%/33%/22% (2%) 115% (1), male 8 (89%), Age at txp: median 16.8 (3-20yrs), 7 (78%) received DDT, all received Induction (4 thymo for pre txp PRA >25%); Time to rejection: median 2.5 yrs (8 days-8 yrs), 2 neg C4D and DSA; 1 de novo anti GBM GN and 1 had ATIR abs+. Infections: 1 oral Herpes+ oral candidiasis+ pneumonia, 1 herpes + atypical mycobacteria+ candida, 3 gastroenteritis and 1 C. difficile colitis, 1 prolonged EBV viremia and 1 cellulitis.(1.4 infections/p) Erythropoietin: time after txp 1-12 yr (median =3.8), post bortezomib = 0.5-9 yrs (median 1.5). Post bortezomib: eGFR improved from 58 to 79 ml/min/1.73M2 (21%) and reduction in DSA = 36%. Other therapies: 1 Rituximab, 1 Cytoscan (anti GBM GN), 4 Thymoglobulin for TCR. Graft survival with Bortezomib: 100% at 1 and 3 yrs. 2 progressed to ESRD at 9 and 12 yrs (22% graft loss). Graft loss in children with no rejection was 8% compared to 47% with rejection (aAMR and TCR). Overall, graft loss was 24% and patient survival 97.4% as of last follow up.

Conclusions: Bortezomib was well tolerated well with few adverse effects; 36% reduction in DSA, 21% improvement in eGFR and graft loss 22%. Graft loss in children with no rejection was 8% compared to 47% with rejection (aAMR and TCR). Overall, graft loss was 24% and patient survival 97.4% as of last follow up.

TH-PO778

Fibroblast Growth Factor 23 and Anemia in Pediatric Renal Transplant Recipients

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Background: Pre-clinical studies have shown that anemia-related factors, specifically iron deficiency and increased erythropoietin (EPO), can induce FGFR23 production. Studies of adult renal transplant recipients (RTR) have demonstrated independent associations between both lower iron levels and higher EPO concentrations and increased FGFR23. In the present study, we evaluated cross-sectional and longitudinal associations between hemoglobin and FGFR23 parameters in pediatric RTR.

Methods: Demographic, clinical, and standard biochemical data were collected from a cross-section of 59 pediatric RTR during routine clinic visits. Iron, EPO, C-terminal (total) FGFR23 (cFGF23), and intact FGFR23 (iFGF23) concentrations were measured in additional blood samples. Follow-up biochemical data and blood samples were collected from a subset of 29 patients six months later.

Results: Demographic, clinical, and baseline serum parameters are shown in Table 1. Neither cFGF23 nor iFGF23 was significantly associated with iron or EPO (Table 2). cFGF23 correlated inversely with hemoglobin (r=-0.38, p<0.003), while iFGF23 correlated positively with hemoglobin (r=0.28, p=0.01). The cFGF23-hemoglobin association remained significant after adjusting for eGFR, iron, and EPO. Change in cFGF23 over time tended to inversely correlate with change in hemoglobin (r=-0.34, p=0.07).

Conclusions: In pediatric RTR, differential associations between hemoglobin and FGFR23 vs. iFGF23 are observed, suggesting complex relationships among anemia, FGFR23 production, and FGFR23 metabolism that warrant further study.
Risk Factors for Early Readmission Post-Pediatric Kidney Transplantation: A Multicenter Study

Shanthi S. Balami,1 Stephanie T. Nguyen,2 Patricia L. Weng,4 Daniel Ranch,2 Jessica L. Brennan,1 Paul R. Brakeman,1 UCSF, San Francisco, CA; 2UT Health Science Center at San Antonio, San Antonio, TX; 3UCSF Medical Center, San Francisco, CA; 4UC, Los Angeles, CA; 5University of California, Davis, Sacramento, CA.

Background: Early hospital readmissions are associated with morbidity, mortality, significant health care costs and poor outcomes. To date, no published studies have evaluated risk factors for early readmission following pediatric kidney transplantation.

Methods: Retrospective chart review was performed for all pediatric kidney transplant recipients from 2012 – 2017 at the UCSF, UCD, UCLA and UT at San Antonio. Early hospital readmissions were defined as any unplanned admission within 30 days of being discharged from the hospital following a kidney transplant; admissions for elective procedures were excluded. Baseline characteristics evaluated included age, insurance type, race, prior dialysis, donor type, ischemia times, placement of transplant, induction agent, length of hospital stay, weekend discharge, hypotensive medications at discharge, tacrolimus levels, hemoglobin, albumin, and creatinine at discharge. Data regarding readmissions was collected, and analyzed using Student t-test for continuous variables and the chi square test for categorical variables.

Results: There were 308 pediatric kidney transplant recipients. The rate of early readmission was 31%. The leading causes for readmission were: elevated creatinine (30%), vomiting/diarrhea with dehydration (13%) and tacrolimus toxicity (8%). Discharge on weekend (p=0.05) and acute change in tacrolimus trough on day of discharge from 24-hours prior to discharge (p<0.05) significantly predicted readmissions. Other predictors that did not meet our criteria for significance for readmission included: elevated tacrolimus level on day of discharge (p=0.08), more than 2 anti-hypertensives at discharge (p=0.07) and presence of ureteral stent at discharge (p=0.07). No difference was seen in readmission rates based on age, donor type, ischemia times, induction agent or length of initial hospitalization.

Conclusions: The rate of early readmissions for our pediatric population was similar to that reported in adult patients. Weekend discharge and change in tacrolimus significantly predicted readmission. Hospital course and discharge level factors were more predictive than patient related factors providing modifiable clinical factors for targeted interventions to reduce rate of readmissions in pediatric patients.

Renal Replacement Therapy of Hyperammonaemia in Pediatric Patients

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Background: Hyperammonemia is the accumulation of ammonia in the blood that may result in an acute life-threatening event in pediatric populations. Management of hyperammonemia proves to be difficult in pediatric populations given the non-specific clinical symptoms, the age-specific etiologies, and the lack of consensus in the treatment plan. In our review, we sought to systematically search the published literature to comprise guidelines for non-renal replacement therapy (RRT) and renal replacement therapy in pediatric patients.

Methods: A database search using PubMed/Embase, Embase and Cochrane was performed to include publications about hyperammonemia and renal replacement therapy in the pediatric population. An expert panel of pediatric nephrologists made up the workgroup and they were responsible to review and propose recommendations for renal replacement therapy guidelines for hyperammonemia children.

Results: The initial search returned a total of 477 citations of which only 25 studies met our inclusion criteria. A total of 132 patients were included in the study. Hemodialysis indications included hyperammonemia refractory to medical management and hyperammonemia coma. The most common of hyperammonemia was inborn errors of metabolism (IEM). Among the type of RRT used, CRRT had a 60% success rate and peritoneal dialysis (PD) had a 65% success rate.

Conclusions: We recommend initiating renal replacement therapy when blood ammonia levels >150µmol/L, with coma or cerebral edema and when blood ammonia level >400µmol/L refractory to non-RRT measures. Intermittent hemodialysis is more effective than PD or CRRT as it clears ammonia faster but associated with rebound hyperammonemia and can cause hypotension and rapid osmotic shifts. PD is a quick alternative to immediate hyperammonemia management if CRRT is not available. Treating with high dose CRRT allows for rapid clearance of ammonia done on a single dialysis run. A hybrid method of CRRT with ECMO support can increase the patient’s blood volumes, allows for use of a larger cannula, avoids hemodynamic instability.
TH-PO778
A Case Series of Iodine-Induced Hypothyroidism in Children on Peritoneal Dialysis
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Background: Young patients with end-stage renal disease who receive chronic peritoneal dialysis (CPD) are at increased risk for thyroid dysfunction. An extremely rare cause of thyroid dysfunction in these patients is iodine exposure. We report four patients who received CPD and developed iodine overload and secondary hypothyroidism.

Methods: case series

Results: The 4 children, 3 weeks to 3.5 years of age, were cared for in two academic institutions in 2017-2019. Three patients were on automated cycler PD and one received manual fluids over a week and was on continuous PD. PD fill volumes ranged from 160 to 880 mL/m2 BSA. They had normal baseline thyroid stimulating hormone (TSH) levels or normal newborn screens. They were on PD for periods of 1 week to 27 months, with median age of 6 months at presentation. 3 out of 4 patients had high TSH values ranging from 15-875 mIU/L, 2 of the 4 had a low free T4 from 0.2- 0.21 ng/dL, and all 4 had high serum iodine levels: 222-557.5 mcg/L (normal: <100 mcg/L). In every case, a transfer set with betadine gauge was utilized as part of their PD procedure. One patient developed overt hypothyroidism and heart failure and one experienced growth failure, while the other two were asymptomatic. Two patients required temporary treatment with levothyroxine (2.5 months – 6 months). Iodine levels decreased in all patients after switching them to continuous manual PD or by withdrawing the first 5 mL of iodine tinged fluid from the transfer set before connecting them to the PD cycler. Despite extensive investigation, no alternative sources of iodine exposure were detected.

Conclusions: Excessive iodine exposure and the potential for thyroid dysfunction, especially during infancy, is a poorly recognized complication of CPD. Increased awareness among nephrologists is needed so that prevention strategies and regular monitoring for this complication can be instituted.

Patient summary table. syringe and PD cap with iodine tinged fluid.

TH-PO779
Physician Practices Regarding Physical Activity Restriction in Pediatric Hemodialysis Patients: A Qualitative Study
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Background: Children with chronic kidney disease (CKD) due to multiple hospitalizations and interventions have less physical activity. This sedentary lifestyle in CKD is associated with a higher cardiovascular mortality risk. In those patients receiving hemodialysis (HD) time spent on dialysis and restrictions on physical activity due to accesses contribute. No consensus exists regarding physical activity restrictions based on vascular access type. The aim of the study is to assess pediatric nephrologists’ practices regarding physical activity restrictions in children receiving HD.

Methods: The study was conducted through the Midwest Pediatric Nephrology Consortium by an anonymous, self-administered survey of pediatric nephrologists to evaluate the activity restrictions placed on HD patients with arteriovenous fistulae (AVF) and central venous catheters (CVC). The survey consisted of 19 items, 6 questions detailed physician characteristics with the subsequent 13 addressing physical activity restrictions. 15 responses (33.3% response rate) were received. Average years in practice after fellowship: 11.5 years (range: 1-35). Dialysis units had 1 – 12 stations (mean 6) Physical activity restrictions by physicians are summarized in tables. None of the participants reported accesses damage or loss that was attributed to physical activity and sport participation. Physicians practice is based on their personal experience, standard practice at their hemodialysis center and the clinical practices they were taught.

Conclusions: There is no consensus amongst pediatric nephrologists about physical activity that can be allowed in children receiving HD. Due to the lack of objective data, individual physician beliefs have been utilized to restrict activities in the absence of any deleterious effects to accesses. This survey clearly demonstrates the need for more prospective and detailed studies and guidelines regarding the physical activity and dialysis access care in order to optimize quality of care in these children.

TH-PO780
Colostomy in Children on Chronic Peritoneal Dialysis
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Background: The aim of this study was to evaluate the outcome of children on chronic peritoneal dialysis (PD) with a concurrent colostomy.

Methods: Patients were identified through the International Pediatric Peritoneal Dialysis Network (IPPN) registry. Age-matched controls were randomly selected from the registry. Data were collected through the IPPN database and a survey disseminated to all participating sites.

Results: 15 centers reported 20 children who received chronic PD with a co-existing colostomy. The commonest cause of end-stage kidney disease was congenital anomalies of kidney and urinary tract (n=16, 80%). The main reason for placement of a colostomy was anorectal malformation (n=13, 65%). The median age at colostomy creation and PD catheter (PDC) insertion were 0.1 [IQR, 0-2.2] and 2.8 [IQR 0-2.2] months, respectively. The colostomies and PDCs were present together for a median 18 [IQR, 4.9-35.8] months. The median age at PDC placement in 46 controls was 4.2 [IQR, 3.6-10.8] months. 14 patients (70%) developed 39 episodes of peritonitis. The annualized peritonitis rate was significantly higher in the colostomy group (1.13 vs 0.70 episodes per patient year; p=0.02). Predominant causative microorganisms were staphylococcus aureus (15%) and pseudomonas aerugiosa (13%). There were 10 exit site infections (ESI) episodes reported exclusively in colostomy patients. Seven children (35%) died during their course of PD, in two cases due to peritonitis.

Conclusions: Although chronic PD is feasible in children with a colostomy, it is associated with an increased risk of peritonitis, ESI, and mortality. Continued efforts to reduce the infection risk for this complex patient population are essential.
TH-PO781

Mortality in Children with ESRD: A Guatemalan Retrospective Cohort Study
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Background: Mortality rates and long-term survival data in ESRD children are sparse although different modalities of RRT have been used during decades We evaluate the mortality overtime in a tertiary hospital in Guatemala (PGT).

Methods: After ethics approval, we performed a single center retrospective cohort study of all patients with ESRD younger than 18 years, between Jan2015 and Dec2017. Mortality rate was expressed as number of deaths/100patient-years Mortality incidence rate, expressed as number of deaths/100patient-years was determined by sex, RRT and age. Long-term survival rates were calculated by Kaplan Meier test and significant confirm by Log Rank and Breslow tests.

Results: A total of 370 charts were reviewed. Of those, 115 were from PD, 221 from HD and 34 from transplant. During the study period 25 patients died. Of those, 52% (13/25) were female, the mean age was 12.7yrs(3.4), 72%(18/25) were from HD and the rest from PD(7/25). No deaths from transplanted patients were reported during the study. The mortality rate in 2015, 2016 and 2017 were 50, 50 and 32/1000 patients. The mortality incidence rate was higher in girls than boys (p < 0.05). There was a significant difference in mortality incidence rate found by sex (female 8/100 patient-year, males 8.4/100 patient-year). The highest incidence of mortality was found in the HD and in the 5-9 age group (17.5/100 patient-years, 20/100 patient-years). When analyzing long-term survival rates using Kaplan Meier, the overall mortality rate at 3 years was 20%, no significant difference was identified by sex (p, 0.509) Nevertheless; a significant difference was found between HD (36.8%) and PD (16%), p, 0.001. Regarding age, no significant difference in mortality rate between the 5-10, 10-14 and 15-18 age groups was identified at 2 years (25%, 15%, 10%), (p, 0.174) Conclusions: In the overall mortality incidence rate was higher than reported in literature Mortality incidence rate and long-term survival were similar between the sexes. Among the 5-9 year group demonstrated the highest mortality rates Regarding RRT, the incidence mortality rates in PD is comparable with literature however, our HD mortality rates are 4 times higher than what has patient-years. Increasing the proportion of children treated with renal transplantation and PD rather than HD can improve survival further and costs in our centre.

TH-PO782

The Effect of Socioeconomic Status and Distance to Specialist Hospital on Access to Paediatric Nephrology Care in England
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Background: For children with end-stage kidney disease (ESKD), transplantation is the preferred treatment of choice, offering improved survival and quality of life. Preemptive transplantation (PET) is advocated as best practice. Access however is limited by whether socio-economic status (SES) or geographical remoteness from centre are associated with 1) timing of presentation to nephrology services and 2) access to PET.

Methods: A cohort study using UK Renal Registry and NHS Blood & Transplant database; however, our HD mortality rates are 4 times higher than what has patient-years. Increasing the proportion of children treated with renal transplantation and PD rather than HD can improve survival further and costs in our centre.

Results: During the study period, 1856 children received RRT (776 females, 41.8%), with a median age of 3.8 years at presentation. Of these, 426 were late presenters. Among age, the 5-9, 10-14 and 15-18 age groups was identified at 2 years (25%,15%,10%), (p, 0.174) Conclusions: In the overall mortality incidence rate was higher than reported in literature Mortality incidence rate and long-term survival were similar between the sexes. Among the 5-9 year group demonstrated the highest mortality rates Regarding RRT, the incidence mortality rates in PD is comparable with literature however, our HD mortality rates are 4 times higher than what has patient-years. Increasing the proportion of children treated with renal transplantation and PD rather than HD can improve survival further and costs in our centre.

TH-PO783

Differential Metabolic Profile Within Primary Hyperoxaluria Patients Cristina Martin Higueiras,1,4 Eduardo C. Salido,1 Bernd Hoppe,2 Christian Kurts,3 University Hospital Bonn, Bonn, Germany; 2Hospital Universitario Canarias, La Laguna, Tenerife, Spain; 3Institute of Experimental Immunology, Bonn, Germany.

Background: The three types of primary hyperoxaluria (PH) are liver specific enzyme defects inducing endogenous oxalate overproduction, thus hyperoxaluria, urolithiasis and/or nephrocalcinosis, as well as intrarenal deposition of calcium oxalate crystals, leading to chronic kidney disease and renal failure (PHI1&2). Severe infantile cases (PHI) directly present systemic crystal deposition (oxalosis), but otherwise the clinical progression of PHI type profoundly differs, for unknown reasons. PH patients bear pathogenic mutations in either AGXT (PH1), GRIHPR (PH2) or HOGA1 (PH3) genes, causing a misbalanced hepatic glyoxylate metabolism that overproduces oxalate. Here, we aimed to unveil other misbalanced metabolites in PH1, PH2 and PH3 both in mouse models and patients to understand the heterogeneous pathogenesis of PH1, to reveal new biomarkers for differential diagnosis and to find modulators of their immune response.

Methods: All patients signed an informed consent. Serum from 19 PH1, 5 PH2, 7 PH3 and 9 control patients as well as plasma from 4 PH1, 4 PH3, 4 PH1/PH3 and 4 wildtype mice were obtained. Samples were analyzed by the global metabolomics technology of Metabolon, and stored sample (PH1, PH3 patients; PH1 and 4 wt mice) by the Institute of Microecology (Germany). Data followed log transformation and Welch’s two-sample test for statistical analysis.

Results: PH3 mice metabolome showed stronger differences to wt than PH1, mostly in aminoacid, carbohydrate and xenobiotic related metabolism. Both PH1 and PH3 mice shared a strong misbalanced lipid metabolism. Xenobiotic metabolism correlated with differential microbiota in PH1 compared to wt mice. Ongoing human metabolome and microbiota analysis is aimed at translating our findings into the human situation.

Conclusions: Further exploration of candidate metabolites in vitro and in vivo will help elucidating their role in mechanisms of disease and their use as biomarkers for diagnosis and treatment.

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TH-PO784

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Background: Reliance on small solute clearance as a measure of dialysis adequacy fails to fully quantify the intended clinical effects of dialysis therapy. We aimed to study the relationship between dialysis adequacy, as measured by single-pool Kt/V (spKt/V) and urea reduction ratio (URR), and patient morbidity as measured by growth, nutrition and anemia.

Methods: We included 391 patients (median age of 14.3 years [range: 1.0 - 18.9]) in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) database receiving chronic hemodialysis three times a week. Using goal sp Kt/V of 1.2-1.5 and UR of 65-75% we compared weight, height, albumin, hemoglobin (HB) and erythropoiesis stimulating agent (ESA) doses at 12 months from initiation of HD (initiated in 2003 to Dec ’18). Kruskal-Wallis test was used to compare these measures in patients at, above, and below goal values of dialysis adequacy.

Results: Results of the univariate analysis are summarized (Table 1A & B). For patients with URR and spKt/V above goal, the median weight z-scores was 0.6 and 0.7 points lower when compared to those with values within goal levels. Similarly, for patients with URR and spKt/V above goal, the height z-scores was 1.0 and 0.8 lower than the within goal levels. Patients with URR < 65% had 0.7 g/dl higher median HB compared to within goal levels of URR. We noted no significant relationship between dialysis adequacy and serum albumin, ESA doses

Conclusions: Preliminary results show significantly lower weight and height in patients with dialysis adequacy above goal values. This may reflect low volumes of distribution (V). Further analysis of the database at multiple time points from initiation of HD with help describe associations between dialysis adequacy and patient morbidity.
TH-PO785

Metabolomic Profiling for Discovery of Biomarkers of Neurocognitive Impairment in Children with CKD

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Background: Mechanisms underlying neurocognitive impairment in CKD remain unknown. We sought to perform the first large-scale discovery of novel blood metabolite biomarkers of neurocognitive impairment in children with CKD.

Methods: Untargeted GC/MS and LC/MS-based metabolomics quantification (Metabolon) was performed on baseline plasma samples from 498 Chronic Kidney Disease in Children (CKID) participants. We applied linear regression models to examine the cross-sectional association between standardized, log transformed metabolites (n=825) and intellectual functioning (IQ score), adjusted for demographics, CKD-related clinical characteristics, and socioeconomic status (SES). Statistical significance was determined using a threshold to keep the false discovery rate (FDR) <0.05.

Results: Cohort characteristics were: 312 (63%) male; median age 12 years (IQR 8,15); median eGFR 52 mL/min/1.73m² (IQR 38, 64); 377 (76%) non-glomerular diagnosis. Median IQ score was 99 (IQR 87, 108). In unadjusted analyses, 13 metabolites were associated with IQ score. (Figure) Two metabolites, 2-hydroxyarachidate (a fatty acid) and xanthurenate (a product of tryptophan metabolism), were positively associated with IQ independent of age, sex, race, BMI z-score, hypertension, low birthweight/ prematurity, glomerular vs. non-glomerular diagnosis, duration of CKD, proteinuria and estimated glomerular filtration rate (eGFR). With additional adjustment for SES, no metabolite associated with IQ were statistically significant.

Conclusions: Untargeted metabolomic profiling identified two metabolites associated with IQ in children with CKD that were independent of most demographic and CKD-related clinical factors, although the inclusion of SES eliminated the statistical significance of these relationships. Further studies are needed to extend these analyses to other neurocognitive domains and delineate mechanisms.

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TH-PO786

Outcomes of Maintenance Dialysis in Children Younger Than 24 Months: A NAPRTCS Report

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Background: Peritoneal dialysis (PD) is the preferred mode of renal replacement therapy (RRT) in infants and young children with end-stage renal disease (ESRD). Hemodialysis (HD) is less used due to technical challenges and risk of complications in smaller patients. There are limited data on the impact of different dialysis modalities on clinical outcomes in this group.

Methods: Data were extracted from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry. Demographic, clinical, and laboratory data on patients < 24 months age between January 1992 and December 2018 were analyzed. We compared patient survival and access to kidney transplantation using log rank test between children treated with PD or HD.

Results: 1014 infants initiated dialysis therapy on PD: 114 on HD. Mean(SD) age at PD onset was 6.9 (6.8) months and at HD onset was 12.0 (7.2) months. Infants treated with PD more often had congenital anomalies of the kidney and urinary tract/obstructive uropathy (55% vs 40%, p<0.05). At 1, 6 and 12 months post dialysis onset, PD patients had significantly lower serum albumin (Figure 1). Hemoglobin was lower in HD patients at 1 and 6 months, but similar at 12 months between the groups. Time to transplant was lower for HD patients, but patient survival on dialysis was similar (Figure 2).

Conclusions: Although HD is not first line modality for RRT in younger children, 10% of children < 2 years of age start maintenance dialysis on HD therapy. Patients starting HD are more likely to be older and non-white. Patient survival on dialysis is similar irrespective of dialysis modality.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Cerebral Oxygenation Changes in Pediatric Chronic Hemodialysis

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Background: Intradialytic circulatory stress has been well described in adults as tissue ischemia to diverse organs (heart, gut and brain) during hemodialysis (HD). We aimed to determine if pediatric patients had intradialytic changes in cerebral oxygenmetry (CEOs) by using near infrared spectroscopy (NIRS), a continuous, non-invasive method that uses infrared light to penetrate the skull and provides real time regional oxygen saturation (SpO2) from the frontal cortex. NIRS correlates well with more invasive measures of cerebral perfusion, doppler ultrasound and MRIs. Methods: Prospective study in 14 patients <21 years old with more than 1 HD on, on room air, without congenital heart disease. We used continuous NIRS and pulse oximetry (SpO2 monitoring), and obtained co-oximeter measured central venous oxygen saturation (SvO2) at the start, middle, and end of HD treatment. CEOs was data extracted at the exact times SpO2 was measured. Data collected over 2 HD treatments for each patient. Results: Continuous monitor of spO2 showed no hypoxia during recorded HD treatments. SpO2 decreased from HD start 73(SD=7.7) to end of treatment 64.8(SD=9.1), mean difference 8.17(CI 2.3 to 14) =0.01; CEOx also decreased from 74(SD=6.3) to 70(SD=5.7) mean difference 3.8(CI 1.5 to 6.2) =0.002. For every 1 unit drop of SpO2 the CEOx decreased by 0.5 at the end of HD (β=1.0 CI -0.2 to 0.4). CEOx, SpO2 and SvO2 falls significantly during HD in the absence of declining SpO2. These data suggest HD leads to cerebral dysoxia, though it is unclear whether the mechanism is related to decreased oxygen delivery, increased extraction or a combination of both at the tissue level. Future studies are needed to explore these physiological changes as well as the impact the cognitive functioning of children receiving chronic HD.

Guidelines on Prescribing Prolonged Intermittent Renal Replacement Therapy (PIRRT) in a Child in an ICU Setting

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Background: Renal replacement therapies (RRT) are a cornerstone in the management of critically ill children who are often hemodynamically compromised. By virtue of their small size and large volume required in the extracorporeal circuit it often becomes difficult to perform conventional hemodialysis to provide RRT support in these children. Continuous renal replacement therapy (CRRT) is the accepted alternative but is associated with the high cost and limited availability. Thus, in resource-poor settings, peritoneal dialysis becomes the mainstay of management but has the disadvantages of increased risk of infections, inability to control the ultrafiltration and interfering with the ventilatory parameters. Prolonged intermittent renal replacement therapy (PIRRT) which is RRT given intermittently over a prolonged session is a modality that provides the advantages of a CRRT in a cost-effective way. PIRRT has been widely accepted in adults but data on PIRRT in children is sparse.

Methods: We searched the PubMed/Medline, Embase and Cochrane Database for all the publications on PIRRT and two experts from the Pediatric Continuous Renal Replacement Therapy (PCRRT) Workgroup assessed titles, abstracts, and full-text articles for extraction of data. The data from the literature search was shared with the PCRRRT workgroup and expert panel recommendations were developed.

Results: We recommend that sustained low-efficiency dialysis (SLED) be initiated for all critically ill children requiring RRT along with introtopic support if necessary. SLED should also be initiated for acute kidney injury (AKI) with multi-organ dysfunction and poor perfusion of the right atrium (PRISM) scores. The rates of blood flow and dialysate flow are decided based on hemodynamic stability and are usually similar to CRRT. Duration of therapy may be anywhere between 6-18 hours and may be performed 3 times a week or more. Any machine that is used for HD may be used for delivering PIRRT provided it has the provision of lowering the blood flow and dialysate flow rates and can prolong the duration of therapy to 6-8 hours. Conclusions: We recommend that sustained low-efficiency dialysis (SLED) be initiated for all critically ill children requiring RRT along with introtopic support if necessary.

Identifying Factors Associated with Mortality in Pediatric Hemodialysis Patients Using a Machine Learning Approach

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Background: Mortality in pediatric end-stage renal disease patients is ≥30 times higher than in healthy children, and higher on chronic dialysis than after kidney transplantation. We aimed to explore factors associated with mortality on chronic hemodialysis (HD) in patients having started HD at pediatric age.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: Mice with experimental AS develop proteinuria at 4 weeks of age and die of AKI by 32 weeks of age. We demonstrated that SMAD3b expression is 7-fold increased in kidneys of AS mice compared to wildtype littermates. We found decreased albumin-to-creatinine ratio (6.09±1.40 vs. 23.59±1.37 mg/mg) in DKO mice compared to AS mice (27.39±5.15 mg/mg). Improved proteinuria was not associated with improved body weight or glucose homeostasis (130.5±51.5 mEq/min/100 g BW in controls and 153.3±4.4 mEq/min/100 g BW in double knockout) or renal histology. DKO mice also significantly reduced significantly lower levels of SIP (0.07±0.01 pmol/ml) in kidney cortexes compared to AS mice (0.17±0.04 pmol/ml). In vivo pharmacologic inhibition of mTOR and p70S6K significantly reduced ANLN -overexpressing podocytes (p<0.0001). GSX3b (KD) also significantly inhibited podocyte apoptosis at 72 hours (p<0.0001). These results confirmed our prior findings. Pharmacologic inhibition of the PERK and e-Jun N-terminal Kinase (JNK) significantly reduced ANLN -mediated apoptosis in podocytes (p<0.0001) highlighting the pathologic contributions of two additional signaling pathways to ANLN-induced podocyte apoptosis.

Conclusions: These findings broaden our understanding of the pathologic role of ER-stress signaling in ANLN -induced podocyte apoptosis and expand the repertoire of potential therapeutic targets for familial FSGS caused by ANLN mutations. In vivo modeling of the effects of the ANLN mutation are needed to confirm the pathologic role of ER-stress signaling to podocyte apoptosis and to evaluate the efficacy of therapies targeting ER-stress pathways for the amelioration of ANLN -induced podocyte loss.

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TH-P0792
The E3-Ubiquitin Ligase HUWE1 is a Central Regulator in Podocyte Homeostasis
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Background: As terminally differentiated cells, podocytes depend on precise regulation of protein turnover and response to cellular stress in order to preserve homeostasis. Disruption of these processes can lead to podocyte damage and loss and subsequently to glomerular scarring and kidney disease. Ubiquitination is a post-translational modification that targets proteins not only to posttranslational degradation but also to different cellular pathways such as DNA repair, cell cycle regulation, and apoptosis. The HECT type E3 ubiquitin ligase HUWE1 has been shown to be a regulator of various intracellular signaling cascades in different cell types. To characterize the effects of HUWE1-mediated ubiquitination in podocyte homeostasis in vivo and in vitro, we generated a podocyte-specific Huwe1-knockout mouse and HUWE1-deficient human podocyte cell lines.

Methods: To phenotype podocyte-specific Huwe1-knockout mice, we analyzed the urine albumin/creatinine ratio and performed immunohistochemistry and electron microscopy. To elucidate the molecular effects of HUWE1 knockdown on podocyte signaling, we generated a CRISPR/Cas9-mediated HUWE1-deficient human podocyte cell line and analyzed protein expression by mass spectrometry and RNA sequencing. To investigate HUWE1 specific alterations of ubiquitination, mass spectrometry after inhibition of ubiquitin enzymes was performed.

Results: Podocyte-specific loss of Huwe1 in mice caused kidney disease beginning at 5 weeks of age. Affected mice developed massive proteinuria and died prematurely of uramnic complications. At the ultrastructural level, we saw extensive foot process effacement, podocyte vacuolization, and cell loss. Proteome and transcriptome analysis of HUWE1-knockout cells revealed significant differential regulation in a number of relevant pathways such as cell division, mitochondrial metabolism and autophagy. Analysis of the ubiquitome is ongoing.

Conclusions: The E3-ubiquitin ligase HUWE1 is pivotal for podocyte function and overall survival in mice. We identified HUWE1 as a central regulator of a multitude of cellular pathways to preserve podocyte signaling and homeostasis. To address the complexity of affected cellular systems within the podocyte, a systems biology approach is required in order to develop new diagnostic and therapeutic strategies.

Funding: Private Foundation Support

TH-P0793
Targeting of Endoplasmic Reticulum Stress Signaling Pathways for the Amelioration of ANLN -Induced Podocyte Apoptosis
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Background: We previously reported that mutations in anillin (ANLN) cause familial FSGS and that the ANLN -mutated mouse shows aberrant activation of the PI3K/AKT/mTOR pathway and increased apoptosis. To identify potential therapeutic targets for ANLN -induced podocyte apoptosis, we sought to further delineate the ER-stress signaling pathways downstream of the PI3K/AKT/mTOR signaling pathway.

Methods: We quantified apoptosis in our established IgF+, ANLN-, and ANLN- in vitroexpressing podocyte lines using the BioTek® Luminex FX automated live cell imaging system. Biochemical pathway analyses were performed in immunoblots across.

Results: ER-stress signaling was activated in ANLN -KO overexpressing podocytes at 24 hours and knockdown (KD) of CCAAT-enhancer-binding protein homologous protein (CHOP), significantly reduced ANLN -induced podocyte apoptosis (p<0.0001). ANLN -mediated overexpressing podocytes showed significantly increased apoptosis relative to ANLN - and GFP-expressing overexpressing podocytes at 56 hours (p<0.0001). Pharmacologic inhibition of p70S6K and p70S6K reduced ANLN -induced podocyte apoptosis at 72 hours (p=0.0001). Similarly, inhibition of calcium sensing and GSK3B, two upstream regulators of CHOP expression, significantly reduced apoptosis in ANLN -induced overexpressing relative to ANLN - and GFP-expressing overexpressing podocytes (p<0.0001). GSX3b (KD) also significantly inhibited podocyte apoptosis at 72 hours (p<0.0001). These results confirmed our prior findings. Pharmacologic inhibition of the PERK and e-Jun N-terminal Kinase (JNK) significantly reduced ANLN-mediated apoptosis in podocytes (p<0.0001) highlighting the pathologic contributions of two additional signaling pathways to ANLN-induced podocyte apoptosis.

Conclusions: These findings broaden our understanding of the pathologic role of ER-stress signaling in ANLN -induced podocyte apoptosis and expand the repertoire of potential therapeutic targets for familial FSGS caused by ANLN mutations. In vivo modeling of the effects of the ANLN mutation are needed to confirm the pathologic role of ER-stress signaling to podocyte apoptosis and to evaluate the efficacy of therapies targeting ER-stress pathways for the amelioration of ANLN-induced podocyte loss.

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TH-P0794
TBC1D9B Mutations Implicate Rab11-Dependent Vesicular Trafficking in the Pathogenesis of Nephrotic Syndrome
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Background: Steroid-resistant nephrotic syndrome (NS) frequently underlies CKD. Mutations in about 50 genes were identified as monogenic causes of NS and these genes render significant insight into podocyte biology. We previously reported mutations in TBC1D9B in two families with NS. TBC1D9B harbors a TBC domain, that commonly confers a functional role as a GTPase-activating protein (GAP) for specific Rab-GTPases. GAPs promote the inactive state of their Rab protein. However, the function of TBC1D9B and its pathogenic role remained unclear.

Methods: To identify additional mutations of TBC1D9B, we performed whole-exome sequencing (WES). We analyzed the functional role of TBC1D9B and its mutations in vitro and in cultured studies in podocytes using a mouse-like Drosophila nephrocyte.

Results: We identified one hemizygous missense mutation (c.1316T>G, p.Phe435Cys) and two hemizygous nonsense mutations (c.1303C>T, p.Arg344* and c.1383G>A, p.Trp61* in patients with NS. To explore the function of TBC1D9B and its targets, Rab9 and Rab11, we used pharmacologically and genetically inhibited Rab proteins. Pharmacologic inhibition of Rab11 and p70S6K significantly reduced ANLN -overexpressing podocytes (p<0.0001).

Conclusions: Novel mutations in TBC1D9B are monogenic causes of NS and our data indicate that TBC1D9B serves as a GAP protein for Rab11. TBC1D9B interacts with nephrin, being required for its trafficking. This connects RAB11-dependent vesicular trafficking of the membrane protein with NS.

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TH-P0795
Disruption of Crb2 in Podocytes After Birth Leads to Proteinuria
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Background: Crumbs 2, Crb2 is one of the components of the Crumbs cell polarity complex and known to be expressed in podocytes. There have been reports that CRB2 mutations were associated with autosomal dominant nphrs syndrome/NS. However, its precise mechanism is still unclear.

Methods: Crb2 floxed mice that had IoxP sites flanking exon 7 and 8 were bred with NPHS2-Cre ERT2 mice to generate NPHS2-Cre ERT2 positive Crb2 floxed mice. Podocyte-specific Cre2 knockout mice after birth were made by injecting tamoxifen or negative control intraperitoneally for three days at two months of age. Urine, blood, and kidneys were analyzed in the two mouse groups at four months of age.

Results: NPHS2-Cre ERT2 positive Crb2 floxed mice that were injected tamoxifen showed increased proteinuria in kidney of mice compared to the (ctrl). We observed potential negative effect. Blood urea nitrogen or serum creatinine at four months of age was comparable between the two groups. Glomerular indices or fibrotic indices at four months of age were similar between the two groups.

Conclusions: Disruption of Crb2 in the podocytes after birth is related to inducing proteinuria.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

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TH-PO796
CRISPR/Cas9 Zebrafish Models Do Not Recapitulate 4 Human Monogenic Causes of Nephrotic Syndrome
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Background: Steroid-resistant nephrotic syndrome (SRNS) is characterized by proteinuria due to disruption of the glomerular filtration barrier and is a frequent cause of chronic kidney disease. Currently, more than 60 monogenic causes of human SRNS are known. Historically, zebrafish have been a commonly used animal model for human monogenic SRNS, using morpholino oligonucleotides. Recently, generation of zebrafish shifted to CRISPR-mediated knockout (KO), which often showed lack of recapitulation of the human disease phenotype in zebrafish (Dev Cell 32:97, 2015). We recapitulated the human SRNS phenotype due to Mag2 mutation (Nat Commun 9:1980, 2018) in a CRISPR model of mag2a (Kidney Int 95:1079, 2019). Recently, we discovered recessive mutations as novel causes of human SRNS in the following genes: avil (WTJ1, Clin Invest 127:4257, 2017), PRDM15, deleted in liver cancer 1 (DLC1) and Insectin1 (ITSN1) (Nat Commun 9:1980, 2018).

Methods: To recapitulate monogenic causes of human SRNS and to study developmental phenotypes by CRISPR/Cas9 KO of the zebrafish orthologues of affected ISK1304164646730, we generated stable KO lines with 4 different KO-alleles for acute knockdown (KD) and stable KO zebrafish lines for these genes. Survival curves as well as phenotype assessments were performed for acute knockdown (KD) and stable KO zebrafish by monitoring larvae for 21 days.

Results: To assay larval onset phenotype, we generated acute KD animals, which did not show a significant difference in survival or phenotype compared to animals injected with a non-binding control guide RNA and wildtype animals. We subsequently generated stable KO lines with 4 different KO-alleles for AVIL, 3 for DLC1, 4 for ITSNI and 6 for PRDM15 respectively. None of these alleles showed a significant phenotypical difference in homoygous fish compared to heterozygous and wildtype controls.

Conclusions: Failure to recapitulate disease phenotypes in CRISPR models is currently predominantly attributed to upregulation of paralogues, triggered by mRNA decay. In this line with these results, CRISPR/Cas9 zebrafish models of the human SRNS genes AVIL, DLC1, PRDM15 and ITSNI do not recapitulate the human phenotype of nephrotic syndrome and do not impede zebrafish larval survival.

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TH-PO797
Biallelic ANK6 and NPHP1 Mutations Alter Ciliary LKB1 Assembly in Late-Onset Ciliopathies
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Background: Nephropathies is a frequent cause of renal failure in children, presenting with progressive renal fibrosis and commonly include extrarenal organ involvement. The use of technological advances in DNA sequencing has led to a better understanding of molecular causes in rare kidney diseases. However, for most of these these cellular pathways involved still need to be identified. ANK6 is a known member of the Inversin compartment and interacts with ANK33. The Liver kinase B1 (LKB1) was recently shown to form a regulatory module in primary cilia with proteins linked to NPHP.

Methods: Genetic testing was performed in affected individuals with CKD of unknown origin. DNA was extracted from whole blood, enriched, and sequenced on a HiSeq2500. Patient-derived fibroblasts were harvested and cultured from skin biopsies of affected individuals, healthy parent and controls. From these patient derived cells functional studies on protein and RNA level using immuno blotting, immunofluorescence and qRT-PCR were performed.

Results: We identified biallelic mutations in the genes NPHP1 and ANK6 in affected individuals with CKD of unknown origin. These segregated with the affected status and were absent from healthy controls. Functional studies in patient derived fibroblasts demonstrate that the identified mutations alter the ciliary assembly of LKB1 as well as downstream signaling pathways, compared to healthy controls and heterozygous parental cells. Moreover, the detected mutations in ANK6 disrupt the Inversin-complex as the mutations lead to a loss of ANK6, NPHP3, Inversin and NEK8 in primary cilia.

Conclusions: We identified the underlying molecular cause in affected individuals with CKD of unknown origin and observed an alteration of the ciliary assembly of LKB1 as well as of downstream signaling in patient derived cells. These findings support the presence of a ciliary LKB1-NPHP3 functional interaction. Moreover the results indicate that an alteration of ciliary LKB1 signaling could be a relevant mechanism for human ciliopathy and may play a wider role in renal disease. Functional studies on patient derived cells with rare inherited kidney diseases may lead to a better understanding of disease mechanisms. This could help to develop novel therapeutic strategies for treatment of such rare disorders.

TH-PO798
Accumulation of Globotriaosylceramide (GL3) in Podocytes (PC) in Fabry Nephropathy (FN) Is Associated with Progressive PC Loss
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Background: Males with classical Fabry disease (FD) have a high incidence of end stage renal disease (ESRD). Processes leading to ESRD are poorly understood. α-galactosidase A gene defects lead to GL3 accumulation in the glomerulus, but this is progressive with age only in PC. PC are relatively resistant to enzyme replacement therapy and replicate poorly when lost. We aimed to examine if PC GL3 accumulation in FN is associated with PC loss.

Methods: Unbiased morphometric electron microscopic renal biopsy studies were performed in 58 males aged 27±13 years with classic FD genotype and/or phenotype.

Results: With increasing age there was a significant increasing fraction of PC cytoplasm occupied by GL3 inclusions (Nv(PC)/glomeruli), but this plateaued at age ~30. However mean PC volume (VPC) and total volume of GL3 inclusions/PC (V[pc]/glomeruli) continued to increase. V[pc]/glomeruli correlated with PC injury and loss evidenced by increased foot process width (FPW) and decreased PC number density per volume of glomerulus (Nv(PC)/glomeruli). The relationship between Nv(PC)/glomeruli vs. V[pc]/glomeruli was best depicted by a power regression [V(pc/glom) = 0.189*Nv(PC/glom)^0.493] or 2 linear regression lines with an initial steep and a later milder slope. Piecewise linear regression analysis explained 81% of the variance of Nv(PC)/glomeruli by V(PC), providing a breakpoint of V(PC) = 2009 µm². Patients with V(PC) > breakpoint showed an inverse correlation between age and Nv(PC)/glomeruli (r = -0.80, p<0.008) and direct correlation between age and V(PC) (r = 0.87, p = 0.004) and VPC (r = 0.87, p = 0.01). Also, urinary protein excretion rate (UPER), a strong predictor of adverse renal outcomes in FD, correlated inversely with Nv(PC)/glomeruli (r = -0.64, p = 0.03) and directly with VPC (r = 0.79, p = 0.002), and FPW correlated inversely with Nv(PC)/glomeruli (−0.74, p = 0.04) in patients with V(PC) > breakpoint. However, in subjects with V(PC) ≤ breakpoint there was no statistically significant relationship between age or UPER and PC parameters.

Conclusions: Given the known association between PC loss and irreversible focal and global glomerulosclerosis, this study supports an important role for PC loss, which beyond a certain point, is associated with the clinical progression of FN and argues for therapeutic intervention before critical PC loss has occurred.

Funding: Other NIH Support - NCI/AT, Commercial Support - Sanofi

TH-PO799
Epigenetic Downregulation of Klotho via H3K27me3 Associated with Suppression of SGK-1 Survival Signaling in Aged Mouse Kidney
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Background: Klotho deficiency is an important mechanistic driver of cell aging. However, the underlying mechanisms by which how Klotho is downregulated by epigenetics in aging cell have not been clearly elucidated.

Methods: In this study, we examined the role of H3K27me3 in the regulation of Klotho gene expression and pathways that influence the cell aging in the kidney of 30-month-old wild type (aged WT) C57BL/6 mice, and Klotho mutant mice compared to 6-months-old WT (young) mice, respectively.

Results: We demonstrated that the level of H3K27me3 was increased in the kidney of aged WT and Klotho mutant mice compared to young WT mice. Elevation of H3K27me3 was largely due to the downregulation of the histone 3 lysine 27 specific demethylase UTx and/or JMD3 in the aging kidneys. Inhibition of Polycomb Repressive Complex C 2 (PRC2) using EED226 and GSK343 decreased the expression of H3K27me3 leading to increase in the expression of Klotho in primary cultured renal tubule cells determined by Western blot and Klotho promoter assay. Inhibition of PRC2 reduced level of H3K27me3 associated with Klotho promoter, suggesting that epigenetic downregulation of Klotho gene expression was due, at least in part, to histone 3 modification in the Klotho promoter region. ChIP qPCR revealed that H3K27me3 was enriched in the Klotho promoter region in the kidney of aged WT and Klotho mutant mice compared to young WT mice. Furthermore, our results showed that aging impaired SGK-1/FOXO3a signaling leading to upregulation of p53 and p16 in the kidney of aged WT and Klotho mutant mice.

Conclusions: We have first shown that epigenetic modification of histone mark H3K27me3 decrease the expression of Klotho gene expression which can directly downregulates Klotho in the kidney of aged wild type mice. Aging exerts renal effects through hyperphosphorylation of mTOR which is independent of Klotho status. The normal aging and Klotho-deficient mediated aging share a common pathway through impaired SGK1 survival signaling leading to upregulation of FOXO3a, p53 and p16 in the kidney of aged WT and Klotho mutant mice. Thus, hormonal action of Klotho may be an alternative approach to activating SGK1 survival signaling for treating aging-mediated kidney disorders.

Funding: Other NIH Support - NIA

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Underline represents presenting author.
Efficacy and Safety of the Long-Acting C5-Inhibitor Ravulizumab in Adult Patients with Atypical Hemolytic Uremic Syndrome (aHUS)  
Eric Rondeau,1 Marie Scully,2 Gemma Ariceta,3 Thomas D. Barbour,4 Spero R. Cattalan,5 Nils Heyne,6 Yoshtika Miyakawa,7 Stephan Ortiz, Eugene Scott Swenson,8 Marc Valleé,9 Sung-Soo Yoon,10 David Kavanagh,10 Hermann G. Haller,10 APHP, University Paris 6, PARIS, France; 2Hospital Universitari Vall d’ Hebron, Barcelona, Spain; 3University College London Hospitals, London, United Kingdom; 4Royal Melbourne Hospital, Parkville, VIC, Australia; 5Ohio State University, Columbus, OH; 6Saitama Medical University, Saitama, Japan; 7Alexion Pharmaceuticals, Inc., Boston, MA; 8Hannover Medical School, Hannover, Germany; 9Seoul National University, Seoul, Republic of Korea; 10National Renal Complement Therapeutics Centre, Newcastle upon Tyne, United Kingdom; 11Tübingen University Hospital, Tübingen, Germany.

Background: Ravulizumab was engineered to achieve extended complement C5 inhibition, given every 8 weeks, while retaining the proven efficacy and safety of eculizumab. Here we evaluate the efficacy and safety of ravulizumab in adults with aHUS.

Methods: This was a phase 3, single arm study (NCT02949128). Complement inhibitor-naive patients (pts) aged ≥18 years who fulfilled diagnostic criteria for aHUS (exclusion of ADAMTS13 <5% activity and Shiga toxin-producing Escherichia coli) and active thrombotic microangiopathy (TMA) received ravulizumab at 8-week intervals during the maintenance phase. The primary endpoint was complete TMA response during the initial 183-day evaluation period. Secondary endpoints included time to complete TMA response, components of complete TMA response over time, CKD stage, dialysis-free status over time and time to dialysis-free status.

Results: Fifty-six eligible pts were analyzed. Median age at baseline was 40 (range, 20–77) years and 36 (66%) were female. Complete TMA response was achieved in 30 pts (54%). 17 (29%) pts stopped dialysis (at a median time of 30 days). Primary endpoint and TMA parameter response over time is shown in the figure. Improvement in CKD stage from baseline was observed in 32/47 (68%) pts at Day 183. The most frequent serious adverse events were hypertension and pneumonia, each reported in 3 (5%) pts; 4 deaths not attributed to treatment occurred. No meningococcal infections were reported.

Conclusions: 8-weekly ravulizumab dosing produced immediate, sustained, and complete complement inhibition resulting in rapid hemolytic and renal response with no unexpected safety concerns.

Funding: Commercial Support - Alexion Pharmaceuticals, Inc.

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Underline represents presenting author.

Risk for TMA Recurrence and Renal Outcomes After Eculizumab Discontinuation in aHUS: Results from the Global aHUS Registry  
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Background: Eculizumab (Ecu) modifies the course of disease in patients (pts) with atypical hemolytic uremic syndrome (aHUS), but there are limited data to describe thrombotic microangiopathy (TMA) recurrence rates and long-term outcomes after Ecu discontinuation (d/c).

Methods: Pts in the Global aHUS Registry (NCT01522183) who received ≥1 month of Ecu with evidence of hemolologic or renal response prior to d/c and with a no of follow-up (f/u) were included. Those on chronic dialysis (a3 mo) at the time of Ecu d/c were excluded. Classification as pediatric (<18 years) or adult was made at time of Ecu d/c.

Results: 151 pts (62% female) were included in the analysis: 34% were pediatric and 66% were adults (median [range] age at enrolment, 6.0 [1.6–7.1] and 35.7 [18.4–81.2], respectively), 11% had a family history of aHUS and 41% had a pathogenic variant or anti-CFH antibody. Median (range) duration of Ecu prior to d/c was 1.0 (0.1–5.1) and f/u was 2.3 (0.1–7.1) years. 24% experienced TMA recurrence after Ecu d/c. More pts required antihypertensives at f/u vs at d/c (24% vs 6%). Pts with a family history of aHUS, pathogenic variants, lower eGFR and extrarenal manifestations appeared to be at a higher risk of TMA recurrence (Table).

Conclusions: Discontinuation of Ecu is not without risk and may lead to TMA recurrence in some pts with aHUS. A careful assessment of risk factors prior to the decision to d/c Ecu is warranted.

Table: Predictive factors for TMA recurrence rates

<table>
<thead>
<tr>
<th>Variable</th>
<th>All pts (n=151)</th>
<th>EMA recurrence (n=66)</th>
<th>No-TMA recurrence (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median range of TMA before discontinuation, months</td>
<td>1.0 (0.1–5.1)</td>
<td>1.0 (0.1–5.1)</td>
<td>1.0 (0.1–5.1)</td>
</tr>
<tr>
<td>Median range to EMA recurrence after EMA discontinuation, months</td>
<td>40 (16–60)</td>
<td>18 (12–25)</td>
<td>40 (16–80)</td>
</tr>
<tr>
<td>PTH, ng/mL</td>
<td>30 (20–50)</td>
<td>30 (20–50)</td>
<td>30 (20–50)</td>
</tr>
<tr>
<td>creatinine, mg/dL</td>
<td>2.0 (1.0–4.0)</td>
<td>2.0 (1.0–4.0)</td>
<td>2.0 (1.0–4.0)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>115 (105–125)</td>
<td>115 (105–125)</td>
<td>115 (105–125)</td>
</tr>
</tbody>
</table>

*P-values were calculated by Chi-squared test or Fisher’s exact test as appropriate.

TMA recurrence status missing for n=3. Baseline was defined as period prior to first dose of Ecu. CV, cardiovascular; pulm, pulmonary; CNS, central nervous system; GI, gastrointestinal

Identifying Thrombotic Microangiopathy Mimics  
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Background: Thrombocytopenia is one of the key diagnostic criteria for the clinical diagnosis of thrombotic microangiopathy (TMA). When thrombocytopenia presents with other hemolytic processes, distinguishing the correct diagnosis can be difficult. In an era of terminal complement blockade, the correct diagnosis is critical to determining the optimal treatment approach. Here we describe a cohort of patients clinically diagnosed with TMA but then incidentally identified to have a pathogenic variant in the glucose-6-phosphate dehydrogenase (G6PD) gene.

Methods: Targeted genomic enrichment with massive parallel sequencing (TGE-MPS) of genes implicated in TMA was used to screen 329 patients. Multiplex-ligation-dependent probe amplification (MLPA) for copy-number variations (CNVs) in the CFH-CFHR5 region was also performed.

Results: Of 329 patients screened, 7 patients were positive for well-described pathogenic G6PD variants including 3 with the Union variant, 3 with the Sassari variant and 1 with the Chatham variant. All variants identified have been described as class II variants (1-10% G6PD residual activity). Of the 7 patients, 5 carry at least one complement gene variant, including 3 variants of unknown significance (1 CFH and 2 CFI), 1 pathogenic variant (NGKDE), and 1 likely pathogenic variant (CFHII). MLPA detected a heterozygous deletion of CFHRI-CFHRII in one patient while the remaining were unremarkable. Our findings indicate that approximately 2% of TMA diagnoses may be accounted for by G6PD deficiency.

Conclusions: G6PD deficiency should be included on the differential for someone diagnosed with a hemolytic anemia associated with thrombocytopenia. It remains unclear if G6PD deficiency plays a primary or a modifier role in the TMA-like presentation. Similarly, if G6PD deficiency is the primary etiologic agent, what role does enzyme deficiency play in the individual features of the underlying pathology of the TMA-like presentation (including thrombocytopenia and renal insufficiency) is unknown. Despite this gap in our understanding, considering G6PD deficiency on the differential has clear diagnostic and treatment implications. We conclude that G6PD gene testing is recommended in the workup of a clinical TMA, and G6PD enzyme testing is warranted when the acute process has resolved.

Funding: NIDDK Support

Familial Pregnancy-Associated aHUS and Acute Heart Failure Successfully Treated with Eculizumab  
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Introduction: Atypical HUS is a rare thrombotic microangiopathy (TMA) characterized by anemia, thrombocytopenia (TP) and AKI. Mutations in genes encoding complement proteins have been identified in ~50% of patients. We report 3 sisters who developed aHUS after pregnancy. ADAMTS13 was normal in all.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Case Description: Sister 1: 25-yr-old Hispanic female (HF) presented 10 days postnatally in 2015 with anemia, T-DNA tagged kidney biopsy showing a TMA that was treated with plasma exchange (PE) and steroids. Later she developed heart failure (HF) from mitral valve perforation requiring intubation, valve replacement & hemodialysis (HD). Eculizumab was initiated. Creatinine improved in 2 wk and HD was discontinued. Sister 2: 18-yr-old female HF presented 7 days pp in 2006 with anemia, TP, and AKI. Kidney biopsy revealed a TMA which was nonresponsive to PE and HD was initiated. Course was complicated by HF due to severe mitral and tricuspid regurgitation. She was not treated with eculizumab since aHUS was not considered until after it was diagnosed in her two sisters (8 years later). Genetic testing for all 3: 1) Splice-site variant (c.287-2A>G) in membrane cofactor protein (MCP) known to be aHUS-associated; 2) A novel variant (G918E) in Factor H (FH) of uncertain significance; 3) A heterozygous variant (K441R) in Factor I, likely benign; 4) A heterozygous variant (N1050Y) in FH, likely benign. Our functional analysis for these variants reveals that the G918E is not secreted and leads to low FH levels. The N1050Y is normally secreted and has normal C3b and heparin binding properties. The K441R has normal secretion and activity. The splice-site variant in MCP is expected to cause decreased expression of MCP leading to low levels.

Discussion: The sisters carry pathogenic mutations in both MCP and FH. It is unusual for a patient with aHUS to carry multiple rare variants. Pregnancy was the trigger for both family (patients’ paternal grandmother lost 10 of 12 pregnancies). Acute heart failure due to valvular disease is novel. Possible mechanism is thrombus formation followed by endocarditis.

TH-PO804 Complement Activation Causes Major Metabolic and Energetic Changes on Endothelial Cells
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Background: Complement dysregulation and formation of the membrane attack complex (MAC, C5b-9) on vascular endothelial cells (ECs) cause EC injury and can lead to thrombotic microangiopathy (TMA). Effects of chronic complement exposure on cellular level are not well established. Here, we especially focused on metabolic and energetic changes as previous data indicated that C5b-9 formation on the surfaces of ECs did not result in cellular necrosis or apoptosis.

Methods: Human blood outgrowth endothelial cells (BOECs) derived from healthy donors were sensitized with an anti-CD59 antibody. Complement activation was initiated by adding normal human serum. Microscopy, lumiocytometry and western blot were used to measure intracellular calcium, ATP, mitochondrial membrane potential as well as autophagy pathways, respectively.

Results: BOECs exposed to complement showed cell surface C5b-9 deposition followed by an abrupt rise in intracellular Ca2+ that was sustained over 6 hours. Under complement stress, cell motility was impaired, which resulted in defective wound healing. We suggested a defect in endothelial cell energy homeostasis as likely cause for the observed functional defects. Indeed, complement activation caused a sustained drop in intracellular ATP levels and mitochondrial membrane potential. These effects were reversible following discontinuation of complement stress (i.e., removal of serum or blocking C5 or C5a receptors). BOECs lacking CD59 skin, lung, liver and brain ECs were more resistant to C5b-9-mediated killing. Overall, these data indicate that C5b-9 formation will cause significant changes in metabolic and energetic function of ECs.

Conclusion: In chronic complement activation leads to an EC energy deficit. BOECs activate a survival machinery to support complement attack, including the re-sealing of the plasma membrane and the activation of autophagy. All cellular effects were reversible, implying a window of opportunity for treatment initiation and recovery of endothelial cell function.

TH-PO807 Epithelial Membrane Protein 2 (EMP2) Is Predominantly Expressed in Vascular Smooth Muscle Cells of the Kidney
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Background: Mutations in human gene Epithelial Membrane Protein 2 (EMP2) have been linked to childhood-onset nephrotic syndrome. However, we have previously reported that loss of EMP2 in mice does not cause nephrotic phenotype and that EMP2 lacks a known role of T-Again. Here, we show that EMP2 has a distinctive vascular pattern of expression in multiple tissues including the kidney. As EMP2 is currently being investigated as a novel target for treatment of pathologic neovascularization and vasculo-proliferative diseases such as diabetes, we studied in detail the angiogenic function of EMP2 across different organs including the kidney.

Methods: We created a conditional floxed EMP2 allele carrying a lacZ cassette that allows whole-mount β-galactosidase (β-gal) histochemical analysis of EMP2 expression. Tissues were evaluated as whole mount and additionally embedded in OCT and cryosectioned for immunohistochemical analysis. We created endothelial-specific knockout mice by breeding floxed Emp2 animals with a Cdh5-Cre/ERT2 driver strain. Emp2 knockout with endogenous Cre expressed using qRT-PCR analysis.

Results: Expression of EMP2 by β-gal histochemistry was seen in the arteriolar vasculature of multiple tissues including the kidney. Within the kidney, β-gal activity is localized to renal arterial vessels where it is expressed in Tagln+/SM22α+ vascular smooth muscle cells and is absent in Podl+/endothelial cells, Eomes+ and veins and glomerular endothelial cells. Emp2 expression within the kidney is unchanged upon endothelial specific knockout of the Emp2 gene consistent with the lack of β-gal activity in the endothelial cells of Emp2-/- reporter mice.

Conclusions: Our analysis revealed that EMP2 expression is largely confined to vascular smooth muscle cells of the arterial vasculature in the kidneys as well as multiple other organs. These findings provide important insights into the specific site of action of therapeutics designed to target Emp2.

Funding: NIDDK Support

TH-PO808 Analysis of Mutant Human MUC1 Transgenic Mice with Mapped Transgene Suggests Systemic Manifestation of ADTKD-MUC1 Jun-Ya Kaimori,1 Satoko Yamamoto,2 Takaji Yoshimura,3 Yoshitaka Isaka.1 Osaka University Graduate School of Medicine, Suita Osaka, Japan; 2Osaka University, Osaka, Japan; 3nara medical university, Kashihara, Japan.

Background: Autosomal dominant tubulointerstitial kidney disease caused by mucin-1 gene mutations (ADTKD-MUC1) is an important cause of end-stage renal disease, the reported manifestations of which have been limited to within the kidneys. However, no reports about ADTKD-MUC1 transgenic model animals have been published. Almost all MUC1 mutations were previously identified in variable-number tandem repeats (VNTRs), within which sequencing is very difficult. However, we previously discovered a novel MUC1 mutation before these VNTRs.

Methods: We thus developed mMUC1 tg mice using this mutated cDNA driven by mouse Muc1 promoter and examined their phenotypes. We identified the transgene integration site by targeted locus amplification.

Results: We identified the transgene integration site by targeted locus amplification, revealing that transgene integration did not disrupt any endogenous genes. Surprisingly, mice with high mutant MUC1 protein expression showed growth retardation with massive interstitial pneumonia, gastrointestinal inflammation, and dermatitis with sebaceous gland inflammation. Almost all growth-retarded mutant mice died after weaning. Interestingly, most animals with high mutant protein were male. Our patient re-examination in response to these tg mouse data revealed that patients had interstitial pneumonia, gastrointestinal inflammation, and dermatitis with sebaceous gland inflammation with mutant protein accumulation and ER stress.

Conclusions: These findings show that ADTKD-MUC1 can exhibit systemic inflammatory manifestations.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO807 A Uromodulin Mutation Resulting in Innate Immune System Activation Matthew D. Plotkin,1 Annjaneet Stone.1 University of Arkansas for Medical Sciences, Little Rock, AR; 1Central Arkansas Veterans Healthcare System, Little Rock, AR.

Background: Uromodulin (Tamm-Horsfall) is secreted by the thick ascending limb of the loop of Henle but also crosses basolateral membranes into the interstitium and blood. Uromodulin may function as part of kidney’s innate immune system with pro and anti-inflammatory effects. Mutations in the UMOD gene are a cause of autosomal dominant tubulointerstitial kidney disease (ADTKD) due to tubular injury and endoplasmic reticulum (ER) stress. We identified a family with a novel UMOD mutation (C106F). Biopsies from affected members showed glomerular and interstitial inflammation atypical for ADTKD.

Methods: To determine if this mutation causes the observed phenotype through changes in immune system targeting and activation of the innate immune system, we examined a kidney epithelial cell line with stable transfection of mutant protein and developed a transgenic (tg) mouse with an orthologous cystine to phenylalanine mutation (C105S) in the UMOD gene using CRISPR-Cas9 gene editing.

Results: LLC-PK1 cells expressing wt and mutant protein had increased basolateral secretion of protein compared with cells expressing wt or mutant protein alone. EM examination of mutant medium showed protein aggregates in contrast to filaments in wt medium. Immunoprecipitation of plasma uromodulin from tg/tg mice demonstrated other immunostaining not seen in control uromodulin depleted or heat inactivated serum, indicating that ECs were still viable. Thus we hypothesized that ECs are able to switch on a survival signaling pathway.

Conclusions: We identified a novel mutation in UMOD that results in systemic inflammatory manifestations.

Funding: Veterans Affairs Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

Conclusions: Kidney disease-associated variants of ApoL1 show gain of function in K+ channel activity. Kidney disease-associated variants of Apolipoprotein L1 show decreased membrane association and increased cytoplasmic expression. We have recently demonstrated that a vitamin D receptor (VDR) agonist (VDA) enhances the expression of Apolipoprotein L1 in human podocytes through down-regulation of miR193a. Results: We recalled 30 AA participants (15 with Apolipoprotein L1 high risk and 15 with Apolipoprotein L1 low risk). The median age was 56, 66% were female and median eGFR was 59 ml/min. The median Pb was 9.2 gm/gm of bone (IQR 2.7-12) and was correlated with lower eGFR (R² = 0.19). There was a trend towards lower Pb in individuals with Apolipoprotein L1 high risk vs. low risk (median 6.9 vs. 10.6 gm/gm; p=0.10). This was more evident in individuals (n=10) with eGFR<45 ml/min (median Pb was 11.5 gm/gm; p=0.07). (Figure 1) Conclusions: Conditional on low eGFR, Individuals with Apolipoprotein L1 high risk have lower Pb compared to those with Apolipoprotein L1 low risk. Although larger studies are needed, this may suggest that CKD risk is potentiating by lower Pb at lower exposure levels in persons with Apolipoprotein L1 high risk. Finally, this also serves as a proof-of-concept study using "recall by genotype" for deep phenotyping of environmental exposures.

Funding: NIDDK Support

TH-PO810

APO1L1: A "Novel" Genetic Variant Associated with Podopathy in Chile

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Background: Apolipoprotein L1 (ApoL1) risk allele (rs73885319) is associated with kidney disease in African Americans. According to EXAC data, the G1 allele has an uneven distribution, reaching a high frequency (23%) in Africans, but is very rare (0.6%) in the Latino population. In 2016-2017, three patients in Southern Chile affected by kidney disease were identified as homo- or heterozygous G1 carriers. Here, we describe a study as a first effort to determine the prevalence and association of the G1 allele with podopathy in Chileans.

Methods: 50 FFPE-DNA samples of adult patients with a biopsy-proven podopathy and 1666 DNA samples of ChileGenomico DNA repository recruited along the whole country were analyzed to determine prevalence of the Apolipoprotein L1 G1 risk allele. Genetic analysis was performed by PCR combined with (NGS+Sanger) sequencing technology. Genetic association between the G1 allele and podopathy was analyzed by a 2x2 contingency table to estimate OR.

Results: Among the 50 cases with a biopsy-proven podopathy, 4 subjects carried one risk allele (G1/G0), while 8 out of the 1666 ChileGenomico subjects carried this genotype, resulting in a positive genetic association between the allele and the podopathy (G1 allele frequency 4% vs. 0.24%; p<0.001). One of the 4 G1/G0 cases was HIV-positive; the second one remains unknown in the other 3 cases. Odds ratio for the effect of the Apolipoprotein L1 G1 risk allele resulted 19.8 (95% CI 5.7-67).

Conclusions: Chilean population has a 1-5% African genetic ancestry that decreases from North to South. To our knowledge, this is the first study in Chile that explores the prevalence of the Apolipoprotein L1 G1 risk allele and its association with a podopathy. We confirmed a very low frequency of the Apolipoprotein L1 G1 risk allele dispersed in the Chilean population, but a significant prevalence among patients with podopathy. The clinical value of Apolipoprotein L1 allele is still uncertain in our population and second hits in some patients remain unknown. More evidence is needed before considering the Apolipoprotein L1 genotype as an input to define clinical management and ethical issues have to be considered, particularly for the Afrodescendant migrants that have arrived in Chile the last years. Grants FONDICYT 11140242 and 1160465.

Funding: Government Support - Non-U.S.

TH-PO808

Kidney Disease-Associated Variants of Apolipoprotein L1 Show Gain-of-Function in Cation Channel Activity

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Background: Variants in Apolipoprotein L1 (ApoL1) are responsible for increased risk of some progressive kidney diseases among people of African ancestry. ApoL1 is known to function as an amphiphilic protein that can insert into phospholipid membranes and facilitate chloride efflux. Various disease-associated variants show increased chloride permeability optional when protein and vesicles are both mixed and assayed at pH 5.0. K permeability is optional when protein and vesicles are mixed at pH 6.0 and assayed at pH 7.5. Whether these activities differ among the variants or contribute to disease pathogenesis is unknown.

Methods: Recombinant WT (G0) or each variant (G1, G2) were purified from E. coli. We used a vesicle-based assay of voltage-driven ion flow. In brief, KCl-loaded vesicles were mixed with protein, extravesicular KCl removed, and voltage-driven efflux initiated by addition of either a K- or Cl-selective ionophore to assess Cl or K permeability, respectively. To assess membrane association, protein was mixed with vesicles under conditions that support K permeability, stripped with alkali, the membranes isolated by flotation through a sucrose cushion, and associated protein determined by quantitative western blotting.

Results: From each of 5 sets of purified protein, the K selective permeance of G1 and G2 isoforms was significantly increased compared to G0. Combining all sets, initial efflux rates were 0.36±0.028 for G0, 0.738±0.081 for G1, and 0.688±0.069 for G2 (%/sec, mean ± SEM; P<0.0025 for comparison of G0 with either G1 or G2). In contrast, we find no difference in the Cl selective permeance activity among the isoforms. Compared to WT, the two disease-associated variants show decreased stable membrane association under conditions that support the K permeable activity (amount bound: 56.2±3.4 for G0, 76.6±5.1 for G1, and 100.2±11.8 for G2 (ng, mean ± SEM, n=8 for each; P<0.006 for G1 vs. G0, G2 vs. G0, G1 vs. G2). Results: Recombinant WT (G0) or each variant (G1, G2) were purified from E. coli. We used a vesicle-based assay of voltage-driven ion flow. In brief, KCl-loaded vesicles were mixed with protein, extravesicular KCl removed, and voltage-driven efflux initiated by addition of either a K- or Cl-selective ionophore to assess Cl or K permeability, respectively. To assess membrane association, protein was mixed with vesicles under conditions that support K permeability, stripped with alkali, the membranes isolated by flotation through a sucrose cushion, and associated protein determined by quantitative western blotting.

Conclusions: Kidney disease-associated variants of ApoL1 show gain of function in the K permeable activity, and show increased capacity to stably associate with vesicle membranes, suggesting that the increased activity may be due to more efficient membrane association and/or insertion. These data support a model in which enhanced potassium permeability may contribute to the progressive kidney diseases associated with high-risk ApoL1 alleles.

Funding: NIDDK Support

TH-PO809

Bifunctional VDR-miR193a Axis Modulates APOL1 Expression in Human Podocytes

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Background: APOL1 plays an important role in the maintenance of podocyte molecular phenotype. We have recently demonstrated that a vitamin D receptor (VDR) agonist (VDA) enhances the expression of APOL1 in human podocytes through down-regulation of miR193a. miR193a plays a vital role in the development of focal segmental glomerulosclerosis (FSGS) in experimental animal models and humans. miR193a induces oxidative stress and negatively regulate the expression of Wilm's Tumor Type (WT) 1 expression in podocytes. We hypothesize that VDR and miR193a inversely regulate each other.

Methods: Differentiated immortalized human podocytes (DPHMs) and human embryonic kidney cells (HEKs) were treated with different concentrations of a VDR agonist (VDA, EBI1089, 0, 5, 10, 50, 100 nM) for 48 hours (n=6); HEKs were transduced with either control or VDR plasma (n=4); DPHMs were transduced with either control of miR193a plasmids (n=4); DPHMs were treated with either an empty vector or a specific miR193a inhibitor for 48 hours (n=4). RNAs and proteins were extracted. Protein blots were probed for VDR, APOL1, WT1, and GAPDH. RNAs were assayed for miR193a cDNAs were amplified for VDR, APOL1, and WT1. To validate the putative binding of miR193a-5p to VDR 3'UTR, Luciferase assay was carried out. To examine the binding of VDR at miR193a promoter, ChIP assay was carried out. To evaluate the role of WT1, HEKs were transduced with control, VDR, or WT1 plasmids and protein blots were probed for VDR, WT1, APOL1, and GAPDH. RNAs were assayed for miR193a. Results: Both VDR-treated DPHMs and HEKs displayed upregulation of APOL1 VDR, and WT1 in a dose-dependent manner. VDR-transfected HEKs as well as DPPD-treated with a miR193a inhibitor also showed an increase in APOL1 and WT1 but attenuated miR193a expressions. DPPD overexpressing miR193a showed diminished APOL1, WT1, and VDR expressions (both protein and mRNA). Interestingly, WT1 transfected HEKs showed disease-associated variants show increased stable membrane association under conditions that support K permeability, stripped with alkali, the membranes isolated by flotation through a sucrose cushion, and associated protein determined by quantitative western blotting. These data support a model in which enhanced potassium permeability may contribute to the progressive kidney diseases associated with high-risk ApoL1 alleles.

Conclusions: Bifunctional VDR-miR193a and WT1 regulates APOL1 directly as well as through modulation of WT1.

Funding: NIDDK Support
Institute, Gaithersburg, MD; 2University of Parma, Parma, Italy; 3National Health, Bethesda, MD; 4Johns Hopkins University, Baltimore, MD; 5Merck & Institute of Diabetes and Digestive and Kidney Disease, National Institute of Genetic Diseases of the Kidney - I

Results: In cystinosis patients' fibroblasts homozygous for the nonsense W138X mutation incubation of ELX-02 at escalating dose for 72 hours resulted in reduced half-cystine levels (at 100 nM) up to normal levels, and significantly increased CTNS mRNA levels (at 200 nM) by 2.5- to 3.5-fold. Treatment of compound heterozygous cystinosis patient human fibroblasts, CTNSW138X/57kbDel and CTNSW138X/F598 frameshift mutations, with ELX-02 resulted in increased CTNS mRNA levels and a trend in reduction of half-cystine levels. In a mouse model of cystinosis bearing a Y226X mutation, the PK of ELX-02 in plasma and kidneys and the renal half-cystine levels were evaluated following single and repeated bi-weekly subcutaneous administration of ELX-02 at 9 mg/kg for up to 21 days. As compared to controls, kidneys showed improved metabolites.

Conclusions: The pharmacodynamic effect of ELX-02 treatment on cystine levels suggests that ELX-02 induced functional read-through of cystinosis and demonstrated that the expressed protein reduced the accumulated lysosomal cysteine by one third in the time frame of the experiment given in vivo. These results support the continued development of ELX-02 for the potential treatment of nephropathic cystinosis and other nonsense mutation mediated diseases of the kidney.

Funding: Commercial Support - Eloxx Pharmaceuticals, Inc

TH-PO814

Studying the Link Between Nephropathic Cystinosis and Tubular Acidosis

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Background: Recently, a 23-month old girl presented with rickets, metabolic acidosis, signs of renal Fanconi syndrome and increased granulocyte cysteine levels. The suspected diagnosis was cystinosis, a disease caused by mutations in the CTNS gene (cystine transporter), leading to the lysosomal accumulation of cystine, causing organ damage, particularly the kidneys. However, genetic testing revealed no mutation in CTNS, but compound heterozygous pathogenic mutations in the ATP6V1B1 gene. ATP6V1B1 encodes the B1 subunit of the lysosomal V1 ATPase, which is deficient in distal renal tubular acidosis type III, but with an unknown link to cystinosis. The present study aimed to determine the link between renal tubular acidosis and nephropathic cystinosis.

Methods: CRISPR/Cas9 technology was used to knock-out the ATP6V1B1 gene in conditionally immortalized proximal tubular epithelial cells (ciPTEC) and cell characteristics were compared to isogenic CTNS-/- cells. An untargeted metabolomics approach based on UPLC/MS/MS was applied for the intracellular quantification of metabolites differentially expressed in knock-out and control cells. Fluorescence-based imaging assays were applied to monitor the lysosomal-autophagy dynamics (TEBF, LC3, and DQ-BSA) in ciPTEC.

Results: The ATP6V1B1/-/- isogenic ciPTEC showed a significant increase in cystine accumulation compared to healthy control cells (0.26 vs. 0.13 nmol/mg protein; p<0.05). But this was significantly lower as compared to cystine accumulation in CTNS-/- cells (6.32 vs. 0.26 nmol/mg protein; p<0.05). Like the CTNS-/- cells, ATP6V1B1-/- cells demonstrated an abnormally increased autophagy as shown by the increased TFEB mRNA (7-fold; p<0.05) and increased lysosomal degradative activity of DQ-BSA (2-fold; p<0.05). Moreover, using metabolomics, we identified several metabolites and pathways that were altered (p<0.05) in both renal acidosis and cystinotic cells.

Conclusions: We successfully developed a new genetically engineered renal tubular acidosis cell model with isogenic controls. These cells provide a novel versatile tool to study the pathology of renal tubular acidosis. Metabolomics allowed us to bridge the gap between pathogenesis and renal tubular acidosis in the future aim of finding drugable targets.

Funding: Government Support - Non-U.S. Grant

TH-PO815

Impact of Enzymatic Degradation of Plasma Cysteine in a Mouse Model of Cystinuria Under Dehydration Challenge

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Background: Cystinuria is a genetic disease resulting from mutations in the SLC3A1 and/or SLC7A9 dibasic amino acid transporter genes. Disruption of transporter function leads to increased urine cystine concentrations that exceed the limit of solubility with cystine precipitation and stone formation. In addition to severe episodic symptoms including abdominal pain, affected patients require multiple procedural interventions with an increased risk of hypertension and chronic kidney disease. Although high fluid intake remains a cornerstone of therapy, these regimes are problematic and can lead to nocturia and increased day time frequency. Maintaining an adequate urine output is particularly challenging in children and oral hydration is compromised or during periods of increased fluid loss including occupational commitments such as troop deployments (PMID:16001591). We previously reported that enzymatic degradation of cystine reduces the propensity for kidney and bladder stone formation in a mouse model of cystinuria. Herein, we investigated the therapeutic potential of cystine enzymatic degradation as a therapeutic approach to prevent cystine stone formation in dehydration prone environments.

Methods: We used a murine model of cystinuria (SLC3A1/-/-) that develops stones between 4 & 7 weeks of age (PMID:28165480) and rationed water to 65% to model
dehydration conditions. During water rationing, mice were administered either vehicle or a cystine degrading enzyme, and urine cystine concentration was monitored at specific time points prior to and after treatment.

**Results:** Pharmacodynamic analysis of urinary cystine demonstrated that enzymatic degradation of plasma cystine results in reduction of total cystine levels in urine despite temporary dehydration.

**Conclusions:** This study demonstrates that enzymatic degradation of cystine is effective at reducing the levels of cystine in urine in a mouse model of cystinuria in temporary dehydration conditions. Given that the incidence of urolithiasis is higher in conditions of dehydration (e.g. warmer climates) (PMID:12709888), enzymatic degradation of cystine warrants further investigation as a new potential approach for disease management of cystinuric patients.

**Funding:** Commercial Support - Aeglea Biotherapeutics, Inc.

**TH-PO816**

Whole-Exome Sequencing Reveals ATP6V1C2 as a Novel Candidate Gene for Recessive Distal Renal Tubular Acidosis

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**Background:** Distal renal tubular acidosis (dRTA) is a rare renal tubular disorder characterized by hyperchloremic metabolic acidosis and impaired urinary acidification. Mutations in 3 genes (ATP6V0A4, ATP6V1B1 and SLC4A1) constitute a monogenic causation in 56-70% of familial childhood-onset dRTA cases. ATP6V0A4 and ATP6V1B1 both encode for subunits of the vacuolar V-ATPase. Just recently, mutations in FOXJ1 have been identified as an additional cause. Therefore, we hypothesized that additional monogenic causes of dRTA remain to be discovered.

**Methods:** We performed panel sequencing and whole exome sequencing (WES) in a cohort of 17 families with 19 affected individuals with pediatric onset dRTA. Yeast growth assays and immunoblot analysis of vacuolar V-ATPase subunits were performed for ATP6V1C2. Transmembranous transport experiments were performed for SLC4A2 after expression in Xenopus oocytes.

**Results:** We identified a causative mutation in 1 of the 3 “classical” known dRTA genes in 10/17 families (58%). Genomic DNA of the 7 unsolved families was then subjected to WES analysis. We identified mutations in 3 genes: ATP6V1C2, which encodes another kidney- specific subunit of the V-type proton ATPase (1 family); WDR72 (2 families) which is an established disease gene for amelogenesis imperfecta, but was also previously implicated in V-ATPase trafficking in cells; and SLC4A2 (1 family), a paralog of known dRTA gene SLC4A1. We then assessed 2 of these mutations for deleteriousness through functional studies: yeast growth assays and immunoblot analysis of vacuolar V-ATPase subunits for ATP6V1C2 revealed loss-of-function for the patient mutation with impairment of V-ATPase stability, strongly supporting ATP6V1C2 as a novel dRTA gene.

In contrast, Xenopus oocyte experiments did not reveal a functional impact of the SLC4A2 mutation after membrane transport experiments.

**Conclusions:** We provided a molecular diagnosis in a known dRTA gene in 10/17 families with dRTA (58%), identified a mutation in ATP6V1C2 as a novel human dRTA candidate gene, and provided further evidence for phenotypic expansion in WDR72 mutations from amelogenesis imperfecta to dRTA.

**Funding:** NIDDK Support, Government Support - Non-U.S.

**TH-PO817**

Proteomic Analysis of Urinary Exosomes in Patients with Gitelman Syndrome

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**Background:** Gitelman syndrome (GS) is hereditary salt-losing tubulopathies resulting from defects of sodium-chloride cotransporter (NCC). Urinary exosome analysis of NCC by western blotting has been evaluated. However, the urine exosomal protein alterations in patients with GS remains unclear. Our purpose to examine urine exosomal protein alterations in patients with GS.

**Methods:** Urinary exosomes were further isolated by ultracentrifugation method. We applied isotopic demethylation labeling coupled with liquid chromatography-tandem mass spectrometry (LC–MS/MS) with CID to discover urinary exosomal target proteins in patients with GS (n=10) compared to healthy controls (n=10).

**Results:** We identified a total of 253 nonredundant proteins that were based on at least two distinct tryptic peptides. Of these, 241 proteins were quantified. Specifically, 90 proteins showed an altered pattern (Log2GS-Control ≥1) in patients with GS including 50 upregulated proteins and 40 down-regulated protein. Renin-angiotensin system was the shared KEGG pathway/biological process in the upregulated differentially genes that compatible with the clinical presentation in GS patients with salt-losing tubulopathy and volume depletion. NCC has been identified in urinary exosome from healthy control but not from patients with GS that was consistent with the finding of NCC mutation in GS. Of interest, there is no significant change in specific exosome markers in CD9, CD81, phosphoglycerate kinase 1 (PGK1), L-lactate dehydrogenase A chain (LDHA), and Alpha- enolase (ENO1) that could be used as an internal control.

**Conclusions:** The identified proteins constitute potential targets for understanding the signal pathway or pathogenesis in in patients with GS. Further target protein needs to be validated in the future.

**Funding:** Government Support - Non-U.S.

**TH-PO818**

Investigating the Pathophysiology and a Potential Therapeutic Approach for Cystinosis

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**Background:** Nephropathic cystinosis is a severe genetic disorder caused by mutations in CTNS gene (cystine transporter), leading to the lysosomal accumulation of cystine and progressive organ damage. To date, no appropriate in vitro isogenic cystinotic cell models exist, a pre-requisite to study the link between the CTNS gene and the disease, and to investigate potential therapeutic strategies. Hence, our aim was to generate a cystinosis phenotype in human kidney cells using CRISPR/ Cas9 and study cystinosis pathology.

**Methods:** We selectively knocked-out the CTNS gene in conditionally immortalized proximal tubular epithelial cells (ciTPEC). An untargeted metabolomics approach based on UHPLC-MS/MS was applied for the intra- and extracellulat quantification of cystine and other metabolites differentially expressed in knock-out and control cells. Various analyses were applied to monitor the lysosomal-autophagy dynamics (TFRB, LC3-II and DQ-BSA) in citPTEC.

**Results:** The CTNS/-/- isogenic cell line of citPTEC showed a significant increase in cystine accumulation compared to healthy control cells (6.32 vs. 0.05 mmol/mg protein; p<0.001). Upon treatment with cystine depleting drug cysteamine, CTNS/-/- cells showed a significant reduction in cystine levels (0.74 mmol/mg protein; p<0.01). Using metabolomics, we identified that not only cystine but also >25 metabolites and 9 metabolic pathways were affected (p<0.05) in cystinotic cells. CTNS/-/- cells demonstrated an abnormally increased autophagy, confirmed by increased LC3-II-lysosome translocation (2-fold; p<0.05), increased accumulation of LC3-II (2.3-fold; p<0.05) and increased lysosomal degradation of DQ-BSA (2-fold; p<0.05). Of note, cysteamine had no effect on the restoration of autophagy, which might explain its limited effect on treating renal Fanconi syndrome. However, a promising registered drug molecule was found to be effective either alone or in combination with cysteamine to reverse cystinosis manifestations.

**Conclusions:** We developed a genetically engineered cystinotic cell model with isogenic controls. These cells provide a novel versatile tool to study the pathology of cystinosis and develop screens for drugs with the potential to reverse the symptoms. Metabolomics allowed an unbiased analysis of potential new targets for treatment of cystinosis.

**Funding:** Government Support - Non-U.S.

**TH-PO819**

Clinical and Genetic Characteristics in Dent Disease 2 and Lowe Syndrome

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**Background:** Dent disease is associated with low molecular weight proteinuria and hypercalciuria and caused by mutations in either two genes of CLCN5 (Dent disease 1) or OCRL (Dent disease 2). On the other hand, Lowe syndrome is characterized by congenital cataract, developmental delay and Fanconi syndrome. Lowe syndrome is also caused by mutations in OCRL gene. However, the clinical and genetic differences between these two diseases. The reason for this difference remains unclear, but previous reports have shown that patients with type of mutations before exon 7 were diagnosed with Dent disease, and those with truncating mutations after exon 8 were diagnosed with Lowe syndrome. The purpose of this study is to investigate the difference in clinical and genetic characters between Dent disease 2 and Lowe syndrome in the Japanese population.

**Methods:** We conducted gene test for clinically suspected cases of Dent disease or Lowe syndrome in total, 22 male cases in 20 families were detected the mutations in OCRL gene. We retrospectively studied these patients to investigate the genotype-phenotype correlation in OCRL disorders.

**Results:** Eleven patients were clinically diagnosed with Lowe syndrome and 11 patients in 9 families with Dent disease 2. Seven novel mutations were identified. Four of these mutations before exon 7, all of which were Dent disease 2. All patients who had truncating mutations or large deletions after exon 8 were diagnosed with Lowe syndrome, whereas missense mutations after exon 8 were associated with both Lowe syndrome and Dent disease 2. In other words, all cases of Dent disease 2 with mutations after exon 8 had missense mutations. Four of the patients diagnosed with Lowe syndrome were able to walk independently. Of these four cases, two had missense mutations and the other two had splice-site mutations.

**Funding:**
Inflammasome Activation in Primary Hyperoxaluria

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Background: In the primary hyperoxalurias (type I - III), increased production of oxalate in the liver consecutively leads to hyperoxaluria, urolithiasis and/or nephrocalcinosis. Hyperoxaluria causes deposition and internalization of calcium oxalate (CaOx) crystals in the epithelial cells of the proximal tubule. As a result, it activates the inflammasome pathway, which is a protein complex in the cytosol of macrophages. In a mouse model of CaOx induced inflammasome activation, the progression of renal damage was delayed by administration of a specific NLRP3 inflammasome pathway inhibitor. The aim of our present study was to investigate inflammasome activation in PH patients.

Methods: Serum samples from 50 PH patients (39 PH I, 6 PH II, 5 PH III) were collected. Thirtyfive patients had preserved renal function, 14 PH I and all PH II patients were on maintenance hemodialysis (HD). In addition, samples from 8 healthy controls and from 9 non HD PH patients were collected. So far, results from 9/6 PH patients with good renal function/HD and from 4 controls are available. Samples were examined for inflammation and organ damage markers by use of a proximity extension assay (PEA) (n=184). In PEA antibody pairs bind to the desired target structure and, if in close proximity to another, form a new PCR target sequence, which can be quantified using real-time PCR.

Results: The preliminary findings have shown no differences in inflammatory/organ damage marks among the three types of PH patients with preserved kidney function. However, there were significant reactions in dialysis dependent PH I patients. So far it is not yet clear whether these differences are caused by the advanced kidney disease or the dialysis therapy per se.

Conclusions: Our current results might allow the following conclusions: 1) the activation of the inflammasome described in the mouse model is only detectable late, e.g. in ESRD, 2) there is no inflammatory reaction to oxalate at all, 3) the response is below the detection limit, 4) all three forms have a comparable inflammation and therefore no difference can be seen. The latter might suggest protective factors in type III or predisposing factors in types I and II.

Funding: Commercial Support - Oxtexa AB, Sweden

TH-PO821

Understanding the Increased Burden of Rarer Primary Hyperoxaluria- Type I (PHI): A Survey of Physician Experiences

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Background: PHI is a genetic disorder characterized by persistent hepatic overproduction of oxalate. Oxalate crystalsize with calcium to ultimately cause renal insufficiency and multi-organ damage. As PHI progresses, patients may require intensive dialysis, and dual liver/kidney transplant is the only option to resolve the underlying insufficiency and multi-organ damage. As PHI progresses, patients may require intensive dialysis, and dual liver/kidney transplant is the only option to resolve the underlying insufficiency and multi-organ damage. As PHI progresses, patients may require intensive dialysis, and dual liver/kidney transplant is the only option to resolve the underlying insufficiency and multi-organ damage. As PHI progresses, patients may require intensive dialysis, and dual liver/kidney transplant is the only option to resolve the underlying insufficiency and multi-organ damage. As PHI progresses, patients may require intensive dialysis, and dual liver/kidney transplant is the only option to resolve the underlying insufficiency and multi-organ damage. As PHI progresses, patients may require intensive dialysis, and dual liver/kidney transplant is the only option to resolve the underlying insufficiency and multi-organ damage. As PHI progresses, patients may require intensive dialysis, and dual liver/kidney transplant is the only option to resolve the underlying insufficiency and multi-organ damage. As PHI progresses, patients may require intensive dialysis, and dual liver/kidney transplant is the only option to resolve the underlying insufficiency and multi-organ damage.

Methods: Select participation criteria included: physicians in practice 2+ years; active role in diagnosing, treating, or managing ≥1 PHI patient(s) within last 5 years; spend ≥50% of time in direct patient care; able to review PHI patient records. Patient history served as basis for further probing in 60-minute interviews involving open-ended questions from a semi-structured interview guide.

Results: 37 physicians reported on 54 PHI patients. By time of diagnosis, 54% (N=29) of patients had progressed to advanced disease. Among patients with preserved renal function at diagnosis (N=25), 20% progressed to dialysis, with many others showing evidence of renal decline since diagnosis. Of all patients, 48% (N=26) required hemodialysis; of these, 47% required dialysis ≥4x/week, and 33% (N=9) required 6x/week. Patients were on dialysis for a mean of 2 range: 0.25-6.5) years. 34% (N=19) of patients ultimately underwent transplant; typically dual liver/kidney transplant.

Conclusions: As PHI progresses, the disease burden increases substantially, necessitating intensive dialysis and transplant. Often, patients progressed to advanced kidney disease before diagnosis, limiting opportunity to modify disease course. While intensive dialysis is intended to be a bridge to transplant, as it cannot keep pace with the oxalate overproduction and systemic deposition of oxalate that occurs at this stage, many patients spent an extended time on dialysis, which is associated with poorer outcomes. Patients require earlier diagnosis and effective therapies to prevent disease progression and the associated burden.

Funding: Commercial Support - Alnylam Pharmaceuticals

TH-PO822

Whole-Exome Sequencing Identifies Nephrolithiasis (NL) Candidate Genes in Large Consanguineous Pakistani Families

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Background: Nephrolithiasis (NL) affects 1 in 11 individuals worldwide and causes high patient morbidity, frequent hospitalizations and surgical interventions. We previously detected a monogenic cause in established NL disease genes in 15% of 268 American NL and European NL families (Halbritter JASN 26:543, 2015) and 73% of 235 Pakistani NL families (Amar Hum Gene 138:211, 2018). We, then, performed whole exome sequencing (WES) in 17 unsolved Pakistani NL families with multiple affected members and prominent consanguinity to discover novel candidate NL genes.

Methods: We performed WES variant analysis by applying multiple recessive and dominant genetic models based on pedigree structure. Candidate disease genes were evaluated further by kidney single-cell mRNA expression (Park Science 360:758, 2018), because known NL genes predominantly exhibit nephron tubular segment expression. Dominant candidate genes were additionally assessed for population variant intolerance, as known dominant NL genes associated with severe phenotypes show high genomic constraint.

Results: We detected deletional mutations in 24 candidate genes in 12/17 total families. In 10 families with significant homozgyosity (>100 Mb in at least 1 affected family member), we detected deleterious recessive mutations in 10 genes. Of these, we identified 2 novel recessive candidate genes (INPP5B, GGTLC1) based on nephron tubular expression. In 8 families with >3 affected members, we evaluated for dominantly inherited variants and detected deleterious mutantions in 14 genes. Of these, we identified 1 dominant candidate gene (HPKIA) based on nephron tubular expression and high population variant intolerance.

Conclusions: By WES of 17 Pakistani NL families, we identified 2 novel recessive and 1 novel dominant candidate NL disease genes.

TH-PO823

Hypophosphatemia Linked to Chromosome X (XLH): Impact on the Quality of Life

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Background: XLH is a rare disease, with dominant inheritance and where the genetic basis is the mutation of the PHEX gene, located in the short arm of chromosome 22. This gene codes for an endopeptidase, homologous named, which causes the overproduction of FGF-23, a counterregulatory hormone of phosphate reabsorption by the sodium/phosphate cotransporters in the renal tubule, as well as increasing catabolism and decreasing the synthesis of the active form of vitamin D. The disease has a wide phenotype variability and different studies have shown a significant impact on the quality of life (QoL) of these patients with reduced mobility and functional disability. A human anti-FGF-23 monoclonal antibody, burosumab, approved in the USA and Europe for the treatment of XLH, corrects the underlying pathophysiology of the disease. It has shown impressive efficacy in children and its study in symptomatic adults with this disease is under study. The objective of this study is to know the impact on the quality of life of a series of patients affected by XLH.

Methods: Longitudinal study with retrospective data collection of a series of patients affected by XLH who were in follow-up in the Department of Nephrology of the Hospital Universitari i Politecnic La Fe (Valencia). Data on the impact of the disease has been collected through a Qol test (EQ-5D-3L), and clinical and radiological variables were collected from the time of diagnosis until 2019.

Results: Data were collected from 18 patients, 38% males of 21.64 ± 11.61 years, of which all had osteomalacia or rickets of some degree, 94.4% short stature, 44% some type of affection joint 16.6%, enthesealopathies, 5.5% stenosis of the medullary canal and none craniosynostosis. Regarding the QoL, 75% referred problems for walking, 50% reported problems to form their daily activities, 25% even for their own self-care, 50% reduced anxiety or depression and 75%, pain. Their average score with respect to their state of health was 63.75 ± 22.86 out of 100.

Conclusions: XLH is a disease with different musculoskeletal manifestations that condition the important impact on the quality of life of patients in both physical and psychological aspects. That is why the appearance of burosumab as a new therapeutic strategy that blocks the physiopathological mechanism of the disease will change this paradigm.
TH-PO824
The Value of Genotypic and Imaging Information to Predict Outcomes in a Large Longitudinal ADPKD Mayo Cohort

Background: Variability in severity of ADPKD is influenced by genetic and allelic factors at the causative locus, plus other genetic and environmental factors. In a mutation characterized ADPKD cohort, we analyzed the predictive ability of the germline mutation and Mayo Imaging Class (MIC) to predict renal functional and structural outcomes.

Methods: Mayo Clinic patients >15 years having a PKD1 or PKD2 pathogenic variant were included (n=1072). Longitudinal eGFR (n=870) and htTKV (n=600) data were collected until ESRD. PKD1 patients were divided into truncating (Mutation Strength Group 1; MSG1), and strongly and weakly predicted non-truncating mutations (MSG2 & 3). The associations between MSG group or MIC and time to 50% loss of eGFR or ESRD was assessed using Cox regression with age as the timescale.

Results: Median time from baseline to 50% eGFR loss/ESRD was 8.1, 8.8, 15.5 and 15.6 years for PKD1 MSG1, 2, 3, and PKD2, and 6.7, 8.2, 10.7 and 17.2 years for MIC classes 1E, 1D, IC & 1B, respectively (MIC class 1A survival was >50% throughout follow-up). This equates to PKD1 MSG2, 3, and PKD2 being associated with a lower risk of 50% eGFR loss/ESRD compared to MSG1 [HR (95% CI): 0.69 (0.51-0.93), 0.35 (0.25-0.49), and 0.28 (0.20-0.40), respectively; P<0.001]. MIC classes 1A-1D were also associated with a lower risk of ESRD compared to class 1E [HR (95% CI): 0.018-0.087], 0.10 (0.065-0.16), 0.19 (0.13-0.28), and 0.44 (0.30-0.63), respectively; P<0.001. A multivariable model including both MSG and MIC had strong discriminatory ability (C-statistic of 0.802). Median time to 50% increase in htTKV was 8.3, 11.1, 12.9, 13.3 & not reached, respectively, for MIC 1A, 1D, 1C, 1B & 1A; hence the other imaging classes had a lower risk of reaching this endpoint than MIC group 1E (P<0.001). However, genotypic class was not found to be associated with a 50% increase in htTKV (p=0.56).

Conclusions: Genotype (MSG) and MIC are strong predictors of functional renal outcome in ADPKD; however, genotype was not associated with htTKV increase of 50%. Utilizing both genotype and imaging class is helpful for identifying patients with severe disease, thereby aiding selection of patients for clinical trials and treatment.

Funding: NIDDK Support

TH-PO825
ADPKD Calculator: A New Tool to Help in the Detection of Patients with Rapid Progression
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Background: Autosomal dominant polycystic kidney disease (ADPKD), a frequent hereditary renal disorder, is the etiology of 10% of dialysis or renal transplant patients and approximately 70% will progress to end-stage renal disease in the fifth decade of life. In 2016 the ERA-EDTA published the Recommendations for the use of Tolvaptan, which included an Algorithm for the recognition of patients with rapid progression, to assess indications for initiation of treatment in ADPKD patients. Starting from this point, we have developed a new App for free use (Scientifically Endorsed by the SCALN), to facilitate detection of rapid progressions. The aim of this App is calculate variables of Renal Function, Total Renal Volume and by means of an Algorithms and Prediction Models, identify ADPKD patients with Rapid Progression.

Methods: Once the conditions of use have been accepted, the patient’s data can be entered in various ways. The methods are described in the App itself in "References and Formulas" button as you can see in attached image.

Results: Body Mass Index. Body Surface. Renal Function (Cockroft Gault BMS corrected; MDRD-4; MDRD-4 IDMS; MDRD-6; CKD-EPI; Urine Albumins/creatinine Ratio; CKD-EPI Cystatin; CKD-EPI Cystatin C Equation). CKD Stage KDIGO 2012 (with graphic representation). KIDNEY TOTAL VOLUME with link to Mayo Clinic Website (The user must be previously accepting Mayo Clinic Terms of Use). Identification of Rapid Progressing patients (through the use of: 1) The Digitalized Algorithm of the ERA-EDTA Workings Groups cited; and 2) PRO-PKD Prediction Model.

Conclusions: ADPKD Calculator, allows the nephrologist to quickly and easily identify patients as Rapid Progressives, in order to proceed to implement those measures that may slow the progression to ESRD. Finally, the free access to this App from www.scal.es, its availability in multplatform and English/Spanish languages, facilitates the use of it.

TH-PO826
Expanded Imaging Classification of Autosomal Dominant Polycystic Kidney Disease (ADPKD)
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Background: Mayo imaging classification of ADPKD is a widely accepted tool that uses height-adjusted total kidney volume (htTKV) and age to identify patients at highest risk for disease progression. The current Mayo classification, however, is applicable only to patients who have typical disease with diffuse cystic involvement (Class 1) by excluding 5-10% of patients (Class 2) with atypical kidney morphology whose htTKV do not appear to predict eGFR decline. Thus, for Class 2 patients, predicting the risk for progression remains uncertain.

Methods: Twenty-one patients of Class 2 with predominant exophytic cyst distribution were identified from the HALT-A study (558 ADPKD adults), and their htTKV were remeasured by excluding exophytic cysts to estimate revised htTKV (rev-hTKV). For the analysis, the odds ratio of reaching CKD3 with and without including class 2 in two logistic models with (1) only Class 1 participants, (2) all participants with original htTKV and (3) all participants with rev-hTKV.

Results: All 6 logistic models showed significant association (p<0.001) between baseline htTKV and reaching CKD3. Estimated odds ratios of reaching CKD3 for all participants increased from rev-hTKV to rev-hTKV adjusted from 1.26 to 1.31 and adjusted (from 1.18 to 1.26) models. Because rev-hTKV was always less than htTKV, the probability of reaching CKD3 decreased for all Class 2 participants. Furthermore, with rev-hTKV, the probability of outcome for Class 2 participants who did not reach CKD3 decreased more than those who reached CKD3.

Conclusions: For Class 2 with predominant exophytic cyst distribution, the association between baseline htTKV and CKD3 outcome became stronger with the use of htTKV reassessed after excluding exophytic cysts, compared to the use of original htTKV.

Funding: NIDDK Support

Comparison of odd ratios of reaching CKD3 with and without including class 2 in two different models

<table>
<thead>
<tr>
<th>Outcome: CKD3</th>
<th>OR (95% CI)</th>
<th>Adjusted model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusive Class 2</td>
<td>4.51 (1.29-15.64)</td>
<td>1.26 (1.04-1.53)</td>
<td>-0.001</td>
</tr>
<tr>
<td>Inclusive Class 2, rev-hTKV</td>
<td>4.51 (1.22-15.64)</td>
<td>1.26 (1.04-1.53)</td>
<td>-0.001</td>
</tr>
</tbody>
</table>

TH-PO827
A Computable Phenotype for ADPKD
Mohammad A. Kale,1 Abdallah El alayli,2 Mohammed N. Alkhathib,7 Kerri A. Georgal,2 Alan S. Yu,2 Reem Mustafa,2 1Washington University Medical center; Kansas city, MO; 2University of Kansas, Kansas City, KS; 3Lebanese American University, Beirut, Lebanon; 4University of Kansas Medical Center, Kansas City, KS; 5University Kansas Medical Center, Kansas, KS.

Background: Autosomal Dominant Polycystic kidney disease (ADPKD) is the most common inherited disease causing of end-stage kidney disease (ESKD). A computable phenotype is an algorithm used to identify a certain set of patients within an electronic

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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 medical record system. Developing a computable phenotype that can identify patients with ADPKD will assist researchers in designing studies and clinical trial recruitment within this population.

Methods: We reviewed a random sample of 1000 medical charts from the University of Kansas Medical Center database. The sample was divided into four groups (A, B, C, and D) of 250 patients each. Group A included patients followed in nephrology clinics who had ICD (International Classification of Diseases) 9 or 10 codes for ADPKD. Group B included those with no ICD codes of ADPKD, but with ICD codes of renal cysts. Group C and D had patients who did not attend the nephrology clinic, with and without ICD 9 or 10 codes for ADPKD respectively. We used ICD 9 code 751.12, CHUNG 05 codes Q61.2-3 for ADPKD. We used the ICD 9 code 593.2 and the ICD 10 code N82.3 for renal cysts. For all medical records, we extracted family history of PKD, hypertension, gomelerous filtration rate, proteinuria, kidney size, number of kidney cysts. Then, we compared the data to internationally accepted diagnostic criteria for ADPKD to determine the diagnosis of ADPKD (reference standard). We calculated test accuracy results for the proposed computable phenotype for ADPKD.

Results: The computable phenotype to identify patients with ADPKD who attended the nephrology clinic has a sensitivity of 98.8% (95% CI 96.4-99.7), a specificity of 84.4% (95% CI 79.4-88.8%), a positive predictive value (PPV) of 83.4% (95% CI 78.4-88.5%), and a negative predictive value (NPV) of 98.8% (95% CI 96.4-99.6). For those who did not attend the nephrology clinic the computable phenotype has a sensitivity of 97.1% (95% CI 93.3-99.0), a specificity of 82.0% (95% CI 77.4-86.1), a PPV of 74.0% (95% CI 69.2-78.3), and a NPV of 98.2% (95% CI 95.7-99.2).

Conclusions: A computable phenotype using the ICD9 and 10 codes can correctly identify most patients with ADPKD, and can be used by researchers to categorize ADPKD patients' cohorts with limited inaccuracy.

TH-PO828
A Convolutional Neural Network for Large-Scale Segmentation of Kidneys in Autosomal Polycystic Kidney Disease
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Background: Total kidney volume (TKV), along with age and Glomerular Filtration Rate (eGFR), is an early prognostic marker of progression in autosomal dominant polycystic kidney disease (ADPKD). Current manual or semi-automated methods for estimation of TKV from imaging data are laborious, time-consuming approximations subject to human perception and experience; this has hampered a widespread adoption of TKV as a biomarker in ADPKD. We report a TKV measurement and processing framework that has a fully automated method for kidney segmentation and TKV estimation from magnetic imaging (MRI) data in patients with ADPKD on a large patient cohort using a deep learning approach. In addition, we describe how such an estimate can be employed for predicting disease progression and monitoring progression, with the aim of supporting clinical management.

Methods: We employ a fully-convolutional neural network based on the volumetric U-net architecture, trained on an extensive dataset of 1620 T2-weighted magnetic resonance imaging scans extracted from the multicenter TEMPO3-4 trial (NCT00429848); expert outlines were available as ground truth. The method is validated on 490 scans, not included in the training dataset, extracted from 179 individual subjects. Based on the data from the same trial, we develop a similarity model for the prediction of the expected TKV growth over time.

Results: We obtained a 90th percentile estimation error of TKV and its change over time of 13% and 11% of the baseline volume, respectively. We predict 3-year TKV based on baseline characteristics with R2 of 0.954 on the TEMPO3-4 placebo data.

Conclusions: The present work represents the first, large-scale example of fully automated TKV estimation in ADPKD that has been trained and validated on a large-scale, multi-centric dataset. When coupled with clinical data from the same trial, we demonstrate the ability of a machine learning algorithm to predict likely TKV progression with high accuracy. This prognostic information combined with other clinical findings may support clinical care.

TH-PO829
Expert-Level Segmentation Using Deep Learning for the Volumetry of Polycystic Kidney and Liver
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, with serious impacts on patients. In polycystic kidney and liver diseases (PKLD), including ADPKD, volumetry is used to assess disease progression and drug efficiency. However, since no rapid and accurate method has been developed, volumetry has not been established in clinical practice, hindering the development of therapies for this disease. This study presents an AI-based PKLD volumetry method that showed powerful performance.

Methods: As a first experiment, the performance of AI was evaluated compared to ground-truth (GT). We trained a V-net based convolutional neural network on 175 ADPKD computed tomography (CT) segmentations (GT) produced by 3 experts using images from 214 patients. The Dice similarity coefficient (DSC), inter-observer correlation coefficient (ICC), and Bland-Altman plots of 39 GT and AI segmentations in the validation set were compared. Next, the performance of AI on the segmentation of 50 random CT images was compared to that of 11 PKLD specialists based on the resulting DSC and ICC.

Results: The DSC and ICC of the AI were 0.961 and 0.999729, respectively. The error rate was within 3% for approximately 95% of CT scans (error <1%, 46.2%, 1% ≤ error <3%, 48.9%). Compared to the specialists, AI showed moderate performance. Furthermore, an outlier in our results confirmed that even PKLD specialists can make mistakes in volumetry.

Conclusions: PKLD volumetry using AI was fast and accurate. AI showed comparable performance to that of human specialists, suggesting its practical use in clinical settings.

Funding: Other NIH Support - NIBIB-216R1DI1A1B103934173

TH-PO830
Total Kidney Volume (TKV) Measurements in Autosomal Dominant Polycystic Kidney Disease (ADPKD) by 3D Ultrasound (3D-US) vs. Ultrasound Ellipsoid (US-EL)
Pedram Akhbar,1 Fatemeh Nasri,1 Crystal F. Quist,1 Elisa Guiard,2 Ioan-Andre Iliuta,3 Syed E. Ahmed,3 Luca Calvaruso,2,4 Mostafa Atri,1 Korosh Khalili,1 York P. Pei,1 University Health Network and University of Toronto, Toronto, ON, Canada; 2University Health Network, Toronto, ON, Canada; 3Toronto General Hospital UHN, Toronto, ON, Canada; 4Università Cattolica del Sacro Cuore, Roma, Roma, Italy.

Background: Total kidney volume (TKV) is a validated prognostic biomarker for risk assessment in ADPKD. TKV by magnetic resonance imaging and manual segmentation (MRI-MS) is the “gold standard”, but it is relatively expensive, time-consuming, and not readily accessible. 3D-US is a new technology which may provide greater precision and accuracy for measuring TKV than US-EL. Here, we report a comparative study of these two US techniques for TKV measurements against MRI-MS.

Methods: We conducted a prospective study of 123 patients recruited at a PKD specialty center who underwent a standardized 3D-US and MRI. Kidney volumes (i.e. single kidney and TKV) by 3D-US and US-EL measured by 5 different experienced ultrasound technicians were compared to those by MRI-MS derived from an experienced radiologist blinded to patient clinical results. Bland-Altman plots were used to assess the agreement of TKV measurements by US vs. MRI.

Results: Table 1 shows the study patient characteristics. We found the accuracy of TKV measurements by US was operator-dependent and varied between different technicians. Compared to MRI-MS, Bland-Altman plots of TKVs by 3D-US and US-EL revealed a similar bias (-9.0% vs. -10.2%), range of diagnosis (-42.25 to 24.31% vs. -41.25 to 20.85%), and difference of greater than 20% (17.2% & 24.3%), respectively. Converting height and age-adjusted TKV’s to the Mayo Class Imaging Class (MCIC) we found a misclassification rate of 22.8% and 23.5% by 3D-US and US-EL, respectively.

Conclusions: TKV measurements by 3D-US and US-EL are less accurate than MRI-MS. Both US techniques displayed similar bias, accuracy, and the operator-dependent; however, TKV by US-EL is simpler to use and more readily available. These factors need to be considered when US-derived TKV is used for risk assessment in ADPKD as classification of MCIC (esp. 1B to 1C) can have important clinical methodological implications.
Table 1. Patient characteristics

| Age (years) mean ± SD | 47±13 |
| Gender, M/F | 14 ± 8 |
| Height (cm) mean ± SD | 169 ± 5.9 |
| TKV (mL) mean ± SD | 1190 ± 522 |

TH-PO831

Simplification of Total Kidney Volume Measurement Procedures for ADPKD
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Background: Total kidney volume (TKV) is an important measure of risk of disease progression in autosomal dominant polycystic kidney disease (ADPKD). Methods to measure TKV are labor-intensive and time-consuming, and not all centers have ability to measure TKV. We developed a technique to provide timely and reliable quantification of TKV using any sequence of abdominal magnetic resonance imaging (MRI).

Methods: Abdominal MRI scans of 74 consecutive patients from the UCSF Polycystic Kidney Disease Center of Excellence were selected. The technique was developed using functionality readily available in an FDA-approved commercial medical imaging analysis software (Zosoft). Scans for the subjects were acquired from different scanner types (GE, Philips) and field strengths (1.5 T, 3 T). On each scan the volumes of left and right kidneys were assessed. Measurements were done on coronal T2-weighted DICOM images (single shot fast spin echo/half-Fourier, slice thickness between 3 and 9 mm). The outer kidney contour was defined manually by tracing on each slice. The contour from each 2D slice was merged to create a true 3D volume of the kidney. The process is calibrated using parameters available in DICOM images. For some cases the cystic volume was measured for each kidney as well via a binary intensity value thresholding. The non-cystic volume was used to assess the agreement of KLs by US vs. MRI. TKV adjusted for age and height was used to derive the Mayo Clinic Imaging Class (MCIC) and used as a “gold standard” for classifying patients into low-risk (1A-1B) vs. high-risk (1C-1E) grouping.

Results: Table 1 shows the study patient characteristics. Good agreement was observed between US- and MRI-derived aKL with 98% of cases within 20% difference. Using aKL >16.5 cm as a diagnostic threshold yielded a sensitivity of 0.53, specificity of 0.92, false positive rate (FPR) of 0.14, false negative rate (FNR) of 0.31, and accuracy of 0.74 for predicting high-risk MCIC (1C-1E).

Conclusions: US-derived aKL >16.5 cm provides a simple approach for risk stratification in ADPKD, but is associated with a FPR of 0.14 (i.e. 14% of low-risk patients misclassified as high-risk) and FNR of 0.31 (i.e. 31% of high-risk patients misclassified as low-risk). When a therapeutic decision (i.e. use of Tolvaptan) is based on accurate risk stratification these errors have clinical consequence.

Funding: Government Support - Non-U.S.

Table 1. Characteristics of Patient Cohort

| Age (years) mean ± SD | 47±13 |
| Gender, M/F | 14 ± 8 |
| Height (cm) mean ± SD | 169 ± 5.9 |
| TKV (mL) mean ± SD | 1190 ± 522 |

TH-PO833

How Well Do Risk Assessment Guidelines Perform for Autosomal Dominant Polycystic Kidney Disease (ADPKD)?
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Background: The approval of Tolvaptan for treatment of ADPKD heralds a new era when mechanism-based therapy is now possible. However, Tolvaptan is an expensive drug that is associated with potentially serious side-effects. Thus, it is currently reserved for patients who are at high-risk for progression. Two sets of risk assessment guidelines for ADPKD are now available based on the consensus of two panels of nephrologists from Canada and Europe. However, how well do these guidelines perform in risk assessment has not been formally assessed.

Methods: We conducted a prospective study in 474 patients with typical imaging pattern of ADPKD by MRI who also had detailed clinical and laboratory data including total kidney volume (TKV). We used age- and height-adjusted TKV to derive Mayo Clinic Imaging Class as a “gold-standard” for risk assessment (i.e. low-risk: 1A-1B; high-risk: 1C-1E). We then applied the revised Canadian guidelines (Can J Kidney Health Dis. 2018; 5:2054358118801589) and European guidelines (NDT 2018; 31: 337-348) to our patient cohort to assess their performance.

Results: Applying the updated Canadian risk assessment algorithm resulted in exclusion of 52% (245/474) of patients in whom 65% were deemed to be low-risk (i.e. MCIC 1A-1B) and 35%, high-risk (MCIC 1C-1E). The resultant cohort (221/503) was enriched with 88% high-risk patients but also included 12% of low-risk patients. The European guidelines provide a 5-step hierarchical algorithm. Applying the first step based on age and CKD stages resulted in exclusion of 74% (351/474) of patients in whom 69% were deemed to be high-risk and 31%, low-risk. The resultant cohort (123/474) was enriched with 72% high-risk patients but also included 28% of low-risk patients. Applying the second step based on rate of eGFR decline resulted in a total exclusion of 93% (440/474) of patients in whom 59% were deemed to be high-risk and 41%, low-risk. The resultant cohort (34/474) was enriched with 82% high-risk patients but also included 18% of low-risk patients.

Conclusions: Risk assessment in ADPKD is an evolving process to be refined by new clinical data and test technologies. Guidelines that enrich “high-risk”, while minimizing “low-risk”, patients, have most clinical utility.

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Long-Term Safety and Tolerability of Tolvaptan (TLV) in Late-Stage ADPKD

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Background: A hepatic safety signal for TLV emerged in the TEMPO clinical ADPKD program with the 1st 18 months (m) of treatment being of greatest susceptibility. This phase 3b, open-label extension study (NCT02251275) evaluated long-term TLV safety in ADPKD pts; liver enzyme monitoring frequency was q1m for the first 18 m of treatment, then q3m thereafter.

Methods: Pts entered from REPRISE, TEMPO 4, 4, or prior trials (9 pts). TLV exposure before entry was ≤5 yrs for TEMPO 4.4 pts and ≤1 yr for REPRISE TLV pts. Hepatic safety was monitored q1m in pts with ≤18 TLV treatment, then q3m thereafter. Starting TLV dose depended on prior trial; maintenance regimens in this study were daily split doses 45/15mg, 60/30mg, and 90/30mg, with down-titration allowed for tolerability.

Results: Of 1803 pts enrolled, 1800 received ≥1 TLV dose. Range of duration TLV exposure in this study was 1-1435 days (d); median exposure 651d (mean 697; SD 334, IQR: 538-924). Percentages of treatment-emergent AEs (TEAEs) were similar across the 3 subgroups but REPRISE PBO pts reported more TEAEs (3678) vs TLV (2965) pts. Most common TEAEs overall: thirst (32%), polyuria (20%), hypertension (17%), nasopharyngitis (15%), nocturia (15%). Aquaretic AEs (AAEs) were most frequent in REPRISE PBO (thirst 32%, polyuria 32%, nocturia 22%). No Hy’s Law cases. TEAE ALT increased 2.8%; AST increased 0.6%. Median 245d exposure before entry was 538-924. Percentages of treatment-emergent AEs (TEAEs) were similar across the 3 subgroups but REPRISE PBO pts reported more TEAEs (3678) vs TLV (2965) pts. Most common TEAEs overall: thirst (32%), polyuria (20%), hypertension (17%), nasopharyngitis (15%), nocturia (15%). Aquaretic AEs (AAEs) were most frequent in REPRISE PBO (thirst 32%, polyuria 32%, nocturia 22%). No Hy’s Law cases. TEAE ALT increased 2.8%; AST increased 0.6%. Median 245d exposure before entry was 538-924. Percentages of treatment-emergent AEs (TEAEs) were similar across the 3 subgroups but REPRISE PBO pts reported more TEAEs (3678) vs TLV (2965) pts. Most common TEAEs overall: thirst (32%), polyuria (20%), hypertension (17%), nasopharyngitis (15%), nocturia (15%). Aquaretic AEs (AAEs) were most frequent in REPRISE PBO (thirst 32%, polyuria 32%, nocturia 22%). No Hy’s Law cases. TEAE ALT increased 2.8%; AST increased 0.6%. Median 245d exposure before entry was 538-924.

Conclusions: Previous HRQoL assessments in ADPKD patients yielded conflicting results. In addition, the impact of tolvaptan treatment on TLV HRQoL outcomes in ADPKD patients is currently unknown.

Methods: The Bern ADPKD registry is an observational cohort study initiated in 2015. Inclusion criteria are age ≥ 18y, clinical diagnosis of ADPKD, informed consent. The main exclusion criterion is need for renal replacement therapy. We assessed HRQoL of ADPKD patients with the validated Short Form-36 (SF-36). This is a part of the KIDSCREEN-10 questionnaire in yearly intervals. The SF-36 consists of 8 multi-item subscales (physical functioning, role-physical, body pain, general health, energy/vitality, social functioning, role-emotional, mental health), and two summary scores: Physical Component Summary (PCS) and Mental Component Summary ( MCS). We transformed raw scores into T-scores (mean=50, SD=10, range 0-100) using contemporaneous Swiss general population norms. Higher scores indicate better HRQoL.

Results: Between October 2015 and May 2019, 121 ADPKD patients were recruited and Tolvaptan treatment has been initiated in 38 patients. In 30 patients (66%) treatment had to be discontinued within the first three months of treatment due to adrenergic side effects (n=4, 11%) or due to elevated liver enzymes (n=3, 5%), and in eight patients (21%) a dose reduction was necessary. We included 93 patients (28 with and 65 without Tolvaptan treatment for whom baseline and 1-year follow-up data were available. Thirty-nine patients were male (42%), median age was 45.7y, median eGFR 47.5 mL/min/1.73 m² and total kidney volume 1197 mL. HRQoL at baseline was similar to the general population with a PCS of 48.6 (95% CI 46.2 – 51.0) and a MCS of 49.6 (95% CI 47.5 – 51.7). Patients with future Tolvaptan treatment had higher PCS scores than patients without future Tolvaptan treatment (52.8 versus 46.8; p<0.05). Individual subscales were not different. At 1 year follow-up HRQoL subscales, MCS and PCS scores were similar to baseline scores in both patients who received Tolvaptan and those who did not.

Conclusions: HRQoL in Swiss ADPKD patients is comparable to HRQoL in the general Swiss population. Furthermore, our data reveal that, beyond an initial adaptation to increased aquarexia, long-term treatment with Tolvaptan does not negatively affect HRQoL of ADPKD patients.

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Could Glomerular Filtration Rate be an Exclusion Criteria to Initiate Tolvaptan Therapy in Those Patients with ADPKD with Risk of Rapid Progression and Predict Renal Outcomes?

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent inherited renal disease and located among the four main causes of end stage renal disease (ESRD) in adult population.

Methods: To analyze the role of tolvaptan (TOLV) along time according with the initial estimated glomerular filtration rate (CKD-EPI) in those patients with CKD 1-4 with risk of rapid progression to ESRD (clinical, analytical and imaging scoring).

Patients AND METHODS: This is an observational and transversal study of our first cohort of 15 pts which initiate in TOLV at a 45±15 mg/d dose and escalating every two weeks until 120 mg/d (13 pts) or maximal tolerated dose (90 mg/d (2 pts)). Controls were made initially every two weeks and randomly every 18 months.

Results: At the time of inclusion all patients 45.4±6.5 years old and 83.0±14.2 kg. 65% were men and the plasma creatinine were 0.98 to 2.58 mg/dl with a CKD-EPI of 53.3±23 mm/min (25.6 to 102.3). Total kidney volume adjusted for age and height ranged from 997 to 2634 cc. After being log-transformed GFR was normally distributed and parametric comparison was made. All treated patients showed a reduction in their GFR in correlation with the used doses (p=0.002). Since in the previous comparison de-escalation patients were included, patients were distributed in quartiles of GFR excluding filtering values correspondent to de-escalated doses as follows: (<30 ml/min: 2 pts; 30-44 ml/min: 5 pts; 45-60 ml/min: 4 pts and >60 ml/min: 4 pts). In this analysis we do not show any correlation between GFR and TOLV treatment, even after one year of therapy. These data are in agreement with the REPRISE study (Torres V et al, NEJM 2010).

Conclusions: The use of TOLV seems to be safe and effective even in those patients older than 50 years and with CKD stage 3b-4. Those patients with a GFR less than 30 ml/min must be on a one-to-one basis evaluated.

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Differential Effects of Tolvaptan on Total Kidney Volume in Autosomal Dominant Polycystic Kidney Disease Patients with PKD1 and PKD2 Mutations

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common renal disease with a genetic origin. The renal prognosis of patients with polycystin 1 (PKD1) mutations was reported to be worse than those with PKD2 mutations. At our hospital, 17 patients with ADPKD with known gene mutation profiles have been treated with the vasopressin antagonist tolvaptan since 2015. However, the relationship between specific gene mutations and the protective effect of tolvaptan on kidney volume and renal function remains unclear. Therefore, we assessed outcomes of patients with different gene mutations in one-year tolvaptan treatment.

Methods: All patients provided consent for genetic analyses. Genetic analysis by Sanger sequencing with a 3730 DNA analyzer was performed in 17 ADPKD patients, including 8 males and 9 females (mean age; 51±11 years), who were treated with tolvaptan for one year. Total kidney volume (TKV) was evaluated using computer tomography using Ziostation 2, an auto-analysis system for TKV measurement.

Results: Mean values for TKV, GFR, %ΔTKV/year, and ΔGFR were 1569±575 ml, 56.0±22.5 ml/min/1.73 m², 14.1±6.1%, and −5.9±7.5 ml/min/1.73 m², respectively. PKD1 and PKD2 mutations were found in 4 and 3 patients, respectively, whereas no mutations in either gene were found in the remaining ten patients. The baseline total TKV, renal function, and changes in TKV did not differ among the patients with PKD1 and PKD2 mutations and those with unknown status (TKV, 1709±212, 1449±277, and 1770±667 ml; GFR, 58.0±22.7, 60.7±11.7, and 53.6±24.4 ml/min/1.73 m²; %ΔTKV/year, 1.7±7.5, 2.3±4.3%, and 15.9±6.7%, respectively). Tolvaptan treatment significantly improved the %ΔTKV/year in patients with PKD1 mutations (%Δ 3.8±10.2% p=0.03) and those with unknown status (−6.8±8.6%, p=0.001), but not in those with PKD2 mutations (−1.7±8.8%, p=0.20). ΔGFR did not change in any of the groups studied.

Conclusions: One-year tolvaptan treatment reduced %ΔTKV/year in patients with ADPKD with PKD1 mutations and those with unknown mutation status but not in those with PKD2 mutations.

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Autosomal Dominant Polycystic Kidney Disease (ADPKD) Patients: Analysis of Pivotal Clinical Trials

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Background: In the TEMPO clinical program, an imbalance in the proportion of pts with elevated amino transferases <-3X upper limit of normal (ULN) was seen vs placebo (PBO). As 3 pts (2 from TEMPO 3-4 [NCT00428948], and 1 from the open-label extension, TEMPO 4-4 [NCT01214421]) met Hy’s Law criteria, increased monitoring frequency was recommended. In the REPRISE clinical program, monitoring was q2m during the first 18m of Tlv exposure and q1m thereafter.

Methods: An independent, blinded Hepatic Adjudication Committee examined data from REPRISE (NCT02160145) and its open-label extension (NCT02251275) in pts with amino transferases >3X ULN using the 5-point U.S. DILI Network classification.

Results: 53 cases were identified. The safety profile of TLV in these studies did not differ from that in TEMPO 3-4 except for the absence of Hy’s Law cases, despite more advanced ADPKD pts being included in REPRISE.

Conclusions: In the REPRISE clinical program all cases of probable liver injury were resolved with dose modification or treatment interruption in TEMPO. No pts met Hy’s Law criteria for more serious liver injury, possibly due to more frequent monitoring and earlier interruption of therapy. (Funding: Otuka)

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Two Years of Follow-Up Experience with Tolvaptan Treatment in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, it accounts for 10% of end renal disease cases. The approval of tolvaptan in 2014 as the first targeted therapy of ADPKD was a significant progress. Since this year there are only a few data reported of the real experience with ADPKD. The objective of our study was to describe the effectiveness and safety profile of patients during the two first years of treatment.

Methods: Retrospective observational study. We included ADPKD patients with chronic kidney disease stage 1-3 and treated with Tolvaptan We collect data baseline data from 15 centres from Madrid (Spain). These data includes lab values and kidney volume.

Results: We included 143 patients. The mean follow up period was 8.7±5.1 months. 51 % women, aged 42±7.10 years with eGFR of 63.8±22.75 ml/min/1.73m2 and urine osmolality 445.89±172.25 mos/m/kg. Baseline CKD: stage 1 (39.6%), 2 (43.4%), 3 (15.9%) and 4 (6.1%) on total kidney volume (TKV) was 1696.47±1399 and class of Mayo Clinic classification: 1B (7%), 1C (23.8%), 1D (31.5%), 1E (24.5%). The urine volume achieved was 100.69±6.54 mg in 4.9±3.8 weeks. The rate of adverse events was 74.1%, 68.5%were those related to increase aquarexia (thirst, polyuria, nocturia and polydipsia). A total of 14 cases (9.8 %) experienced an elevation of liver-enzyme levels, but no cases of severe liver injury was reported. 31 patients (21.6 %) discontinued treatment after a period of 10.9±5.4 months. The main reasons to discontinue were: aquarexia effects (86%), elevations of liver-enzyme levels 7% and 3% of the patients. 9 patients (29.6%) used the treatment after a medium period of 10.9±11 months. Adherence to the therapy was 94.6%. Renal function (Egfr) at 1.6, 12, 18, 21 and 24 months was respectively: 59.8±21.71 ml/min, 56.58±20.22 ml/min, 58.38±19.5 mln, 60.21±21.85 and 62.87±21.83.

Conclusions: In our experience Tolvaptan could be considered as a safety drug in patients with ADPKD. The adherence of the treatment was good, with similar data.
PH-0842


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Background: In TEMPO 3:4 (NCT00428948), Tolvaptan slowed the increase in TKV and renal function decline over a 3-year period in patients with ADPKD. We conducted a posthoc analysis of TEMPO 3:4 in the Japanese cohort to determine if there was an association between change in TKV and renal function in patients treated with tolvaptan.

Methods: The Tolvaptan-treated group of the Japanese cohort of TEMPO 3:4 was subdivided into responders (R; net TKV decrease) and non-responders (NR; net TKV increase) at Year 3. An analysis of potential correlations between TKV treatment and the effects on TKV and eGFR were performed.

Results: 147 patients (placebo (PBO); 55; TKV: 92 [R: 37; NR: 55]) were analyzed. At Year 3, the mean changes in TKV for PBO, Tolvaptan R, and Tolvaptan NR were 16.99%, -8.33% and 13.95%, mean changes in eGFR were -12.61, -8.47 and -8.38 mL/min/1.73 m². Female gender was a significant predictive factor for Tolvaptan inhibition of TKV growth. Compared with PBO, eGFR decline was significantly reduced in both R and NR groups (p<0.05), however, no difference was seen between R and NR. No difference in urine osmolality at Year 1, 2, and 3 was observed between R and NR.

Conclusions: Tolvaptan slowed the decline in renal function over a 3-year period in the Japanese cohort of patients irrespective to the effect of TKV on TKV. Tolvaptan treatment should not be terminated by the short-term growth of TKV.

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Glucocorticoid Metabolism in ADPKD Patients and the Effect of Treatment with a Vasopressin V2 Receptor Antagonist

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Background: Vasopressin concentration is increased in Autosomal Dominant Polycystic Kidney Disease (ADPKD), and increases even further when a vasopressin V2 receptor antagonist (V2RA) is used as renoprotective treatment. We investigated the stimulatory function of these elevated vasopressin levels on the hypothalamic-pituitary-adrenal axis.

Methods: 24-hour urinary excretion of total cortisol, cortisone, THE, THF and aTHF were measured in 27 ADPKD patients using a validated high-performance LC/MS/MS assay. Results were compared to those in healthy controls (HC, n=81) and in IgA nephropathy patients (IgAN, n=27) that were matched for sex, age and kidney function. Next, in the ADPKD patients the effect of the V2RA tolvaptan (3 weeks of 90/30 mg split dose) was investigated on both urine and plasma glucocorticoid levels.

Results: In comparison to HC, ADPKD patients demonstrated lower 24 hour urinary total cortisol (p<0.001), cortisone (p<0.001), THE, THF and aTHF excretion (p<0.001), without changing the urinary excretion of other glucocorticoid compounds or plasma levels.

Conclusions: ADPKD patients demonstrated a decreased urinary excretion of glucocorticoids compared to HC, both of biologically active and inactive compounds. This is not disease specific, but likely caused by their impaired kidney function. The V2RA increased excretion of glucocorticoids in the form of the inactive glucocorticoid cortisone, but without increasing active cortisol, neither in urine nor in plasma. Overall, renal function appears to have a stronger effect on glucocorticoid metabolism than vasopressin function appears to have a stronger effect on glucocorticoid metabolism than vasopressin.

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TH-PO844

Effect of Lixivaptan on Pharmacokinetic (PK) and Pharmacodynamic (PD) End Points in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) in the ELISA Study (PA-102)

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Background: Blockade of the vasopressin V2 receptor has beneficial effects in non-clinical and clinical studies of patients with ADPKD. Lixivaptan is a novel, potent antagonist of the V2 receptor in Phase 3 development for treatment of ADPKD. We report the PK and PD results of the ELISA study, the first clinical study with lixivaptan in ADPKD patients.

Methods: 32 subjects, Chronic Kidney Disease (CKD) Stages 1, 2, and 3, were enrolled at 14 sites in the US. Subjects received lixivaptan for 7 days at 1 of 2 BID dose levels to assess PK and PD endpoints after 1 and 7 days of treatment. AM and PM doses were separated by 10 hours. Full 24 hour PK profiles were obtained on Days 1 and 7 of dosing. PD endpoints were urine osmolality (Uosm), total kidney volume measured by MRI, eGFR, serum sodium, and plasma copeptin. Adverse events were assessed. Aqureatic tolerability was assessed through a specially designed questionnaire.

Results: 1. At the high dose, lixivaptan caused profound declines in Uosm below the iso-osmolar level (300 mOsm/kg), indicating effective V2 receptor inhibition over extended time periods. Mean Uosm declined 80% to a minimum value of 84 mOsm/kg 2 hours after the first dose of lixivaptan. Importantly, 100% of subjects in CKD Stages 2 and 3 maintained Uosm below 300 mOsm/kg over 24 hours. The high dose of lixivaptan showed a strong, reversible effect on other PD variables, including serum sodium (mean increase of 1.9% from baseline) and serum copeptin (2.5 fold increase from baseline). The effect of lixivaptan on all PD endpoints tested compares favorably with historical data for tolvaptan. Conversely, the low dose of lixivaptan tested in this study acutely reduced Uosm but did not provide continued suppression below iso-osmolar levels over an extended period of time.

Conclusions: These Phase 2 data confirm that the high dose of lixivaptan is tested is a fully pharmacologically effective dose of lixivaptan for ADPKD, whereas the low dose is emerging as the starting dose of lixivaptan. These results form the appropriate titration doses for the upcoming pivotal Phase 3 study with lixivaptan in ADPKD patients.

Funding: Commercial Support - Palladio Biosciences, Inc.

TH-PO845

Safety and Efficacy Results from the SILK (Safety in Larger Kidneys) Cohort of KDO919-101: A Phase 1b/2a Trial of the Tyrosine Kinase Inhibitor Tesevatinib in Patients with ADPKD

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Background: The KDO919-101 trial has evaluated safety and efficacy of tesevatinib in ADPKD patients. Tesevatinib is a tyrosine kinase inhibitor targeting the EGFr receptor pathway previously implicated in the pathogenesis of ADPKD. Tesevatinib has been demonstrated to inhibit the growth of kidneys and preserve kidney function in PKD animal models.

Methods: The SILK cohort enrolled patients with eGFR a 35 but a 80 mL/min/1.73m² and hTKV a 1000mL. Subjects were treated with 50 mg tesevatinib QD for up to 24 months. Subjects had MRIs to determine TKV at baseline and 6, 12, 18, and 24 months. Future eGFR prediction was performed using the Mayo Foundation and Medical Education and Research online tool.

Results: Thirty patients (6M/7F) were enrolled. Ten of 13 subjects received at least 12 months of tesevatinib and are included in efficacy analysis. All subjects are included in safety analysis. Over 24 months the increase in hTKV was 8.7% per year. The mean slope of the best-fit line through eGFR measurements was -0.03 mL/min/1.73m². Modelled data using matching subject baseline criteria produced a line with a mean slope of -0.33. Similarly, while modelled data for a matched population predicts a 13.8% loss in eGFR, the mean decrease in eGFR over the treatment period was 6.6%. Commonly reported AEs were HTN, UTI, CPK increase, muscle spasm, and sinusitis. Grade 3 AEs were reported in 3 patients (CHF, HTN, and Herpes zoster) and were considered unlikely or unrelated to study drug. The CHF and Herpes zoster were considered SAEs. Four subjects discontinued treatment before 24 months, 2 due to AEs (increased amylase, fatigue), 1 to withdrawal of consent, and 1 lost to follow-up.

Conclusions: Tesevatinib 50 mg QD is well tolerated by ADPKD patients. Tesevatinib treatment results in preservation of kidney function as measured by eGFR when compared to predicting model data. An ongoing randomized placebo controlled trial is actively recruiting.

Funding: Commercial Support - Kadmon Corporation LLC.

mean a SD or median [IQR], * p<0.05 vs healthy controls, # p<0.05 vs ADPKD baseline.
Background: In chronic kidney disease salt restriction is advocated as renoprotective treatment, especially in proteinuric diseases. Whether protein restriction is beneficial remains controversial. It has been suggested that in autosomal dominant polycystic kidney disease (ADPKD), a mostly non-proteinuric disease, moderate salt restriction may also be beneficial. We investigated the association of sodium and protein intake with rate of disease progression in ADPKD, and what mediating factors could be.

Methods: We performed a post-hoc analysis of the DIPAK-1 trial, in which 305 ADPKD patients were randomized to 2.5 years treatment with lanarotide or standard care. Blood was collected every 3 months for eGFR assessment and 3 MRI-scans were performed to analyze total kidney volume (TKV). Blood pressure and plasma copeptin (a surrogate for vasopressin) were measured at baseline. Salt and protein intake were estimated from 24h urines, which were collected 6 times and calculated per kg ideal body weight. The effect of salt and protein intake on eGFR decline and TKV growth was analyzed with mixed models. We performed mediation analyses to elucidate potential mechanisms.

Results: Of the participants 53% was female, with an age of 48±7 yr, eGFR 51±11 ml/min/1.73m², TKV 2.4±1.6 L, salt intake 9.5±3.9 g/day and protein intake of 87±25 g/day. Salt intake was associated with annual eGFR decline during follow-up (-0.18 ml/min/1.73m² per gram of salt, p=0.02), whereas protein intake was not (p=0.3). Results were similar per kg ideal body weight (p=0.02 and p=0.3, respectively). The association between salt intake and annual change in TKV did not reach statistical significance (0.30% per gram of salt, p=0.07). There was also no association between total protein intake and TKV growth (p=0.1). The effect of salt intake on eGFR slope was not mediated by systolic blood pressure (3.5% mediation, p=0.3), but was significantly mediated by plasma copeptin (53% mediation, p=0.02).

Conclusions: Higher salt intake, but not higher protein intake may be detrimental in ADPKD. A five grams lower salt intake was associated with a 0.9 ml/min/1.73m² lower rate of annual eGFR decline. The substantial mediation by plasma copeptin suggests that this effect is primarily a consequence of a sodium-induced rise in vasopressin.

Self-Monitoring of Urine Specific Gravity Using Study Smartphone Applications Promotes Adherence to High Water Therapy and Facilitates Remote Data Capture in the DRINK Randomised Trial

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Background: High water (HW) intake inhibits vasopressin, a key promoter of disease progression in ADPKD and Autosomal Dominant Polycystic Liver Disease (ADPLD). Maintaining HW intake requires patient motivation and commitment to self-management. We evaluated the role of a smartphone application to facilitate adherence in ‘DRINK’, a randomised feasibility trial of HW versus ad libitum water intake in ADPKD (NCT02933268).

Methods: We developed a cross-platform smartphone application for home monitoring and remote submission of twice weekly urine specific gravity (uSG) results for participants enrolled in ‘DRINK’. Participants targeted uSG ≤1.010 (HW) or >1.010 (AW) for ≥6 months. Fluid intake instructions were embedded in the app. Submitted data were transferred in real time to a central administration portal.

Results: 8% (34/42) of trial participants (HW n=16, AW n=18) used the app. Over 2.8 weeks of follow-up, HW participants used the app to submit uSG data 92% (165/179) of the time compared to 91% (199/219) in the AW group, p=0.38. Baseline characteristics were similar between groups amongst app users (female 53% vs 56%; median age 57.5 yrs, White British 81% vs 83% p=0.82, mean age 47±11 vs 43±11 years p=0.38, in the HW and AW groups respectively). Plasma osmolality was 296±9 mOsm/l (HW) vs 289±7 mOsm/kg (p=0.68) with a corresponding median uSG 1.010 IQR 1.010-1.015 (HW) and 1.010 IQR 1.010-1.015 (AW), p=0.82. Target achievement for uSG was achieved 79% of the time in the AW group and 80% in the HW group, p=0.75 (Figure).

Conclusions: Smartphone technology resulted in high levels of adherence to the study intervention, reliable remote data collection and attainment of target USG with separation between treatment arms. Incorporation of this methodology into future trials is feasible and enhances research efficiency.

Funding: Government Support - Non-U.S.

Sotradecol Foam Sclerotherapy for Treatment of Symptomatic Cysts in ADPKD and Autosomal Dominant Polycystic Liver Disease

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Background: Patients frequently describe mass symptoms & reduced quality of life (QoL) that correlate with visible large liver/kidney cysts in ADPKD/ADPLD. Since 1/18/2017 we have used cyst drainage followed by sotradecol foam sclerotherapy (SFS) to treat symptomatic, large (≥5 cm in diameter) cysts. Small volumes (20cc max) of sotradecol sclerosant admixed with air were injected under fluoroscopy to ablate the epithelial cyst lining. We studied its safety & impact on QoL & organ volumes.

Methods: In this single-center, single-arm, prospective observational study, ADPKD and ADPLD patients with compressive symptoms due to dominant (liver or kidney) cysts are referred for SFS with 3% sotradecol performed under local anesthesia. QoL using linear analog scale assessment tool (LASA), SF-12, the polycystic liver disease QoL tool (PLD-Q), equivalent opioid dose (mg/24hr), & organ volumes (planimetry using CT/MR) are recorded at baseline & 6 months post-SFS. Changes over time were tested using Wilcoxon tests and confirmed using repeated measures mixed models. Improvements >0.5 SD were considered clinically meaningful.

Results: 45 patients (mean age 55y, 84% female) are enrolled: 12 (27%) with ADPKD, 36 (82%) with ADPLD, & 2 (4%) with cystic disease NOS. 31 (69%) & 14 (31%) underwent first SFS for symptomatic liver & kidney cysts, respectively. 56 SFS procedures (mean 1.24 per patient) have been performed to treat 68 cysts (mean 1.51 per patient). Total PLD-Q, overall QoL, physical well-being, bodily pain, & vitality improved at month 6 (Table). Non-significant reductions in organ volumes seen at 6 months is likely due to small numbers. Longer term follow-up to 12 months is ongoing.

Conclusions: SFS directed at symptomatic large cysts was well tolerated, improved QoL at 6 months, & decreased early satiety, SOB, pain & fullness. Smaller volume instillations of SFS have replaced alcohol sclerotherapy in our practice and are a safe option for directed therapy of symptomatic large cysts in ADPKD and ADPLD.

Funding: Private Foundation Support
Cystic Kidney Diseases: Clinical

TH-PO850
AD(H)PKD-Copeptin as Biomarker in Patients with Autosomal-Dominant Polycystic Kidney Disease (ADPKD)
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Background: Prediction of disease progression in ADPKD is a challenging task. While there are established biomarkers such as total kidney volume (TKV), the identification of new and easily obtainable biomarkers is required to facilitate both prognostic assessment and patient selection regarding targeted therapy. Moreover, new biomarkers would ideally allow the prediction of long-term treatment response. Post-hoc analyses of the TEMPO 3:4 study showed that copeptin could be one of those biomarkers. We investigated copeptin as a possible new biomarker in participants of the AD(H)PKD study.

Methods: Copeptin was tested in serum samples from patients of the AD(H)PKD study. These were collected and analyzed at first presentation as well as at follow-up visits. In total, we collected copeptin values from 369 patients, 54 of these during treatment with Tolvaptan. Copeptin values were analysed for both, their distribution in different patient groups (e.g. age, Mayo Class) as well as their response to Tolvaptan treatment.

Results: Copeptin values from 315 patients without tolvaptan treatment were significantly lower than copeptin values from patients receiving tolvaptan (8.65 pmol/l vs. 19.74 pmol/l; p < 0.0001). A consistent trend towards higher copeptin values with increasing stages of chronic kidney disease (CKD) was observed in both groups. This trend also applied for increasing TKV. Patients receiving tolvaptan showed higher copeptin values than patients without Tolvaptan treatment in all stages of CKD as well as all Mayo classes. In 8 patients longitudinal copeptin measurements prior to tolvaptan administration and on a dose of 90/30mg were available and revealed a significant increase after start of tolvaptan treatment (copeptin before tolvaptan: 5.6 pmol/l, copeptin while receiving tolvaptan 21.25 pmol/l; p = 0.0007).

Conclusions: Our findings in the real-life setting are in line with the results from the post-hoc analysis of the TEMPO 3:4 study. Copeptin may serve as a new biomarker in ADPKD regarding both disease progression and response to tolvaptan treatment. Future analyses of our finding disease outcome in correlation to copeptin will help to support the use of copeptin as an easily obtainable biomarker in daily clinical routine.

TH-PO851
Association Between Baseline Renal Blood Flow and CKD Progression in Autosomal Dominant Polycystic Kidney Disease
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Background: Previous Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) studies have shown height-adjusted total kidney volume (htTKV) and renal blood flow (RBF) were independent predictors of renal disease progression. Here we describe an extended study to identify and evaluate the prognostic value of baseline RBF in ADPKD.

Methods: Linear mixed models were utilized to model the effect of baseline RBF on changes in GFR over time adjusting for baseline variables (age, htTKV, gender, mean arterial pressure, hypertension status, genotype, serum HDL cholesterol, serum LDL cholesterol, filtration fraction and protein intake) and (1) either urine albumin, sodium or phosphorus excretions and (2) either BSA or BMI. Logistic regression models were applied to predict CKD using baseline RBF adjusting for baseline age and htTKV. Likelihood ratio tests were conducted to assess the significance of the variables. Area under ROC curve (AUROC) were calculated to assess the model's prognostic ability for reaching ESKD outcomes (stage 5 CKD) using the AICc method. Significant associations were found between baseline RBF and progression of disease (p < 0.001; AICc). The model was then adjusted for age, sex, height, and blood pressure, and the associations were confirmed (p < 0.001; AICc). The model was then further adjusted for baseline age, sex, height, and blood pressure, and the associations were confirmed (p < 0.001; AICc).

Results: Higher baseline RBF is significantly (p < 0.001) associated with higher GFR in ADPKD patients over time when adjusting for the baseline variables: (1) either urine albumin, sodium or phosphorus excretions and (2) either BSA or BMI. Baseline RBF was an independent predictor of CKD outcomes in both an unadjusted model (p < 0.001; AUROC, from 0.75 to 0.78), or after adjustment for baseline age (p < 0.01; AUROC, 0.82 to 0.85), with similar results across CKD stages 3A, 3B or 4. The combination of baseline RBF and htTKV showed strong prognostic value for CKD progression (p < 0.001) and was adjusted for age, sex, and blood pressure (p < 0.001) to predict ESKD outcomes.

Conclusions: Baseline RBF is a strong independent prognostic marker for renal disease progression in ADPKD. Renal blood flow could be used as a prognostic and potentially monitoring biomarker in this disease.

Funding: NIDDK Support

TH-PO852
Peak Renal Blood Flow Rate Correlates with Renal Function in Adults with ADPKD
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Background: Changes in renal blood flow (RBF) occur early in the course of autosomal dominant polycystic kidney disease (ADPKD) and precede the decline in glomerular filtration rate (GFR). The specific hemodynamic factors responsible for the decline in RBF and GFR in ADPKD are poorly defined. The objective of this study was to determine the relationships between flow hemodynamic parameters and GFR in adults with ADPKD.

Methods: All participants provided informed consent and studies were performed in accordance with the Helsinki guidelines. Renal flow indices were obtained by phase-contrast MRI situated in the mid-section of renal arteries. Images were acquired as previously described by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). GFR was measured by 125I-iothalamate clearance.

Results: Forty-five participants (18 male and 27 female) with a confirmed diagnosis of ADPKD were included in the study. The participant characteristics are shown in Table 1. Both Max Q (ml/s) (peak renal RBF) (r = 0.52, p = 0.05) and Min Q (ml/s) (minimum RBF) (r = 0.52, p = 0.04) were significantly positively correlated with measured absolute GFR ml/min. This relationship was independent of age, sex, systolic blood pressure and body mass index. However, neither total blood flow volume (ml) or maximum flow velocity (cm/s) correlated with measured GFR.

Conclusions: In this cohort of people with ADPKD with preserved kidney function both peak and minimum RBF rates significantly correlated with measured GFR. These data suggest that early hemodynamic alterations may be useful biomarkers of kidney function in early disease.

Funding: Other U.S. Government Support

TH-PO853
Effect of Clinical, Radiological, and Genetic Factors on Progression to ESKD in Autosomal Dominant Polycystic Kidney Disease
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Background: Cystic expansion damaging the renal parenchyma is thought to lead to end-stage kidney disease (ESKD) in autosomal dominant polycystic kidney disease (ADPKD). Here we examined (1) whether factors independent of cystic growth contribute to disease progression and (2) their role in Pkd1 compared to Pkd2 associated disease.

Methods: We designed a cross-sectional study using ADPKD seen at the Mayo Clinic between 1992 and 2018 with available abdominal imaging at or near ESKD (n=294). Clinical, laboratory, genetic, and radiological data at the time of ESKD were obtained from electronic medical records. Kidney volumes were measured and adjusted to height (htTKV).

Results: Compared to females (n=154, 52%), males had similar mean age of ESKD (54.6 vs 54.9 years), larger htTKV (2440 vs 1594 ml/m², p<0.01) and higher incidence of macrovascular disease (27% vs 17%, p=0.03). In the univariate analysis, age (p<0.01) and HDL cholesterol (p<0.02) were negatively associated whereas male sex (p<0.01) and ischemic heart disease (p=0.03) were positively associated with HTKVI at ESKD. In the multivariate analysis, only age, sex and ischemic heart disease were significantly
associated with hTKV at ESKD. ADPKD genotype was known in 182 patients (110 PKD1, 55 PKD2, 17 other mutations). Age at ESKD was 49.8±6.4 years in patients with PKD1, 57.4±10.4 in those with PKD1 NT, and 65.2±10.3 in those with PKD2 mutations (p=0.01). hTKV was 2129±1141, 1835±1331 and 2019±1162 ml/min in patients with PKD1T, PKD1NT and PKD2, respectively (p=0.02). A negative correlation between age and hTKV at ESKD was observed in the PKD1 T group (r=−0.32, p=0.01) but not in the smaller and older PKD1 NT and PKD2 groups.

Conclusions: ADPKD patients who reach ESKD at an older age have smaller kidney volumes. This suggests that cyst burden is the main cause of GFR decline in patients reaching ESKD at younger age, whereas additional factors associated with aging (e.g. vascular remodeling) may contribute significantly to hTKV in older patients.

**TH-PO854**

Serum Bicarbonate but Not Urine Ammonium Predicts Renal Outcomes in Autosomal Polycystic Kidney Disease

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Background: Recently, urine ammonium (uNH4+) has been shown to better predict renal outcomes in CKD than serum bicarbonate (sBic). Urinary acidification is impaired in PKD1 mutation, treatment group, hospital, BMI, cardiovascular disease, hypertension, net DIPAK-1 trial (lanreotide vs. placebo). Secondary outcomes were eGFR slope and change kidney function (30% decrease in eGFR or ESRD) in 305 ADPKD patients from the causes of CKD.

Secondary outcomes in both the unadjusted and adjusted models (Figure).

**TH-PO855**

Biomarker Identification Using Serum Proteomics in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: The variable course of autosomal dominant polycystic kidney disease (ADPKD) makes it important to identify biomarkers that predict disease progression to allow optimal counseling and selection of patients for targeted therapies. Current MRI-based volumetric analysis is used as a standard diagnostic tool. In order to identify easily measurable biomarkers of ADPKD progression, we used mass spectrometric quantification of the serum proteome.

Methods: Serum proteome analysis was performed by MALDI-TOF MS using label-free quantification. We compared ADPKD patients (n = 292) with healthy control subjects (n = 58) and IgA nephritis patients (n = 30) as an independent CKD control. Differences in protein expression were assessed by ANOVA and the multiple comparison procedure of Dunnett. The newly identified markers will now be investigated for their predictive potential and their role in the pathogenesis of ADPKD.

**TH-PO856**

Urinary Adenosine and Adenosine/Xanthine Ratio Associate with the Rate of eGFR Decline in a Cohort of Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: The variable course of autosomal dominant polycystic kidney disease (ADPKD), and the advent of renoprotective treatment make it important to discover novel biomarkers for predicting renal disease progression. Based on in vivo data, we hypothesised that urinary ATP excretion is increased in ADPKD, which might contribute to disease progression. We applied urinary metabolomics to explore differences in purine metabolism compounds, as an indirect readout of ATP, and the association with estimated glomerular filtration rate (eGFR, CKD-EPI equation), and progressive loss of eGFR.

Methods: Targeted metabolic profiling using Liquid Chromatography-Mass Spectrometry was performed on single, spot urine samples of 187 ADPKD patients (mean age 48±10 years, 53% female, mean eGFR 53±20 ml/min/1.73m²), and 139 chronic, renal disease patients (mean age 56±17 years, 48% female, mean eGFR 54±33 ml/min/1.73m²). Multiple regression analysis was used to describe the association between a pre-selected set of the metabolites and actual eGFR, and annual change in eGFR.

Results: Abundances of adenosine, inosine, hypoxanthine, xanthine, and uric acid were determined and normalized. For all metabolites, no differences were found between ADPKD and non-ADPKD patients. Adenosine was most strongly associated with eGFR in the total cohort (R²=0.35, P<2.2e-16, r²=0.222) as well as in patients with ADPKD. In an exploratory analysis, additionally indicating that selected serum proteome markers may contribute to the improvement of ADPKD management and disease severity assessment in the future.

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Cystic Kidney Diseases: Clinical

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Underline represents presenting author.

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TH-PO858
Risk of Hospital Encounters for Kidney Stones in Autosomal Dominant Polycystic Kidney Disease: A Cohort Study
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Background: Patients with autosomal dominant polycystic kidney disease (ADPKD) are more likely to develop kidney stones than the general population. However, empirical evidence to this effect is lacking in the current literature. We studied the incidence of (i) a de novo hospital encounter with kidney stones, and (ii) stone interventions among patients with ADPKD compared to patients without ADPKD who were similar in their baseline health indicators.

Methods: Using large healthcare databases from Ontario, Canada, patients with and without ADPKD were identified using hospital encounters between April 1st, 2000 and March 31st, 2016. We used inverse probability of treatment weighting (IPTW) based on propensity score to ensure characteristics of baseline health indicators between the two groups were similar. We followed patients from cohort entry until the first recorded hospital encounter with a de novo stone, death, emigration from Ontario, or March 31st, 2017. We used a weighted Cox proportional hazards model to compare stone rates between the two groups. Death was treated as a censoring event in the primary analysis, and as a competing event in secondary analyses. We also performed analyses for time to first recorded stone intervention and abdominal imaging across all settings. Patients were followed for a mean (maximum) of 7.5 (15.6) years.

Results: ADPKD compared to no ADPKD was not associated with a higher risk of a hospital encounter with stones (92 patients of 2094 with ADPKD [4.3%] vs 80 patients of 2096 without ADPKD [3.8%]; 7.4 vs 6.2 events per 1000 person-years; hazard ratio 1.2 [95% CI, 0.9 to 1.6]). Similarly, ADPKD compared to no ADPKD was not associated with the development of stone intervention (52 of 2094 [2.5%] vs 62 of 2096 [3.0%]; 4.1 vs 4.7 events per 1000 person-years; hazard ratio 0.9 [95% CI 0.6 to 1.2]). The results were similar when treating death as a competing event. ADPKD compared to no ADPKD was associated with a significantly higher rate of abdominal imaging (hazard ratio 1.2 [95% CI 1.1 to 1.3]).

Conclusions: ADPKD was not a significant risk factor for a hospital encounter with kidney stones. The perception that patients with ADPKD are more likely to develop stones may be due to increased surveillance.

Funding: Government Support - Non-U.S.

TH-PO859
Outcome of Kidney Transplantation in Patients with Polycystic Kidney Disease: A Single-Center Study
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Background: Renal transplant (RTx) is the best choice of life-quality of renal replacement therapy for patients with end-stage renal disease (ESRD). Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder and common cause of ESRD. Different from other causes of ESRD, ADPKD patients need more delicate pre-RTx evaluation for intracranial aneurisms, cardiac manifestation, and complications of liver and renal cysts. The outcome of RTx with ADPKD is still unknown in Taiwan.

Methods: We retrieved our 1327 RTx recipients with 1382 times (two recipients with 3 times, 48 recipients with 2 times) of RTx in the past 35 years. There were 41 recipients with ADPKD. This study evaluated the demographics, outcomes, and complications of RTx in patients with ADPKD compared with other cohorts.

Results: The mean recipient age at first RTx was 42.9 ± 12.6 years, however, the ADPKD group (52.5 ± 10.1 yrs) was elder than other group (42.7 ± 12.7 yrs; P = 0.001). The gender of RTx recipients was female 586 (44.2%) and male 741 (55.8%), though, ADPKD group had higher male gender (28; 68.3%) than other group (713; 55.4%) without statistically significance (P = 0.245). Interestingly, the new onset diabetes after transplant (NODAT) was higher in ADPKD group (21; 51.2%) than other group (326; 25.3%; P = 0.005), and more malignancy (18; 43.9% vs. 360; 28.0%; P = 0.041). The patient survival was inferior in ADPKD group (38.9% vs. 70.0%; P = 0.018).

Conclusions: Further studies with multiple centers and greater numbers of patients are needed to compare more precisely the complications and results of transplant between patients with ADPKD and other recipients in Taiwan.

TH-PO860
Post-Kidney Transplant Intracranial Aneurysm and Hemorrhagic Stroke in Polycystic Kidney Disease
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Background: Polycystic Kidney Disease (PKD) is associated with 6-9 times higher prevalence of intracranial aneurysm (ICA) and consequently, of hemorrhagic stroke than the general population. An appropriate screening strategy for ICAs in PKD post-kidney transplantation is not known.

Methods: The Wisconsin Allograft Recipient Database was queried to identify adult patients who received a primary kidney transplant at University of Wisconsin between 1/1/2000-12/31/2015. Causes of ESRD among kidney transplant recipients (KTRs) was categorized as PKD or non-PKD. History of ICA and hemorrhagic stroke at the time of transplant and incidence post-transplant were compared between PKD vs non-PKD using logistic regression and survival analysis.

Results: PKD recipients (N=520) were, in comparison to non-PKD (N=3494), older (52.9 vs 49.4 years), more often female (45% vs 38.8%) and white (93.5% vs 90.2%; p<0.01). Pre-transplant dialysis was less common in PKD KTRs (56% vs 77%; p<0.01). No significant difference was observed in pre-transplant hypertension (97.5% in PKD vs 96.2% in non-PKD KTRs; p=0.15). A history of ICA and prior hemorrhagic stroke was significantly higher in PKD recipients compared to non-PKD KTRs (2.7% and 1.92% vs 0.3% and 0.63%;p<0.01) even after adjusting for demographics and pre-transplant hypertension. Over a median post-transplant follow up 5.4 years (2.4-9.1) in PKD and 5 years (2.1-8.1) in non-PKD recipients, the incidence of ICA was higher in PKD (1.6 vs 0.3 per 1000 person years in non-PKD; p=0.02). The incidence of hemorrhagic stroke was similar between PKD and non-PKD recipients (0.3 vs 0.8 per 1000 person years; p=0.36).

No strokes occurred at time of transplant.

Conclusions: Our findings show that incidence of hemorrhagic stroke in PKD KTRs was low. Regular interval screening for new ICA may not be necessary in PKD patients following kidney transplantation. The factors contributing to change in frequency of hemorrhagic stroke in PKD and non-PKD group in the post-transplant setting need further investigation.
lack of support, helplessness, the need to lie about their condition, and victimization. Participants unanimously described lack of trust-worthy easy to understand educational resources for minorities as a main barrier to engagement.

Conclusions: With a treatment now approved for use in the US, it is important to be aware of patients’ values and barriers to engagement which have pivotal effects on care. Additionally, it is essential to utilize resources to help activate patients of all racial and ethnic groups to be prepared for future treatments.

Funding: Private Foundation Support

TH-PO862

Frequency of Polycystic Kidney Disease in Patients with Intracranial Aneurysm

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Background: Polycystic kidney disease (PKD) is characterized by the multiple cystic formation in the bilateral kidneys. It is also famous for the highly accompanying extrarenal manifestations such as intracranial aneurysm, valvular heart disease, liver cysts, pancreatic cysts, or intestinal diverticulum. The underlying and unifying mechanism of PKD is the abnormality of cilia. The frequency of intracranial aneurysm in patients with PKD is reported to be approximately 4 to 12%. However, the rate of PKD in patients with intracranial aneurysm is not known. Here, we aimed to investigate the frequency of PKD in patients with intracranial aneurysm.

Methods: Seventy-two patients with intracranial aneurysm who visited department of neurosurgery in our hospital, also visited department of nephrology between Nov 2017 and May 2019 for PKD screening. The screening modality was basically kidney ultrasound. If abdominal CT or MRI was already performed, we utilized them to diagnose whether or not the patients have PKD. In cases where PKD is highly suspected by questionnaire to the patients, we performed abdominal MRI or CT. We also investigated the family history of kidney disease, dialysis, intracranial hemorrhage, intracranial aneurysm, sudden death, or liver cysts. Thus we retrospectively investigated the PKD rate in cases with intracranial aneurysm. The ethics committee in our hospital approved this retrospective study.

Results: The patients’ characteristics were as follows; age median 69 IQR (53-76) y.o., male 60, female 12, eGFR 69 (61-81) mL/min/1.73m². Out of the 72 cases, 43 patients had single intracranial aneurysm and 29 patients had plural intracranial aneurysm. Of 72 patients, typical PKD was detected in 1 patient and atypical PKD in another patient. Family history taking showed that 9 patients had relatives with kidney diseases, 4 had those with dialysis, 7 had those with intracranial aneurysm, 14 had those with intracranial hemorrhage, 14 had those with sudden deaths, and 2 had those with liver cysts.

Conclusions: PKD screening indicated that approximately 1-3% of patients with intracranial aneurysm had PKD.

TH-PO863

Clinical Characteristics of Patients with Early-Onset ESKD in Autosomal Dominant Polycystic Kidney Disease: A Case Series

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) has high phenotypic variance. Mutations in PKD2 versus PKD1 lead to milder disease, with average ages at End-Stage Kidney Disease (ESKD) of 79.7 and 58.1yrs, respectively. Some patients reach ESKD in early adulthood, but factors leading to such poor prognosis are unclear.

Methods: This is a cross-sectional study of patients with ADPKD presenting between 1992 and 2018 to Mayo Clinic who reached ESKD by age ≤35 and had detailed clinical information pre-ESKD. Among 4307 patients with ADPKD, 1079 reached ESKD with 18 by age 35. Clinical, genetic and radiological data prior to ESKD onset were collected. Kidney volumes were measured and adjusted by height (HTKV).

Results: Ten patients (55%) were male and 16 (89%) were Caucasian. The average age at ESKD was 30.3 (± 4.3) yrs. Average body mass index was 27.3(±5.6) Kg/m². Among the 13 patients with genetic screening, 8 (61%) had PKD1 truncating and 5 (38%) had PKD2 non-truncating mutations, and one had a possible in trans PKD2 modifying allele. Seventeen patients were hypertensive (94%) with average age of onset of 23 (±6.5) yrs. Among 16 patients with abdominal imaging, 13 (81%) were classified as Mayo Class 1E and 3 (19%) as 1D. Mean HTKV was 2148 (±1169) mL/m². Mean PROPKD score was 7.4 (± 1.5). The majority of patients had cyst hemorrhage (89%) and more than half had ≥2 episodes (55%). The average age of the cyst hemorrhage occurrence was 22 ± 8.5 yrs. Four (22%) patients had cyst infections, and 13 (72%) had at least a history of one episode of acute kidney injury. Seven patients (38%) had bilateral nephrectomies at time of ESKD due to recurrent cyst hemorrhage, three of whom were done concomitantly with their kidney transplantation.

Conclusions: We describe a series of patients with ADPKD who reached ESKD before age 35. All patients had PKD1 mutations and large kidney volumes (Mayo Class 1E and 1D). The majority of the patients had one or two episode of cyst hemorrhage. Prospective studies would be helpful in ascertaining the role of cyst hemorrhage in accelerating the decline of kidney function in patients with ADPKD.
TH-PO865
RAPID-ADPKD, the Retrospective Epidemiological Study of Asian-Pacific Patients with Rapid Progression Disease of Autosomal Dominant Polycystic Kidney Disease: Design and Methods
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Background: For effective treatment and early intervention in Autosomal dominant polycystic kidney disease (ADPKD) patients, identifying subgroups with rapid renal progression is important in ADPKD. This study was designed to identify the clinical characteristics of rapidly progressing ADPKD patients in Asia-Pacific area.

Methods: The RAPID-ADPKD is a multinational retrospective observational cohort study of ADPKD patients in the Asia-Pacific area.

Results: Six hospitals from six regions (Australia, China, Hong Kong, South Korea, Taipei and Turkey) are participating in this study. Adult ADPKD patients, diagnosed by the unified criteria and with eGFR ≥45 mL/min/1.73m2 at baseline will be included. Patients with other comorbidities that can affect renal function will be excluded. Demographic information, clinical characteristics, premorbid condition, medications, GFR, radiologic findings that can calculate height adjusted total kidney volume (htTKV), PKD-related complications and the PRO-PKD score will be collected. Rapid progression will be defined as when any of following criteria are met: (i) an annual eGFR decline ≥0.5 mL/min/1.73m2 in 1-year and ≤2.5 mL/min/1.73m2 per year over a period of 5-years, (ii) an increase in htTKV ≥5% per year from a3 radiologic images; (iii)Mayo classification 1C, 1D, or 1E or kidney length from ultrasonography of >16.5 cm (iv)/PKD1 truncated mutation with early symptoms (PRO-PKD score ≥6). All other patients without any of the criteria are considered as slow progression. The clinical characteristics of rapidly progressing ADPKD group will be compared to slow progression group. In addition, the incidence rate, age of diagnosis, treatment complications between rapid and slow progression will be analyzed. The planned sample size of the cohort is 1,000 patients, and as Feb 28th 2018, data from 400 patients have been collected.

Conclusions: RAPID-ADPKD is the first large-scale multinational retrospective observational study of ADPKD in Asia-Pacific region and will identify the clinical characteristics, risk factors for disease progression and patterns of complications in Asian populations with ADPKD.

Funding: Commercial Support - Korea OIAA

TH-PO866
Neurological Complications After Very Early Bilateral Nephrectomies in Patients with Autosomal Recessive Polycystic Kidney Disease (ARPKD)
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Background: Autosomal recessive polycystic kidney disease (ARPKD) is a pediatric disorder with pronounced phenotypic variability. Severely affected patients may undergo bilateral nephrectomies in the first months of life. The neurological outcome of these patients has not been studied in defined cohorts.

Methods: In a single center international registry study AREgPKD 18 patients with very early (≤3 months of age at second nephrectomy, VEBNE) and 9 with early (3–15 months, EBNE) bilateral nephrectomies as well as 13 patients with very early dialysis onset (<3 months, VED) not receiving bilateral nephrectomies were identified. Eleven patients with total kidney volume (TKV) comparable to TKV of VEBNE patients but without bilateral nephrectomies served as an additional control group. Descriptive statistics, multivariate and Kaplan-Meier analyses evaluated the neurological outcome and potential risk factors of the cohorts.

Results: Mean (SD) follow-up time ranged from 1.6(2.6) years for VED patients to 7.8±5.8 years for EBNE patients. VEBNE patients suffered more frequently from seizures (67%) and severe neurological complications (61%) in comparison to EBNE patients (seizures 11%, severe neurological complications 11%), VED patients (seizures 31%, severe neurological complications 15%) and patients of the TKV control group (seizures 27%, severe neurological complications 6%). In total, 5/11 (45%) patients suffered from severe hypertensive episodes. Multivariable Cox regression analysis revealed the report of a severe hypertensive episode as well as very early bilateral nephrectomies to be independent risk factors for severe neurological complications. Mortality, including mortality after palliative care, was highest among patients with very early onset of dialysis without bilateral nephrectomies.

Conclusions: Bilateral nephrectomies within the first three months of life may be associated with severe neurological sequelae. The indication for very early bilateral nephrectomy must be carefully considered.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Cystic Kidney Diseases: Clinical
Poster/Thursday
Cystic Kidney Diseases: Clinical

TH-PO867
Genetic and Functional Investigation of Neprhin Number on Diabetic Kidney Disease
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Background: Low neprhin number has been linked with susceptibility to hypertension and CKD, but a clear connection between neprhin number and hyperglycemic renal injury is lacking. Our current work seeks to investigate the association between neprhin deficiency and the development of diabetic CKD using a unique model of neprhin deficiency, the HSRA rat. HSRA are born with a single kidney 50-75% of the time while the remaining pups are born with two. The model provides a unique advantage for direct comparison of congenital one-kidney, neprhin-deficient animals (HSRA-S, ~20,400 neprhons), nephrectomized two-kidney animals (HSRA-UNX, ~25,100 neprhons) and two-kidney littermates (HSRA-C, ~50,000 neprhons). Previous work demonstrated that HSRA-S developed increased renal dysfunction with age compared to HSRA-UNX and HSRA-C, which is greatly exacerbated in the presence of DOCA hypertension. This suggests that even slight neprhin differences (≤ vs ~UNX) are important driver of elevated blood pressure, kidney injury and accelerate decline in kidney function.

Methods: To investigate the impact of hyperglycemia on renal injury in the HSRA rat, streptozotocin (STZ) was administered at 9 weeks of age in all three groups; animals were followed for 15 weeks.

Results: Despite overt hyperglycemia (350-450 mg/dl), the diabetic groups did not develop increased proteinuria compared to their non-diabetic counterparts, contrary to the impact of second insult of hypertension.

Conclusions: Current studies are investigating the impact of hyperglycemia after overt injury (“late insult”) in HSRA-S (week ~24) is observed. Additionally, studies to revisit the “early insult” of hyperglycemia with the addition of modest hypertension (130 mmHg) will be completed to better understand the underlying genetic contribution of renal agenesis, altered nephrogenesis in the solitary kidney, and perhaps the differential response of injury to hypertension and hyperglycemia, genetic linkage analysis has been initiated in the HSRA model to map the quantitative trait loci/modifier genes. This work, in conjunction with completed whole genome sequencing and annotation of HSRA genome will hopefully identify new genes/pathways relevant to nephrogenesis and provide insight into differences in the interaction between neprhin number and secondary insults of hypertension and hyperglycemia.

Funding: Other NIH Support - NIGMS

TH-PO868
Genetic Susceptibility of Diabetic Kidney Disease in Mice Is Linked to a Promoter Variant of XOR
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Background: Diabetic kidney disease (DKD) is the leading single cause of ESRD in the United States. Approximately 10-30% of diabetic patients develop DKD with comparable and glucose levels, indicating a significant genetic contribution to disease susceptibility. Differential susceptibilities are also observed in well-defined inbred mice strains. The glomerulus is the primary site of injury with hypertrophy and podocyte depletion being the hallmarks for progressive DKD. We have demonstrated that ROS and mitochondrial oxidative damage accumulation in glomerular endothelial cells (GECs), podocyte foot process effacement and depletion, basement membrane thickening, developing endothelial injury, with increased ROS and mitochondrial oxidative stress in diabetics. However, the underlying mechanisms that contribute to differential susceptibility to DKD are poorly understood.

Methods: Ibed B12/1 (D2) mice are susceptible, while C57BL/6 (B6) mice resistant to diabetes-induced podocyte depletion. We used the 39 strains of BXD (B6XD2) recombinant inbred and parental strains to map genetic loci associated with podocyte numbers after long-term diabetes (6-month). We identified a cis-acting regulatory (promoter) of the Udr gene encoding xanthine dehydrogenase XDH/XO (xanthine oxidoreductase (XOR)). XORs catalyze the oxidation of purine substrates, xanthine and hypoxanthine, producing uric acid, and are a major enzymatic source of ROS.

Results: XOR expression in the kidney and XOR circulating activity were significantly increased in diabetic D2 but not B6 mice. XOR inhibition in diabetic D2 mice significantly reduced albuminuria, oxidative damage in glomeruli and prevented podocyte loss. The two nucleotide variant was shown to influence XOR activity in vitro. To determine whether the variant in XOR promoter underlie the differential responses to diabetes, we used CRISPR/Cas9 to knock-in the XOR variant of D2 into B6 mice. Indeed, the mutant B6-Xor mice had significantly higher XOR activity than the wild-type B6 mice, developed endothelial injury, with increased ROS and mitochondrial oxidative stress in GECs, podocyte foot process effacement and depletion, basement membrane thickening, albuminuria, glomerular sclerotic lesions and tubular injury, furthermore DKKD in B6-Xor mice was prevented with XOR specific inhibition.

Conclusions: These data suggest that the identified promoter variant regulates XOR activity, and may be critical for DKD susceptibility.

Funding: NIDDK Support
TH-PO869  
Genes Involved in Diabetic Nephropathy in a Greek Population of Diabetic Type 2 Patients  


Background: The incidence and prevalence of diabetic nephropathy (DN), the major cause of end-stage renal disease in diabetic type 2 patients (DM2), are continuously rising. Important role in the pathogenesis of DN play metabolic factors, the oxidative stress (OS) pathway and the patient’s genetic substrate. Nevertheless, genome-wide association studies regarding the genetic causes of DN are few and inconclusive. The aim of our study was to find a possible genetic association between the single-nucleotide polymorphisms on the array of OS studied and DN development.

Methods: Data from a genome-wide association study were utilized to perform a study between 240 DM2-DN (cases) and 230 DM2-Non-DN (controls) diabetic type 2 patients of greek origin. 

Results: The polymorphisms that exhibited a significant correlation with DN development were 44 and the corresponding genes were 20. Some polymorphisms are probably potentially protective and others could be implicated in DN development. The genes with an odds ratio below 1, possibly exhibiting a protective role, were: SPP1 (p=0.001), CCs (p=0.019), ALOX12 (p=0.04), OPR (p=0.049). Genes with an OR>1, possibly contributing to DN development, were: TPO (p=0.002), AOX1 (p=0.005), NOS3 (p=0.005), PDLIM1 (p=0.005), EPHX2 (p=0.013), GPX4 (p=0.019), TXNRD2 (p=0.033), EPX (p=0.035), GPX3 (p=0.036), IPECF1 (p=0.041), GAST7 (p=0.041), GPX6 (p=0.044), VKORC1 (p=0.044), TNR1 (p=0.048).

Conclusions: In our study 44 polymorphisms with their 20 genes on the oxidative stress pathway were found to be potentially associated with DN in greek DM2 patients.

To determine the mechanism of depot downregulation, we considered the epigenetic repression of the protein-coding gene mTORC2 in which EZH2 is responsible for the trimethylation (H3Me) of histone H3 at K27. HG increased the expression of EZH2 concomitant with increased H3K27 Me3. Deazanoploacin (DNzep), an inhibitor of EZH2, blocked H3K27 Me3 and depot downregulation induced by HG. Also, Dznep inhibited HG-stimulated mTORC1 and C2 activities, similar to HG treatment. Furthermore, Dznep and shEZH2 significantly inhibited HG downregulation and expression of fibronectin and plasminogen activator inhibitor-1 (PAI-1). On the other hand, EZH2 increased fibronectin and PAI-1 expression similar to HG. To address the in vivo relevance of our observations, we used OVE26 diabetic mice. In the renal cortex of these mice expression of EZH2 was significantly increased concomitant with HG and mTORC1 and C2 activities, and fibronectin and PAI-1 expression.

Conclusions: Our results for the first time uncover a precisely tuned balance between depot suppression by EZH2 and activation of mTORC1 and C2 for HG-induced MC hypertrophy and matrix accumulation. The data lend support for testing EZH2 inhibitors in a real model for attenuation of complications of DN.

Funding: Veterans Affairs Support

TH-PO871  
Urinary Kidney-Specific DNA Methylation Signature Correlates with Renal Function Decline in Diabetes  

Takeshi Marumo, Tatsuo Mitsuhiro A, Takeshi Renal Function Decline in Diabetes Hypertrophy and Matrix Expansion in Diabetic Nephropathy (DN) Launches Deptor Downregulation for Mesangial Cell (MC) Hypertrophy and Matrix Expansion in Diabetic Nephropathy

Background: Renal tubular injury contributes to the silent decline in kidney function in patients with diabetes. Cell type-specific DNA methylation patterns have been used to calculate proportions of particular cell types. In this study, we developed a method to detect renal tubular injury in diabetic patients based on tubule-specific DNA methylation patterns in urine sediment.

Methods: To identify gene loci exhibiting proximal tubule-specific DNA methylation in the human urinary system, we used two approaches: genome-wide DNA methylation analysis using the Infinium MethylationEPIC BeadChip Kit and extrapolation from mouse CpG data obtained in our previous study. We next determined the methylation levels of tubal-genome-spanning loci in urine sediment of diabetic patients and analyzed correlation with clinical variables.

Results: Genomic loci in gene A and G6PC were selectively unmethylated in proximal tubular cells compared to other parts of micro-dissected tissues obtained from normal kidney and normal kidney. The methylation levels of gene A and G6PC in urine sediment, deemed to reflect the proportion of exfoliated proximal tubular cells, correlated well with each other. Multivariate analysis with classic tubular injury markers and known risk factors of renal insufficiency in diabetic patients revealed that lower eGFR and lower methylation levels of gene A were independently associated with larger annual decline in estimated glomerular filtration rate (eGFR). Moreover, addition of urinary gene A methylation to a model containing eGFR and urinary albumin/ Cr improved discrimination of diabetic patients with faster eGFR decline, which were defined as those losing eGFR at a rate more than the 25th percentile of annual eGFR decline, with c-statistics from 0.698 to 0.756 and a significant improvement in reclassification with category-free net reclassification improvement.

Conclusions: This study demonstrates that diabetic patients with continual loss in kidney function may be stratified by a specific DNA methylation signature and provides the approach for using kidney cells in the urine for the non-invasive diagnosis of kidney diseases through epigenetic urinalysis.

Funding: Government Support - Non-U.S.

TH-PO872  
Analysis of DNA Repair Factor KAT5 and DNA Methylation Modulators in Urinary Shedding Cells of Patients with Diabetic Kidney Disease  

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Background: Diabetic kidney disease (DKD) is the leading cause of ESRD worldwide. Therefore, early diagnosis is needed. We have recently discovered that DNA repair factor KAT5 is decreased in DKD podocytes, which may lead to impaired DNA repair with aberrant DNA methylation (Cell Rep 2019). Here we investigated the expression profiles of KAT5 and DNA methylation modulators in urinary shedding cells of patients with DKD as a potential diagnostic marker.

Methods: 60 outpatients who visited the nephrology department at Keio University Hospital were enrolled (Gender [Male 39, Female 21], Age 63±2, patients with diabetes 17 [eGFR 59±4.5], patients without diabetes 43 [eGFR 63±4.3]). 35ml of urine samples were collected and centrifuged, and mRNA was extracted to analyze the expression of DNA repair factors and DNA repair with aberrant DNA methylation (Cell Rep 2019). Here we investigated the expression profiles of KAT5 and DNA methylation modulators in urinary shedding cells of patients with DKD as a potential diagnostic marker.

Conclusions: This study demonstrates that diabetic patients with continual loss in kidney function may be stratified by a specific DNA methylation signature and provides the approach for using kidney cells in the urine for the non-invasive diagnosis of kidney diseases through epigenetic urinalysis.

Funding: Government Support - Non-U.S.

TH-PO870  
Enhancer of Zeste Homolog-2 (EZH2), a Histone H3 Methyltransferase, Launches Depor Downregulation for Mesangial Cell (MC) Hypertrophy and Matrix Expansion in Diabetic Nephropathy (DN)  

Falguni Das, Nandini Ghosh-choudhury, Balakantalam S. Kasinath, Goutam Ghosh-Choudhury. University of Texas Health Science Center, San Antonio, TX.

Background: mTOR has emerged as a centerpiece in pathogenesis of DN. Depor is an inhibitory component of both mTOR complexes (C1 and C2). We investigated epigenetic control of depot expression and its relevance to mesangial cell hypertrophy and matrix protein expansion during the progression of DN.

Methods: Human MCs and OVE26 mice were used. Activation-specific antibodies, real time qRT-PCR, immunoblotting, plasmid-derived expression vector and shRNA transfection were employed.

Results: In MCs, 25 mM glucose (HG) decreased expression of depot mRNA and protein in a time-dependent manner, resulting in increased activation of mTORC1 and C2 as judged by phosphorylation of S6 kinases (T389) and Akt (S473), respectively.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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clinical data including presence of diabetes (DM) or hypertension (HT) was investigated using multivariate logistic regression analysis.

Results: Urine KAT5/nephrin was decreased in diabetic patients (p<0.04) consistent with our previous basic study. On the other hand, KAT5/nephrin was increased in HT patients without DM (p<0.08), whereas it decreased in HT patients with DM (p<0.02). In addition, gene chip data showed a number of differentially expressed genes (DEGs) between 16-week-old female and male UNx mice. Among these, TET1, 3 expression adjusted with AQP1 or AQ2 was respectively increased in patients with HT. These expression tendencies correlated with the severity of HT especially in AQP11 adjustment. Moreover, DNMT1/AQP1 and DNMT3A/AQP1 had positive correlation with 1-year eGFR reduction rate suggesting its possible role as a predictor of renal prognosis.

Conclusions: Urine KAT5/nephrin may be a potential diagnostic marker of DKD. Urine DNMT1, 3A/AQP1 is increased in HT patients and associated with 1-year eGFR reduction rate suggesting its possible role as a predictor of renal prognosis.

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**TH-PO873**

**Epigenetic Regulation of Grem1-1, A Key Player in Diabetic Nephropathy Development**

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**Background:** Grem1 (Growth differentiation factor 5) is a protein highly expressed in the kidney of both diabetic nephropathy (DN) patients and experimental models. However, the molecular mechanisms underlying the upregulation of Grem1 in DN remains only partially understood. Emerging evidence supports a role for epigenetic regulation in the pathogenesis of diabetic nephropathy, but the epigenetic regulation of Grem1 has not been explored. This work aimed to study the role of epigenetic mechanisms in the control of renal expression of Grem1 and its association with diabetic nephropathy.

**Methods:** We first evaluated the renal expression of Grem1 in 4, 8, 12, and 16-week-old mice from a diabetic nephropathy model (BTBR ob/ob) and in 8-week-old mice from an epidemic disruption model (Meep2-null) by RT-qPCR. Additionally, we determined renal expression levels of Meep2 in 16-week-old BTBR ob/ob mice by Western Blot. Next, the DNA sequence of Grem1 was analyzed with bioinformatics tools to identify potential methylatable CpG islands (CGI). Chromatin immunoprecipitation using anti-Meep2 antibody followed by PCR was performed to assess the binding of Meep2 to the Grem1 CGI previously identified. Methylated DNA enrichment by MBD-capture was performed to evaluate the methylation level of the Grem1 CGI.

**Results:** We observed that Grem1 renal expression is increased in BTBR ob/ob mice starting from 8 weeks of age and according to the progression of the phenotype associated with DN. Renal expression of Meep2 in 16-week-old BTBR ob/ob mice was also increased. Additionally, Grem1 renal expression was increased in Meep2-null mice compared to wild-type. Next, we identified a ~2 kb CGI in Grem1 sequence, that includes its transcription start site. We found that in the kidney of wild-type mice, there is a ~4% of basal methylation in two zones of Grem1 CGI and Meep2 binds to several regions of the Grem1 CGI.

**Conclusions:** Our results strongly suggest that Meep2 epigenetically represses Grem1 expression by binding to a methylated CpG island in Grem1 promoter and coding gene. These results allow us to propose that an epigenetic mechanism underlies the induction of Grem1 gene expression in diabetic nephropathy development. Funding acknowledgement: PF/CECs 01/2007, FONDECYT 1160465, FONDECYT 1181574, CONICYT-PFCHA 21160495.

**Funding:** Government Support - Non-U.S.

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**TH-PO874**

**Comparison of Kidney Transcriptomic Profiles Between Patients with Early and Advanced Diabetic Nephropathy Reveals Potential New Mechanisms for Disease Progression**

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**Background:** Genome-wide gene expression profiling can be useful in providing a global picture of the disease pathogenesis and to identify potentially new biomarkers and drug targets for DN.

**Methods:** We performed RNA sequencing of the whole kidney biopsy samples from 28 patients with early DN (n=6), advanced DN (n=22) and normal kidney tissues (n=9) from nephrectomy samples. Correlation of differentially expressed genes (DEGs) with renal function (eGFR) and histological parameters in the DN patients was analyzed. We took advantage of the recently published sRNA-seq data to perform a computational deconvolution analysis of the gene expression data from whole kidney to estimate the contribution of each cell type in the differentially expressed genes (DEGs). We additionally performed a meta-analysis on the DEGs from different sequencing platforms to identify potential novel biomarkers and drug targets for DN.

**Results:** We found that a group of genes were upregulated at early DN but downregulated in late DN, many of which were shown to be renoprotective, including those in the retinoic acid and glucagon-like peptide-1 receptor (GLP1R) pathways. Another group of genes that were downregulated at early DN, but highly upregulated in advanced DN, consisted mostly of genes known to be involved in progression of DN, such as those related to immune response and fibrosis. We found that the DEGs in the pathways of iron transport and metabolism were positively associated with eGFR, while those in the immune response and fibrosis pathways were negatively associated. We also found that individual renal pathology features were associated with the DEGs belonging to the unique GO terms and pathways. We performed deconvolution analysis of the RNA sequencing data and found that the relative abundance of different cell types in DN by using recently published single-cell transcriptome datasets, which showed a significant increase in monocytes/macrophages, fibroblasts, and myofibroblasts in the kidneys from patients with advanced DN. Finally, we validated the expression of RBP4 and GLP1R and the markers of immune cells in the kidney of these patients using direct comparisons.

**Conclusions:** Our study provides potential molecular mechanisms for DN progression as well as the associations of DEGs with the functional and structural changes observed in patients with both early and advanced DN.

**Funding:** Government Support - Non-U.S.

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**TH-PO875**

**Bioinformatic Analysis of Kidney Transcriptome Sequencing from Patients with Diabetic Nephropathy Based on Different Sequencing Platforms**

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**Background:** Diabetic Nephropathy (DN) is one of serious complications of diabetes mellitus. The changes in kidney gene expression profile in patients with DN remain unclear. The field has seen studies of kidney transcriptome sequencing data from patients with DN using different sequencing platforms with varied results. Our aim is to combine those sequencing data and find the differentially expressed genes (DEGs) profile in the kidney of DN patients analyzed by bioinformatics and functional analysis.

**Methods:** The microarray data of human diabetic glomeruli and tubules were screened in GEO database. The selection criteria were as follows: 1. The samples include both DN tissue and normal ones; 2. The samples must be detected after the confirmation of diagnosis. DN tissue is not subject to other experimental biological factors. In total, 82 cases of glomeruli and 77 cases of kidney tubules, coming from GPL11670, GPL14663, GPL30122 platforms, were included to identify the DEGs. The contrast model is constructed on the DN and CTL data from the three platforms using limma function package in R software. We performed Bayesian Test according to contrast Model (Log FC < 1 and P < 0.05 were defined as DEGs). The results of gene intersection between different sequencing platforms were analyzed with STRING and DAVID on-line tools. Cytoscape was used to screen proteins with stable differential expression trend.

**Results:** There were 134 common DEGs with multiple sequencing platforms in the glomerular of DN patients which were enriched in the exosome process and Rap1 signaling pathway. Among them, 7 genes (WNT1,FGF9,IGF1,ALB,TIP1,EFG,BMP7) exhibited the most stable protein interaction. 20 genes show a consistent trend of differential expression in kidney tubule. Exosome process is the most enriched biological process in functional analysis. Moreover, 3 genes (LUM,THBS2,VCAN) exhibited the most stable interaction. We confirmed the expression of these genes in the human protein library (HPA) and verified the different expressions in the kidneys of DN patients by RT-qPCR.

**Conclusions:** DEGs of microarray data in glomeruli and tubules of DN patients are not the same. DEGs from different sequencing platforms are inconsistent. The function of common DEGs in different platforms may be more closely related to the pathogenesis of DN.

**Funding:** Other U.S. Government Support, Government Support - Non-U.S.

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**TH-PO876**

**Whole-Kidney 3D Imaging and Transcriptomic Assessement in the Unx db/db Mouse Model of Diabetic Nephropathy**

Frederikke E. Sembach, Brandon B. Boland, Lisbeth N. Fink, Urmas Roostalu, Jacob L. Skytte, Thomas Secher, Keld Fosgerau, Niels Vrang, Jacob Jelsing, Jacob Hecksher-Sørensen, Tanja X. Pedersen. Guba, Harsholm, Denmark.

**Background:** Diabetic nephropathy (DN) is associated with increased cardiovascular risk and shortened survival. The DN therapeutic landscape has remained almost completely unchanged for decades, largely due to the lack of transferrable preclinical models. In this study, we assessed renal changes in uninephrectomized (Unx) db/db mice using a combination of transcriptomic analysis and functional histology, in order to define the structural and functional changes associated with early progression of DN.

**Methods:** Unx was performed in 7-8 week old male and female db/db mice. Sham-operated db/db mice served as controls. Kidneys were preserved for histology, stereology, and RNA sequencing. In a separate study, Unx were performed in 18 week old male db/db mice. Mice were injected with lectin-594 immediately prior to termination to visualize glomerular morphology and to assess glomerular permeability via LSM. All mice were terminated at 24 weeks.

**Results:** Male and female Unx db/db mice showed similar progression of type 2 diabetes and urine albumin to creatinine ratio (UACR). Glomerular volume was increased in both genders relative to non-diabetic controls. Tubulointerstitial collagen III was increased in female Unx db/db vs. control mice, whereas glomerulosclerosis, as assessed by PAS and Podocin colocalization, was significantly increased in male Unx db/db mice. Kidney RNAseq revealed increased expression of the glomerular marker Nephr1 and the tubule markers Lcn2, Spp1, Haver1, confirming glomerular hypertrophy and kidney injury. Glomerular number was determined by LCM and subsequent stereological assessment of the same kidney sections as the mRNA expression analysis. Unx and control mice demonstrated similar glomerular numbers (~16,000), whereas Unx...
Early Changes in Urinary Transcriptomics and Proteomics in Streptozotocin-Induced Diabetes Model

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Background: Diabetic kidney disease (DKD) is a progressive and feared microvascular damage in diabetes patients. It is the leading cause of end-stage kidney disease (ESKD) globally. There is strong evidence that cellular insulin resistance is a major contributor to DKD.

Methods: To induce diabetes, one dose of STZ (50 mg/kg) was administered in the intraperitoneal cavity to fasted overnight. Urine and kidneys were collected as days 1, 7 and 15 post injection. Sections of cut kidney cortex were used to validate normal and RNA sequencing. For protein analysis, tissue was homogenized in 7M urea, 2M thiourea, 10x Genomics Chromium system. Results were correlated with kidney tissue pathology.

Results: 1 day after injection of STZ, an increase in serum glucose levels and urine volumes was detected in STZ treated groups as expected. Distinct differences between diabetic and control groups in regard to miRNA, mRNA, and proteins, respectively, were observed as early as day seven and also at day 15 post injection. At day 15, the gene enrichment analysis (GO: Biological process) of proteins reflected many known pathways involved in diabetes type II. These included pathways modulated at the onset of diabetes and involved in glucose homeostasis, glycolysis/gluconeogenesis and others. Analysis of transcriptional expression pattern was seen at each timepoint which should be very valuable to establish new molecular targets now available for verification in human DKD.

Conclusions: Our approach describes early molecular changes of DKD at transcriptomics and proteomics level. These results are valuable to define previously unidentifed pathways involved and novel molecular targets in DKD.

Diabetic Kidney Disease: Basic - I

MicroRNA-155 Upregulation Induces Podocyte Insulin Resistance: A New Therapeutic Target in Diabetic Nephropathy?

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Background: Loss of podocyte-specific insulin-sensitivity results in histological features of diabetic nephropathy (DN) in mice, implicating this pathway in disease development. MicroRNAs (miRNAs) regulate expression of most mammalian protein coding genes at the post-transcriptional level, and are critical regulators of insulin responses in “traditionally” insulin-sensitive tissues, liver, fat and muscle. The role of miRNAs in podocyte insulin-signalling is unknown. We hypothesise that miRNA-driven loss of podocyte insulin responsiveness is a key event in DN development.

Methods: Podocytes were rendered insulin-resistant by culture in diabeticogenic media containing high dose insulin, glucose and inflammatory cytokines. Microarray analysis was performed to compare miRNA expression profiles of wild type and insulin-resistant podocytes. Differential expression of selected miRNAs was validated by RT-qPCR. In vitro manipulation of differentially expressed miRNAs was achieved using miRNA mimics and inhibitors, and insulin responses assessed by Western Blot and tritiated glucose uptake assay.

Results: Differential expression of 103 miRNAs was detected. Five miRNAs were selected for a series of studies background

Conclusions: MicroRNA-155 is upregulated in podocyte insulin-resistance in vitro. Insulin-resistance may be affected by targeting this miRNA using inhibitors, which may have therapeutic potential in DN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

*Temp*
Exosome-mediated tubulointerstitial communication promotes renal fibrosis in diabetic kidney disease

**Jin Wen,1,2 Man J. Livingston,3 Wei Zhang,4 Chunyuan Guo,5 Yanggang Yuan,6 Ping Fu,7 Zheng Dong,8 Yongchuan Hospital of Chongqing Medical University, Chongqing, China; West China Hospital of Sichuan University, Chengdu, China; 4Augusta University Medical College of Georgia, Augusta, GA.**

**Background:** Renal tubular injury initiates fibroblast activation and drives overproduction of extracellular matrix, leading to renal fibrosis which is a final common pathway in progressive kidney diseases including diabetic kidney disease (DKD). However, it is unclear how injured tubular epithelial cells relay signals to neighboring fibroblasts and trigger the differentiation of fibroblasts to myofibroblasts. Recently, exosomes have been recognized as crucial mediators of intercellular communication. We hypothesized that exosomes might be involved in the communication between injured tubular cells and fibroblasts during the progression of DKD.

**Methods:** Exosomes were isolated from kidney tissues and mouse proximal tubular cells (MDCK cells) in response to angiotensin II (Ang II) + high glucose (HG). In co-culture experiments, MDCK cells were placed in the bottom chamber of a transwell and human renal fibroblasts were cultured in the top chamber. Exosome-mediated signaling was assessed using an ELISA-based cytokine array, real-time polymerase chain reaction (RT-PCR), western blot, and immunofluorescence (IF). A total of 107 metabolic features were identified by MALDI-MSI in mouse kidney tissue samples.

**Results:** We found that MDCK cells significantly increased the production of exosomes in response to Ang II + HG, which was accompanied by upregulation of exosome-related genes (e.g., ABCA1, ABCG1). Exosomes isolated from Ang II + HG-treated MDCK cells increased the production of TGF-β1 and collagen Iα1 (Col1α1) in fibroblasts. Moreover, exosomes isolated from Ang II + HG-treated MDCK cells expressing higher Levels of PGE2 and S1PR1 increased the production of TGF-β1 and Col1α1 in fibroblasts, indicating a positive feedback loop between exosomes and fibroblasts.

**Conclusions:** These findings suggest that exosomes play a crucial role in the development of diabetic kidney disease by mediating intercellular communication between injured tubular cells and fibroblasts, ultimately contributing to the progression of renal fibrosis. The study also highlights the importance of studying exosome-mediated signaling in the context of diabetic kidney disease.
Conclusions: The metabolic function of PTEC and their response to sex hormones are impaired in cell sex. Male PTEC show higher glycolysis, oxygen consumption, and respiratory capacity than female PTEC. These differences are related to increased oxidative stress and apoptosis, and to enhanced AR and SRY expression. In male PTEC, DHT-induced protein changes are linked to a more glycolytic and oxidative phenotype, higher glucose consumption, oxidative stress, apoptosis, and H-6-MCP1 secretion.

TH-PO886
Alteration of Tryptophan-Kynurenine Metabolites in the Serum and Kidney in Diabetic Nephropathy
Shoko Matsushita, Kazuo Takahashi, Ryosuke Umeda, Naotake Tsuobi, Kazuhito Sakagami, Kanako Kumamota, Masanori Kugita, Hidetsugu Fujigaki, Akihito Mouri, Yasuko Yamamoto, Toshitaka Nabeshima, Mitsushi Setou, Shizuo Nagao, Kunici Saito, Yukio Yuzawa, Fujita Health University, Toyoake, Japan; Hamamatsu University School of Medicine, Hamamatsu, Japan.

Background: It has recently been suggested that several metabolic pathways associated with diabetes interact to influence systemic function, humoral response, and chronic inflammation, contributing to complications of diabetes. Tryptophan-kynurenine (TRP-KYN) metabolites play a vital role in several physiological and pathological conditions including diabetes. However, the contribution of TRP-KYN metabolites to the pathogenesis of diabetic nephropathy has not been established. Metabolomic data analysis was used to detect pathways of systemic interaction associated with the pathogenesis of diabetic nephropathy. We identified that TRP-KYN metabolism was one such pathway that contributed to the progression of diabetic nephropathy.

Methods: To identify TRP-KYN metabolites associated with diabetic nephropathy, we analyzed serum, urine, and tissue levels of TRP-KYN metabolites in a animal model of diabetic nephropathy using un-nephrectomized spontaneously diabetic Torii fatty rats on 0.3% salt supplementation. Distinctive TRP-KYN metabolites in the kidney were analyzed using matrix-assisted laser desorption/ionization imaging mass spectrometry. Finally, we identified serum TRP-KYN metabolites in patients with diabetic nephropathy prone to ESRD.

Results: Profiling of TRP-KYN metabolites in a diabetic nephropathy revealed activation of the KYN pathway and accumulation of metabolites in kidney tissues. Changes in levels of TRP-KYN metabolites were also observed in patients with diabetic nephropathy. Additionally, the concentration of some metabolites was related to the severity of proteinuria, percentage of glomerular sclerosis, and grade of interstitial cellular infiltration.

Conclusions: Changes in the profile of TRP-KYN metabolites were observed both in animal models and in patients with diabetic nephropathy progressing to ESRD.

Funding: Government Support - Non-U.S.

TH-PO887
Impact of Angiotensin Receptor Blockade on Metabolic Profiles in a Mouse Model of Diabetic Nephropathy
Kengo Azushima, Jean-Paul Kovalik, Jianhong Ching, Susan B. Gurley, Thomas M. Coffman. Cardiovascular and Metabolic Disorders Program, Duke-NUS Medical School, Singapore, Singapore; Medical Science and Cardiovrenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan; Oregon Health and Science University, Portland, OR; Duke University Medical Center, Durham, NC.

Background: Changes in energy metabolism have been associated with susceptibility to diabetic nephropathy (DN). Blockade of the renin-angiotensin system (RAS) is renoprotective in DN, but effects of RAS inhibition on metabolic profiles in DN have not been clearly defined. To investigate this issue, we carried out metabolomics profiling to identify metabolic alterations occurring in the early stages of diabetic nephropathy using uni-nephrectomized spontaneously diabetic Torii fatty rats. The concentrations of TRP-KYN metabolites may be associated with the progression of diabetic nephropathy.

Results: Profiling of TRP-KYN metabolites in an animal model of diabetic nephropathy revealed activation of the KYN pathway and accumulation of metabolites in kidney tissues. Changes in levels of TRP-KYN metabolites were also observed in patients with diabetic nephropathy. Additionally, the concentration of some metabolites was related to the severity of proteinuria, percentage of glomerular sclerosis, and grade of interstitial cellular infiltration.

Conclusions: Changes in the profile of TRP-KYN metabolites were observed both in animal models and in patients with diabetic nephropathy progressing to ESRD.

Funding: Government Support - Non-U.S.

TH-PO889
Selection of Suitable Housekeeping Genes for Mesangial Cell Studies with High Glucose and Angiotensin II Receptor Blocker
Riccardo Tomasso, Ana C. Anauate, Mariana R. Boim. Nephrology Division, Universidade Federal de São Paulo, São Paulo, Brazil.

Background: Real-time PCR (qPCR) is currently the gold standard method to gene expression studies. Identification of the best reference gene is a key point to provide high quality qPCR, being able to provide strong support for results, as well as acting as a source of bias when inappropriately chosen. Mesangial cells (MC), as an essential cell line in diabetic kidney disease (DKD) pathophysiology, demand accurate analysis of the most excellent housekeeping (HK) gene to enhance validity of gene expression studies, especially regarding high glucose (HG) and DKD treatments, being angiotensin II receptor blockers (ex. Losartan) the most commonly used. Our objective was to evaluate the suitability and define the most stable reference gene for MC studies of an in vitro DKD model of disease and its treatment.

Methods: Five software packages (RefFinder, NormFinder, GeNorm, Bestkeeper, and DataAssist) and the comparative ΔCt method were used to analyze six different candidate genes: HKT, ACTB, PGAM-1, GAPDH, PPIA, and B2M. RNA was extracted and cDNA was synthesized from immortalized mouse MC cultured in 4 groups: control (n=5; 5mM glucose), mannitol (n=5; 30mM, as osmotic control), HG (n=5; 30mM glucose), and HG+Losartan (n=5; 30mM glucose and 10-4 M of losartan). qPCR was performed according to MIQE guidelines in QuantStudio 7Flex (Applied Biosystems).

Results: HKT presented higher stability values in RefFinder, ANOVA method, and NormFinder softwares (Table 1), while frequently used HK such as GAPDH and ACTB showed lower scores compared to HKT.

Conclusions: This analysis provides support to the use of HKT as a HK gene in mouse mesangial cell studies of gene expression via qPCR technique.

Funding: Government Support - Non-U.S.
Ranking of the candidate reference genes by each method used. Lower values indicate higher stability in gene expression. SD, standard deviation; CV, coefficient of variation.

*Best reference genes analyzed by NormFinder considering the intra- and intergroup variations.

TH-P0890
A Comprehensive Bioinformatics Analysis Reveals the Pivotal Role of Tubulopathy in Diabetic Nephropathy
Leting Zhou, Xiaobin Liu, Zhijian Zhang, Xiran Zhang, Jin Xue, Lin Liu, Liang Wang, Zuxing Sun. Wuxi People’s Hospital affiliated to Nanjing Medical University, Wuxi, China.

Background: Diabetic nephropathy (DN) is one of the main causes of ESKD worldwide. However, there is still a lack of a comprehensive understanding of the unique molecular mechanism of DN.

Methods: Over 250 Affymetrix microarray datasets of human glomerular and tubulointerstitial tissues were collected (Table 1). Next, a linear model was constructed, and the empirical Bayes method was used to select the unique differentially expressed genes (DEGs) of DN. The DEGs were further analyzed using the enrichment analysis. Finally, the protein-protein interaction networks (PINs) with established physical interaction were constructed, and based on the networks, hub genes were selected.

Results: A total of 980 unique DEGs were identified. Enrichment analysis revealed that a wide array of pathways are dysregulated in the pathogenesis of DN. Notably, the upregulated DEGs of tubulointerstitial compartment are mainly enriched in pathways that a wide arrange of pathways are dysregulated in the pathogenesis of DN. Notably, the protein-protein interaction networks were constructed, and based on the networks, hub genes were selected.

Conclusions: This bioinformatic analysis suggests that tubulopathy might play a pivotal role in the pathogenesis of DN.

Funding: Government Support - Non-U.S.

Table 1

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Pathway analysis of upregulated(A) and downregulated(B) DEGs in tubulointerstitial compartment

TH-P0891
Small RNA Sequencing Identifies Circulating sncRNAs That Are Differentially Expressed in Type 1 Diabetic Patients at Risk of Progressive Renal Decline
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Background: Progressive renal decline is the fundamental disease process that underlies the development of end-stage renal disease (ESRD) in Type 1 diabetes (T1D). Work by our group and others has demonstrated that microRNA (miRNA) expression profiles are altered in T1D patients with diabetic nephropathy. In the present study, we used small RNA sequencing (sRNA-Seq) to identify circulating small non-coding RNAs (sncRNAs), non-coding regulatory RNAs typically 18-200 nucleotides in length, that are associated with progressive renal decline in T1D patients with normal renal function (eGFR > 60 ml/min per 1.73m²) from the Joslin Kidney Study (J KS).

Methods: sRNA-Seq was used to determine circulating sncRNA expression profiles in baseline plasma specimens obtained from two sub-groups of patients who were followed for 5-10 years from entry to the JKS: 76 rapid progressors, who experienced significant loss of renal function over the course of their follow-up (eGFR slope = -12.61 ml/min/1.73m²/year), and 70 non-progressors, who experienced minimal decline in eGFR during their follow-up (eGFR slope = -1.43 ml/min/1.73m²/year).

Results: Differential expression analysis identified more than 50 sncRNAs, including miRNAs, small nucleolar RNAs (snoRNAs), and small nuclear RNAs (snRNAs), that were significantly differentially expressed among rapid progressors and non-progressors, including miR-3168 (P = 8.7x10⁻¹⁰), SNORD36C (P = 1.1x10⁻⁰⁸), and SNORD30 (P = 3.7x10⁻¹⁰). Interestingly, we also found miR-3168 to be differentially expressed in an independent cohort of non-progressors and rapid progressors with impaired renal function from the JKS (P-value = 0.0006).

Conclusions: These data suggest that sncRNAs, including miR-3168, SNORD36C, and SNORD30, may be able to distinguish diabetic individuals who are at the greatest risk of losing renal function from those who are protected against these complications. The differentially expressed sncRNAs identified in this study represent novel therapeutic targets that may prove useful in inhibiting renal function decline in T1D.

Funding: NIDDK Support

TH-P0892
A Novel Deep Learning Model Outperforms Cox Regression Model to Predict Renal and Cardiovascular Risk in Patients with Diabetic Kidney Disease
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Background: Predicting long-term risk in patients with type 2 diabetes and chronic kidney disease is important in clinical practice. We hypothesize that by using short-term dynamic changes in clinical characteristics, deep learning algorithm can accurately predict long-term renal and cardiovascular risk.

Methods: In total 3228 patients with type 2 diabetes and chronic kidney disease from two randomized controlled trials were used in this study: RENAAL (= 1513), IDNT (= 1715). IDNT were used to construct a 2D convolutional neural network (CNN) to predict renal (doubling of serum creatinine and/or end-stage renal disease) and cardiovascular (CV; myocardial infarction, stroke and cardiovascular death) outcomes. We compared the prediction performance with a traditional Cox proportional hazard regression (Cox) model. Eighteen clinical characteristics from baseline until 6 months follow-up were used as predictors to train the model on RENAAL data. The model was then externally validated on the IDNT trial. The area under the receiver operator curve (AUC) was used to assess the performance of the CNN and Cox model in the IDNT trial.

Results: A total of 462 (27%) and 518 (30%) of patients in IDNT experienced a renal or CV outcome respectively during a median follow-up of 2.6 years. The AUC of the CNN model, including UACR, HbA1c, SBP, albumin and uric acid as important predictors, was significantly higher compared to the Cox regression model (figure) and obtained the state-of-the-art performance to predict the long-term renal and CV outcome respectively during a median follow-up of 2.6 years. The AUC of the CNN model, including UACR, HbA1c, SBP, albumin and uric acid as important predictors, was significantly higher compared to the Cox regression model (figure) and obtained the state-of-the-art performance to predict the long-term renal and CV outcomes.

Conclusions: Using 6-month short-term dynamic changes in clinical characteristics, a deep learning algorithm identifies patterns to accurately predict long-term renal and CV risk. The proposed method offers the potential to create accurate and automated risk predictions model to identify high-risk patients who could benefit from intensified therapy.

The performance comparison (mean AUC ± standard deviation) of CNN and Cox model for the prediction of renal and cardiovascular risks.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Inhibition of Yap/Taz Ameliorates Renal Fibrosis in Type 2 Diabetic Mice. The p21-Mediated and Senescence-Associated Hyperglycemic Memory in Diabetic Nephropathy Is Therapeutically Amenable

Background: Diabetic nephropathy (DN) is a major cause of end-stage renal disease. A major challenge in DN is the failure of renal recovery upon improved blood glucose levels. It is now understood that the memory underlying the metabolic memory, remains unknown. We aimed to identify mechanisms contributing to the metabolic memory in DN.

Methods: Two mouse models with established DN (16 weeks after STZ-induced persistent hyperglycemia or 16 weeks old db/db mice) were used. Blood glucose was normalized for 6 weeks using an SGLT2-inhibitor. An unbiased approach (mRNA-seq) was used to establish pathways involved in metabolic memory. Candidate genes were studied in human diabetic patients and mice after lowering blood glucose. In vitro and in vivo studies were conducted to determine mechanistic and translational relevance.

Results: Despite a marked reduction of blood glucose levels, albuminuria and glucose induced changes in renal gene expression persisted, enabling to study mechanisms contributing to metabolic memory. P3K-kinase-Akt signaling, cellular proliferation and senescence, and complement-coagulation cascades were linked with metabolic memory. Sustained tubular expression of p21—a senescence-associated cyclin-dependent kinase inhibitor—was confirmed in humans (histology, urinary p21) and mice (histology, RNA, protein) despite blood glucose lowering. Sustained p21 expression was linked with promoter demethylation and reduced DNMT activity and DNMTI expression. In silico and in vitro analyses identified miR-148a as a potential regulator of DNMT1. The nephroprotective zymogen protein C was among the genes persistently repressed in DN. Increased tubular senescence, interstitial fibrosis, and albuminuria was confirmed in diabetic mice with a superimposed genetic deficiency of protein C activation. Substituting the protease activated protein C (APC), mimicking biased aPC-signaling (paranmodulin-2), or reducing miR-148a in addition to normalizing blood glucose reversed sustained tubular p21 expression, senescence, and renal damage in DN.

Conclusions: Epigenetically sustained p21-expression and associated senescence contribute to the metabolic memory in DN. This regulatory mechanism can be targeted by inhibiting miR-148a or by mimicking cytoprotective aPC-signaling.

Funding: Government Support - Non-U.S.

Inhibition of Yap/Taz Ameliorates Renal Fibrosis in Type 2 Diabetic Mice

TH-PO893

The p21-Mediated and Senescence-Associated Hyperglycemic Memory in Diabetic Nephropathy Is Therapeutically Amenable

Shrey Kohli,1,2 Moh’d Mohanad A. Al-Dabet,1,2 Ahmed Elwakil,1,2 Ihsan K. Gadi,3 Alba Sulja,3 Chris Dockendorff,4 Peter R. Mertens,4 Berend H. Isermann,1,2 Institute of Clinical Chemistry and Pathobioclinics, Otto-von-Guericke University, Magdeburg, Germany; 1Institute for Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, Leipzig University, Leipzig, Germany; 2University Hospital Heidelberg, Heidelberg, Germany; 3Marquette University, Milwaukee, WI; 4Department of Nephrology, Hypertension, Diabetes and Endocrinology, Otto-von-Guericke-University, Magdeburg, Germany.

The expression of p21 was determined in human renal proximal tubule cells obtained from 18 patients with early or advanced DN and in normal renal tissues from patients with renal-cell carcinoma. Effects of TUG-891 on development of DN was investigated in male C57BLKS/J db/db mice and podocytes. TUG-891 was administrated by oral treatment at 15 mg/kg/day for 4 weeks or every other day for 4 weeks. Murine podocytes (MPC5) were cultured in high glucose (30mmol/L) and with TUG-891 (10umol/L). Collagen type 4, fibronectin, αSMA and TGF-β/αsmad2/3 were examined in vivo and in vitro. Furthermore, GPR120/β-arrestin2/TAK1 binding protein-1 pathway was measured.

Results: Decrease levels of p21 were detected in renal tissues from patients with DN. The intensity of p21 staining was negatively correlated with the progression of the disease. In db/db mice, administration of GPR120 agonist, TUG-891, attenuated urinary albumin excretion and delay the extent of glomerulosclerosis and tubulointerstitial fibrosis. Renal fibronectin, collagen type 4 and TGF-β/αsmad2/3 expressions were reduced by TUG-891. Nevertheless, GPR120 and β-arrestin2 expression were increased after TUG-891 treatment. The coexpression of p21 and nephrin were detected in kidney. In high-glucose treating murine podocytes (MPC5), TUG-891 decreased the subsequent expression of collagen type 4, fibronectin, αSMA and TGF-β/αsmad2/3. It upregulated expression of GPR120 and β-arrestin2, suppressed the downstream TAK1/IKK/JNK/NFκB signaling pathway of TAK1 binding protein-1, thus restored podocytes dysfunction.

Conclusions: Our results show that TUG-891 ameliorates kidney fibrosis and podocyte injury by activating the intracellular GPR120/β-arrestin2/TAK1 binding protein-1 pathway, which suggests its efficacy for treating type 2 diabetes associated DN.

Funding: Government Support - Non-U.S.

Angpt4 Is a Critical Mesenchymal Inducer That Contributes to Renal Fibrosis

Angpt4 Is a Critical Mesenchymal Inducer That Contributes to Renal Fibrosis

Shwamy P. Srivastava, Julie Goodwin. Yale University School of Medicine, New Haven, CT.

Background: Kidney fibrosis is characterized by excess deposition of extracellular matrix leading to renal function deterioration and kidney injury. Several angiopoietin-like proteins (ANGPTLs) regulate lipid metabolism in the kidneys. However, the role of angiopoietin-4 like-4 (ANGPTL4) protein has not been explored yet. We hypothesized that loss of ANGPTL4 would be protective against renal fibrosis.

Methods: Two mouse models were used to recapitulate renal fibrosis. In one model, a single subcutaneous streptozotocin (STZ) was used to induce diabetes and diabetic nephropathy in global Angpt4 knockout mouse (ANGPTL4 KO) mice and wild-type littermates; mice were monitored for 4 months post-STZ. In the second model, the surgical procedure of unilateral ureteral obstruction (UUO) was used to induce renal fibrosis in 10-week-old global ANGPTL4 KO mice and wild-type littermates. Interstitial fibrosis was analyzed by Masson’s trichrome staining of the kidneys. Immunofluorescent staining of kidney tissue for mesenchymal markers was also performed. Blood glucose, kidney weight, and severity of proteinuria as measured by albumin-to-creatinine ratios were measured in animals subjected to both models. One way Anova with Tukey’s post-test was performed for the analysis of statistical significance.

Results: At the time of sacrifice, diabetic global ANGPTL4 KO mice did not show any significant difference in blood glucose compared to controls. However, kidney weight (+14.5%), collagen deposition (-5.5%), and albumin-to-creatinine ratios (-5.9%) were significantly lower in global ANGPTL4 KO mice when compared to wild-type controls (n=6; genotype; p<0.05). Similarly, in the UUO model, we observed that the UUO-operated kidneys of global ANGPTL4 KO mice showed less collagen deposition (-48.9%) and interstitial fibrosis (-45.2%) when compared to those of the controls (n=7; genotype, p<0.05). Immunofluorescence analysis of kidney tissue from both genotypes revealed suppression of fibronectin and collagen-1 deposition in global ANGPTL4 KO mice compared to controls, in both models, suggesting suppression of mesenchymal activation.

Conclusions: We conclude that ANGPTL4-associated mesenchymal activation is critical for disruption of kidney homeostasis and contributes to renal fibrosis.

Funding: Government Support - Non-U.S.
expression and increased pro-fibrotic signaling in the kidney. Current studies identified signaling mechanisms by which TGF-β regulates target cell surface response in vivo to HFLC diet and leads to renal fibrosis which may lead to generation of new therapies.

**Methods:** HK-11 cells were treated with 10 ng/ml of TGF-β for 24 h or pre-treated with p38 and ERK inhibitors MG132 (0.125 μM, 0.25 μM, 0.5 μM and 1 μM) for an hour prior to treatment with TGF-β. Cell lysates were immunoblotted with appropriate antibodies. HK-11 cells were transfected with pSer vector/pSerNF-E2 or with control siRNA or NF-E2 siRNA for 24 h followed by treatment with vehicle or TGF-β for additional 24 h. Kidney tissues were collected with appropriate antibodies. Kidney homogenates from STZ-type 1 diabetic mice, OVE26 type 1 diabetic mice treated with vehicle/MG132, and db/db type 2 diabetic mice, were immunoblotted with appropriate antibodies.

**Results:** NF-E2 expression was decreased in kidney homogenates from STZ, OVE26, and db/db cells pre-treated with TGF-β for 24 h; treatment with TGF-β for additional 24 h. Kidney tissues were collected with appropriate antibodies. Kidney homogenates from type 1 diabetic mice were treated with TGF-β for 24 h. Cell lysates were immunoblotted with appropriate antibodies. Kidney homogenates from STZ-type 1 diabetic mice, OVE26 type 1 diabetic mice treated with vehicle/MG132, and db/db type 2 diabetic mice, were immunoblotted with appropriate antibodies.

**Conclusions:** Blockade of p38 and MEK/ERK pathways and proteinasal activation during diabetes and TGF-β treatment of HK-11 cells prevents NF-E2 degradation and attenuates pro-fibrotic signaling in kidney cells.
15.6% cornstarch, 15.5% alpha-cornstarch, 4% soybean oil. All other dietary ingredients were then mixed together (100g/kg body wt) was injected at 17 and 18 weeks of age. Fasting blood glucose (FBG) was measured before and after STZ injection. After termination, kidneys were obtained for histology.

**Results:** Terminal body weight, total intake of food and energy, and serum creatinine level were not different between all groups. FBG was higher in HFLC but not in NFHS compared with CONT mice both before (at 17 weeks of age) and after STZ injection (at 20weeks of age). In kidney, the number of LAMPI (lysosome-associated membrane protein 1)-positive vacuoles was significantly higher in HFLC compared with CONT and NFHS mice.

**Conclusions:** The present results suggest that the high fat diet, but not the high sugar diet, induces renal injury with impaired lysosome-mediated autophagic degradation, when total energy intake is identical in pre-diabetic mice.

**Funding:** Government Support - Non-U.S.

**TH-PO902**

**Targeting the Gut-Kidney Axis Through Dietary Modification in Experimental Diabetic Nephropathy**

Yan J. Li,1 Xiaochen Chen,1 Yik W. Loh,1 Jian Tan,2 Laurence Macia,3 Stevenson of palm,1 Huling Wu,1,3 Kidney Node, Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia; 2Renal Medicine, Royal Prince Alfred Hospital, Sydney, Australia; 3Nutritional Immuno-metabolism Laboratory, University of Sydney, Sydney, NSW, Australia.

**Background:** Dietary fibre has been associated with decreased inflammation and mortality in CKD, with short-chain fatty acids (SCFA) derived from gut microbial fermentation of fibre proposed to mediate this effect. Here we explore the impact of dietary fibre content on the development of experimental diabetic nephropathy (DN).

**Methods:** Diabetics was induced using streptozotocin (STZ) in wild-type (WT) B6 and GPR43/-/- mice. Diabetic mice were randomized to 4 diets; resistant starch (RS), high fibre (HF), zero fibre (ZF), control diet (NF), or supplemented with oral SCFAs (acetate 150mM, propionate 100mM, butyrate 50mM). Gut microbiota composition was assessed by 16S rRNA sequencing of fecal DNA.

**Results:** All STZ treated mice developed diabetes and remained similarly hyperglycaemic. HF and RS fed mice were protected from DN, with reduced albuminuria (p<0.01), glomerular hyper trophy (p<0.001), interstitial fibrosis (p<0.001) and podocyte injury (p<0.01) reduced to those in NF and ZF. Diet markedly altered gut microbial composition by weighted UniFrac, with cluster separation of diabetic mice according to diet (ANOSIM p=0.0001, R=0.93). HF and RS feeding increased relative abundance of phylum Bacteroidetes at the expense of Firmicutes and expanded the SCFA acetate (p<0.001) and Propionate (p<0.001) pathways compared to controls. This change in microbial ecology correlated with a significant increase in faecal SCFAs and serum acetate. Supplementation with SCFAs in diabetic mice achieved similar degrees of protection from albuminuria and histological injury. Acetate reduced expression of NFκB and increased activation of two gut barrier ligases, atrogin-1 and murf-1. The levels of urinary L-FABP and the degree of renal tissue TBARS (indicative of liperoxidation) (232.3±7.2 vs 282.0±4.82 vs 45.42±3.0) and urinary TBARS (indicative of lipoperoxidation) (232.3±28.83 vs 282.0±7.2) when compared with untreated ones.

**Funding:** Our data suggest that decreased P2X2, perhaps via increasing Klotho, could be one of possible pathways for esculin to promote beneficial effects on the kidneys of diabetic animals.

**Funding:** Government Support - Non-U.S.

**TH-PO904**

**The Effect of A1AR on Diabetic Megalin Loss-Associated Albuminuria by Inhibiting Caspase-1/IL8 Signaling**

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**Background:** The mechanism of exacerbation of albuminuria observed in A1 adenosine receptor knock-out (A1AR-) mice with diabetic nephropathy (DN) is unclear. Here, we investigated the relationship of megalin loss and albuminuria, to identify the effect of A1AR in the pyroptosis signaling caspase-1/IL-18 of DN.

**Methods:** Successfully collected diabetic nephropathy patients’ samples and built streptozotocin-induced diabetes mice model. Megalin, cubulin, and A1AR expression were detected in kidney samples from DN patients and mice through immunohistochemical and immunofluorescent staining. A1AR, caspase-1, Interleukin -18 (IL-18) expression were analyzed using western blotting in wild-type and A1AR mice. Human renal proximal tubular epithelial cells (PTC) were cultured with high glucose to observe the effect of A1AR agonist and antagonist on caspase-1/IL-18 and megalin injury. The loss of megalin, co-localized with A1AR at PTC, was associated with the level of albuminuria in diabetic patients and mice. The injury of megalin-cubulin was accompanied by the A1AR upregulation and the caspase-1/IL-18 signaling activation in mice with DN. More severe pathologic injury, albuminuria, and megalin-cubulin loss were observed in A1AR-/- DN mice with more pronounced caspase-1 and IL-18 secretion. High glucose could stimulate the secretion of caspase-1 and IL-18, which was completely abolished by A1AR agonist and further aggravated by A1AR antagonist.

**Conclusions:** A1AR played an important role in protecting megalin loss associated albuminuria by inhibiting the pyroptosis signaling caspase-1/IL-18 in DN.

**Funding:** Government Support - Non-U.S.

**TH-PO905**

**Urinary L-FABP Reflects the Degree of Sarcopenia in a Diabetic Kidney Disease Model**

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**Background:** Diabetic kidney disease (DKD) is a high-risk factor for onset of sarcopenia which leads to increase in all-cause mortality in patients with type 2 diabetes. Although the sarcopenia in DKD should be focused just before a super-aging society, there had not been a useful biomarker for monitoring the sarcopenia. The aim of this study is to reveal the correlation between urinary L-type fatty acids binding protein (L-FABP) known as a tubular marker and sarcopenia using novel model of DKD with sarcopenia.

**Methods:** Male spontaneously diabetic tori (STZ) fatty rats (n = 5) were used as an animal model of type 2 diabetes with sarcopenia. Age- and sex-matched Sprague–Dawley rats (SD) (n = 7) were used as controls. Urine samples were obtained from the rats at 8, 12, 16, 20, and 24 weeks of age. Their kidney, and soleus and extensor digitorum longus (EDL) muscles were obtained at 24 weeks of age.

**Results:** Urinary L-FABP increased and muscle strength decreased along with age in the SDT rats. Renal tissue damage and accumulation of renal oxidative protein were observed at 24 weeks of age of the SDT fatty rats. Muscle weight, and cross-sectional areas of both type I and type IIb muscle fibers were significantly decreased in the SDT fatty rats compared to the SD rats. The muscle atrophy in the SDT fatty rats was induced due to decreased phosphorylation of 56k1 and increased expression of E3 ubiquitin ligase MuRF-1 and atrogin-1. The levels of urinary L-FABP and the degree of renal tissue damage were significantly correlated with muscle weight, diameter of muscle fibers and muscle strength.

**Conclusions:** Urinary L-FABP increased along with the progression of sarcopenia and the degree of sarcopenia in DKD. In clinical practice, urinary L-FABP may be useful for monitoring the sarcopenia as well as DKD in the type 2 diabetic patients.

**Funding:** Government Support - Non-U.S.
Diabetic Kidney Disease: Basic - I

Cindy Ralf Laura

Intercalated Cells

Insulin Resistance Impacts the Host Defense Transcriptome in Kidney

TH-PO906

glomerular apoptosis was observed in Alk1Δ and induces podocyte loss. Alk1 haploinsufficiency also increases extracellular matrix

patients biopsies were compared with patients already diagnosed with diabetic nephropaty

serological analyzes were performed, along with immunohistochemical studies. Healthy

mice. Mice were euthanized four months after the onset of diabetes and urine and

Enrichr tool and DA VID.

p

expressed genes (DEG) using the R package edgeR. DEGs with fold-change >1.5 and

was performed on FACS-isolated ICs and read count data were analyzed for differentially

 sorting (FACS) of ICs and visualize IC-specific Cre-recombination. Limited cell RNAseq

in vivo

pH, releasing cytokines, secreting antimicrobial peptides (AMPs), and creating a barrier

populations have increased UTI risk, including those with insulin resistance and diabetes.

These studies may uncover new immune targets to prevent/treat diabetes-

resistance, and adipocytokine signaling. Gene ontology terms involved in innate immunity

upregulation of 232 genes in IRKO IC vs IRflox IC. A decrease in

in vivo

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mRNA and protein levels compared to normal glucose cultured podocytes. Isolated podocytes from diabetic (Leprdb/db) mice had increased ARF6 expression compared to control (Lepr+/-) mice. Furthermore, podocyte-specific ARF6KO mice had decreased uric acid to creatinine ratio (UACR). To determine whether ARF6 might serve as a molecular target for pharmacological inhibition in DKD, diabetic mice were treated with an ARF6 inhibitor (NAV2729 or vehicle) at 8 weeks of age. NAV2729-treated diabetic mice demonstrated significant improvement in the UACR compared to diabetic mice treated with vehicle suggesting a renal-protective effect of ARF6 inhibition.

Conclusions: These results suggest that ARF6 is an important protein involved in podocyte health and DKD. Inhibition of ARF6 might serve as a molecular target to prevent podocyte injury, albuminuria, and progressive renal functional decline.

Funding: NIDDK Support, Private Foundation Support

TH-PO909

Akt/bmp9 Signaling as a New Target of Therapy in Diabetic Nephropathy

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Background: Diabetic kidney disease one of the most frequent microvascular long-
term complications in diabetic patients and is a major cause for the need of dialysis.

Currently therapies in diabetic nephropathy are focusing on glycemia control and adequate arterial pressure levels in order to maintain an adequate glomerular filtration rate. However, a few of them are targeting the endothelial damage or podocyte-endothelial crosstalk, which play a critical role in diabetic kidney disease progression. We have previously shown that Akt1, along with its ligand BMP9, plays an important function to maintain vascular integrity in diabetic animals. Loss of Akt1 signaling in diabetic animals led to dissociation ofvascular junctions and increased vascular leakage. Given its role in the maintenance of endothelial quiescence and integrity, we evaluated the effects of Akt1 suppression on kidney integrity and renal function in diabetic mice.

Methods: We used mice with conditional deletion of Akt1 in the endothelium (Akt1ΔEC) to evaluate the role of Akt1 in glomerular filtration in STZ-induced diabetic mice. We euthanized four months after the onset of diabetes and urine and serological analyses were performed, along with immunohistochemical studies. Healthy patients biopsies were compared with patients already diagnosed with diabetic nephropathy

Results: We demonstrated that Akt1 haploinsufficiency worsens microalbuminuria and increases podocyte loss. Akt1 haploinsufficiency also increases extracellular matrix expression at the glomerular basement membrane. Furthermore, a significant increase in glomerular apoptosis was observed in Akt1ΔEC mice. Analysis of homozygous Akt1ΔEC mice also revealed a significant loss of glomerular endothelial cells. Akt1 expression in the glomeruli was observed in patients diagnosed with diabetic nephropathy compared to the healthy patients.

Conclusions: 1. Partial loss of Akt1 in type I diabetic mice leads an increase in microalbuminuria compared to WT mice. 2. Heterozygous diabetic mice have an increase in glomerular injury and albuminuria, and Akt1 loss. 3. Partial Akt1 deficiency in diabetic mice induces an increase in extracellular matrix synthesis. 4. The Akt1 / bmp9 signaling could be a potential target of therapy because it plays a critical role in the maintenance of glomerular endothelial cells and has an important functions to maintain glomerular integrity through a crosstalk between podocytes and endothelial cells.

Funding: Clinical Revenue Support

TH-PO908

Deletion or Inhibition of ARF6 Improves Albuminuria in Type 2 Diabetic Mice

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Background: Podocytes are key glomerular cells that determine the progression of diabetic kidney disease (DKD), the leading cause of renal failure in the U.S. Small GTPase ARF6, which is activated in podocytes in response to in vivo glomerular injury, plays a role in podocyte cell-cell interactions. Since ARF6 is involved in diverse cellular events (e.g. actin remodeling or endocytic trafficking) we hypothesized that hyperglycemia might result in alterations in ARF6 activity and contribute to the progression of DKD.

Methods: To investigate the in vivo role of ARF6 in diabetes, we generated an inducible-cre-lox mutant diabetic animal model. We also explored whether pharmacological intervention of ARF6 using an ARF6 inhibitor, NAV2729 (R&D Systems), might recapitulate the observations from our aforementioned transgenic animal model.

Results: High glucose cultured podocytes expressed significantly higher ARF6 mRNA and protein levels compared to normal glucose cultured podocytes. Isolated podocytes from diabetic (Leprdb/db) mice had increased ARF6 expression compared to control (Lepr+/-) mice. Furthermore, podocyte-specific ARF6KO mice had decreased uric acid to creatinine ratio (UACR). To determine whether ARF6 might serve as a molecular target for pharmacological inhibition in DKD, diabetic mice were treated with an ARF6 inhibitor (NAV2729 or vehicle) at 8 weeks of age. NAV2729-treated diabetic mice demonstrated significant improvement in the UACR compared to diabetic mice treated with vehicle suggesting a renal-protective effect of ARF6 inhibition.

Conclusions: These results suggest that ARF6 is an important protein involved in podocyte health and DKD. Inhibition of ARF6 might serve as a molecular target to prevent podocyte injury, albuminuria, and progressive renal functional decline.

Funding: NIDDK Support, Private Foundation Support

TH-PO909

Activation of Notch Signaling in Podocytes by Growth Hormone

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Background: Growth hormone (GH) plays a significant role in normal renal function and overactive GH signaling has been implicated in nephropathy particularly in diabetes and obesity. Previous results have shown that podocytes, which play an essential role in kidney filtration, express the GH receptor (GHR), suggesting the direct action of GH on these cells. Activation of Notch signaling, which is crucial in early podocyte development, contributes to the glomerular disease upon maturation. In this study, we investigated whether GH activates Notch1 signaling in podocytes in γ-secretase dependent manner.

Methods: Swiss Webster male mice were infused with GH i.p (1.5mg/kg/day) for 4 weeks. Another group of mice was administered GH and DAPT (10 mg/kg/day) while control mice received PBS. Renal functional and histological studies were performed at the end of the experimental period. Simultaneously, human podocytes (HPC) were treated with GH (500ng/ml) in the absence or presence of DAPT (5µg/ml) and assessed the expression of Notch signaling and its downstream targets.

Results: Employing HPC in vitro and GH-injected mouse model in vivo, we demonstrate that GH activates Notch1 signaling in a γ-secretase-dependent manner in podocytes. Pharmacological inhibition of Notch1 by a γ-secretase inhibitor (DAPT) abrogated GH-induced epithelial to mesenchymal transition (EMT) and associated podocyte injury. Importantly, our results show that DAPT treatment blocked the GH-induced cytokine release and attenuated glomerulosclerosis. Further, DAPT prevented glomerular basement membrane thickening as well as proteinuria induced by GH. Kidney biopsy sections from diabetic nephropathy patients reveal activation of Notch signaling in podocytes.

Conclusions: GH induces Notch1 signaling in podocytes, which may contribute to proteinuria through podocyte EMT as well as renal fibrosis. Blocking Notch activation with γ-secretase inhibitors ameliorates glomerular injury and proteinuria in conditions of GH-associated nephropathy.

Funding: Government Support - Non-U.S.

TH-PO910

Empagliflozin as an Add-On to Linagliptin Ameliorates Renal Interstitial Fibrosis in Spontaneously Diabetic Tori Fatty Rats

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Background: Recent clinical trials have shown that SGLT2 inhibitor significantly attenuates the rapid decline in eGFR and enhances blood pressure control. Further, DPP4-inhibitor has become the first-line therapy of blood glucose control in patients with diabetic kidney disease (DKD). However, whether dual therapy could prevent the development and progression of DKD are yet to be elucidated. Therefore, we investigated the effects of

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Underline represents presenting author.

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empagliflozin as an add-on to linagliptin or vice versa on diabetes-induced renal injury in SDT fatty rats: a type 2 diabetic model of DKD.

Methods: Eight-week-old SDT fatty rats were divided into 5 groups, 1) SDT fatty rats untreated (SDT), 2) SDT fatty rats given 30 mg/kg of empagliflozin for 12 weeks (EMPA), 3) SDT fatty rats given 3 mg/kg of linagliptin for 12 weeks (LINA), 4) SDT fatty rats given empagliflozin for 6 weeks in addition with linagliptin for 6 weeks (EMPA-EMPA+LINA), and 5) SDT fatty rats given linagliptin for 6 weeks in addition with empagliflozin for 6 weeks (LINA-EMPA). All experimental groups were given water supplemented with 0.5% salt. All animals (20 weeks of age) were euthanized and parameters such as urine and blood chemistry, blood pressure (BP), renal pathology, and GFR were measured.

Results: At 14 weeks of age, SDT exhibited hypertension, which was not ameliorated in EMPA and LINA groups. However, at 20 weeks of age, BP decreased in all treated groups. Treatment with empagliflozin showed glycosuria and increased urinary sodium excretion. SDT showed albuminuria and glomerulosclerosis, which were not ameliorated in all the treated groups. Compared with SD, GFR was significantly higher in SDT, suggesting hyperfiltration, and it further increased in LINA. SDT manifested dramatically increased urinary L-type fatty acid binding protein levels, which were attenuated in LINA−LINA+EMPA (p<0.05 vs SDT). Besides, renal interstitial fibrosis was ameliorated in EMPA, EMPA−EMPA+LINA, and further reduced in LINA−LINA+EMPA, as evidenced by the Masson trichrome staining. Diabetes-associated interstitial TGF-β expression was inhibited only in LINA−LINA+EMPA (p<0.05 vs SDT).

Conclusions: Empagliflozin as an add-on to linagliptin might be a better therapy for diabetes-induced renal fibrosis than linagliptin as an add-on to empagliflozin and each drug.

TH-PO911 Stakeholder Perspectives on Implementing Precision Medicine in Diabetic Kidney Disease Michelle Pena1, Julia Czaja2, Joao M. Nabaïs2, Francesc Xavier Cos claramunt3, John J. Nolan4, Thorsten Vetter5, Matthias Kreutzler6, Maria F. Gomez7, Friedrich Schulze8, Dick de Zeeuw9, Hiddo L. Heerspink10, Peter G. Mol11, BEAT-DKD Consortium12 University Medical Center Groningen, Groningen, Netherlands; 2Associação Proteutora dos Diabéticos de Portugal, Lisboa, Portugal; 3Primary Care Diabetes Europe, Barcelona, Spain; 4European Diabetes Forum, Dublin, Ireland; 5European Medicines Agency, Amsterdam, Netherlands; 6U.Michigan, Ann Arbor, MI; 7Land University, Malmö, Sweden; 8Boehringer Ingelheim International GmbH, Ingelheim, Germany.

Background: One of the important aims of the Innovative Medicine Initiative BEAT-DKD consortium is to promote implementation of Precision Medicine (PM) in treating diabetic kidney disease (DKD). Engaging stakeholders is crucial in this process. We held a consensus workshop and conducted a survey of diabetes stakeholders to identify benefits and obstacles of PM, and to strategize solutions.

Methods: Seventy-one participants from 26 countries met in Amsterdam, the Netherlands over 2 days to develop a strategy to move PM forward in DKD. Represented stakeholder groups included patients with diabetes and advocates (n=11), academia (n=18), drug regulators (n=7), health technology assessors (HTAs)(n=6), industry (n=11), and health care providers (HCPs)(n=18). A survey was developed and pilot tested prior to implementation. Respondents were asked about their opinions on needs, benefits, and obstacles for introducing PM in DKD. A consensus discussion was held to strategize solutions.

Results: Stakeholders were mostly positive for PM in DKD (Figure). HTAs least agreed, while HCPs most agreed. Obstacles and concerns for PM included data safety, time constraints, and increased burden for assessments. Keys to successful implementation of PM would be increased engagement with patients, specific training for HCPs in PM, and early collaboration between stakeholders. All stakeholders responded that quality of life outcomes would be important to assess the impact of PM.

Conclusions: Diabetes stakeholders view PM in DKD positively. Implementing PM is complex as different stakeholders have different priorities. The consensus of all stakeholders was that early engagement and aligning stakeholders goals are critical to implement PM in DKD.

TH-PO912 Urinary Complement-Enriched Inflammatory Proteome of an Overt Progressive Diabetic Kidney Disease Salina Moon1, Heather L. Donsky2,3, John J. Tsay2,3, Edward P. Feenner,4 Simon T. Dillon,4 Monica A. Newczias,4 Jostin Diabetes Center, Boston, MA; 2Beth Israel Deaconess Medical Center, Boston, MA; 3KalVista Pharmaceuticals, Inc., Cambridge, MA; 4Harvard Medical School, Boston, MA.

Background: We aimed to advance our knowledge of the role of the local kidney proteome in the progressive diabetic kidney disease (DKD) reflected by the urinary profiles of the inflammatory proteome.

Methods: We conducted a nested case-control study comprising a discovery panel of Jostin subjects with T1D and a validation panel of Jostin subjects with T2D (total n=112). All study subjects had an overt DKD at baseline (CKD stage 3-4 and albuminuria (median GFR: 46 ml/min/1.73m²; median ACR: 653)). Subjects experiencing renal function loss of eGFR > 40% within 5 years were defined as progressive DKD cases. 194 inflammatory proteins were measured in baseline urine samples using aptamer proteomics (SOMAscan).

Results: In the multivariate screen we identified a urinary proteomic profile consistently associated with progressive DKD in T1D and T2D. Complement proteins (CPL) accounted for almost half of our profile (twelve out of 26 (46%); enrichment: p<0.001). Chemokines (CHK) comprised the second-most abundant group of our profile (enrichment: p-vs; Fig A - needleplot). In the adjusted mediation model (ACR - intermediate phenotype), all 26 proteins were associated with the renal slope. The protein effects were mainly independent from albuminuria (median proportion mediated (PM): 25%). One unit change in these proteins resulted in renal function loss between 1.5-7.3 ml/min/1.73m²/yr. These protein effects markedly correlated between the T1D and T2D panels (p<10^-6; Fig B - β estimates).

Conclusions: We have identified a significant urinary profile of the inflammatory proteome strongly associated with progressive DKD in subjects with an overt disease in both types of diabetes. Our data suggest that the complement system and chemokines seem to be important players of the disease process. Larger studies including subjects with early DKD are needed to evaluate the dynamic of these processes across DKD stages.

Funding: Private Foundation Support

TH-PO913 Proteomic Study of Circulating Proteins to Identify Novel Surrogate Markers for Progressive Renal Decline Jan Skupien1, Katsuhiro Ikara2, Zaipul 1 Md Dom2, Kristina V. O’Neil3, Andrzej S. Krolewski4, 5Jagellonian University Medical College, Krakow, Poland; 6Jostin Diabetes Center, Harvard Medical School, Boston, MA.

Background: Clinical trials of renoprotection in diabetic nephropathy have been limited to high-risk patients with impaired renal function due to low incidence of clinical and traditional surrogate end-points. End-points based on serum creatinine may be affected by its high variation, especially in patients with normal renal function. No efficient trial design exists to test early interventions in moderate-risk patients with eGFR > 60 ml/min.

Methods: We followed 196 patients (44% female) with type 1 diabetes from Jostin Proteinuria Cohort (median albumin/creatinine ratio 852 mg/g) with normal baseline renal function (median eGFR 100 ml/min). During median 10 years of follow-up there were 110 cases of end-stage renal disease (ESRD) and 15 deaths. We quantified 455 proteins in baseline plasma samples using OLINK (Uppsala, Sweden) Proximity Extension Assay. In 110 patients we measured these proteins in a second sample collected after median 4 years of follow-up. Annualized proteins’ increments (DELTA) were tested as surrogate of ESRD using Cox regression models.

Results: In regression models adjusted for the change in eGFR the DELTAS of 13 proteins were significantly (Bonferroni-corrected) associated with time to ESRD. Also, their baseline concentrations were associated with time to ESRD independently from eGFR. DELTAS of these proteins than with the change in eGFR (for example C-statistic for baseline eGFR. Surrogate outcomes derived from these candidate proteins may help designing efficient clinical trials. Replication of the findings in independent cohorts is under way.

Funding: NIDDK Support, Private Foundation Support
Candidate surrogate outcome proteins, adjusted for baseline GFR and DELTA of eGFR

**TH-PO914**

Multi-Omics Data Integration Identifies Molecular Pathways Associated with Renal Response to Atrasentan

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**Background:** The endothelin-1 receptor antagonist atrasentan lowers urinary albumin:creatinine ratio (UACR) and reduces renal risk in patients with type 2 diabetes and chronic kidney disease (CKD). This effect markedly varies among patients. Aim of this study was to identify molecular pathways and biomarkers predicting the renoprotective effect of atrasentan.

**Methods:** In vivo and in vitro transcriptomics profiling was performed in kidney tissue from atrasentan treated BTBR ob/ob mice and human mesangial cells respectively. A transcriptomic dataset from human diabetic kidney biopsies was used to calculate RPF.

**Results:** Here we seek to determine which MRI markers are independent predictors of mGFR and UACR. We here we seek to determine which MRI markers are independent predictors of mGFR and UACR.

**Methods:** Subjects: The study included 2 CKD2, 16 CKD3, and 20 CKD4 subjects with DKD, 18-79 years old, and 20 age- and gender-matched healthy controls. GFR was measured using iohexol clearance. MRI was previously used to measure FF in kidney samples, CKD3 and CKD4 (p < 0.0001), and CKD3 vs CKD4 (p < 0.05) using Bonferroni/Dunn multiple testing correction. Differences in FF in controls vs both CKD3 and CKD4 (p < 0.0001), and CKD3 vs CKD4 (p < 0.005) were significant.

**Conclusions:** Standard deviations in the CKD 2 group were relatively large as there were only 2 subjects in this group. All MRI FF comparisons between control healthy subjects and DKD subjects were statistically significant. This MRI FF measurement can be further improved by correcting RBF for extracellular volume in order to calculate RPF. References 1 Costanzo L. (2007) Physiology. Lippincott Williams and Wilkins; Philadelphia; 2 Eikefjord, et al AFR (2016) 207, 1022-1030; 3 Cutajar, et al. Eur Radiol (2015) 25: 2390.

**Funding:** Commercial Support - Atrasan Medical; AstraZeneca

**TH-PO915**

Magnetic Resonance Imaging Biomarkers Independently Predict GFR and Urine Albumin Creatinine Ratio

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**Background:** Filtration fraction (FF) is the ratio of the glomerular filtration rate (GFR) to renal plasma flow (RPF) and therefore an important marker of glomerular filtration. FF is not normally measured, as estimation of RPF requires constant infusion of para-aminohippurate over 8 h (1). Therefore, quicker, simpler assays of FF are needed. We assessed a novel magnetic resonance imaging (MRI) technique to measure FF in patients with type 2 diabetes and diabetic kidney disease (DKD). MRI was previously used to measure FF in kidney donors (2,3).

**Methods:** The study included 2 CKD2, 16 CKD3, and 20 CKD4 patients with DKD, 18-79 years old, eGFR between 15-60 ml/min/1.73 m² and 20 age-, gender-matched healthy controls. GFR was measured using iohexol clearance (mGFR). Renal blood flow (RBF) (ml/min) was measured by phase contrast MRI. The phase contrast MRI scan is a 5 minutes add-on to an MRI examination. MRI FF = (mGFR x BSA)/(RBF x 1.73) RBF was corrected for Body Surface Area (BSA) to use the same units as GFR. EVF (hematocrit) was not available and therefore RPF was not calculated.

**Results:** MRI FF % (Mean (SD)) was 8.28 (1.00) % for Healthy Controls; 6.57 (2.62) % for CKD2; 6.30 (0.93%) for CKD3; and 5.13 (1.36%) for CKD4. We tested for significant differences between groups (p = 0.05) using Bonferroni/Dunn multiple testing correction; p-values less than 0.05 were significant. Differences in FF in controls vs both CKD3 and CKD4 (p < 0.0001), and CKD3 vs CKD4 (p < 0.005) were significant.

**Conclusions:** Standard deviations in the CKD 2 group were relatively large as there were only 2 subjects in this group. All MRI FF comparisons between control healthy subjects and DKD subjects were statistically significant. This MRI FF measurement can be further improved by correcting RBF for extracellular volume in order to calculate RPF. References 1 Costanzo L. (2007) Physiology. Lippincott Williams and Wilkins; Philadelphia; 2 Eikefjord, et al AFR (2016) 207, 1022-1030; 3 Cutajar, et al. Eur Radiol (2015) 25: 2390.

**Funding:** Commercial Support - Atrasan Medical; AstraZeneca

**TH-PO917**

Prediction of Rapid Kidney Function Decline in Type 2 Diabetes Using Machine Learning Combining Blood Biomarkers and Electronic Health Record Data

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**Background:** Individuals with type 2 diabetes (T2DM) are at increased risk of rapid kidney function decline (RKFD). The application of machine learning to integrate biomarkers with EHR data may lead to improved prediction of RKFD.

**Methods:** We selected individuals with T2DM with a baseline eGFR ≥85 and <90 ml/min/1.73 m² from the Mount Sinai BioMe Biobank (n=871). We measured plasma levels of tumor necrosis factor (TNFR)1 & 2, and kidney injury molecule(KIM)-1 and employed resonance imaging (MRI) markers correlated strongly to both measured GFR (mGFR) and UACR. Here we seek to determine which MRI markers are independent predictors of mGFR and UACR.

**Methods:** Subjects: The study included 2 CKD2, 16 CKD3, and 20 CKD4 subjects with DKD, 18-79 years old, and 20 age- and gender-matched healthy controls. GFR was measured using iohexol clearance. MRI was previously used to measure FF in kidney samples, CKD3 and CKD4 (p < 0.0001), and CKD3 vs CKD4 (p < 0.005) were significant.

**Conclusions:** It is well known that GFR is strongly linked to renal blood flow and therefore not surprising to see mean arterial flow emerge as an independent predictor of mGFR. The strong link between cortical Rf and UACR indicates that cortical Rf, a measure of cellular infiltration in the cortex where the filtration barrier exists, may be a novel biomarker of kidney damage and warrants further investigation.

**Funding:** Commercial Support - Antares Medical; AstraZeneca

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random forest (RF) models to combine the biomarkers with longitudinal clinical features extracted from the electronic health record (EHR) to predict RKFD (eGFR decline of $\geq 5$ ml/min/1.73 m$^2$/year).

**Results:** In 871 participants, baseline eGFR was 74 ml/min/1.73 m$^2$, and median UACR was 15 mg/g. Overall, 164 (19%) of individuals experienced RKFD over a median follow-up of 4.7 years from the baseline specimen collection. In the training and test sets respectively, the combined RF model (clinical features plus biomarkers) had an AUC of 0.82 (95% CI, 0.81-0.83) and 0.80 (95% CI, 0.78-0.82), which outperformed a standard clinical model via logistic regression (AUC 0.64, 95% CI 0.63-0.65), a biomarker model alone (AUC 0.76, 95% CI 0.72-0.79), and RF model using clinical features alone (AUC 0.74, 95% CI 0.73-0.76). The RKFD score stratified 18%, 49%, and 33% of patients in the entire cohort to high, intermediate, and low-probability strata, respectively, with a PPV of 53% in the high-probability group and an NPV of 97% in the low-probability group (Figure).

**Conclusions:** In patients with type 2 DM, a RF model combining plasma biomarkers and longitudinal EHR data significantly improved prediction of RKFD over standard clinical or biomarker-only models. Further validation of such approaches is needed.

**Funding:** NIDDK Support, Commercial Support - RenalytixAI

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**TH-PO919**

**Urinary Glyceraldehyde Predicts Kidney Function Decline in Type 1 Diabetic Subjects**

**Manjula Darski,1 Jiwan J. Kim,2 Tarunveer S. Ahluwalia,3 Peter Rossing,1 Per-Fritiof Nyberg,2 Kumar Sharma.2 Center for Renal Precise Medicine, Steno Diabetes Center, Copenhagen, Gentofte, Denmark; 2University of Texas Health Science Center at San Antonio, San Antonio, TX; 3University of Helsinki and Helsinki University Hospital, Helsinki, Finland.

**Background:** Diabetes is the common cause of chronic kidney disease (CKD) and end-stage renal failure. Albuminuria and eGFR are widely approved biomarkers to identify disease progression. However, due to considerable heterogeneity not all subjects progress at the same rate. Here we evaluated a set of urine metabolites toward prediction of rapid progression of CKD in patients with type 1 diabetes.

**Methods:** We used a nested cohort study in four diverse cohorts (CACTI, EDC, FinnDiane, and Steno) with long-standing type 1 diabetes and normal kidney function. Subjects were classified into slow decliners (controls) with eGFR decline slower than 1% per year or rapid progressors/cases with eGFR decline of $\geq 1.5$% per year. We included 95 controls and 95 cases (n=212) were 91.97 (sd 18.68) and 9.44 (IQR 30), and 98.37 (sd 25.44) and 33.49 (IQR 283.01), respectively. Analysis with clinical variables revealed age, baseline A1c, antihypertensives, estimated glomerular filtration rate (eGFR: ≥ 90, 90–60, 60–30, <30 ml/min/1.73 m$^2$), and urine albumin to creatinine ratio (UACR: ≥ 300, >90–<130, <10) as significant factors. We used a metabolomics analysis to study urinary metabolites using liquid chromatography with high-resolution mass spectrometry (LC-HRMS). We performed feature detection and mass spectrometry-based quantification to identify metabolites that were significantly associated with RKFDeGFR decline.

**Results:** We identified 223 significantly altered urinary metabolites between the 2 groups of 95 controls and 95 cases. We validated the results in 200 subjects in an independent cohort. A total of 19 metabolites were significantly associated with RKFDeGFR decline. We built two models: 1) a clinical-only model and 2) a clinical plus biomarker model. Both models were validated on additional 200 subjects from the same 4 cohorts. Logistic regression model was used to predict rapid eGFR decline. Area under the curve (AUC) was 0.64 (95% CI 0.63-0.65) for a clinical-only model and 0.82 (95% CI 0.81-0.83) for the combined clinical plus biomarker model. The AUC of the clinical plus biomarker model was improved from 0.64 (95% CI 0.63-0.65) to 0.82 (95% CI 0.81-0.83) with the biomarker model. The AUC of the combined clinical plus biomarker model was improved from 0.64 (95% CI 0.63-0.65) to 0.82 (95% CI 0.81-0.83) with the biomarker model.

**Conclusions:** In patients with type 1 diabetes, urinary metabolomics analysis can help identify patients at high risk for rapid progression of CKD. Further validation of such approaches is needed.

**Funding:** NIDDK Support

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**TH-PO920**

**Metabolomics Analysis of Urinary Biomarkers That Correlate with Kidney Injury in Diabetic African American Men**

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**Background:** African Americans (AA) are disproportionately burdened by diabetes and diabetic kidney disease (DKD). However, little is known about the cellular and molecular mechanisms underlying the onset and progression of DKD in this population. This is due, in part, to the fact that AAs are often underrepresented in biomedical research. We recently reported undiagnosed kidney injury in a significant proportion of diabetic AA men served by a community clinic in Greensboro, NC. The goal of the current study was to determine the association between specific metabolites and kidney injury in this population.

**Methods:** We used Biocrates Absolute IDP q400 kits together with high-resolution liquid chromatography-mass spectrometry to analyze fasting urine samples from three groups of AA men; 1) diabetics with DKD (n=10), 2) diabetics but no diagnosed DKD (DM; n=55), and 3) age-matched non-diabetic controls (ND; n=15). Patients in the DM group were further stratified based on their urinary albumin-to-creatinine ratios (UACR) into normo- (UACR<30 mg/g; n=28), micro- (30-<300 mg/g; n=20), and macroalbuminuria (UACR>300 mg/g; n=7). The concentrations of metabolites were normalized to the urinary creatinine levels, and compared through linear mixed models.

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underline represents presenting author.**
Results: The differentiating metabolites included glyceraldehydes, cholesteryl esters, sphingomyelins, glycero-phosphodiyols, biogenic amines and amino acids. The levels of several metabolites correlated with UACR. These include the Pro and the Arg derivative, citrulline, and three biogenic amines (kynurenine, 4-hydroxyproline, and α-amino acid). 87 urine metabolites exhibited above the limit of detection of the assay.

Conclusions: The current data suggest that key metabolic pathways are altered in diabetes and DKD for this population. For instance, proline is a precursor during the biosynthesis of both 4-hydroxyproline and citrulline. Likewise, citrulline is also involved in nitric oxide production, consistent with our previous observation that inflammation markers are dysregulated during the development of DKD in this population. Together, the metabolic biomarkers offer insights into the cellular and metabolic pathways that are dysregulated during the development of DKD in this population.

Funding: NIDDK Support, Other NIH Support - NIMHD, NIGMS

TH-PO921

LC-MS/MS-Based Proteomics Analysis Reveals Correlations Between Kidney Injury and Mediators of Vascular Pathology, and Oxidative Stress in Diabetic African American Men

Elimelech M. Oyewole,1 Aldelisha D. Smith,1 Falihaa Ahmed,1 Heather A. Newman,1 Oluyemisi A. Jegede,2 Robert H. Newman,1 H. H. Harrison,1 Bioloay, North Carolina A&T State University, Greensboro, NC;2Community Health and Wellness Center, Cone Health, Greensboro, NC.

Background: The prevalence of diabetic nephropathy (DN) is disproportionately high among minority ethnic groups in the US. African American (AA) men are especially underrepresented in research to identify biomarkers of DN which are then used for the development of diagnostic tools and therapeutics targets. The goal of the current study was to identify biomarkers present in the serum of diabetic AA men which correlate with kidney injury and thus gain insights on the cellular and molecular mechanisms underlying the progression of DN in this population.

Methods: Fasting blood and urine samples were obtained from AA men aged 18-65 years; (i) non-diabetic controls (n=22), (ii) diabetics (n=65), and (iii) diabetics with nephropathy (n=15). Assays included eGFR, albumin, creatinine, individual, kidney injury molecule 1 (KIM-1) and neutrophil gelatinase associated lipocidin (NGAL) were used for evaluation of kidney function. The serum samples were depleted of abundant proteins then subjected to global LC-MS/MS-based analysis. The data were searched using Proteome Discoverer 2.2 utilizing Sequest HT search algorithm. Linear regression modeling was conducted for screening changes in association with urinary albumin and creatinine ratio (UACR), and odds and fold changes calculated across groups.

Results: 29 of the identified proteins correlated with UACR. Among these are proteins related to vascular pathology (vascular cell adhesion protein 1), oxidative stress (protein disulfide-isomerase, tenasin-X, vascular cell adhesion protein 1), oxidative stress (sulfhydryl oxidase 1), and ECM/fibrosis (tenascin-X, fibulin-1).

Conclusions: The data suggest that the progression of kidney injury in AA men is associated with vascular pathology, inflammation, and oxidative stress. Vasodilator glomerular localization and is down-regulated during vessel repair. Reversal of vasodilator down-regulation inhibits TGF-β signaling diminishing injury-induced vascular lesions. AGES, which are linked to DN, suppress the expression of neprilysin-1 in podocytes. Tenasin X, localizes in the mesangial zone of kidney glomeruli, activates latent TGF-β, and induces TFG-β/Smad signaling. Increased levels of fibulin-1 also associate with impaired kidney function.

Funding: NIDDK Support, Other NIH Support - NIGMS, NIMHD

TH-PO922

Prediction and Validation of Exenatide Risk Marker Effects on Progression of Renal Disease: Insights from EXSCEL

Lindsay Clegg,1 Nienke Tijdsera,2 George L. Bakris,2 Robert C. Pendland,2 David W. Boulton,2 Hiddo J. L. Heerspink.1 1University of Genova IRCCS AOU San Martino, Genova, Italy; 2University of Genova, Hospital IRCCS-IST San Martino, Genova, Italy; 3University of Genova, IRCCS-IST San Martino, Genova, Italy; 4University of Genova, IRCCS CCTO, Genova, Italy; 5Kanazawa University, Ishikawa, Japan; 6Tohoku University Graduate School of Medical Dentistry and Pharmaceutical Sciences, Okayama, Japan; 7AstraZeneca Pharmaceuticals, Watertown, MA.

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RA) may slow progression of renal disease in patients with type 2 diabetes (T2D). We previously developed the PRE score that translates multiple short-term drug effects into a predicted score which could predict the renal effects of exenatide observed in the EXSCEL cardiovascular trial. The PRE score, integrating multiple short-term risk marker changes, predicted observed renal outcomes with exenatide treatment as observed in the EXSCEL trial. The results of the present study support further clinical trials to prospectively assess the renal efficacy of exenatide.

Funding: Commercial Support - AstraZeneca

TH-PO923

Myostatin Promotes Tubular Inflammation in Diabetic Nephropathy

Daniela Vezzola,1 Annalisa Carta,2 Samantha Milanesi,2 Michela Saio,4 Francesca Vuzzi,3 Daniela Picciotto,2 Francesca Costigliola,3 Chiara Barisone,3 Giacomo Garibotto.3 1University of Genova Di.M.I. Nephrology, Genoa, Italy; 2University of Genova IRCCS San Martino, Abbasanta, Italy; 3University of Genova, IRCCS CCTO, Genova, Italy; 4University of Genova, Hospital IRCCS-IST San Martino, Genova, Italy; 5University of Genova, Genova, Italy.

Background: Inflammation contributes to the tubulointerstitial lesions of diabetic nephropathy. Myostatin (MSTN), a member of the Transforming growth factor-β family, has been identified as a mediator of inflammation and insulin resistance in type 2 diabetes. MSTN has also been identified in the tubulointerstitium of porcine kidney, but its role in the human kidney is not known. The aims of the current study were (i) to investigate MSTN expression in the normal kidney and in kidney biopsies with documented diabetic nephropathy (DN); (ii) to the functional role of MSTN in tubular inflammation and fibrosis, using an established PTEC culture system.

Methods: MSTN mRNA levels were evaluated in microdissected tubular and glomeruli from normal kidneys (N=19), DN patients (n=23, proteinuria 3.8±1.0 g/d, eGFR= 33±7 ml/min) and IgA biopsies (n=12, proteinuria 2.7 g/d, eGFR= 39±5 ml/min) and protein was studied by immunohistochemistry. In vitro, HK-2 (human PTEC line) was exposed to MSTN (500 µg/ml) for 48 hours. We evaluated mRNAs by rt PCR, proteins by western blot, cell proliferation by CFSE incorporation, oxidative stress by CellROX staining.

Results: Laser capture microdissection showed an overexpression of MSTN mRNA (~8- to 10-fold increase) in the tubulointerstitium compartment in DN. Immunoreactive MSTN (~4-8 fold increase) was not detected in nondiabetic control subjects and co-localized with interstitial infiltrating CD45+ cells. The intensity of tubulointerstitial MSTN expression correlated directly with tubular atrophy (R=0.64, p<0.001). When proximal tubule HK-2 cells were treated with MSTN, they showed a decrease in proliferation, together with NF-kB activation and upregulation of downstream inflammatory chemokines, SMAD 3/2 and fibropeptin mRNA and protein. In addition, MSTN induced intracellular ROS release and upregulated NADPH oxidase, an effect which was mediated by ERK activation.

Conclusions: In conclusion, our data show that MSTN is upregulated in the tubulointerstitium of DN and associates with tubulointerstitial fibrosis. Its proinflammatory and profibrotic effects in human tubular cells suggest that MSTN plays a role in the progression of DN.

Funding: Government Support - Non-U.S.

TH-PO924

Gut Microbiome-Derived Phenyl Sulfate Contributes to Albuminuria in Diabetic Kidney Disease (Part 2)

Takahito Abe,1 Koichi Kishida,1 Daisuke Saigusa,2 Koki Miso,3 Tomonori Nakamura,1 Jeff D. Kopp,4 Takafumi Toyohara,1 Ekan Mishima,1 Takehiro Suzuki,1 Atsushi Hozawa,2 Takashi Wada,3 Jun Wada,3 Yoshihisa Tomioka.1 1Tohoku University Graduate School of Medicine, Aoba-ku, Sendai, Japan; 2Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan; 3Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; 4NIDDK, NIH, Bethesda, MD; 5Kanazawa University, Ishikawa, Japan; 6Tohoku University Graduate School of Pharmaceutical Sciences, Sendai, Japan.

Background: Diabetic kidney disease (DKD) represents a major cause of ESRD. However, since it is difficult to identify patients who are at risk of progression, specific biomarker is needed.

Methods: 362 patients in a multi-center clinical study in diabetic nephropathy (U-CARE) with full data were selected. The plasma PS level was measured by LC-MS/MS. In addition, PS was also assessed in urinary samples between two groups using Spearman Rank-Order Correlation. Multiple regression analysis and logistic regression analysis were used to identify the factors independently associated with PS or the development of 2-year ACR deterioration, respectively.

Results: Participants had a mean age of 63.3 years and 56.9% were male. The blood glucose was 154.2± 56.4 mg/dl and the HbA1c was 7.2± 1.1%. The eGFR was 73.8 (17.1 – 115.4) ml/min/1.73 m2 and the albumin to creatinine ratio (ACR) was 11.0 (1.0 – 6407.4) mg/g/Cre. The serum PS level was 3.3 µM (9 – 68.1 µM) and suPAR was 660.1 (456.0 – 2740.2) pg/ml. The usual plasma PS level was induced in renal outcomes.

Results: Compared with placebo, mean HbA1c, BMI, SBP, and total cholesterol were lower at six months with exenatide, as was the incidence of micro- or macroalbuminuria. The PRE score predicted a relative risk reduction for the 30% eGFR decline / ESRD endpoint of 11.3% (HR 0.89; 95%CI 0.83 to 0.94), compared with 12.7% (HR 0.87; 95%CI 0.72 to 1.04) for the 40% eGFR / ESARD endpoint, the predicted and observed risk reductions were 11.0% (HR 0.89; 95%CI 0.82 to 0.97) and 13.7% (HR 0.86; 95%CI 0.72 to 1.04), respectively.

Conclusions: The PRE score, integrating multiple short-term risk marker changes, predicted observed renal outcomes with exenatide treatment as observed in the EXSCEL trial. The results of the present study support further clinical trials to prospectively assess the renal efficacy of exenatide.

Funding: Commercial Support - AstraZeneca

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
with known factors increased the c-statistics value and the value were further increased with the PS combination.

**Conclusions:** PS is related to ACR and could predict the 2-year ACR deterioration in DKD patients, especially with microalbuminuria (Nature Commun. 10: 1835, 2019).

**Funding:** Government Support - Non-U.S.

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**TH-PO925**

The Acute Effect of Selonsertib on eGFR Is a Result of Creatinine Transport Inhibition, Not Alteration of Renal Function


**Background:** Selonsertib (SEL) is a first-in-class small molecule inhibitor of apoptosis signal-regulating kinase 1 (ASK1) in clinical development for the treatment of diabetic kidney disease (DKD). As small, dose-dependent, and reversible increases in serum creatinine were observed across clinical studies, an analysis of in vitro and clinical data was conducted to identify and confirm the mechanism by which SEL decreases estimated GFR (eGFR) without changing measured GFR (mGFR).

**Methods:** In vitro studies assessed the potential for SEL and its inactive metabolite, GS-607509, to inhibit renal transporters (OCT2, MATE1, and MATE2K) and determined their IC50 values. Clinical studies in healthy subjects included a multiple ascending dose (MAD) study (SEL 1 to 100 mg or placebo, QD) to assess the effects of SEL on eGFR. Additionally, a mechanistic study (SEL 18 mg or placebo, QD) evaluated the effect of SEL on renal function using iohexol to measure GFR before, during, and after treatment for 2 weeks. Meta-analyses of clinical studies were conducted to quantify the magnitude and consistency of the acute effect across patient populations.

**Results:** Based on the 2017 FDA drug interaction guidance, SEL and GS-607509 demonstrate low potential for inhibition of OCT2 (Cmax,IC50 > 0.1). SEL, but not GS-607509, is a potential inhibitor of MATE1 and MATE2K (Cmax,IC50 < 0.02). In the MAD study, a dose-dependent reduction in GFR was observed and was reversible upon washout of SEL (A). Results from the mechanistic study showed no change in mGFR for subjects taking SEL or placebo (B). Regardless of baseline eGFR, meta-analyses showed at the 18 mg dose, a consistent acute percent decrease (median 7.3%) in eGFR across patient populations.

**Conclusions:** The totality of data from in vitro and clinical studies indicate that the acute effect of SEL on eGFR is dose-dependent, reversible, and a result of inhibition of renal creatinine transporters without altering mGFR. Clinical trials evaluating the efficacy of SEL on slowing the loss of kidney function will need to account for these acute effects.

**Funding:** Commercial Support - Gilead Sciences, Inc.

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**TH-PO926**

Genome-Wide Expression Quantitative Trait Loci Analysis for Circulating miR-1275-5p and miR-339-5p and ESRD in Type 1 Diabetes

Eiichiro Satake,1 Marcus G. Pezzolesi,2 Zaipul I Md Dom,3 Kristina V. O’Neill,1 Hiroki Kobayashi,1 Katsuhiro Ibara,1 Andrzej S. Krolewski,1 Joslin Diabetes Center, Boston, MA; 2University of Utah, Salt Lake City, UT; 3Joslin Diabetes Center, Harvard Medical School, Boston, MA.

**Background:** microRNAs are short endogenous non-coding RNA molecules that are involved in gene regulation and play important roles in the pathogenesis of various kidney diseases. Previously, we identified risk and protective miRNAs (miR-1287-5p and miR-339-5p) strongly associated with progression to end stage renal disease (ESRD) in diabetic patients. To identify expression quantitative trait loci (eQTL) that influence plasma levels of these miRNAs and onset of ESRD in Type 1 diabetes (T1D), we performed a genome-wide miR-eQTL analysis.

**Methods:** Plasma levels of the two miRNAs were measured using HTG Molecular Diagnostics’ EdgeSeq platform and genotyping of 325,735 single nucleotide polymorphisms (SNPs) was performed using Illumina’s HumanCoreExome BeadArray in 240 T1D patients. Association analyses between plasma levels of miR-1287-5p and miR-339-5p were used to identify eQTL using linear regression implemented in PLINK. To assess the relationship between the candidate eQTLs and the development of ESRD, we applied logistic regression using an additive model in 437 T1D patients.

**Results:** Trans miR-eQTL analysis revealed that 13 SNPs that affect plasma levels of miR-1287-5p or miR-339-5p (P<5e-5). Among them, in logistic models, we identified 2 SNPs associated with onset of ESRD: rs4624519 in the LINC0203 (OR: 0.64 (95%CI=0.48-0.83); p=0.0024) and rs10963040 in the CNTLN gene (OR: 1.43 (95%CI=1.04-1.96); p=0.028).

**Conclusions:** We identified SNPs that have regulatory effects on circulating miRNAs and play roles in progression to ESRD in T1D.

**Funding:** NIDDK Support, Private Foundation Support

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**TH-PO927**

The Circulating Exosomal MicroRNAs Related to Albuminuria in Patients with Diabetic Nephropathy

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**Background:** Diabetic nephropathy (DN) is associated with high risk of cardiovascular disease and mortality. Exosomal microRNAs (miRNAs) regulate gene expression in a variety of tissues and play important roles in the pathology of various diseases. We hypothesized that the exosomal miRNA profile would differ between DN patients and patients without nephropathy.

**Methods:** We prospectively enrolled 74 participants, including healthy volunteers (HV), diabetic patients without nephropathy, and those with DN. The serum exosomal miRNA profiles of participants were examined using RNA sequencing.

**Results:** The expression levels of 107 miRNAs differ between HVs and patients without DN, whereas the expression levels of 95 miRNAs differed between HVs and patients with DN. Among these miRNAs, we found 7 miRNAs (miR-1246, miR-642a-3p, let-7c-5p, miR-1255b-5p, let-7i-3p, miR-3010-5p, miR-150-3p) that were uniquely up-regulated in DN patients compared to HVs, and miR-4449 that was highly expressed in DN patients compared to patients without DN. A pathway analysis revealed that these eight miRNAs are likely involved in MAPK signaling, integrin function in angiogenesis, and regulation of the AP-1 transcription factor. Moreover, we also significantly correlated with the degree of albuminuria (figure 1).

**Conclusions:** Patients with DN have a different serum exosomal miRNA profile compared to HVs and these miRNAs may be promising candidates for the diagnosis and treatment of DN and cardiovascular disease.

**Correlation between miRNAs and albuminuria**

<table>
<thead>
<tr>
<th>Mature miRNA</th>
<th>albuminuria (mpgċ/dl)</th>
</tr>
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<tbody>
<tr>
<td>miR-1246</td>
<td>0.73 (90.0)</td>
</tr>
<tr>
<td>miR-642a-3p</td>
<td>0.92 (p=0.002)</td>
</tr>
<tr>
<td>let-7c-5p</td>
<td>0.42 (p=0.002)</td>
</tr>
<tr>
<td>miR-1255b-5p</td>
<td>0.24 (p=0.13)</td>
</tr>
<tr>
<td>let-7i-3p</td>
<td>0.90 (p=0.002)</td>
</tr>
<tr>
<td>miR-3010-5p</td>
<td>0.74 (p=0.029)</td>
</tr>
<tr>
<td>miR-150-3p</td>
<td>0.14 (p=0.02)</td>
</tr>
<tr>
<td>miR-4449</td>
<td>0.47 (p=0.001)</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Hypoxia in Individuals with Type 1 Diabetes and Macroalbuminuria Is Associated with Autonomic Dysfunction

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Background: Blood oxygen saturation (SpO2) in the supine position is lower in individuals with type 1 diabetes (T1D) compared to healthy controls (CON). This has been suggested to be linked with cardiovascular autonomic dysfunction (CAD). Presence of CAD in individuals with T1D and diabetic nephropathy is associated with cardiovascular mortality. Our aims were to investigate SpO2 levels in individuals with T1D and different albuminuria-stages compared to CON and to explore associations between SpO2 and baroreflex sensitivity (BRS), a sensitive measure of CAD.

Methods: One-hundred-and-five individuals with T1D and normalalbuminuria (NORMO) and 24 individuals with T1D and macroalbuminuria (MACRO) were compared to 55 CON. SpO2 was assessed for at least 5 min in the supine position and then for five minutes in the standing position. A linear mixed-effects model was fitted with SpO2 as outcome and albuminuria-status as exposure, adjusted for sex, age and smoking, with a random person effect. Association between SpO2 and BRS was tested with linear regression analysis and adjusted for albuminuria-status, sex, age, and smoking.

Results: In CON, NORMO and MACRO respectively, mean (SD) age was 47.2±12.6, 43.9±11.1 and 56.8±11.0 years; HbA1c was 33.2±2.4, 63.9±12.0 and 63.1±11.7 mmol/mol; BRS was 15.2±9.5, 13.8±10.6 and 4.9±3.2 mmHg/mL per second; serum creatinine was 79.0±41.5, 91.7±53.1 and 81.8±52.6 µmol/L; and baseline SBP was 97.5±14.0 and 96.2±14.0 ms/mmHg. From supine to standing position, SpO2 increased in CON and NORMO, but not in MACRO. Overall, in mixed effects model mean difference in SpO2 between NORMO and CON was -0.7% (p=0.03) and mean difference in SpO2 between MACRO and CON was -1.4% (p=0.001). In all participants together, SpO2 was positively correlated with BRS (p=0.03).

Conclusions: Individuals with T1D and normalalbuminuria had lower SpO2 than healthy controls and the macroalbuminuria-group had even lower SpO2. SpO2 was positively correlated with BRS. Additional studies in larger cohorts and in the lungs of T1D and diabetic nephropathy patients may lead to hypoxia contributing to autonomic dysfunction. It remains to be investigated if low SpO2 contributes to excess cardiovascular mortality in individuals with T1D and diabetic nephropathy.

Funding: Private Foundation Support.

Diabetic Kidney Disease (DKD) is the leading cause of end-stage renal disease. As the most common microvascular complication of diabetes, DKD is a knoty clinical problem in terms of its diagnosis and management. Currently, renal biopsy remains the most reliable method to distinguish a true DKD, non-DKD, or mixed form. Our present study focuses on early biomarker identification to monitor the onset of DKD in type 2 diabetes (T2D) patients. We expect the identified biomarker could eventually be translated into the solid troubleshooting resources to avoid invasive biopsy in patients.

Method: Based on our previous findings, combine with the data refine in the supine position and then for five minutes in the standing position. A linear mixed-effects model was fitted with SpO2 as outcome and albuminuria-status as exposure, adjusted for sex, age and smoking, with a random person effect. Association between SpO2 and BRS was tested with linear regression analysis and adjusted for albuminuria-status, sex, age, and smoking.

Results: In CON, NORMO and MACRO respectively, mean (SD) age was 47.2±12.6, 43.9±11.1 and 56.8±11.0 years; HbA1c was 33.2±2.4, 63.9±12.0 and 63.1±11.7 mmol/mol; BRS was 15.2±9.5, 13.8±10.6 and 4.9±3.2 mmHg/mL per second; serum creatinine was 79.0±41.5, 91.7±53.1 and 81.8±52.6 µmol/L; and baseline SBP was 97.5±14.0 and 96.2±14.0 ms/mmHg. From supine to standing position, SpO2 increased in CON and NORMO, but not in MACRO. Overall, in mixed effects model mean difference in SpO2 between NORMO and CON was -0.7% (p=0.03) and mean difference in SpO2 between MACRO and CON was -1.4% (p=0.001). In all participants together, SpO2 was positively correlated with BRS (p=0.03).

Conclusions: Individuals with T1D and normalalbuminuria had lower SpO2 than healthy controls and the macroalbuminuria-group had even lower SpO2. SpO2 was positively correlated with BRS. Additional studies in larger cohorts and in the lungs of T1D and diabetic nephropathy patients may lead to hypoxia contributing to autonomic dysfunction. It remains to be investigated if low SpO2 contributes to excess cardiovascular mortality in individuals with T1D and diabetic nephropathy.

Funding: Private Foundation Support.
TH-PO932

Urine Myo-Inositol, the Novel Prognostic Biomarker for Diabetic Kidney Disease: A Targeted Metabolomics Study Using Nuclear Magnetic Resonance

Soo Kwon, Jung Nam An, Jeonghwan Lee, Yong Chul Kim, Dong Ki Kim, Yon Su Kim, Jung Pyo Lee.

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Background: Estimated GFR (eGFR) and urine proteinuria are currently the strongest predictive biomarker of CKD regardless of the cause. For more precise prediction according to the cause of CKD and to identify treatment options, metabolomics has been increasingly applied to identifying new biomarkers of diseases specific CDK.

Methods: Based on previous our animal study, targeted metabolomics (n=26) was performed using nuclear magnetic resonance. Prospectively stored urine samples consecutive patients with CKD stage 1 to 5 (n=208) and their healthy controls (n=26) were analyzed. Cross-sectional association between measured metabolites and eGFR were compared. Multivariate cox models were conducted for the risk of ESRD and mortality.

Results: ESRD occurred in 103 (40.4%) patients and the number of death was 65 (27.8%). The median fold change of metabolites compared with control groups, 7 metabolites (glucose, mannose, myoinositol, lactate, succinate, fumarate and choline) revealed a trend according to CKD stages. Linear regression identified myo-inositol is best-associated metabolite with eGFR. The relationship between competitive metabolites and outcomes was investigated by multivariate cox models after adjusting for the baseline covariates (Table1). Of which, 4 metabolites (myoinositol, glycerol, fumarate, oxosaccharopate) had predictive value for eGFR and only myo-inositol retained predictive significance in multivariate analysis.

Conclusions: Our results suggest the myoinositol, previously defined as vitamin B8, can be a predictive biomarker to predict the risk of ESRD progression in DKD. Myoinositol, as a secondary messenger of insulin and confirmed safe compound, further mechanism study is needed.

Table 1. Risk of end-stage renal disease according to the urinary metabolites

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Myoinositol</td>
<td>1.005 (1.000-1.010)</td>
<td>1.001 (0.996-1.006)</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.001 (0.999-1.002)</td>
<td>1.001 (0.999-1.002)</td>
</tr>
<tr>
<td>Fumarate</td>
<td>1.001 (0.999-1.002)</td>
<td>1.001 (0.999-1.002)</td>
</tr>
</tbody>
</table>

Only 4 significant metabolites were described: Model 1: adjusted for age, sex, HTN, eGFR; Model 2: adjusted for model 1 plus laboratory findings.

TH-PO934

Polys and Branched Chained Amino Acids Are Associated with Present and Future Renal Impairment in Type 1 Diabetes

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Background: Improved understanding of the pathophysiology causing diabetic nephropathy is imperative. The aim of this study was to uncover associations between serum metabolites and renal outcomes in patients with type 1 diabetes.

Methods: In total, 637 persons with type 1 diabetes were included. Non-targeted serum metabolomics analyses were performed using two-dimensional gas chromatography coupled to time-of-flight mass-spectrometry. Longitudinal data at follow-up on development of renal events were obtained from national Danish health registries over a median of 5.5 years. A composite renal endpoint (n=123) was defined as an estimated glomerular filtration rate (eGFR) decline from baseline (<30%), development of end-stage renal disease (eGFR < 15 ml/min/1.73m², dialysis or renal transplantation) and all-cause mortality. Metabolites with significant associations (p<0.05) were validated in cross-sectional analyses with Cox proportional hazards models for either specific or composite endpoint. Adjustments included traditional cardiovascular risk factors and correction for multiple testing.

Results: A data-driven partial correlation analysis revealed a dense fabric of co-regulated metabolites and clinical variables dominated by eGFR. After statistical analyses, ribonic acid and myoinositol were inversely associated with eGFR and positively associated with macroalbuminuria (urinary albumin excretion rate (UAER) a 300 mg/24h (p=0.02). Longitudinally, ribonic acid was associated with the combined renal endpoint (HR 1.8, CI 1[3.2-3.3], p=0.001). Further, ribonic acid (HR 2.2, CI [1.6-3.0], p=0.001) and myo-inositol (HR 2.7, CI [1.6-4.3], p=0.001) were both associated with higher risk of eGFR decline a30%. The hydroxy butyrate 3,4-dihydroxybutanoic acid was cross-sectionally associated with micro- (UAER 30-299 mg/24h) and macroalbuminuria, UAER and inversely associated with eGFR (p<0.04), while branched amino acids were associated with eGFR and lower risk of the combined renal endpoint (p<0.02).

Conclusions: Alterations in serum metabolites, particularly polys and amino acids, were associated with renal endpoints in type 1 diabetes highlighting molecular pathways associated with development of kidney disease.

Funding: Private Foundation Support

TH-PO935

Circulating Long Noncoding RNAs Are Associated with Diabetic Nephropathy and Normalize After Simultaneous Pancreas-Kidney Transplantation

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Background: Diabetes mellitus can lead to end-stage renal disease and cardiovascular injury. Simultaneous pancreas kidney transplantation (SPKT) replaces kidney function and restores endogenous insulin secretion. Circulating long noncoding RNAs (LncRNAs) are promising biomarkers in (cardiovascular) disease and can provide insight into pathogenesis. However little is known about these markers in vascular injury in the context of diabetic nephropathy (DN) and after SPKT.

Methods: We performed a pilot study of 40.173 LncRNAs in plasma of healthy controls and patients with diabetic nephropathy. Based on these results, as well as a dedicated literature search, we assessed 14 candidate LncRNAs of which 9 were detectable in plasma samples in DN (n=14), SPKT (n=35) and healthy controls (n=15). All DN patients were studied longitudinally before and 1, 6 and 12 months after SPKT. LncRNAs that were detected in less than 95% of the samples were excluded from the study. Assays for LncRNA2 and soluble thrombomodulin (sTM) were measured using ELISA As a markers for vascular injury.

Conclusions: LncRNA1 was significantly higher (p<0.002) in patients with DN (median 13.8, IQR 2.9-16.3) compared with healthy controls (median 0.16, IQR 0.1-1.3). The first month after SPKT LncRNA1 normalized from 13.8 to 0.3 (p=0.016). EPHA6, LIPCAR

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
and G003293 showed a similar pattern with significant decline after SPKT (resp. p=0.01, p=0.03 vs. post). TNFα was also upregulated in MALAT1, EPH-A6 and LIPCAR with blood pressure and vascular injury marker sTM.

**Conclusions:** Circulating IncRNAs associate with DN and vascular injury and normalize after SPKT. As such, IncRNAs are potentially interesting biomarkers for disease progression in diabetic nephropathy and may provide insight into the underlying pathophysiology.

**TH-PO936**

**Systemic Inflammation Precedes New-Onset Microalbuminuria in Diabetic Mellitus Type II: A Post Hoc Analysis of the ROADMAP Study**

Christos D. Chatziyannakos,1 Jan Menne,2 Sabine Brandt,3 Anja Bernhardt,4 Peter R. Mertens,4 Hermann G. Haller,1 Florian G. Scurt,5 Universitätsklinikum Magdeburg, Magdeburg, Germany; 2Medical School Hannover, Hannover, Germany; 3University Hospital Magdeburg, Magdeburg, Germany; 4Universitätsklinikum Magdeburg, Magdeburg, Germany; 5Otto von Goerike University Magdeburg - Medical Faculty, Magdeburg, Germany.

**Background:** The aim of the case-control study was to investigate if serum biomarkers indicative of vascular inflammation and endothelial dysfunction can predict the development of microalbuminuria in patients with diabetes mellitus type II.

**Methods:** Amongst participants enrolled in the ROADMAP (Randomized Olmesartan And Diabetes Microalbuminuria Prevention) and observational follow-up (OPU) studies, a panel of 15 serum biomarkers was quantified from samples obtained at initial study visit and tested for associations with development of new-onset microalbuminuria (defined as a urinary albumin to creatinine ratio (UACR) of more than 35 mg/g in women or more than 25 mg/g in men) during follow-up. A case-control study was conducted with inclusion of 172 patients with microalbuminuria and 188 matched controls.

**Results:** Non-parametric inferential, nonlinear regression, mediation and bootstrapping statistical methods were used for the analysis

**Results:** The mean follow-up time was 37 months. At baseline, mean concentrations of CXCL-16, TGF-β1 and angiopeptin-2 were higher in patients with subsequent microalbuminuria. In the multivariate analysis, after adjustment for age, sex, BMI, HbA1c, duration of diabetes, LDL, smoking status, blood pressure, baseline UACR, eGFR, time of follow-up and cardiovascular disease, CXCL-16 (OR 2.60, 95% CI 1.71-3.96), angiopeptin-2 (OR 1.50, 95% CI 1.14-1.98) and TGF-β1 (OR 1.03, 95% CI 1.00-1.04) remained significant predictors of new-onset microalbuminuria (p<0.001). Inclusion of these biomarkers in conventional clinical risk models for prediction of microalbuminuria increased the AUC from 0.638 to 0.760 (p<0.001).

**Conclusions:** In type II diabetes patients elevated plasma levels of CXCL-16, angiopeptin-2 and TGF-β1 are independently predictive of microalbuminuria. Thus, these serum markers improve renal risk models beyond established clinical risk factors.

**TH-PO937**

**Soluble Urokinase Receptor Level as Biomarker in Biopsy-Confirmed Diabetic Nephropathy**

Gabriela Lupusoru,1 Andreea G. Andronescu,1 Ioana Allincai,1 Georgia Micu,1 Bogdan M. Sorohan,1 Bogdan Obrisca,1 Mircea Lupusoru,1 Georgiana Fratila,1 Oana Ion,1 Danut Andronescu,1 Ioan Ficior,1 Fundeni Clinical Institute, Bucharest, Romania; 2UMF Carol Davila Bucharest, Bucharest, Romania.

**Background:** Diabetic nephropathy (DN) is the leading cause of end-stage renal disease worldwide associated with significant cardiovascular morbidity and mortality. The serum levels of soluble form of podocyte membrane urokinase activator receptor (suPAR) were recently elevated in patients with DN, making it a potential biomarker for assessing the severity of disease in these patients. The aim of this study was to explore the association between suPAR levels and renal pathological findings in patients with biopsy-confirmed DN.

**Methods:** We performed a cross-sectional study on 33 patients with biopsy-confirmed DN admitted in our department. The following clinical variables and laboratory parameters were assessed at the time of kidney biopsy: age, gender, time since DM diagnosis, BMI, arterial blood pressure (BP) values, treatment, serum creatinine, estimated glomerular filtration rate (eGFR, calculated by CKD-EPI equation), 24-hour proteinuria and suPAR levels. Histological scoring was made according to that of Tervaert et al (JASN, 2010, 21 (4) S56).

**Results:** 33 patients were included (8 F, 25 M), with mean age 56.6±11.5 y, BMI 28.1±3.4kg/m2, DM1 (n=14) and DM2 (n=29), months since DM diagnosis (140.7±97.9m), hypertension (n=30), SHP (151.5±23.4mmHg), DBP (83.7±11.3mmHg), eGFR (34.4±24.8ml/min), serum creatinine (2.74±1.78mg/dl), 24-hour proteinuria (2.62±2.92g/24h), ACEI or ARB use (20/33). Serum suPAR levels were 7.41±3ng/ml. SuPAR levels were positively correlated with age of diabetes (r=0.363, p=0.038), serum creatinine (r=0.493, p=0.004), degree of glomerulosclerosis (r=0.405, p=0.024), degree of tubular atrophy/intertstitial fibrosis (r=0.740, p<0.001), degree of arteriosclerosis (r=0.694, p<0.001), and negatively correlated with eGFR (r=−0.675, p<0.001).

**Conclusions:** Our study confirmed the presence of high serum levels of suPAR in patients with DN and we suggested that these are associated with age of DM, renal function, degree of glomerulosclerosis, tubular atrophy/intertstitial fibrosis and arteriosclerosis. Serum suPAR might be a useful biomarker for assessing severity of renal impairment in DN, but requires future validation on larger series of patients.

**TH-PO938**

**Association of Angiogenic Markers with Kidney Outcomes in Patients with Type 2 Diabetes**

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**Background:** Deregulated angiogenesis may play a role in kidney disease in type 2 diabetes (T2D). We assessed the associations of 7 angiogenesis biomarkers with kidney outcomes in a contemporary clinical cohort.

**Methods:** We used banked plasma specimens from a cohort of patients with T2D from the EMR and USRDS-linked Mount Sinai BioMe Biobank (n=870). We measured the angiogenesis biomarkers (FLT-1, PI GF, TIE-2, VEGF, VEGF-C, VEGF-D, and bFGF) in plasma specimens banked from the time of enrollment in BioMe using the Mesoscale multiplex platform. Using multivariable Cox Regression, we evaluated the association of biomarkers with a composite kidney outcome of sustained 40% decline in eGFR or ESRD. We also examined the association between biomarker ratios and kidney outcomes.

**Results:** Median follow-up time for the population was 4.5 (IQR, 3.3-6.1) years, baseline eGFR was 68 (IQR, 55-80) ml/min/1.73 m², and UACR was 13 (IQR, 4-66) mg/g. After adjusting for demographics, comorbidities, medications, and baseline eGFR, PI GF (adjusted HR 2.1 per doubling; 95% CI 1.5-3.1) and FLT-1 (adjusted HR 1.6 per doubling; 95% CI 1.1-2.2) were independently associated with the kidney outcomes (Figure). However, when adjusted for TNFRI, TNFRII, and KIM-1, the independent associations between biomarkers and the kidney outcomes were attenuated to null. There were no associations between the biomarker ratios and kidney outcomes.

**Conclusions:** Higher baseline plasma PI GF and FLT-1 are associated with kidney outcomes during follow-up in patients with T2D. Since models including TNFRI, TNFRII, and KIM-1 nullified the association of FLT-1 and PI GF with kidney outcomes, this indicates the possibilities of shared pathways between these biomarkers. More studies are needed to find a definite association between these biomarkers and kidney outcomes in T2D population.

**Funding:** NIDDK Support

**Angiogenesis Markers**

**TH-PO939**

**Characteristics of 24-Hour Ambulatory Blood Pressure in Non-Dialysis Patients with Diabetic Kidney Disease**

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**Background:** Data about characteristics of 24-hour ambulatory blood pressure in non-dialysis patients with diabetic kidney disease was limited.

**Methods:** We monitored 24-hour ambulatory blood pressure in non-dialysis patients with diabetic kidney disease from the nephrology division, the fifth affiliated hospital of Sun Yat-sen University from August 2000 to October 2018, and compared with primary chronic glomerulonephritis patients matching in age(±5 years old), sex and CKD stages. The target organ damages were measured by carotid intima-media thickness, left ventricular hypertrophy, diastolic dysfunction, eGFR<60ml/min and massive proteinuria. Blood pressure loads, circadian rhythm and target organ damages in two groups were evaluated and compared. Multivariate logistic analyses were used to evaluate the relationship between blood pressure loads and target organ damage parameters.

**Results:** 202 patients with diabetic kidney disease were enrolled in this study. The mean age of the patients was 57.9±9 years and 66.3%(134/203) were men. Compared with control patients, patients with diabetic kidney disease had a higher level of systolic blood pressure in clinic, daytime, nighttime or 24-hour ambulatory measurement. They also had a higher proportion in reversed dippers(34.2% vs. 24.8%, P=0.038) and target organ damage evaluations, like the carotid intima-media thickness(69.3% vs. 26.2%, P<0.001), left ventricular hypertrophy(63.4% vs. 50.0%, P=0.009), diastolic dysfunction(74.3% vs. 48.0%, P=0.001) and massive proteinuria(51.0% vs. 25.7%, P<0.001). Multivariate logistic analyses, which included both clinic and ambulatory blood pressure, showed that only 24-hour systolic blood pressure independent significantly the target organ damage.
The Triple Whammy: An Unexpected Case of Leukocyte Chemotactic Factor 2 Amyloidosis (ALECT2) with Diabetic and Hypertensive Nephropathy

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Introduction: Amyloidosis is a disorder resulting from abnormal deposition of misfolded beta-sheet fibrils. ALECT2 is a recently identified entity with high incidence in certain ethnic populations.

Case Description: A 56 year old Hispanic female with history of Diabetes Mellitus (not on therapy for a few years), presented with lower extremity edema and elevated blood pressure. Patient was noted to have nephrotic range proteinuria of >4 g/dm², and elevated Creatinine of 3.6 mg/dL. Serological work up for glomerulonephritis was negative. We proceeded with kidney biopsy given lack of proper explanation for her presentation. Biopsy showed evidence of amyloid deposition, but in the context of negative immunofluorescence study, and patient’s ethnicity, LECT2 type amyloid deposition was suspected, which was further identified by Liquid Chromatography (LC) with tandem Mass Spectrometry (MS). Renal biopsy also showed changes consistent with diabetic and hypertensive nephropathy.

Discussion: ALECT2 mostly involves the liver and kidneys. Renal involvement usually presents with slow, progressive renal failure, bland urine sediment, and variable proteinuria. Prognosis of ALECT2 is better than other forms of Amyloidosis, with 1/3rd usually presenting with slow, progressive renal failure, bland urine sediment, and variable proteinuria. We proceeded with kidney biopsy given lack of proper explanation for her presentation. Biopsy showed evidence of amyloid deposition, but in the context of negative immunofluorescence study, and patient’s ethnicity, LECT2 type amyloid deposition was suspected, which was further identified by Liquid Chromatography (LC) with tandem Mass Spectrometry (MS). Renal biopsy also showed changes consistent with diabetic and hypertensive nephropathy.

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Immunofluorescence (IF) demonstrated diffuse granular capillary and mesangial staining for IgG (3+), C3 (2+), IgA (1+), C1q (trace), kappa (4+) and lambda (4+). IF staining for IgM was negative. Immunoelectron microscopy showed segmental mild BM thickening and subepithelial granular deposits, with diffuse effacement of foot processes (>90%). In addition, there were regions of mesangial and para-mesangial intramembranous non-branching fibrillary deposits, 12-nm diameter. The renal disease was treated with furosemide, lisinopril, prednisone, and tacrolimus with improvement in proteinuria and lower extremity edema. CDP was treated with IVIG. The patient is currently in clinical remission with stable CKD.

Discussion: While FGN may have granular subepithelial deposits that mimic MN, positivity for anti-PLA2R is unique, suggesting dual glomerulopathy with coincidental ANCA vasculitis. FGN is a rare disease found in 1% of renal biopsies. Although renal damage of FGN is caused by immune complexes, only approximately 17% of the cases are positive for M-protein, and 2% have hypocomplementemia. As the diagnosis required electron microscopy examination, some cases may have been overlooked. DNAJB9, a recently discovered histological marker of FGN, is expected to improve diagnostic accuracy and therefore increase the number of reported cases.

TH-PO943

IgA Nephropathy Associated with Intravesical Bacillus Calmette-Guerin: A Case Report

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Introduction: BCG immunotherapy has remained crucial in the treatment of non-muscle invasive bladder cancer. Serious systemic complications can occur including granulomatous inflammation in various organs (BCGosis), reactive arthritis, and disseminated BCG. We present a unique case of BCGosis associated with new onset IgA nephropathy (IgAN).

Case Description: A 79-year-old man with type 2 diabetes, chronic kidney disease stage 3A received intravesical BCG therapy two months prior to presentation and developed caseating granulomas of the liver thought secondary to Mycobacterium bovis abdominal infection. He subsequently presented with altered mental status, dyspepsia, abdominal pain, and acute kidney injury two weeks after starting antitubercular therapy. RIPE therapy was discontinued, however his creatinine continued to rise. He developed uremic symptoms with a creatinine peaking at 4.0 mg/dL, nephrotic-range proteinuria and an active urine sediment with many dysmorphic RBCs and mixed cellular casts. Prednisone 50 mg daily was started, and a kidney biopsy was arranged. Serologic investigations/therapy.

Discussion: From the histological findings, it was considered that the patient’s renal dysfunction was caused by either FGN alone or from concomitant AAV and FGN. FGN is a rare disease found in 1% of renal biopsies. Although renal damage of FGN is caused by immune complexes, only approximately 17% of the cases are positive for M-protein, and 2% have hypocomplementemia. As the diagnosis required electron microscopy examination, some cases may have been overlooked. DNAJB9, a recently discovered histological marker of FGN, is expected to improve diagnostic accuracy and therefore increase the number of reported cases.

TH-PO942

A Rare Case of Dual Glomerulopathy: Fibrillary Glomerulonephritis (FGN) and Membranous Nephropathy (MN) in a Patient with Chronic Inflammatory Demyclininating Polynuepolyathritis

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Introduction: FGN is a rare glomerular disease characterized by random fibrillary deposits. Usually idiopathic, it can be associated with malignancy, monoclonal gammopathy, or autoimmune disease. Its association with MN with CIDP is rare.

Case Description: A 68-year-old Burmese female presented with lower extremity edema and paraparesis of a 3-month duration. Her history was significant for latent tuberculosis, HTN and uncontrolled DM2 (last A1c of 14.5%). On exam, hypertension, renal anasarca and paraparesis were noted. Labs were significant for hypoalbuminemia (1.8) and nephrotic range proteinuria (6.8g/24hr). Serum Cr was at baseline (0.6). ANA (320), C3, C4, and Kappa/Lambda ratio (1.86) were mildly elevated. HIV, hepatitis panel, RPR, anti-dsDNA Abs, SFP, UPEP, antiphospholipid Abs, cryoglobulins were negative. CT scan showed left renal vein thrombus. Electromyography showed mixed axonal polyneuropathy and she was diagnosed with CIDP. Renal biopsy revealed diffuse diffuse mesangial expansion, Congo red negative. No Kimmelstiel-Wilson nodules were seen. Immunofluorescence (IF) demonstrated diffuse granular capillary and mesangial staining for IgG (3+), C3 (2+), IgA (1+), C1q (trace), kappa (4+) and lambda (4+). IF staining for M-type PLA2R showed 3+ diffuse, granular staining predominantly in subepithelial distribution. EM showed segmental mild BM thickening and subepithelial granular deposits with diffuse effacement of foot processes (~90%). In addition, there were regions of mesangial and para-mesangial intramembranous non-branching fibrillary deposits, 12-28nm in diameter. The renal disease was treated with furosemide, lisinopril, prednisone, and tacrolimus with improvement in proteinuria and lower extremity edema. CDP was treated with IVIG. The patient is currently in clinical remission with stable CKD.

Discussion: While FGN may have granular subepithelial deposits that mimic MN, positivity for anti-PLA2R is unique, suggesting dual glomerulopathy with coincidental ANCA vasculitis. FGN is a rare disease found in 1% of renal biopsies. Although renal damage of FGN is caused by immune complexes, only approximately 17% of the cases are positive for M-protein, and 2% have hypocomplementemia. As the diagnosis required electron microscopy examination, some cases may have been overlooked. DNAJB9, a recently discovered histological marker of FGN, is expected to improve diagnostic accuracy and therefore increase the number of reported cases.

TH-PO940

A Case of Fibrillary Glomerulonephritis with a High Level of Myeloperoxidase-ANCA

Tomohiko Asakawa, Makoto Araki. Suwa Central Hospital, Chino, Japan.

Introduction: Gross hematuria with renal dysfunction suggests the possibility of rapidly progressive glomerulonephritis (RPGN) and requires urgent attention. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents RPGN and is characterized by elevated serum ANCA levels and pauci-immune crescentic glomerulonephritis. But it is well known that the presence of a high titer of ANCA does not imply the presence of disease.

Case Description: A 71-year-old woman was admitted with the chief complaint of gross hematuria. Her laboratory values included a Cr 1.52 mg/dL and advanced proteinuria of 7.5 g/g Cr. There was no fever, and her white blood cells were within the normal range. Further examination revealed a high myeloperoxidase (MPO)-ANCA level (96.6 U/mL, normal < 3.5), no monoclonal proteins, and normal complement levels. Thus, a renal biopsy was performed; it showed mesangial proliferation in all 13 glomeruli and crescents formation in 5 glomeruli. Immunofluorescent staining was positive for IgG, C3, and C1q. The deposition of fibrils was recognized in the glomeruli by electron microscopy. In addition, immunohistochemical staining for DNA-J heat shock protein family member B9 (DNAJB9) was strongly positive in the glomeruli. These results indicated the presence of fibrillary glomerulonephritis (FGN).

Hence, we performed induction therapy with prednisolone and intravenous cyclophosphamide, and subsequently the patient’s renal function improved.
A Rare Case Report of Systemic Lupus Erythematosus (SLE) with Acute Nephritis, Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis, and Thrombotic Thrombocytopenic Purpura (TTP)

Olalekan Adesida,1 Sarah M. Ziegler,1 Timotheo W. A. Wee,2 Oleksiy Yudinskyy,2 Liran Uziel,3,4 Robert M. Calabro,1 Berlinprotocol,1 James R. Galloway,5 Min X. Xie,5 Richard M. spine,1 and Jonathan D. Fedorak,1,2

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a potentially fatal disorder that requires urgent identification and treatment. The association of TTP with systemic lupus erythematosus (SLE) and vasculitis has been reported, however, never simultaneously.

Case Description: A 33-year-old woman with history of SLE presented with acute abdominal pain, fever, arthralgias, and skin rash. She had severe hyperkalemia, diffuse abdominal tenderness, and peritoneal rash. Diagnostic work-up revealed active urine sediment with proteinuria and hematuria, elevated creatinine, anemia, and thrombocytopenia. She was diagnosed with acute lupus nephritis and early microangiopathic hemolytic anemia in the setting of hypersensitive urticaria and started on intravenous methylprednisolone 500 mg once a day. Within 48 hours she developed shock with multiorgan dysfunction and succumbed to her illness. Laboratory tests later showed ADAMTS13 activity less than 10% consistent with TTP and p-antineutrophil cytoplasmic antibody (ANCA) positivity. Autopsy revealed small vessel vasculitis of the visceral organs. Kidney biopsy demonstrated diffuse proliferative glomerulonephritis.

Discussion: This case illustrates the occurrence of SLE nephritis, p-ANCA vasculitis, and severe TTP with rapidly fatal course, and the importance of having a low threshold for initiating plasma exchange therapy. Based on our literature search, this is the first case report on these three afflictions occurring at the same time. The nonspecific signs and symptoms of TTP may hamper a physician’s ability to suspect it on clinical grounds alone, especially in patients with underlying autoimmune conditions. Therefore, when patients with SLE present with thrombocytopenia and features of MAHA, the possibility of TTP should be considered with prompt initiation of empiric plasmapheresis while awaiting test results for confirmation.

TH-PO945

Leukocyte Chemotactic Factor 2 Amyloidosis (ALC2) in a Young Female

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Introduction: ALEC2, initially described in 2008 is now the third most common cause of renal amyloidosis. Patients typically present in the seventh decade of life. We describe a unique case of ALEC2 presenting in a young female after a previous biopsy diagnosis of IgA Nephropathy.

Case Description: A 46-year-old Hispanic female with CKD 3 due to IgA nephropathy was evaluated for rising creatinine from 1.7 to 2.7 mg/dL and proteinuria (Urine protein/creatinine 3.5 g/g). She was on losartan, triamterene-hydrochlorothiazide. Repeat kidney biopsy showed moderate to severe interstitial fibrosis and tubular atrophy with 70% globally sclerotic glomeruli on light microscopy. Immunohistochemistry was positive for Ig A and equivalent lambda and kappa stains. Electron microscopy revealed abundant fibrillary deposits and a Congo red stain for amyloid was strongly positive. Liquid chromatography mass spectrometry analysis was consistent with ALECT2. Her creatinine improved (1.7-2.2 mg/dL) although with persistently elevated proteinuria at 3.7 g/day.

Discussion: Most cases of ALEC2 described are in older population and it is unclear if age at diagnosis affects prognosis. There is yet no specific treatment for ALEC2. For patients who progress to ESRD, renal transplantation has been shown to be a good therapeutic option. So far, very few studies have described patients with IgA nephropathy and ALEC2. We describe an uncommon case in a young patient, and it highlights the need for thorough re-evaluation of patients with acutely worsening renal function or proteinuria, in the setting of known renal disease. A repeat biopsy is often required in such cases as a different pathology is a possibility.

TH-PO946

IgA Nephropathy in Patients with Psoriatic Arthritis: A Case Series and Systematic Review of the Literature

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Introduction: There are cases in the literature of patients with IgAN and PsA, leading to the hypothesis that they may be biologically associated. Here, we present 2 cases and a systematic review of the literature of IgAN coexisting with PsA.

Case Description: Case 1: A 26 year-old man with a history of psoriasis in childhood was diagnosed with PsA at age 20 after developing back pain and bilateral dactylitis. NSAIDs and leflunomide were ineffective, but arthralgias improved on oral methotrexate and adalimumab. SCr was 1.1-1.3 mg/dL (eGFR 52 mL/min) and UA showed 2+ blood, trace protein, 10-20 RBCs/hpf and no WBCs. UPVR ranged from 300-300 mg. Microhematuria persisted and Cr increased to 1.6. A kidney biopsy showed IgAN (Oxford M1, E1, S0, T0, C1). He continued on methotrexate and adalimumab. 3 years later, Scr is 1.1, he has normal proteinuria and no hematuria. Case 2: A 56 year-old woman had severe psoriasis since childhood and a 10-year history of PsA (axial and non-axial joints) controlled with infliximab until she stopped treatment due to atypical mycobacterial pneumonia. She then presented with ARF requiring hemodialysis. Kidney biopsy showed IgAN (M1, E1, S1, T0) and AIN, attributed to rifampin or ethambutol. She was treated with prednisone and recovered kidney function after 20 days. One year later, she presented with shortness of breath, edema, eGFR 9 mL/min, UPVR 3.64, and microhematuria. Repeat kidney biopsy showed IgAN (M1, E1, S1, T1). She was treated with steroids and cyclophosphamide, with improvement to eGFR 22 mL/min. Four months later, she expired with unknown cause of death.

Discussion: Literature Review Our systematic review of the literature identified 16 additional cases of coexisting IgAN and PsA dating back to 1982. Including our two, the cases comprise 14 male and 4 female patients from the USA, Europe, and Japan. Median age of diagnosis of PsA and IgAN were 42 and 47, respectively, with only 1 pediatric case. PsA preceded IgAN in 10 patients (median time from PsA to IgAN diagnosis in these patients 5 years). Serum IgA levels were elevated in 7/8 patients for whom this was described. There is heterogeneity in these patients presentations, treatments, and outcomes. Conclusion Further study is warranted to determine whether there is a pathophysiological link between IgAN and PsA.

TH-PO947

The Cryo Menace

Sri Mahathi Kalipatnapu,1 Chandra Kanth Chaturvedula,1 Maria M. Pickern,1 Julia Schneider,1 Loyola University Medical Center, Maywood, IL,1 MacNeal Hospital, Berwyn, IL

Introduction: Membranoproliferative glomerulonephritis (MPGN) and cryoglobulinemia is a well-recognized complication of HCV infection. We present an interesting case of persistent cryoglobulinemia and MPGN despite sustained remission of hepatitis C treated with Harvoni (direct-acting antiviral).

Case Description: 56 year old man with a history of Hepatitis C cirrhosis, previously treated with Harvoni, was referred for proteinuria and hematuria. Besides mildly elevated transaminases and indirect Bilirubin, his metabolic profile was unremarkable. Protein creatinine ratio was 2gm/gm. Hepatitis C PCR was undetectable. Serology showed low complement levels and normal values of HBAlc, ANA, Anti ds-DNA, ANCA, ASL, and anti nuclear autoantibodies.
Anti-PLA2R abs, and hepatitis B and C antibody. Serum and urine, protein electrophoresis with immunofixation, failed to reveal any monoclonals. Interestingly, cryoglobulins were detected in the serum and a renal biopsy demonstrated membranoproliferative glomerulonephritis with abundant, non-organized, predominantly subendothelial deposits (Fig A).

**Discussion:** MPGN is a pattern of glomerular injury that is characterized by mesangial hypercellularity, endocapillary proliferation, and double-contour formation along the glomerular capillary walls associated with cryoglobulinemia and Hepatitis C infection. Treatment with direct-acting antivirals (DAAs) has been shown to demonstrate cryoglobulinemic quiescence. Our case is unique given the persistence of circulating cryoglobulins and continued glomerular injury, despite SVR. Case of vasculitis and DAH in a patient with Hepatitis C treated with Harvoni was previously reported. This probably suggests that these antibodies propagate injury, despite SVR. Case of vasculitis and DAH in a patient with Hepatitis C treated with Harvoni was previously reported. This probably suggests that these antibodies propagate injury, despite SVR.

**Conclusion:** Our patient had acute HCV with negative cryoglobulins; previous cases had both chronic HCV infection and cryoglobulinemia or cryoglobulinuria. Electron microscopy in our patient did not show cryoglobulinemic immune deposits. The hepatitis C virus may be causally involved in MPGN with monoclonal IgM associated with MCL by a mechanism independent of the production of cryoglobulins. Our patient did not show cryoglobulinemic immune deposits. The hepatitis C virus may be causally involved in MPGN with monoclonal IgM associated with MCL by a mechanism independent of the production of cryoglobulins. References 1 Chelioti E, Efthimiou E et al Neutrophil Mon 2014 (Jul; 6 (4) e18391 2 Yamada M, Deitzer, D et al Am J Kidney Disease 2016, 67 (5) A1-A118 3 Bracci, P, Benavente, Y et al J Natl Cancer Inst monographs 2014 48, 52-66;

**Fig A**

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**TH-PO948**

**Acute Lupus Hemophagocytic Syndrome as Initial Presentation of Membranous Lupus Nephritis: Case Report with Successful Treatment**

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**Introduction:** Acute Lupus Hemophagocytic Syndrome (ALHS) is a rare entity. It is highly unusual to diagnose lupus nephritis in an adult presenting as ALHS. Both ALHS and SLE responded well to therapy with MMF with steroids, which has rarely been described in literature.

**Case Description:** 40-year-old Hispanic lady with fibromyalgia, hypothyroidism and hypertension, presented with fever, weakness, myalgia and photosensitivity. Physical examination was significant for alopecia and 3/5 muscle strength in lower extremities. No evidence of synovitis or organomegaly. Investigation: creatinine 0.4, albumin 2.4, AST 168, ALT 52, LDH 387, ALP 108, triglycerides 674, ferritin 3211, hemoglobin 7.1, WBC 9.0, platelets 127, ANA (+1:160), AntiDNA, +smAb, low C3 and C4. UA was positive for RBC and protein. Urine protein/creatinine ratio was 1.2 g/day. Bone marrow biopsy was done, showing erythrophagocytosis. Soluble IL-2 receptor (CD25) level and CD8 immune competence panel were normal. She fulfilled SLICC criteria for SLE.

Renal biopsy showed membranous lupus nephritis class V She was started on prednisone 60 mg daily and MMF 500 mg twice a day and later increased to 1000 mg twice a day and gradually, prednisone was tapered down to 5 mg daily. Significant improvement in symptoms noted and labs including ferritin, triglycerides and blood counts became normal and proteinuria resolved. 

**Discussion:** HLH (Hemophagocytic lymphohistiocytosis) is a life-threatening disorder associated with high mortality. Secondary HLH results from underlying infections, malignant and autoimmune conditions. When HLH is attributed to SLE, it is called Acute Lupus Hemophagocytic Syndrome (ALHS). Incidence of HLH in SLE is estimated to be around 0.9% to 4.6% with a mortality rate varying from 5% to 35%. Clinical manifestations include high-grade fever, hepatosplenomegaly, lymphadenopathy and coagulopathy. Abnormal laboratory findings include cytopenias, hyperferritinemia and hypertriglyceridemia. There are no randomized trials to guide therapy. Treatment in ALHS is aimed at managing the underlying condition. If unresponsive Etoposide is used. This case highlights the importance of early recognition of ALHS, to prevent high morbidity and mortality. MMF and prednisolone induction and maintenance therapy is a viable option in patients with ALHS.

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**TH-PO950**

**Congophilic Fibrillary Glomerulonephritis: A Diagnostic Challenge**

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**Introduction:** Fibrillary glomerulonephritis is characterised by the presence of randomly orientated nonbranching fibrils larger than those found in amyloid and lack the histochemical staining of amyloid. The absence of Congo Red reactivity has traditionally been a defining feature to differentiate it from amyloid glomerulopathy. We examined two cases showing the existence of Congophilic fibrillary glomerulopathy.

**Case Description:** Case 1: A 67 year old man presented with peripheral oedema and subnephrotic proteinuria on a background of poorly controlled hypertension. Initial renal biopsy suggested a focal segmental glomerulosclerosis with 13.9 nm fibrils on electron microscopy in the previous year. Despite treatment with rituximab, cyclosporin and cyclophosphamide, there was ongoing proteinuria with repeat renal biopsy showing Congo Red positive staining with 15.9 nm fibrils present. A monoclonal gammopathy of uncertain significance with IgM lambda was found. Case 2: A 51 year old man presented with newly diagnosed diabetes and was found to have subnephrotic proteinuria and microscopic haematuria. He underwent a renal biopsy finding Congo Red positive deposits with ultrastructural findings of 20 nm fibrils. Subsequent screening for malignancy and lymphoproliferative disease were negative. Despite immunosuppression with rituximab, cyclophosphamide and prednisone, the patient continues to have ongoing proteinuria.

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Underline represents presenting author.
TH-P0951
Double Troubleshooting: Pulmonary-Renal Syndrome due to IgG4-RD and Myeloperoxidase-ANCA Vasculitis

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Introduction: IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition that could be similar or overlap with ANCA-associated vasculitis (AAV).
Case Description: 38-year-old female with a history of inflammatory arthritis and high ANA titers, but no definite diagnosis of lupus on hydroxychloroquine presentation with dyspnea and hemoptysis for one month. She also reported recurrent sinusitis, arthritis, and Raynaud’s symptoms. Urinalysis revealed hematuria and cellular casts. Urine protein/creatinine was 2.8 grams. Serum creatinine rose from 0.7 to 1.08 mg/dL. CT Chest showed right upper lobe consolidation with cavitation. Anti MPO antibody was positive for >100 U/ml (0.0-9.0 U/mL). Serum complements were normal and anti-double strand DNA was negative. Initially, the patient was diagnosed with microscopic polyangiitis (MPA). However, lung biopsy noted a fibro-inflammatory lesion with elevated IgG4 positive plasma cells (20-30 per HPF) typical of IgG4-RD. Serum IgG4 level was elevated. Kidney biopsy showed IgG4-related glomerulonephritis with cellular crescents and numerous subepithelial and intramembranous deposits that were negative for PLA2R immunofluorescence. Acute tubulointerstitial fibrosis was noted. Lack of C1q deposition and absence of tubuloreticular inclusions argued against lupus membranous disease. Patient was subsequently found to have p-ANCA with positive ANCA. Anti-GBM and RNP antibodies were negative. The patient was treated with rituximab and cyclophosphamide.

Discussion: In the literature, two entities have been described: IgG4-RD with ANCA positivity and AAV associated with increased IgG4-positive plasma cells. Our patient presented with crescentic membranous GN and a very high anti MPO antibody. The histological features of lung biopsy however showed characteristics of IgG4-RD. Although membranous GN is reported both with AAV and IgG4-RD, it is not a typical renal biopsy finding of either of those diseases. Corticosteroids are the first line therapy in IgG4-RD. Our case highlights the importance of recognising such cases of overlap and the potential role of treatment for both diseases.

TH-P0952
IgG4 Positive Linear Deposition Anti-Glomerular Basement Membrane Nephritis with Negative Glomerular Basement Membrane Antibody (GBM Ab)
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Introduction: Anti-glomerular basement membrane (anti-GBM) nephritis is an antibody mediated small vessel vasculitis usually caused by IgG antibodies with predominance of IgG1 and IgG3 directed against basement membrane antigens.
Case Description: 22 years old morbidly obese male with history of asthma, recurrent ear infections requiring Eustachian tubes, smoking and exposure to polyvinyl chloride, presented with 3 months of fatigue and was found to have proteinuria on urinalysis. He denied fever, chills, chest pain, cough or hemoptysis, abdominal pain, melena, arthralgias, edema, dysuria, hematuria or tea-colored urine. On physical exam, he was afebrile with stable vital signs and absence of sinus tenderness, lymphadenopathy, synovitis, rash and edema. Chest, cardiovascular and abdominal exam were unremarkable. 24-hour urine protein was 3.8g and albumin was 2.4g. Urine sediments showed red cell casts. Labs showed a serum creatinine 1.1-2mg/dL, serum albumin 3.7g/dL, BUN 15.2% and negative anti-dsDNA, ANA, cANCA, pANCA, PR3, MPO, anti-GBM, RF, Jo-1, cryoglobulins, HIV, HBV, HCV, SPEP and UPEP. Serum complement levels and free light chains ratio were normal. Renal ultrasound showed normal size kidneys. Chest CT showed no pulmonary nodules < 5 mm. Renal biopsy showed proliferative glomerulonephritis with 2/17 glomeruli involved. Three glomeruli were positive for IgG4 along the GBM in immunofluorescence and foot process effacement in electron microscopy. He was started on prednisone 80mg and cyclophosphamide 2.5mg/kg/d; plasmapheresis was not done due to negative anti-GBM titers. Few months later he was started on lisinopril 40mg. After 19 months of treatment, 24-hour urine protein decreased to 8 g/day.
Discussion: Usually anti-GBM nephritis presents as rapidly progressive GN rather than with nephrotic range proteinuria. Patients with deposition of IgG on the GBM on immunofluorescence and negative for circulating antibodies by conventional assays, may be positive when tested by highly sensitive bioassays or ELISA. In anti-GBM disease, IgG1 and IgG3 subclasses are the usual antibodies but barely IgG4 as these antibodies may not be detected on routine assays. Patients with diabetic nephropathy may present with linear IgG but should not have crescents or cellular casts as noted in our patient.

TH-P0953
A Case of Familial Fibrillar Glomerulonephritis in Living Related Kidney Transplantation (LRKT)
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Introduction: Fibrillar glomerulonephritis(FGN) is a rare form of kidney disease found in ~1.0% of adult native kidney biopsies with only 4 reported cases of familial FGN. The discovery of protein DNAJ heat shock protein family (Hsp40) member 9 (DNAJB9) has aided diagnosis of FGN.
Case Description: A 49-year-old African-American man was found to have proteinuria on routine exam with UPCR 6 g/g and serum creatinine(1.0) mg/dL. Renal biopsy later revealed FGN. Light microscopy(LM) showed diffuse mesangial matrix expansion with thickened glomerular capillary walls(GCW) (Fig 1A) with negative Congo red stain. Immunofluorescence(IF) showed 3+ staining for IgG, C3 and lambda(L), 2+ staining for kappa(K). Electron microscopy(EM) showed linear, randomly arranged fibrils with average diameter of 16 nm. DNAJB9 stain done later was strongly positive (Fig 1B). Further workup did not reveal monoclonal gammopathy and he had no known family history of kidney disease. He was treated with steroids as immunosuppressive therapy(IST). He presented to Columbia 5 years later with CKD Stage 5, further IST was held. At age 55, he underwent LRKT from his son. Prior to organ donation, his son had Scr of 0.88mg/dL, UA with negative blood and trace protein, UPCR 15mg/dL. Post revascularization kidney biopsy showed FGN. LM showed mild mesangial proliferation with scattered double contours (Fig 2A) and negative Congo red stain. IF showed IgG4-RD with segmental GCW staining for IgG3 (Fig 2C). DNAJB9 stain was positive (Fig 2B). EM showed randomly oriented fibrils with mean diameter of 18 nm (Fig 2C). These findings are consistent with donor-derived FGN, indicating a familial form of FGN.
Discussion: We described here a case of familial FGN confirmed by DNAJB9 staining on biopsy. Presence of well-formed fibrils and glomerular changes in the donor kidney despite minimal clinical findings suggest in-depth evaluation of related donors may be important in FGN.

TH-P0954
A Case of Poststreptococcal Glomerulonephritis with Concurrent ANCA-Associated Vasculitis and Aortitis: Challenges in Diagnosis and Treatment
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Introduction: Aortitis is an uncommon condition with either infectious or rheumatologic etiology. Common rheumatologic causes of aortitis include the large vessel vasculitides, Takayasu’s arteritis and giant cell arteritis; however, other rheumatologic causes exist, such as ANCA-associated vasculitides (AAV). A few previous cases of aortitis associated with perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and myeloperoxidase-ANCA (MPO-ANCA) have been reported, however, in medical literature, AAV is infrequently discussed in association with large vessel involvement. It is rare to find cases of post-streptococcal glomerulonephritis (PSGN) in which there is concurrent AAV affecting large vessels.
Case Description: We report a case of a 36-year old Hispanic woman with an initial presentation of right leg cellulitis with positive antistreptolysin-O titer. Her past medical history was significant for previous right leg skin lesion and right groin lymph node abscesses. She developed hematuria during her admission and severe epistaxis. Due to worsening kidney function and persistent hyperkalemia, hemodialysis was initiated. Kidney biopsy results supported PSGN. P-ANCA, MPO, and proteinase-3 (PR3) antibody assays were positive. Magnetic resonance angiography results supported aortitis. Due to treatment for active infection, immunotherapy was postponed. Repeat P-ANCA, PR3, and MPO were persistently positive. Subsequently, she developed a cough and dyspnea and underwent bronchoscopy which revealed no significant findings. A case of paraneoplastic AAV with concurrent PSGN was suspected and Rituximab was initiated. Rituximab therapy was followed by significant improvement in her dyspnea and hematuria.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Discussion: This case highlights a diagnostic dilemma in vasculitis classification: determining whether the disease is due to ANCA-associated vasculitis, large vessel arteritis, or an infectious process. Renal biopsy and clinical picture supported an infectious etiology of glomerulonephritis, thus the positive p-ANCA and MPO antibody assay were initially thought to be induced by infection, however, our patient had persistently positive ANCA and MPO titers and developed DAH. This case also highlights the challenge in starting immunosuppressive treatments during infection, and, finally, the response to Rituximab and plasmapheresis therapies.

TH-P0955

Collapsing Glomerulopathy in an APOL1 Compound Heterozygous Patient with CMV Infection: The Double Hit Theory
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Introduction: Collapsing glomerulopathy (CG) is a rare and aggressive variant of focal segmental glomerulosclerosis (FSGS). Commonly associated with human immune deficiency virus (HIV). We present a case of CG in an HIV-negative African American (AA) patient with Cytomegalovirus (CMV) infection. The patient is compound heterozygous for APOL1 risk variants. We propose that CMV can act as a “second hit” in the pathogenesis of CG in the genetically predisposed individuals.

Case Description: A 31-year-old AA female with sickle cell disease was admitted with 2 weeks of fever, malaise, nausea, vomiting, cough and chest wall tenderness. On admission her serum creatinine was 2.39 mg/dl and peaked at 7.19mg/dl. Urine investigations revealed nephrotic range proteinuria. CMV DNA PCR was positive in plasma and urine. Renal biopsy showed features of collapsing glomerulopathy, characterized by collapse of the capillary loops, prominence of the overlying epithelial cells and extensive effacement of foot processes. Genetic testing showed compound heterozygous mutations in the APOL1 gene. The patient was treated with high dose steroids and anti-viral therapy with ganciclovir. With resolution of CMV infection, she made full renal recovery.

Discussion: CG as well as other nephropathies have well established racial disparity, probably due to the genetic variants affecting AA patients. The discovery of apolipoprotein L1 gene (APOL1) helped improve our understanding of genetic predisposition to renal disease. Increased risk can be attributed to the presence of two specific variants in the APOL1 gene (G1 and G2). These variants are present in about 30% of APOL1 alleles in the AA population. Individuals with one or two risk alleles are at greater risk for developing FSGS, hypertension-associated ESRD, sickle cell-associated kidney disease, HIV-associated nephropathy, and shortened graft survival of kidney transplants. CG was initially described in HIV patients but also associated with viral infections (e.g. parvovirus B19 and CMV), lymphoproliferative disorders, autoimmune diseases and sickle cell disease. CMV infection could be a second hit in the genetically susceptible patient. Identification of CMV infection in patients with CG is important as they usually improve with treatment of the viral infection.

TH-P0956

Favorable Effect of Bortezomib in Patients with Noninfectious Mixed Cryoglobulinemia Complicated with B Cell Lymphoma: Experience of Two Cases
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Introduction: Non-infectious mixed cryoglobulinemia (MC) is rare disorder associated with autoimmune or hematological diseases, eventually causing systemic vasculitis and glomerulonephritis. Due to the low frequency of this disease, there is no established strategy for non-infectious MC has not been established. Here we report that two cases with non-infectious MC complicated with B cell lymphoma who had good response to a combination of corticosteroid and bortezomib (BTZ), a proteasome inhibitor used for the treatment of multiple myeloma and B-cell Lymphoma.

Case Description: Case1. A 61-year-old man with a medical history of mucosa-associated lymphoid tissue (MALT) lymphoma presented with nephritic syndrome, purpura, and congestive heart failure. Laboratory tests revealed monoclonal IgM-κ and presence of cryoglobulins (CG). A renal biopsy showed glomerulonephritis with deposits of IgM-κ. A diagnosis of non-infectious cryoglobinemic glomerulonephritis was made and treatment was initiated with corticosteroid, rituximab and plasma exchange with no improvement of clinical manifestations. After the informed consent, the patient received lenalidomide with BTZ containing therapy for treatment of MALT lymphoma. He was treated with a combination therapy of BTZ with corticosteroid, and achieved clinical remission of nephritic syndrome.

Case Description: We presented two case of non-infectious MC complicated with lymphoma in whom BTZ was added in the treatment protocol to ameliorate renal manifestations. The improvement of renal function was associated with the disappearance of serum CG and decrease of serum levels of monoclonal IgM-κ. These findings suggest that BTZ suppresses the IgM-κ producing plasma cells and the deposition of CG in glomeruli, leading to improvement of nephritis. BTZ had anti-inflammatory effects as well, presumably involved in the protection of renal injury. This is a first report to show that treatment protocol including BTZ lead favourable outcome in patients with non-infectious MC with B cell lymphoma.

TH-P0957

Recurrent C3 Glomerulonephritis
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Introduction: C3 glomerulopathy encompasses dense deposit disease and C3 glomerulonephritis. On electron microscopy it is defined as C3 deposits more than 2 orders of other immunoglobulins. Pathogenesis involves activation of alternative complement pathway due to genetic or acquired mutations. Post infectious glomerulonephritis with current hematuria or proteinuria is termed as atypical. We present a case of C3 glomerulonephritis presenting as post infectious glomerulonephritis then crescentic C3 treated with immunosuppression.

Case Description: A 54 year old female with history of glomerulonephritis (2008, 2016) presented with hematuria. Labs significant for creatinine 3mg/dl (baseline 1.7), protein excretion 2g/day, C3 9mg/dl and C4 20mg/dl. Urine analysis with 4000 red blood cells. Workup for acquired factors showed normal factor H, serum C3b-9, negative C3 nephritic factor and CH50 less than 10mg/dl. Urine and blood cultures, antibodies to Proteus-1, myeloperoxidase and genetic testing was negative. Steroid 1mg/kg/d and plasmapheresis were given twice daily for 4 days, transitioned to prednisone. Due to increased creatinine hemodialysis was initiated. Biopsy showed crescentic C3 dominant proliferative glomerulonephritis. Immunofluorescence 3+ C3, 2+kappa and 1+ lambda. Electron microscopy showed scattered subepithelial hump-like intermembranous and mesangial deposits. After 6 doses of cyclophosphamide 750mg, in 3 months renal function stabilized with creatinine 1.34mg/dl, urine protein excretion 0.8g and C3 153mg/dl. In 2008, kidney biopsy showed post-infectious glomerulonephritis, low C3 and CH50 responsive to steroids. In 2016 she presented with pyelonephritis, creatinine 2.8mg/dl, protein excretion 2 g/day, urinalysis 3+ red blood cells, low C3 and normal C4. Biopsy showed membranoproliferative glomerulonephritis with crescents. Immunofluorescence positive for IgG 2+, C3 2+, kappa 1+ and lambda 2+. Creatinine and C3 levels normalized post steroid therapy.

Discussion: Atypical Post infectious glomerulonephritis and C3 glomerulopathy are two sides of the same coin involving alternative complement pathway activation as shown by our patient’s biopsy findings. Due to repetitive steroid and immunosuppression responsiveness we conclude that recurrent cases of atypical post infectious glomerulonephritis be investigated for alternate pathway mutations. Novel anticomplement medications such as eculizumab may also be used.

TH-P0958

Anti-GBM Disease: A Case Report of an Atypical Presentation
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Introduction: Anti GBM disease is a rarely encountered, but well known entity. It can present with nephritic syndrome, alveolar hemorrhage, or both. It is typically associated with positive circulating anti GMB antibodies. We are reporting a case of seronegative anti GMB antibody disease presenting with RPCR picture.

Case Description: A 59 year old female with a history of hemochromatosis presented with complaints of night sweats and fever. She was sent to the hospital by her PCP with abnormal labs and hypertension. Her physical exam was unremarkable. Her labs were notable for creatinine of 0.03mg/dl, BUN of 32 mg/dl, hgb of 23 ml/m2, 1.71 mg/dl, and CRP of 113. Dipstick urinalysis was positive for blood and protein. Urine sediment exam showed dysmorphic RBCs. Measured urine microalbuminuria was 299 mg/g of creatinine. Extensive serological workup, including testing for anti GMB antibodies, was negative. Extensive workup of anti GBM disease was negative and showed atypical presentation of anti glomerulonephritis as well as focal interstitial granulomatous inflammation with giant cells. The immunofluorescence studies revealed findings consistent with IgG type anti-glomerular basement membrane disease. After pulse methylprednisolone was started, the creatinine started to trend down. The patient was eventually treated with prednisone taper and rituximab with continuous improvement in her GFR.

Discussion: Anti GBM disease is frequently associated circulating IgG antibodies that commonly target cryptic, conformational epitopes within the NC1 domain of the alpha 3 chain of Type IV Collagen. These antibodies are usually detected in sera using different conventional serological methods. Seronegativity in anti GBM disease is extremely rare. We identified less than 10 cases describing this atypical presentation in the literature. In one case, anti GBM detection was variable with each relapse. Sero negative anti GMB disease has also been described to recur in renal allografts. Anti GMB antibodies are known to be heterogeneous with respect to collagen type IV domain reactivity in the sera of patients with anti GMB antibody disease. This could explain the seronegativity of anti GBM disease when conventional serological methods are used. Cases with sero negative anti GMB disease present challenges not only for diagnosis but also management, since anti GMB titers cannot be used to monitor these patients.

TH-P0959

Hydralazine-Induced Crescentic Pauic-IImune Glomerulonephritis Associated with Multi-Antigenity
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Introduction: Hydralazine use is common for treatment of hypertension, and heart failure with the ability to induce lupus as a rare complication. Though mechanisms are not understood, it may also be a causal factor in antinuclear cytoplasmic antibody (ANCA) vasculitis (AAV). This emerging syndrome is characterized by crescentic pauci-immune
glomerulonephritis and classically positive antibodies, including anti-myeloperoxidase (MPO) and anti-histone. We report a case notable for the wide array of auto antibodies, the combination of which has not been previously reported.

**Case Description:** A 71 year old male presented to the hospital with a two month history of fatigue. His past medical history included hypertension for which he was taking Hydralazine, and an ischemic cardiomyopathy. His lab results showed an elevation in serum creatinine of 3.2 mg/dl from a baseline of 1.2 – 1.3 mg/dL. Urinalysis revealed proteinuria and hematuria with accompanying red blood cells. Serologies returned positive not only anti-histone antibodies, but also for both MPO and anti-proteinase 3 (PR3) antibodies. In addition, was a high titer ANA, double stranded DNA, low C3, presence of lupus anticoagulant, and anti-cardiolipin IgG. Kidney biopsy revealed focal segmental necrotizing and crescentic glomerulonephritis, pauci-immune type, acute and subacute. CT chest was negative for pulmonary hemorrhage. Taken together, these findings seemed consistent with a drug induced AAV. Deemed to be the culprit, Hydralazine was discontinued and treatment rendered with pulse dose steroids, transitioning to tapering Prednisone and two doses of Rituximab. This led to a marked clinical and serologic improvement, which was not only rapid, but also proved durable.

**Discussion:** Drug induced AAV has been linked to certain agents, including Hydralazine. The presentation may be severe, and often associated antibody positivity such as MPO and anti-histone may hold the key to the diagnosis. For the treatment of drug-induced MN, early diagnosis is critical to prevent progression to chronic kidney disease. With careful monitoring and a prompt change in immunosuppressive therapy, patients can achieve a durable response and may avoid the need for dialysis or transplantation.

**Conclusion:** This case highlights the importance of early identification and prompt discontinuation of suspected drugs in the management of drug-induced MN. Early intervention with immunosuppressive therapy, such as pulse doses of corticosteroids and rituximab, can lead to significant improvement in renal function and reduce the risk of progression to chronic kidney disease. The significance of drug-induced MN is underscored by the potential for recovery with timely intervention, emphasizing the importance of clinical vigilance and timely drug discontinuation in such cases.

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**TH-PO961**

Is Liposorber an Option for Lipoprotein Glomerulopathy in Pediatric African American Males?

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**Introduction:** Lipoprotein glomerulopathy is a rare inherited renal disease that is characterized by the accumulation of lipoproteins leading to the formation of lipoprotein thrombi with markedly dilated glomerular capillaries. The disorder is associated with an accelerated progression leading to massive proteinuria and dyslipidemia with high chance of progression to chronic kidney disease. The first publication of a case was reported in 1989 by Saito, and has since been commonly reported in adult individuals of Japanese and Chinese descent.

**Case Description:** Interestingly, our report looks into the presentation of lipoprotein glomerulopathy in a 7 year old African American male who has been followed since birth for hypertension, hypercholesterolemia, nephrotic range proteinuria, and multiple past episodes of renal AKI. A renal biopsy was performed and diagnosis of lipoprotein glomerulopathy was confirmed. Results of immunohistological diagnosis revealed a heterogeneous mutation of ApoE2. The patient also presented with hemihyperplasia of the right lower extremity, increasing our suspicion for a possible accompanying WT gene mutation. Treatment has been focused on controlling hypertension and symptoms of chronic kidney disease. Patient has been taking a beta blocker, angiotensin converting enzyme inhibitor, and calcium channel blockers for hypertension. These medications have been effective in reducing the blood pressure from 140-150/100 to 120-130/80. To treat for hypercholesterolemia that imposes continued damage on the kidneys of patients with this disease, he has been taking fibrates and statins, but his cholesterol levels continue to be elevated, while triglyceride levels are well controlled. Further treatment evaluation is being focused on the possibility of beginning patient on Liposorber once per month to remove the high levels of LDL. Kidney transplant consideration is low due to recurrence being reported in all post transplanted kidneys.

**Discussion:** This case illustrates the possible expansion of a rare renal disease outside of commonly targeted population. Recognition of lipoprotein glomerulopathy and its clinical features will become critical in future evaluation of nephrotic syndromes in the pediatric population.

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**TH-PO962**

Minimal Change Disease in an 82-Year-Old Man with Type 2 Diabetes Without Histologic Evidence of Diabetic Glomerulosclerosis on Renal Biopsy

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**Introduction:** Minimal change disease (MCD) in adults with type 2 diabetes mellitus (T2DM) is a rare occurrence. Finding MCD in this population without diabetic glomerulosclerosis (DGS) is even more uncommon. We found only 16 reported cases of MCD in the setting of adult type 2 diabetes. Only 4 of those were confirmed to have MCD in the absence of DGS. We report a case of MCD in an 82 year old man with type 2 diabetes whose kidney biopsy showed no histologic evidence of diabetic glomerulosclerosis.

**Case Description:** An 82 year old man with a 10-year history of T2DM on insulin for 1 year presented with a one week history of lower extremity edema and shortness of breath. On physical examination his serum creatinine was 1.4 mg/dl and his serum albumin was 2.4 grams per deciliter. Protein in 24-hour urine was 14 grams. Serology and serum protein electrophoresis were normal. Kidney biopsy was performed. Light microscopy showed normal glomeruli with no evidence of glomerulosclerosis. Electron microscopy revealed diffuse effacement of foot processes diagnostic of minimal change disease. Patient was started on prednisone and achieved complete remission in 5 weeks. At his six-month follow up he was doing well. His creatinine was down to 1.0 and urine protein/creatinine was 0.07 g/g.

**Discussion:** This case illustrates the value of kidney biopsy in the diagnosis of severe nephrotic syndrome in adults with T2DM. Nephrotic syndrome occurring in a patient with diabetes is often presumed to be due to diabetic glomerulosclerosis and renal biopsy is usually not performed. However, in this patient there were a number of pivot points that suggested further exploration was necessary, including the degree of proteinuria and abruptness of the onset. This case is of clinical significance because MCD in an older diabetic can be easily missed, but if diagnosed, is almost always curable as it was in this patient. Our patient adds to the literature of MCD presenting in older adults with T2DM and provides a new upper age of reported occurrence. It is uncertain as to whether this is a truly rare occurrence or the result of under-reporting because kidney biopsy is infrequently performed in older adults with minimal change disease. The true incidence of MCD in older adults with T2DM may be less rare than the literature suggests.

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**TH-PO963**

Unusual Presentation of Cryoglobulin-Positive Fibrillary Glomerulonephritis

Edward G. Medeiros,1 Nathan Calabro-Kailukaitis,2 3 Matthew R. Lynch.

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**Introduction:** Fibrillary glomerulonephritis encompasses approximately 1% of adult native kidney biopsies. Although considered a predominantly idiopathic disease, up to 1/3 reveal a secondary cause such as monoclonal gammopathy, autoimmune disease or malignancy. In the two largest case series published to date, over 22% of histologically positive serum cryoglobulins; it is unclear if these patients had concurrent HCV infection. A
Using Rituximab: A Case Report

Remission of Refractory THSD7A-Associated Membranous Nephropathy

Case Description: A 72-year-old male was admitted to Xinhua Hospital because of proteinuria and hematuria. His serum creatinine was 1.2 mg/dL. On examination, he had a rash and swelling of the lower extremities. The patient had a history of chronic kidney disease due to membranous nephropathy.

Introduction: Rituximab (RTX) is reported to induce clinical remission in 60-80% of primary membranous nephropathy (MN) patients. Due to the rarity, only four thrombocytopenia type-1 domain-containing 7A (THSD7A) associated cases were recorded in clinical trials of RTX treating MN, without detailed description of clinical information or treatment outcome. Here, we reported the successful RTX treatment of a THSD7A-associated MN patient non-responsive to tacrolimus and glucocorticoids.

Case Description: A 72-year-old male was admitted to Xinhua Hospital because of persistent nephrotic-range proteinuria and non-responsive to tacrolimus and glucocorticoids. Laboratory results included 24hr proteinuria 6.2g, serum albumin 2.15g/dL and serum creatinine 1.39mg/dL. Renal biopsy results suggested MN with negative glomerular staining of phospholipase A2 receptor and IgG4 but positive THSD7A by immunohistochemistry. Serum THSD7A-antibody titer was 1:100 by indirect immunofluorescence. The patient had a rash of 7 years without metastasis. Renal biopsy was reviewed and weakly positive THSD7A staining was found, which can be seen in 43% of renal tumors. Extensive screening ruled out cancer recurrence or metastasis and RTX was given at a weekly dose of 375mg/m2 for four weeks. At month 6, the patient had a successful partial proteinuria remission and THSD7A-antibody titer decreased to 1:10.

Discussion: In this refractory case, the treatment of RTX achieved partial remission of proteinuria and circulating THSD7A antibody depletion at month 6, supporting its good efficacy on THSD7A-associated MN. We also emphasize that screening for malignancy is warranted in THSD7A-associated MN before immunosuppressive therapy.

Fig 2 A summary of the clinical course.

Fig 2 Histological findings.

TH-PO966
Renal Manifestations Associated with Bartonella Infection

Case Description: A 56 y/o man with LVAD presented with a vasculitis rash and AKI. He had a 2-week history of fever, malaise, and myalgia. His blood pressure was 170/90 mmHg, and his serum creatinine was 1.5 mg/dL. Urine analysis showed 2+ protein and 2+ blood. The patient had a history of IE due to Staphylococcus aureus.

Introduction: Culture negative endocarditis constitutes about 8% of all cases. Bartonella henselae is a common causative organism. Here we discuss 3 cases of GN associated with B.henselae infections masquerading as vasculitis, IgA and focal necrotizing C3 GN.

Case Description: Case 1: A 56 y/o man with LVAD presented with SOB and AKI with rapid rise in SCr from 1 to 3.45mg/dL over 3 weeks. Lab showed positive ANA, ANCA (+PR3) and normal complements (Table). Renal pathology was highly suggestive of infection-associated GN. Additional w/s revealed B.henselae Ab IgG > 1:1024 and TEE revealed possible vegetation in RV pacemaker lead. He was treated with Doxycycline and rifampin, plus oral prednisone. F/U SCr in 1 year was 1.1mg/dL.

Case 2: A 42 y/o man with bioprosthetic AV valve presented with a vasculitis rash and AKI and presented with a vasculitis rash and AKI. The patient had a history of IE due to Staphylococcus aureus.

TH-PO965
Tubular Basement Membrane Deposits in Lupus Nephritis

Case Description: A 66 year-old female with history of longstanding diabetes mellitus, hypertension and stage III chronic kidney disease with serum creatinine 1.6mg/dl, six months prior was admitted with abnormal labs including serum creatinine of 7mg/dl on routine testing. She denied localizing symptoms to explain worsening renal function. She was afebrile and initial blood pressure was 170/90mmHg. On physical exam, lungs were clear and there was no rash or edema. Repeat labs revealed serum creatinine 7.49mg/dl, BUN 57mg/dl, serum albumin 3.3g/dl and 7 grams of protein on 24hr collection. Urine sediment showed hematuria with dysmorphic RBCs and numerous WBCs. Further tests for HBV, HCV, HIV, ANA, ANCA, and anti-GBM were negative. Hypocomplementemia with undetectable C4 and normal C3 was present, along with elevated rheumatoid factor at 152 IU/mL. Serum cryoglobulins were positive. SPEP was weakly positive for IgG lambda. Renal biopsy exhibited global glomerular sclerosis, and diffuse deposition of haphazardly arranged 15nm filaments within glomerular capillary walls and mesangial matrix on electron microscopy. Staining for DNAJB9 was positive. Despite treatment with Rituximab for 4 weeks, her disease progressed and required renal replacement therapy. Serum cryoglobulins remained positive after treatment.

Discussion: Fibrillary GN is a rare disease associated with poor renal outcomes and progression to ESRD. Only two previous cases of Fibrillary GN had positive serum cryoglobulins. There is little evidence to guide therapy in this disease, and even less is known about those with positive serum cryoglobulins. Efforts to identify secondary causes in such patients should include viral illness, malignancy and autoimmune disease. Further investigations to evaluate more effective therapeutic options are needed.

Fig 2 Histological findings.

TH-PO964
Remission of Refractory THSD7A-Associated Membranous Nephropathy Using Rituximab: A Case Report

Case Description: A 66 year-old female with history of longstanding diabetes mellitus, hypertension and stage III chronic kidney disease with serum creatinine 1.6mg/dl, six months prior was admitted with abnormal labs including serum creatinine of 7mg/dl on routine testing. She denied localizing symptoms to explain worsening renal function. She was afebrile and initial blood pressure was 170/90mmHg. On physical exam, lungs were clear and there was no rash or edema. Repeat labs revealed serum creatinine 7.49mg/dl, BUN 57mg/dl, serum albumin 3.3g/dl and 7 grams of protein on 24hr collection. Urine sediment showed hematuria with dysmorphic RBCs and numerous WBCs. Further tests for HBV, HCV, HIV, ANA, ANCA, and anti-GBM were negative. Hypocomplementemia with undetectable C4 and normal C3 was present, along with elevated rheumatoid factor at 152 IU/mL. Serum cryoglobulins were positive. SPEP was weakly positive for IgG lambda. Renal biopsy exhibited global glomerular sclerosis, and diffuse deposition of haphazardly arranged 15nm filaments within glomerular capillary walls and mesangial matrix on electron microscopy. Staining for DNAJB9 was positive. Despite treatment with Rituximab for 4 weeks, her disease progressed and required renal replacement therapy. Serum cryoglobulins remained positive after treatment.

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Case Description: A 38-year-old woman was admitted to our department with a 7-month history of proteinuria and without a substantial past medical history. A 24 hour urine test showed proteinuria excretion of 1.2 g/day with no microscopic hematuria. A blood test showed 0.63 mg/dL of creatinine, 5.98 g/dL of total protein and 3.54 g/dL of albumin. Cryoglobulinemia was not detected. A renal biopsy showed membranous nephropathy by light microscopy, IgM and C3 deposits along the glomerular basement membrane, in subendothelial, subepithelial, and intra-glomerular basement membranes by electron microscopy. An immunofluorescence (IF) study showed restricted IgG-1 Kappa deposition, which was validated by MS/MS spectrometry using several glomeruli dissected by LMD from the same sample which showed deposits of a V-chain variable lesion. Therefore, we were able to diagnose the patient with PGNMID, and initiate treatment with an angiotensin converting enzyme inhibitor. The patient’s renal function has been stable up to the time of writing this report.

The evidence of pathogenic deposits shown by immunostaining was consistent with the result of MS/MS spectrometry. Based on the observations of this case, we validated MS/MS spectrometry to be a sensitive tool for detecting glomerular basement membrane deposits and might enable a better understanding of GDDs. <Acknowledgment> LMD and MS/MS analysis was performed by Drs. Yoshinaga, Yazaki, Sekijama (Shinshu University)

TH-PO969

Mercury in Natural Health Products as a Cause of Membranous Nephropathy
Stephen B. Tanner, Vivek Sharma, John W. Idoux. Nephrology, Baylor Scott and White, Temple, TX.

Introduction: Membranous nephropathy (MN) is characterized by subepithelial deposits along the glomerular basement membrane and it is the most common cause of nephrotic syndrome in white adults (1, 2). 80% of cases are primary with antibodies to specificity type-1 domain-containing 7A (THSD7A). An emerging concern is use of natural health products (NHPs) including vitamins, supplements, and herbal remedies. The composition of these products is not tightly regulated and some have been shown to contain mercury (4). We present a case of MN due to mercury intoxication related to use of NHPs.

Case Description: 39-year-old white male with past medical history of depression presented with worsening bilateral lower extremity edema and abdominal distension over the past month. He was taking multiple herbal supplements daily for 6 months. He denied changes in urine output, use of non-steroidal anti-inflammatory drugs, illicit drugs, or alcohol. He reported eating fish 1 meal per month. On evaluation, He demonstrated anasarca. No other abnormalities noted on physical examination. Lab work demonstrated normal renal function, nephritic range proteinuria, hypalbuminemia, and hyperlipidemia. Urine protein-to-creatinine ratio was elevated at 14.3 (ref 0.00 - 0.19). ANA, hepatitis B and C, and C3, C4 were normal. Full house staining was IgG predominant and numerous subepithelial, paramesangial deposits and tubulocortical inclusions were seen. PL2AR stain was positive but serum anti-PL2AR antibody was negative. Although she had a positive ANA, she had no other clinical signs or symptoms of lupus. In the absence of another etiology, we concluded she had a primary, idiopathic, subepithelial membranous nephropathy possibly associated with her infection. Despite conservative treatment for 6 months, proteinuria worsened to 7.1 gms. She was subsequently treated with rituximab. Within 2 months, her proteinuria improved to 3.1 gms consistent with partial remission.

Discussion: Lupus-like glomerulonephritis with a membranous pattern has been rarely described in HIV infection. Our patient had a positive ANA but no other serological or clinical features of lupus. Although full house immune staining was seen, IgG3 predominated with mostly subepithelial deposits and her PL2AR stain was positive, suggesting this may be primary membranous nephropathy with atypical features. There are a variety of glomerular diseases observed in HIV positive individuals and this case highlights the importance of the renal biopsy for appropriate diagnosis and treatment

TH-PO968

Laser Microdissection and Tandem Mass Spectrometry, a Valuable Method to Identify Components of Glomerular Deposition Diseases: A Case Report

Introduction: The diagnosis of glomerular deposition diseases (GDDs), including proliferative glomerulonephritis with monoclonal IgG deposition (PGNMID), requires evidence of pathogenic deposits in the glomeruli. Laser microdissection (LMD) and Tandem mass (MS/MS) spectrometry, which can identify the deposit’s structure, might be valuable for this purpose in theory. Here, we report a case of PGNMID suggesting the applicability of MS/MS spectrometry in the diagnosis of GDDs.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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return to baseline after 2 months, during which she was supported by dialysis, but PU persisted despite steroids. Subsequent addition of mycophenolic acid led to partial PU remission.

Discussion: Unlike prior sparse case reports documenting celecoxib-associated MCD, our patient did not initially have any IF or TA, nor did her PU remit spontaneously after celecoxib discontinuation. Although MCD responded well to prednisone, it eventually became steroid-resistant. While IgA deposits were deemed incidental and benign, our patient did not initially have any IF or TA, nor did her PU remit spontaneously after return to baseline after 2 months, during which she was supported by dialysis, but PU remained. While IgA deposits were deemed incidental and benign, our patient did not initially have any IF or TA, nor did her PU remit spontaneously after return to baseline after 2 months, during which she was supported by dialysis, but PU remained.

Discussion: Anti-TNF-α agents have been associated with different renal pathologies including AIN, as well as glomerular processes such as pauci-immune crescentic GN. Determining causality is a challenge because RA is independently linked to AAV as an overlap syndrome. In our patient, lack of clinically evident RA flare and concomitant presence of AIN on biopsy more strongly supported etanercept as the underlying etiology. A high index of suspicion for drug-related vasculitis is required in patients with primary rheumatic disorders treated with biologic agents. Discontinuation of anti-TNF-α therapy and prompt initiation of immunosuppression for treatment of vasculitis are the cornerstone of management.

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initiated, massive proteinuria persisted and hypalbuminemia had deteriorated over the following months. She was diagnosed as nephrotic syndrome. Kidney biopsy demonstrated thickening of GBM with a diffuse granular pattern of IgG and C3 staining along GBM on immunofluorescence microscopy. Electron microscopy revealed subepithelial and intramembranous electron-dense deposits, which led to the diagnosis of MN (stage II-III). At age 42, she underwent anti-GBM antibody was not detected in her serum. One month post-surgery, she was admitted with persistent fever and oliguria. She got anuric soon after the admission and hemodialysis (HD) therapy was initiated. Laboratory test revealed a high titer of anti-GBM antibody (276 IU/mL), and plasminogen deficiency combined with corticosteroids was also suggested. The second kidney biopsy revealed membranous nephropathy with variable glomeruli with cellular crescents. Immunofluorescence microscopy demonstrated deposition of IgA along GBM in both linear and granular patterns. Her renal function did not recover in spite of decrease in titer of anti-GBM antibody, and she has been eventually on maintenance HD.

Discussion: The conformational change of GBM by MN can unmask hidden epitope in the non-collagenous domain 1 of type Vcollagen, which could induce autoimmunity response. Further studies are needed to determine whether MN could cause such autoimmunity.

TH-PO975
IgA Dominant Infection-Related Glomerulonephritis in the Setting of Acute Ehrlichiosis
Zafira Chowdhury, Yevgeniy Borschenko, Michael B. Stokes, Minesh Khatri, Naveed N. Masani.

**Introduction:** IgA-Dominant staining on immunofluorescence (IF) with diffuse endocapillary proliferation and mesangial (M) and endocapillary proliferative nephritis (LMN) has a differential diagnosis that includes primary IgA nephropathy, Henoch-Schönlein purpura (HSP), and IgA dominant infection related GN. We report a case of acute ehrlichiosis infection with concomitant GN. To date, there have been no reported cases of ehrlichiosis associated GN.

**Case Description:** A 37-year-old man with a petechial rash, 13 pound weight gain, bilateral lower extremity edema, and serum creatinine 1.6 mg/dl (12 months prior to presentation was 0.9 mg/dl). Urinalysis revealed 3+ protein, 2+ blood; protein:creatinine ratio of 5.3 g/g (urinalysis 12 months previously was negative for blood and protein).

**Discussion:** Glomerular lesions included complete collapse and segmental fibrosis with partial tubular atrophy. Immunofluorescence microscopy demonstrated IgA in glomeruli without significant IgM or C3. IgM was either normal or negative. An IgM titer for Ehrlichiosis chaffensis was strongly positive at 3.7 (normal ≈ 1.0). Renal biopsy findings revealed diffuse endocapillary proliferation, widespread mesangial and global endocapillary hypercellularity, endothelial swelling, and mild activity. Of note, there was significant intracapillary leukocyte accumulation including neutrophils. There was minimal patchy tubular atrophy and interstitial fibrosis, comprising 10% of the cortex. IF was significant for 2+ IgA and 1+ C3. Electron microscopy revealed electron dense deposits in the mesangium and subendothelial locations, along with 40% foot process effacement. No subepithelial humps were identified. Given the patient’s clinical timing of acute ehrlichiosis infection and GN, these findings support the diagnosis of an IgA-dominant infection related GN. The presence of neutrophils on LM and 1+ C3 staining on IF, albeit less than the IgA staining of 2+, also support the diagnosis.

Discussion: The LM pattern of proliferative GN with IgA dominance requires clinical correlation. Specific laboratory and biopsy findings including degree of IgA and C3 staining and presence of neutrophils can help distinguish this entity from HSP and IgA nephropathy, as well as timing of renal dysfunction with relationship to onset of infection.

**TH-PO976**

Case Report of Membranous Glomerulonephritis Secondary to Papillary Thyroid Carcinoma
Khalid M. Elharrar, Farah Abifaraj, Marjan Afrozian, Hania Kassem.

**Introduction:** Secondary Membranous glomerulonephritis is most commonly seen in the setting of autoimmune disease, infection, neoplasia, and with certain therapeutic agents. Malignancies associated with secondary membranous GN are solid tumors such as solid tumors and less commonly hematological malignancy. We present a unique case of MGN, secondary to PTC, with dramatic improvement of proteinuria post thyroidectomy. This case emphasizes the importance of clinical workup after a diagnosis of secondary MGN, which in our patient, led to the discovery of an unexpected PTC and its successful treatment.

**TH-PO977**

Doxycycline-Associated Minimal Change Disease
Rushang Parikh, Nupur N. Uppal, Vanessa Bijol, Zacker School of Medicine at Hofstra/Northwell, NY; Manhasset, NY; Hofstra Northwell School of Medicine, Great Neck, NY; Northwell Health Hofstra University, Lake Success, NY.

**Introduction:** Minimal Change Disease (MCD) is a disease that usually affects adolescents, however 10-25% of nephrotic syndrome in adults is also caused by MCD. Malignancies associated with secondary membranous GN are solid tumors such as solid tumors and less commonly hematological malignancy. We present a rare case of MCD associated with doxycycline use.

**Case Description:** A 24-year-old Caucasian female with history of IBD presented to emergency department (ED) with worsening swelling of lower extremities. 4 weeks prior, she was diagnosed with Influenza A, treated with Oseltamivir, and the week before presentation had mild fever when was diagnosed with acute sinusitis and initiated on doxycycline therapy. After taking doxycycline for 4 days, she started having “dizzy spells” followed by appearance of severe swelling over lower extremities with palpalpable and pitting edema. Her systolic BP was 150 which was unusual for her. UA performed at Urgent Care center revealed RBC’s in the urine and protein of 300 mg. She was transferred to ED, where was noted to have persistently elevated BP, with repeat UA also showing RBC’s and protein. Spot urine protein:creatinine was elevated at 10.3, with a serum creatinine of 0.62 mg/dl and albumin of 2.1 g/dl. Patient underwent kidney biopsy which showed “extensive effacement of visceral epithelial cell foot processes, suggestive of minimal change disease, and thin glomerular basement membranes, suggesting an inherited abnormality of basement membrane collagens.” She was started on high-dose prednisone, 1 mg/kg, to which she responded well. Her lower extremity swelling and proteinuria completely resolved within 2 weeks of corticosteroid therapy, and prednisone was subsequently tapered.

Discussion: Doxycycline is a widely available antibiotic that is readily used in the treatment of multiple pathologies. It is not typically associated with MCD however it has been shown to cause MCD in mice due to causing overexpression of VEGF-A in the kidneys which results in albuminuria and minimal change disease. To our knowledge, there has been only one reported case of doxycycline related MCD in humans. Physicians including internists, infectious disease specialists and nephrologists need to be aware of this potential adverse effect of doxycycline.

**TH-PO978**

Collapsing Focal Segmental Glomerulosclerosis and Diffuse Infiltrative Lymphocytosis Syndrome with Renal Involvement in Acute HIV Infection
Erum Z. Malik, Duncan B. Johnstone.

**Introduction:** Human Immunodeficiency Virus (HIV) infects and damages podocytes leading to HIVAN, a collapsing form of focal and segmental glomerulosclerosis. HIV also causes dysregulation of the immune system, which rarely can cause CD8+ T-cells to infiltrate and attack various organs, leading to Diffuse Infiltrative Lymphocytosis Syndrome (DILS).

We present the first case of simultaneous HIVAN and DILS with renal involvement, occurring only 6-8 weeks after infection during the initial phase of acute HIV seroconversion.

**Case Description:** A 20-year old Hispanic male was diagnosed with acute HIV because of drug exposure, negative serology, and positive p24 antigen. Three weeks later, he was admitted with fever, chills, myalgias, severe dry mouth, neuropathic pain of both legs, and declining urine output. Compared to labwork three weeks prior, new labs showed seroconversion of HIV, a 10-fold increase in CD8+ T-cells, new hyponatremia (123 mEq/L), and hyperkalemia (creatinine 5.24 mg/dl, prior 0.98). Urinalysis showed 300+ protein (while oliguric). Sonogram showed bilaterally enlarged and echogenic kidneys suggestive of interstitial nephritis. He denied using any medications including herbs. Biopsy showed collapsing FSGS with severe interstitial inflammation, and staining demonstrated these were CD8+ T-cells. He started steroids, losartan and anti-retrovirals. His symptoms of xerostomia and neuropathy improved daily, along with an increase in urine output.

Discussion: This report is the first to describe both HIVAN and DILS simultaneously, and of additional significance, both conditions arose early at the time of HIV seroconversion. HIVAN typically occurs in advanced HIV as an AIDS defining illness but was reported twice in early HIV. DILS is a multi-organ disorder of increased, dysregulated CD8+ T-cells that infiltrate one or more organs, most often the salivary glands and lungs. When kidneys are affected, DILS shows similarities to allergic interstitial nephritis (enlarged and echogenic kidneys, tubular proteinuria, eosinophilic interstitial nephritis), but with DILS the cells are CD8+ T-cells. Renal and extra-renal symptoms of DILS can respond to HAART and prolonged steroids.

**TH-PO979**

Clinical Course of a Patient Treated for Dense Deposition Disease (Monoclonal Protein Associated)
Yevgeniv Borschenko, Win Win Mo, Kamal Nayyar, Antonia Tharian, James Drakakis.

**Introduction:** Dense deposition disease (DDD), a subclassity of C3 glomerulopathy is a rare entity characterized by uncontrolled activation of the alternative pathway (AP) of the complement cascade. When diagnosed in the older population, there is often an...
accompanying monoclonal gammopathy of undetermined significance (MGUS). As the monoclonal protein may perturb AP regulation, treating with chemotherapy need be considered. We report a case of DDD (MGUS associated) first treated with bortezomib, later switched bortezomib plus cyclophosphamide and dexamethasone (CyBorD). As there was no histologic or serologic improvement, daratumumab was introduced with stability of kidney function.

Case Description: A 62 year old male was evaluated for a serum creatinine (Cr) of 1.3 mg/dL with urine protein of 3 g/g. There were low C3 and C4 levels. Urinalysis showed 3+ blood with 86 red blood cells. Serum immunofixation detected an IgG kappa monoclonal protein. Plasma cell count on bone marrow biopsy was 8%. Renal biopsy showed diffuse mesangial and segmental endocapillary proliferative glomerulonephritis with membranoproliferative features. Immunofluorescence had intense deposition of C3. Global, marked electron dense deposits were seen. As findings were consistent with DDD, bortezomib was initiated. After 3 months, this was held for observation. Cr then was 2.5 mg/dL with urine protein/creatinine of 4.5 g/g. Six months later, bortezomib was resumed but not effective. CyBorD followed, but Cr rose to 3.5 mg/dL. Second kidney biopsy revealed severe tubular atrophy and interstitial fibrosis. At this point, weekly daratumumab with bortezomib was started. After several months, renal function has not declined further and proteinuria reached nadir of 2.9 g/g.

Discussion: Monoclonal gammopathy has emerged as a potential driver of the complement dysregulation, known to characterize DDD. Although there have been several strategies reported, there is no standard approach to guide therapy. While chemotherapy is not used to treat MGUS, it is appropriate in cases whereby the monoclonal protein manifests as a form of C3 glomerulopathy (DDD). This case demonstrates various options which may be utilized to curtail renal morbidity. While bortezomib alone and CyBorD were not effective, our patient has achieved ongoing clinical and laboratory stability with daratumumab.

TH-PO980

Chronic Inflammatory Demyelinating Polyneuropathy and Concurrent Membranous Nephropathy Associated with Anti-Contactin-1 Antibodies

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Introduction: MN is a common cause of nephrotic syndrome in nondiabetic adults. CIDP is an acquired disorder of peripheral nerves. Antibodies directed against the paranodal axonal cellular adhesion molecule contactin-1 and its binding partner neurofascin have been identified in some severe cases of CIDP. Case reports of patients with co-existing MN and CIDP have been published, but an underlying disease mechanism has not been described in these patients.

Case Description: A 45-year old male was diagnosed with CIDP in March 2015. He was treated with prednisone, IVIG and azathioprine with good response. In September 2016, he presented with nephrotic syndrome with 22 g/day of protein. He underwent a renal biopsy which showed stage 2 MN. Renal function was normal and anti-phospholipase 2 antibody was negative. Malignancy, infectious, and routine autoimmune investigations were negative. Additional serology was positive for IgG4 anti-contactin-1 antibody. Neurofascin antibody was negative. We examined renal tissue for the presence of contactin-1 antigen. The patient’s biopsy was strongly positive for this antigen, while 2 control were negative. Cyclosporine was added to the patient’s regimen with good resolution of proteinuria.

Discussion: Anti-contactin-1 antibodies have been identified as a cause of CIDP. This is the first report of these antibodies being identified in a case of secondary membranous nephropathy. Anti-contactin 1 antibody may be a novel diagnostic test in this condition.
TH-PO982

Urinary angiotensinogen predicts renal disease activity in lupus nephritis
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Background: A non-invasive indicator of renal histological lesions and disease activity in lupus nephritis (LN) is needed for timely and targeted treatment before overt renal injury. Here, we tested the utility of urinary angiotensinogen (UAGT) to predict renal disease activity in LN.

Methods: A prospective, three-stage study was performed in patients with LN. In stage I, UAGT was measured in 140 newly-diagnosed LN patients. In stage II, UAGT was monitored in 61 subjects from stage I for up to 12 months. In stage III, UAGT was monitored in 12 LN patients before, during and after the onset of renal flares.

Results: In stage I, UAGT significantly increased in LN patients, correlating well with kidney AGT expression and histological activity. Patients with LN Class IV exhibited the highest UAGT compared with other histopathological classes of LN. For identifying LN class IV, a particularly aggressive type of LN, UAGT outperformed the conventional clinical measures and improved their performances. In stage II, UAGT decreased after immunotherapy and remained low in patients with LN remission during follow-up. In stage III, an elevation in UAGT predicted recurrence of LN, and a decline in UAGT after a renal flare heralded the remission of disease before conventional clinical measures.

Conclusions: UAGT in LN is a promising indicator for dynamical surveillance of renal disease activity and prediction of renal flares.

Funding: Government Support - Non-U.S.

TH-PO983

Association Between Kidney Tissue Estrogen Gene Signature and Nephrotic Syndrome Remission
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Background: Kidney disease severity and rate of progression are reported to be higher in males than females, which may in part be mediated by glomerular sex hormone receptor expression. We developed a kidney tissue estrogen gene signature to examine associations between estrogen signaling and remission from nephrotic syndrome.

Methods: Patients with active FSGS, MCD, MN, or other nephrotic syndrome at enrollment in NEPTUNE, a multi-center observational cohort study were studied. Our outcome of interest was complete remission, defined as a uPCR ≤0.3 g/g. Our exposure of interest was a novel estrogen z-score. First, genes affected by estrogen signaling were defined as any gene related to ESR1 and 2 in both the HumanBase (Flatiron Institute) and MSigDB (Broad Institute) databases. Genes were limited to only those with estrogen response elements in the promoter region and 21 genes of interest were identified. Genome wide RNA expression data from the glomerular compartment of kidney tissue were used to calculate a z-score (X-mean/SD) for each gene. Each patient’s overall z-score was generated from the average of the individual gene z-scores.

Results: Among the 177 patients, 67% were male, mean age was 34 years, mean eGFR was 86 ml/min/1.73m2, and mean uPCR was 2.8 g/g. A cox proportional hazards model was used to calculate a z-score (X-mean/SD) for each gene. Each patient’s overall z-score was generated from the average of the individual gene z-scores.

Figure 1 shows unadjusted association of z-score median split with time to remission. Overall Z score and time to complete remission (HR 4.59; 95% Cl 1.4-15.1; p=0.012).

Conclusions: Higher estrogen score was associated with a higher hazard for complete remission. This estrogen gene signature could be used in both research and clinical practice to more carefully risk stratify patients. These findings also identify the estrogen receptor as a potential therapeutic target in glomerular disease.

Funding: NIDDK Support

TH-PO984

Proximal tubular cell isolation during human acute kidney injury
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Background: There is an urgent need to discover and validate the pathophysiological pathways involved in human acute kidney injury (AKI). Proximal tubular cells (PTCs) are the cells primarily injured during AKI and their maladaptive repair contribute to AKI to chronic kidney disease (CKD) transition. It is very important to develop non-invasive tools that will help to improve our understanding of the signaling pathways contributing to the maladaptive repair.

Methods: We collected urine from patients hospitalized in the ICU of University Hospital of Geneva, presenting or not AKI. We here propose a novel method to isolate specifically PTCs from human urine using a combination of Magnetic-Activated Cell Sorting (MACS) sorting and Fluorescent-Activated Cell Sorting (FACS). We have characterized the sorted cells, and show how these cells can be used to determine pathophysiological pathways in human AKI.

Results: Isolated PTCs are viable, can be cultured for at least three passages (a) and retain the expression of several proximal tubule specific markers at the level protein (b) and of mRNA (c). We report that our technique is more sensitive than routine microscopic approach used to identify the presence of tubular cells in the urine during clinical AKI (d). There is a clear correlation between isolated PTC cell numbers and the severity of AKI as defined by KDIGO staging guidelines (e). RNA sequencing and pathway analysis confirmed alterations in PTCs cell cycle in AKI patients, which correlated to the severity of AKI (f).

Conclusions: We show that isolation of PT cells from urine is possible during human AKI episode. These cells can be used to study the pathways involved in AKI and we could confirm alterations of the cell cycle in PTCs collected from AKI patients. Thus, we believe that PTCs isolated from human urine will allow the identification and characterization of novel pathways in AKI and the AKI to CKD transition.

Funding: Private Foundation Support
Background: Racial/ethnic disparities exist among glomerular disease patients with respect to access to care and patient outcomes. However, few data exist on how race/ethnicity influences protocol adherence and data completeness in clinical research studies. Identification of such disparities will improve trial design and enhance generalizability of research findings.

Methods: CureGN is a 70-center prospective cohort study of patients with MCD, FSGS, MN, IgA nephropathy, or IgA vasculitis. We compared metrics on retention, visit completion, data completeness, and immuno- and biosample collection [urine, blood, including RNA and DNA] across racial/ethnic groups using proportional-hazards models.

Results: Overall protocol adherence was high (80-97%) for all races and ethnicities. Few data exist on how race/ethnicity influences protocol adherence and data completeness in clinical research studies. Identification of such disparities will improve trial design and enhance generalizability of research findings.

Conclusions: Significant racial/ethnic differences in protocol adherence exist among enrollees with glomerular disease in CureGN. Rates were significantly lower in blacks and Hispanics. The diversity of research staff and site investigators may influence these disparities. Creation of a diverse Patient Advisory Council might reduce disparities.

Funding: NIDDK Support

TH-PO986

Rapid Genome Sequencing to Guide Clinical Decision Making in FSGS

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Background: About 30% of children with focal segmental glomerulosclerosis (FSGS) have a genetic cause. While genetic forms are usually resistant to immunosuppressants, steroids are still the first-line treatment regardless of individual genetic make-up. We hypothesized that rapid whole genome sequencing (WGS) at diagnosis will help guide clinical management by a) improving diagnosis, b) sparing immunosuppressive treatment in cases with Mendelian mutations, c) identifying cases responsive to targeted therapy, d) improving counseling for both renal and extrarenal disease, and e) improving transplant evaluation and outcome.

Methods: We conducted CLIA-certified rapid WGS to guide decision-making in 10 children and young adults affected by biopsy-proven FSGS where a genetic diagnosis could affect therapeutic decision. Return of results (ROR) included therapeutic, familial and pre-transplant counseling.

Results: Turn-around time from consent to ROR averaged 20 days (15-42). WGS identified a diagnostic genotype in 5/10 patients and prompted biopsy revision in 2 cases leading to management change in virtually all cases, including holding/stopping immunosuppression in 6/10 cases, new treatment in 5/10 cases and improved transplant evaluation in 2 cases (Fig. 1). Genetic diagnosis also prompted early screening for subclinical neurological disease in a patient.

Conclusions: Rapid WGS in FSGS can improve medical management and possibly outcome by sparing ineffective and toxic treatment, identifying forms amenable to etiologic treatment, and inform familial counseling and pre-transplant evaluation thus optimizing organ allocation.

Funding: Other NNI Support - NNI CTSA Program

TH-PO987

The Soluble VEGF Receptor sFlt-1 Contributes to Endothelial Dysfunction in IgA Nephropathy

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Background: Endothelial injury is a common manifestation in IgA nephropathy (IgAN). After the previous identification of the upregulated solute free-fab version of the vascular endothelial growth factor receptor-1 (sFlt-1) correlates with endothelial injury in IgAN, in the present study, we further explored the role of sFlt-1 in endothelial injury in IgAN.

Methods: We enrolled 72 patients with IgAN and detected the sFlt-1 levels. The polymorphism IgA1 (plgA1) complexes were isolated from the pooled plasma samples of another 10 patients with IgAN. Apoptosis proteins were detected in cultured human umbilical vein endothelial cells (HUVECs) with recombinant sFlt-1 or the caspase-9 inhibitor, Z-LEHD-FMK stimulation.

Results: We identified there were positive correlations between sFlt-1 and IgA-IgG complex as well as vWF levels in patients with IgAN. The sFlt-1 levels in HUVECs were...
The Levels of Plasma suPAR May Not Discriminate the Patients with Poor Therapeutic Reactivity Among Adult Japanese Focal Segmental Glomerulosclerosis and Minimal Change Disease

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Background: Soluble urinase-type plasminogen activator receptor (suPAR) is a negative regulator of thrombosis. Intracellular accumulation of suPAR in podocytes can lead to podocyte apoptosis. However, there are few reports investigating the impact of suPAR as a marker for predicting therapeutic reactivity among adult minimal change disease (MCD) and FSGS.

Methods: Multicenter retrospective cohort study. Among the biopsy-proven MCD/FSGS patients during 2005-2015 at Nagoya University and 14 affiliated hospitals, the patients who collected their plasma at biopsy according to their consent were included. The patients with preserved renal function, plasma suPAR levels were still higher than those in diagnosed with FSGS, the levels were not different between non-responders and responders. However, we cannot ignore the affection from the patients' kidney function. Among patients with preserved renal function, plasma suPAR levels were still significantly upregulated by podocyte injury.

Results: Ninety-nine cases (MCD/FSGS: 65/34, responders/non-responders: 67/32) were included to the analyses. The patients with FSGS or non-responders demonstrated more impaired kidney function at baseline. The median value of plasma suPAR was MCD/ FSGS: 225.3±3290.9 μg/ml (p=0.001) and responder/non-responders: 233.4±3080.7 μg/ml (p=0.55).

Conclusions: Plasma suPAR level was observed significantly higher among FSGS and non-responders. However, we cannot ignore the affection from the patients' kidney function. Among patients with preserved renal function, plasma suPAR levels were still higher than those in diagnosed with FSGS, the levels were not different between non-responders and responders. We plan to present additional results including urine specimen of same patients.

Funding: Clinical Revenue Support

TH-PO989

Association Between Histologic Variants of Focal Segmental Glomerulosclerosis and Outcomes: Results from the Japan Renal Biopsy Registry

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Background: Focal Segmental Glomerulosclerosis (FSGS) is a leading cause of end stage kidney disease (ESKD). The previous studies suggested that FSGS histologic variants of the Columbia classification were associated with clinical outcomes, but the impact of FSGS variants on outcomes has not comprehensively been investigated in Japan.

Methods: Data on 383 patients with biopsy-proven FSGS from Japan Renal Biopsy Registry from 2010 to 2013 were analyzed. The outcome measures were 30% decline in estimated glomerular filtration rate (eGFR30), progression to ESKD, and the first clinical reanimation (CR: proteinuria>0.3g/day) during 60 months after the biopsy. Multivariable Cox models were used to compare the outcomes among variants, adjusted for age, sex, baseline eGFR, nephrotic proteinuria (NP), and immunosuppressive treatment (IS).

Results: 311 patients were enrolled [median age: 52 (IQR 33, 66) years, male: 63%; baseline eGFR: 58 (IQR 40, 80) ml/min/1.73m², NP: 54%, IS: 54%]. The distribution of variants was 47% (n=147) FSGS not otherwise specified (NOS), 19% (n=59) tip (TIP), 16% (n=50) perihilar (PERI), 13% (n=40) cellular (CEL), and 5% (n=15) collapsing (COL). During the follow-up, 87 patients (28%) developed GFR30, 25 (8%) ESKD, and 118 (38%) reached CR. No significant differences in GFR30 and ESKD were found among variants, but TIP was significantly associated with CR compared with PERI (adjusted HR (95% CI), 2.2 (1.0, 4.8) (Figure). The variant types were associated with CR. Larger sample size, especially for COL, and longer follow-up may be needed to detect a statistically significant difference in the outcomes among FSGS variants.

Funding: Government Support - Non-U.S.
A Pilot Study of a Gluten-Free Dairy-Free Dietary Intervention in Children with Steroid-Resistant Nephrotic Syndrome

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Background: Steroid-resistant nephrotic syndrome (SRNS) in children often fails immunosuppression and progresses to kidney failure. Case reports have suggested potential beneficial effects of dietary changes on SRNS, especially gluten-dairy restrictions. Zonulin is a circulating protein upregulated in gluten sensitivity, which regulates intestinal barrier. We hypothesize that zonulin might also alter permeability of podocyte tight junctions and contribute to SRNS activity.

Methods: Prospective non-randomized pilot study to investigate the effect of a gluten and dairy-free (GF/DF) diet in children with SRNS. The study was organized as a four-week summer camp with prospective collection of blood, urine and stool.

Results: 16 patients (mean age 7 years, range 2-21) met the eligibility criteria. Ten patients had FSGS, while six minimal change disease. Whole exome sequencing did not reveal any SRNS-associated variants. Complete remission following implementation of GF/DF diet occurred in two patients (13%, Fig A –marked in blue and red). Furthermore, GF/DF diet showed anti-inflammatory effects on the immune system in all participants, reducing circulating Th17 cells by 78% (Fig B) and decreasing levels of pro-inflammatory cytokines (Fig C). Microbiota analysis revealed a higher fraction of Faecalibacterium prausnitzii upon dietary intervention. Circulating zonulin levels over 106 ng/mL differentiated responders from non-responders (Fig D).

Conclusions: GF/DF may be an effective candidate diet treatment in a subset of children with SRNS, in particular those with high zonulin levels. Diet intervention can also have anti-inflammatory benefits. A summer camp is a feasible way to implement dietary interventions in children and assess its short-term effect.

Funding: Private Foundation Support
that new therapeutic options are mandatory. The main objective of our study is to describe the prospective features of young patients who used rituximab in our Primary Care setting.

Methods: This is a retrospective cohort including 18-year-old or older patients with kidney biopsy showing MCD or FSGS who have used at least 1 dose of rituximab between 2012 and 2018, with a minimum of 6 months of follow up after infusion. Epidemiological, clinical and histological variables were analyzed. We compared responders patients with at least a 35% reduction in proteinuria and an increment of 0.5 g/dl of serum albumin.

Results: Twenty-eight patients fulfilled the inclusion criteria, 57% female, median creatinine of 1.27 mg/dl, and the median of the first infusion was 1 mg/dl and 33 years-old, respectively. The main indications were lack of response to traditional immunosuppressors and frequent relapse during or after corticosteroid withdrawal, with previous use of cyclosporine in 76% and prednisone in 96%. Median 24-h urinary protein at infusion were 8.40 g (5.30 - 12.64, IQR) in non-responders and 7.65 g (1.34 - 17.63, IQR). After 3 months they resulted 7.06 g (5.62 - 9.97, IQR) and 0.25 g (10 - 5.51, IQR), respectively. The complete remission rate in 3 was 24% and in 6 months was 10%. Partial remission was present after 3 months in 33% of the cases. Evaluating non steroid resistant patients, 58% of them had partial remission at 3 months while no steroid resistant individual had any type of remission. In relation to side effects, 18% had an infection episode up to 6 months after infusion and 2 patients presented rash, with no severe drug reaction. Conclusions: Rituximab is a possible option to use in FSGS and MCD especially in individuals considered steroid-sensitive and dependent and with an acceptable safety profile.

TH-PO995
Rituximab Treatment of Minimal Change Disease (MCD) and Focal Segmental Glomerulosclerosis (FSGS) in Adults
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Background: Previous smaller retrospective and prospective studies have suggested that rituximab may be an effective treatment for adult patients with MCD and FSGS who have steroid dependent nephrotic syndrome.

Methods: We reviewed the charts of 82 adults seen at Columbia University Medical Center between 2014 to 2019 who received rituximab for treatment of MCD or FSGS. We analyzed clinical, biopsies, and laboratory data pre-infusion and at follow up after (FU). We categorized patients as frequently relapsing/steroid dependent (FRSD), infrequently relapsing (IR), steroid resistant (SR), and multi-drug resistant (MDR, failed 2 or more prior immunosuppressive medications(IS)) based on their clinical course.

Results: Of 80 patients biopsied, 41 patients had MCD, 34 had FSGS, 5 had podycopathology associated with another diagnosis, 2 patients had nephrotic syndrome without previous biopsy. Median age was 40 years and 60% were male. 48 patients were Caucasian, 11 African-American, 17 Hispanic and 6 Asian. Disease categories included 41 FRSD, 7 IR, 9 SR and 25 MDR. The median duration of FU was 30 months (range 1-156 months). 51/82 (62%) patients achieved complete remission (CR, UPCR <0.5 g/g) and 11/82 (13%) achieved partial remission (PR, UPCR 0.5-3.5 g/g) at FU. All CR/PR occurred by 7 months after infusion of rituximab. 20/82 (24%) did not achieve CR/PR. Of the 61 patients in CR, PR, 48 (79%) patients were off all other IS at FU. 36/41 (88%) FRSD patients achieved CR/PR, and while 11/25 (44%) MDR patients achieved PR, none achieved CR. 13/82 (16%) patients progressed to ESRD, 8/13 (62%) of these patients were MDR. 52/82 (65%) patients relapsed, median time to relapse was 22 months from last rituximab infusion. 18 patients were retreated with rituximab. Those with relapse after rituximab (13/87%) achieved a higher remission rate compared to those with relapse after steroids (8/137%).

Conclusions: This large study confirms the benefit of rituximab in achieving remission of proteinuria and reduction of immunosuppression in adults with MCD or FSGS. Patients with MDR disease were less likely to respond to rituximab.

TH-PO996
Study of Long-Term Recurrence and Adverse Effects of Rituximab Treatment in Adults with Steroid-Dependent Minimal-Change Nephrotic Syndrome
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Background: The effect of rituximab treatment on the minimal-change nephrotic syndrome came to be known widely. However, there are few reports investigating the incidence of infectious complications and its timing during immunosuppressive therapies.

Methods: Multicenter retrospective cohort study. MCD/FSGS diagnosed by kidney biopsy from 2005 to 2015 at Nagoya university and 15 affiliated hospitals were included. Age>20, non-nephrotic cases, secondary cases, patients who did not receive any immunosuppressive treatment or patients who dropped-out within 4 weeks were excluded from the analyses. The incidence and its timing of infections that were treated under hospitalization were evaluated using Kaplan-Meier method.

Results: Among 298 cases (MCD/FSGS: 243/55 cases), 270 (89.9%, MCD/FSGS: 212/48) achieved complete remission (CR). The median values of duration for CR were 14 days in MCD and 38 days in FSGS (p=0.05). Thirty-nine (13.1%) patients suffered from infections at least once during entire observation and pneumonia was the most common (11 cases). Twenty-two out of 39 (56.4%) cases had infections within 6 months from the initiation of immunosuppressive treatment. In Kaplan-Meier analysis, the risk for infections were higher in FSGS patients (p=0.034 vs. MCD) or elderly patients (age<65, p<0.001 vs. age>64). When patients were categorized into 4 subgroups according to the duration for CR (patients who attained CR within 4 weeks, 4-8 weeks, 8-16 weeks and >16 weeks), poor-responders (CR over 16 weeks) demonstrated the highest risk and early-responders (CR within 4 weeks) showed the lowest risk for infections (p<0.001 in log-rank test). Multivariate Cox proportional hazard model showed that elderly patients (adjusted HR: 3.35, 95% CI: 1.61-6.97, p<0.001), baseline eGFR (adjusted HR: 0.83 for every 10ml/min decrease in baseline eGFR, 95% CI: 0.63-0.99, p=0.038) and poor-responders (adjusted HR: 4.80, 95% CI: 1.86-12.35, p=0.001) were associated to infections.

Conclusions: Among patients with adult MCD/FSGS, infections relating to immunosuppressive therapies should be taken in mind especially in poor-responders as well.

Funding: Commercial Support - Chugai Pharmaceutical Co

TH-PO998
Incremental Reduction of Proteinuria and Kidney Survival in FSGS
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Background: Proteinuria remission has been shown to predict disease progression in focal and segmental glomerulosclerosis (FSGS). This study examines if incremental reductions in proteinuria are associated with improved kidney survival even if a complete or partial remission is not reached.

Methods: Data are from the NIH/NIDDK FSGS clinical trial of 138 steroid resistant patients randomized to cyclosporine or mycophenolate mofetil (no difference in trial endpoint of proteinuria remission). Linear-mixed effects models tested if week 26 proteinuria was associated with subsequent slope of estimated glomerular filtration rate (eGFR). Stratified Cox-proportional hazards models tested if time-varying proteinuria was associated with time to kidney failure. Model interaction terms and sensitivity analyses tested for an incremental impact of proteinuria on outcome for those with urine protein: creatinine ratio >1.5g/g. Analyses were adjusted for age, race, baseline proteinuria and eGFR, and treatment arm.

Results: A 1log change in proteinuria was associated with a -5.1/mlyear difference in change in eGFR per year (95% CI=−8.3 to −2.0 p=0.001). There was an analogous relationship between time-varying proteinuria and time to kidney failure: HR per log-proteinuria=3.94 (95% CI=1.79 to 8.68 p=0.001). Findings remained the same when limited to those with proteinuria >100mg/dl at week 26.

Conclusions: These findings agree with previous reports of an important proteinuria threshold at approximately 1.5g/g associated with a large clinical benefit, but also support that a reduction in proteinuria—even if not to below 1.5g/g—is still associated with improved survival. Clinical trials should consider reductions in proteinuria as a marker of future preservation of kidney function.

Funding: NIDDK Support, Commercial Support - Goldfinch Bio, Pfizer inc.
Methods: Participants (PTS) were recruited from nephrology practices, Kidney Research Network registry and NephCare Kidney International social media. Eligibility criteria: proteinuria (UPC ≥ 1) within the prior 12 months, eGFR > 30 ml/min and no other severe health condition. Interviews for concept elicitation were conducted in-person for children < 14 yrs and in-person or by phone for ≥ 14 yrs. Interviews were transcribed and reviewed by 2 investigators who developed a hierarchical taxonomy through an ongoing, iterative, deductive and inductive analytical process. Concepts were pooled with those elicited from 30 adults with FSGS participating in the initial FSGS PRO development initiative.

Results: 43 interviews with FSGS children (n=11) and adults (n=11), and MCD children (n=8) and adults (n=13) were completed. MCD interviews are ongoing. Latent content analysis suggests FSGS and MCD impact physical, social and mental HRQOL regardless of age or diagnosis. Physical complaints of swelling, fatigue and pain were endorsed by the majority of PTS. PTS described their experiences with medications and associated side effects, as well as lifestyle changes made to manage disease (i.e., diet and medical visits). Interviews often detailed a profound impact on physical abilities and life participation. PTS described the negative impact these symptoms had on their mood and sense of self with a majority of PTS endorsing feelings of anxiety. Depression was common in MCD and about half of expressed feelings of frustration. Finally, PTS with MCD also talked about the toll that frequent and unpredictable relapse had on leisure and work/school activities.

Conclusions: FSGS and MCD can have a profound impact on HRQOL in children and adults. While there is an existing PRO for adults with FSGS, our results suggest that there are commonalities to the FSGS-MCD patient experience that will enable the generation of a disease specific FSGS-MCD PRO for use in children and adults. Measure validation initiatives will be required prior to broad spectrum use.

Funding: Commercial Support - Goldfinch Biosciences.

TH-PO1001
Alport Syndrome: Phenotype-Genotype Correlation in Lithuanian Families
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Background: Alport syndrome (AS) is a rare inherited collagen IV nephropathy, caused by mutation in COL4 genes leading to progressive kidney injury with extrarenal manifestations including ocular and hearing abnormalities. Exact incidence of AS is not well known due to clinical and genetic heterogeneity. Most cases of AS is confirmed by a pathogenic mutation in the COL4A5 gene, associated with X-linked AS or pathogenic mutations in COL4A3 or COL4A4 genes inherited in autosomal pattern.

Methods: Data analysis of the clinical, histological and genetic records of the patients with suspected AS was made. Inclusion criteria were associated with a high grade suspicion for AS such as positive family history, hematuria as an early sign of the disease, progressive chronic kidney disease (CKD), sensorineural hearing loss and several ocular abnormalities.

Results: 87 patients with suspected Alport syndrome (23 children and 64 adults), 51 females and 36 males were included. 33 patients were suggested to have Alport syndrome due to specific renal biopsy findings. Other patients had positive family history. Diagnosis of AS was genetically confirmed in 74 % patients, with COL4A3, COL4A4 and COL4A5 genes 82 %, 8 %, 10 % respectively. In total 20 different familial mutations were found. All patients had hematuria. Progressing chronic kidney disease was seen in 39 % of the patients with an average age at diagnosis 15,4 years (14 – 40 y), whereas 36 % patients with CKD had end-stage renal disease and underwent on dialysis. CKD was significantly more frequent than in COL4A5 compared with COL4A1 and COL4A4 genes mutations. Disease progression correlated with the age (p<0.05). Hearing abnormalities were presented in 22,4 % of all AS cases. Ocular abnormalities and vision alterations were seen in 18,4 % patients and were strongly associated with COL4A5 gene mutations.

Conclusions: COL4A5 mutations cause more severe phenotypic manifestation in male patients, specially related with a more severe renal phenotype while mutations in COL4A3 or COL4A4 are related with autosomal AS with milder clinical alterations. Further epidemiological studies are needed for better understanding of AS manifestations.

TH-PO1002
Description of Alport Disease in Female Children and Adolescents
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Background: Alport disease (AD) is a multi-system disease historically thought to be presymptomatic in young females given inheritance is most commonly X-linked. Prior descriptive studies and outcome data have focused mainly on males and adult women. The aim of this study was to describe the clinical presentation and course of the females with AD in a large pediatric medical center.

Methods: A single center retrospective review of pediatric females with AD seen at Children's Hospital of Philadelphia between 1987 - 2018. All females with ECD 910 codes for Alport, familial hematuria and hereditary nephritis were identified. GFR was calculated using the bedside CKD equation. Hypertension was defined as systolic or diastolic blood pressure ≥95th percentile for age, gender and height. Proteinuria was defined as a ≥ 30 mg/ dl of protein.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Results: 217 subjects were identified, 164 of them excluded for an incorrect diagnosis. 16 charts were missing. 37 female patients were confirmed to have AD and included in the analysis. Mean age of presentation was 5.4 ± 3 yrs with mean follow-up of 6.3 ± 4 yrs. 14 patients had genetic testing, with 80% demonstrating heterozygous mutations in the COL4A5 gene. Biopsies were performed in 11 patients. The remaining patients were diagnosed based on clinical manifestation and family history. At the end of follow up at least one episode of gross hematuria was observed in 15 patients, proteinuria in 21 patients, and GFR <90 ml/min/1.73 m2 in 3 patients. Seven patients had an abnormal audiogram. See Table 1 for pertinent clinical findings. One patient required dialysis and received a deceased donor transplant.

Conclusions: Most females diagnosed with AD in childhood have persistent microscopic hematuria and normal renal function. Gross hematuria, proteinuria, and subclinical hearing involvement were common findings suggesting that AD should not be overlooked in girls with nephritis.

Funding: Other NIH Support - T32 DK07006-43

Clinical Characteristics of Females with AD

<table>
<thead>
<tr>
<th>Family History</th>
<th>Renal Function</th>
<th>Renal Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present (n=77)</td>
<td>29 ± 8.4</td>
<td>13 ± 7.8</td>
</tr>
<tr>
<td>End of Follow Epo (n=77)</td>
<td>29 ± 8.4</td>
<td>17 ± 9.8</td>
</tr>
</tbody>
</table>

*Serum creatinine available for this number of subjects

TH-PO1003

Genetic Polymorphism in C3 is Associated with CKD Progression in IgA Nephropathy

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Background: A single nucleotide polymorphism (SNP) in complement factors can harmfully affect their activity. The commonest SNP in C3 is R102G, causing two allelotypic variants: C3 fast (C3F) and C3 slow (C3S). C3F has been shown to be prevalent in CKD, especially IgA nephropathy but no study has explored its role in CKD progression.

Methods: Delta (Δ) eGFR (ml/min/1.73m2/yr) for 2038 patients in the Salford Kidney Study (SKS) was calculated by linear regression, with ΔGFR defined as rapid progressors (RP) and those between -0.5 and +1 ml/min/1.73m2 as slow progressors (SP). There were 37 patients with IgA nephropathy (21 RP and 16 SP), in this group there was a two group as whole: C3F 27% in RP vs. 24.3% in SP p = 0.32. In the subgroups analysis there were 37 patients with IgA nephropathy (21 RP and 16 SP), in this group there was a significantly higher frequency in C3 allelic frequency between the two groups as a whole: C3F 27% in RP vs. 24.3% in SP, p = 0.32. In the subgroups analysis there were 37 patients with IgA nephropathy (21 RP and 16 SP), in this group there was a significantly higher frequency in C3 allelic frequency between the two groups as a whole: C3F 27% in RP vs. 24.3% in SP, p = 0.32. In the subgroups analysis there were 37 patients with IgA nephropathy (21 RP and 16 SP), in this group there was a significantly higher frequency in C3 allelic frequency between the two groups as a whole: C3F 27% in RP vs. 24.3% in SP, p = 0.32. In the subgroups analysis there were 37 patients with IgA nephropathy (21 RP and 16 SP), in this group there was a significantly higher frequency in C3 allelic frequency between the two groups as a whole: C3F 27% in RP vs. 24.3% in SP, p = 0.32. In the subgroups analysis there were 37 patients with IgA nephropathy (21 RP and 16 SP), in this group there was a significantly higher frequency in C3 allelic frequency between the two groups as a whole: C3F 27% in RP vs. 24.3% in SP, p = 0.32. In the subgroups analysis there were 37 patients with IgA nephropathy (21 RP and 16 SP), in this group there was a significantly higher frequency in C3 allelic frequency between the two groups as a whole: C3F 27% in RP vs. 24.3% in SP, p = 0.32.

Conclusions: C3 SNP, R102G, is associated with CKD progression in patients with IgA nephropathy but not in other causes of CKD.

Funding: Government Support - Non-U.S.

TH-PO1004

The Study of the FUT2 Gene Carrying a Nonsense Mutation in IgA Nephropathy

Jieshuang Jin, Shanghai General Hospital, Shanghai, China.

Background: The pathogenesis of IgA nephropathy is related to the dysbacteriosis, but FUT2 gene carrying nonsense mutation plays a role in the intestinal flora disorder.

Methods: To verify that FUT2 gene with nonsense mutation is associated with IgA nephropathy. We collected 104 cases of physical examination and 56 cases of IgA nephropathy diagnosed by renal biopsy from June 2017 to December 2018. We extracted genomic DNA to detect FUT2 gene, test serum biochemical markers, intestinal barrier function indicators (diamine oxidase DAO and D-lactic acid DL), and collected the blood pressure(BP), 24 hour urinary protein and renal pathology.

Results: 1. We found that 5 patients (8.9%) of IgA nephropathy carry a nonsense mutation on FUT2 gene and there is no nonsense mutation in 104 healthy people. 2. The levels of the BP 146 ± 14.9 vs. 140 ± 12.91 mmHg, serum creatinine(Cr)138.34 ± 23.54 vs. 175.5 ± 5.59, serum uric acid(UA)243.9 ± 116.4 vs. 248 ± 6.1 mg/L, 24 hour urinary protein2.69 ± 1.8 vs. 0.89 ± 0.55mg/L, and the number of eGFR 75.71 ± 11.8 vs. 76.2 ± 8.9 ml/min/1.73m2. In the non-mutation group is obviously decreased than that in the mutation group. 3. The number of eGFR 75.71 ± 11.8 vs. 76.2 ± 8.9 ml/min/1.73m2. In the non-mutation group is obviously decreased than that in the mutation group. 4. The melanocyte proliferation, glomerular sclerosis, and interstitial fibrosis were significantly observed in the mutation group, the score was 3.6 ± 4.5. In the non-mutation group, the score was 1.6 ± 0.6 (P=0.05).

Conclusions: 8.9% of patients with IgA nephropathy have nonsense mutations on FUT2 gene. Compared with the non-mutation group, the BP, serum Cr, UA, 24 hour urinary protein, DAO and DL are significantly higher in the mutation group, but eGFR is obviously decreased. Renal pathology suggests that the score of mesangial cell proliferation, glomerular sclerosis and interstitial fibrosis are increased in the mutation group. Studies of IgA nephropathy have shown that higher serum Cr, 24 hour urinary protein, BP and lower eGFR are positively correlated with disease progression and that the higher score of the renal pathology suggest a poor prognosis. Finally we infer that nonsense mutations on FUT2 gene can affect the intestinal barrier function and accelerate the progression of IgA nephropathy, and its mechanism still needs further study.

TH-PO1005

Significant Intestinal Flora Disturbance Is Discovered in IgA Nephropathy Patients

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Background: IgA nephropathy (IgAN) is an autoimmune glomerular disease, manifested by hematuria with or without proteinuria. The pathogenesis has not been clarified yet. This study investigated the relationship between IgAN and gut microbiota composition to understand gut-kidney axis.

Methods: 44 patients with biopsy-proven IgAN and 15 healthy controls were enrolled. The patients were divided into two groups based on levels of urine red blood cells (urRBC). Compositions of intestinal flora were assessed by 16sRNA microbial profiling approach.

Results: The proportions of Escherichia-Shigella (5.16% ± 0.83% vs. 8.25% ± 0.89%, P=0.06), Bacteroides (19.9% ± 3.51% vs 12.07% ± 3.78%, P=0.03) and Bacteroides (19.9% ± 3.51% vs 12.07% ± 3.78%, P=0.03) increased significantly in IgAN patients, compared with normal control. Conversely, Bifidobacterium (1.29% ± 0.54% vs 0.07% ± 0.01%, P=0.01) and Megamonas (2.36% ± 0.76% vs 13.2% ± 25.7%, P=0.01) was markedly decreased.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
TH-PO1006
BAFF-Dependent IgA Production Does Not Play a Pivotal Role in the Pathogenesis of Murine IgA Nephropathy
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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Although our understanding of this disease has improved by remarkable progress, its pathogenesis has not yet clearly understood. Recent studies suggested B cell activating factor belonging to the TNF family (BAFF), which participates in the activation of B cells and class switch of IgA, as a potential disease marker of IgAN. However, the role of BAFF in the development and progression of IgAN remains unclear. In this study, we investigated the pathological role of BAFF in IgAN using a grouped ddY mice which is the spontaneous murine model of IgAN.

Methods: Mice with IgAN designated grouped ddY were treated with PBS or anti-BAFF monoclonal antibody (anti-BAFF Ab) by intraperitoneal injection every three days for four weeks. We measured the levels of urinary albumin, serum immunoglobulins (IgA, IgG, and IgM), and serum IgA-IgG immune complex at the beginning and end of the treatment. The levels of serum abnormally glycosylated IgA were also measured using biotinylated Ricinus communis agglutinin-1 (RCA-I) and Sambucus nigra bark lectin (SNA). We further assessed glomerular deposits of IgA and C3 by immunofluorescence staining, and analyzed changes of B cell population in spleen and bone marrow using flow cytometric analysis.

Results: Anti-BAFF Ab treatment significantly decreased serum levels of IgA, IgG, and IgM as compared with PBS treatment in the murine IgAN model (p < 0.001, p = 0.003, and p = 0.002, respectively). However, it did not affect urinary albumin excretion, serum levels of IgA-IgG immune complex, and serum levels of abnormally glycosylated IgA. Glomerular deposits of IgA and C3 as well as B cell population in spleen and bone marrow were also not affected by anti-BAFF Ab treatment.

Conclusions: Anti-BAFF Ab treatment was effective in inhibiting the production of immunoglobulins, but not nephritogenic IgA in murine IgAN model. Our results suggest that BAFF-dependent IgA production may not play a pivotal role in the pathogenesis of IgAN.

TH-PO1007
High Serum IgA/C3 Ratio Better Predicts a Diagnosis of IgA Nephropathy Among Primary Glomerular Nephropathy with Proteinuria ≤1 g/d: An Observational Cross-Sectional Study
Jun Zhang. Department of Nephrology, The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China.

Background: Serum immunoglobulin A (IgA)/C3 ratio is considered to be an effective predictor of IgA nephropathy (IgAN). This study aims to explore the diagnostic value of serum IgA/C3 ratio in IgAN among primary glomerular nephropathy in China.

Methods: We recruited 1095 biopsy-diagnosed primary glomerular nephropathy patients including 757 IgAN patients and 338 Non-IgAN patients. Social demography, serum immunological indexes and other clinical examinations were measured. IgAN cases were propensity scored matched (PSM) to Non-IgAN cases on the logit of the propensity score using nearest neighbor matching in a 1:1 fashion with a caliper of 0.02 without any replacements, according to age, gender, BMI, proteinuria and eGFR.

Results: We found that, both in the full cohort and PSM cohort, serum IgA/C3 ratio in IgAN group was significantly higher than those in Non-IgAN group. The same results were also obtained at different levels of proteinuria and renal function stratification. In the PSM cohort, there was no difference in IgA/C3 ratio in patients with IgAN between different proteinuria groups and different CKD groups. The area under the ROC curve (AUCORC) for IgA/C3 ratio in distinguishing IgAN among primary glomerular disease was 0.767 in the full cohort and 0.734 in the PSM cohort. The highest AUCORC of IgA/C3 ratio was in the proteinuria ≤ g/d group (0.801 in the full cohort, and 0.803 in the PSM cohort); however, there was no difference between all the CKD groups. Meanwhile, the diagnose accordance rate of diagnostic of IgAN among all those patients with IgA/C3 ratio ≥ 3.5304 was as high as 92.02% in the full cohort. Multivariate logistic regression analysis showed, IgAN was independently correlated with age, albumin, CKD 2 stage and CKD 3-5 stage (versus CKD 1 stage) and IgA/C3 ratio.

Conclusions: The present study provided clear evidence that IgA/C3 ratio is an effective predictor of IgA diagnosis, especially in patients with proteinuria ≥ 1 g/d. In order to study the effectiveness of this biomarker and to determine a standardized cut-off value, large-scale studies are necessary.

TH-PO1008
Single Nephron Parameters in Patients with IgA Nephropathy
Hirokazu Marumoto, Nobuo Tsuibo, Takaya Sasaki, Yusuke Okabayashi, Kotaro Harahara, Go Kanzaki, Kentaro Koike, Tetsuya Kawamura, Takashi Yokoo. Division of Nephrology and Hypertension, The Jikei University School of Medicine, Tokyo, Japan.

Background: The progression of IgA nephropathy (IgAN) may be characterized by progressive loss of functional nephrons and subsequent alterations in single nephron function in remnant nephrons. In this study, we estimated total nephron number and examined the related single nephron parameters in patients with IgAN at different renal function stages of the disease.

Methods: The total nephron number was calculated using a simplified method based on the combined use of unenhanced computed tomography and stereology-based estimation of non-sclerotic glomerular density on renal biopsy (Sasaki T et al. 2018, ASN). Single-nephron glomerular filtration rate (SNGFR) and single-nephron urinary protein excretion (SNUPE) were calculated by dividing the estimated glomerular filtration rate (eGFR) and urinary protein excretion by total nephron number, respectively. The glomerular volume (GV) was estimated from the measured mean glomerular area.

Results: We recruited 1095 biopsy-diagnosed primary glomerular nephropathy patients including 757 IgAN patients (age 43, male 54%, eGFR 61.5 ± 378,000 on average). In order to study the effectiveness of this biomarker and to determine a standardized cut-off value, large-scale studies are necessary.
Urinary Cytokines as Non-Invasive Biomarkers of IgA Nephropathy

Ptin Hye Kang,1 Jin sug Kim,1 Hyeon Seok Hwang,1 Yang gun Kim,2 Su Woong Jung,2 Won-Hee Cho,2 Kyung hwan Jeong.1 Kyunghee University Hospital, Seoul, Republic of Korea; 1Kyung Hee University Hospital at Gang-Dong, Seoul, Republic of Korea.

Background: Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Although renal biopsy is the gold standard of diagnosis, accessibility in clinical practice is poor. Therefore, need for development of non-invasive diagnostic tools such as biomarker has emerged. In this study, we investigated the clinical relevance of 16 urinary cytokines in patients with IgAN.

Methods: The levels of 16 urinary cytokines from 110 biopsy-proven IgAN patients, 15 non-IgAN glomerulonephritis, and 15 normal controls were measured using multiplex assays. Samples were collected from the first spot urine of the morning on the day of renal biopsy. To account for variations in urine concentration, urinary cytokine levels were normalized to urine creatinine. We analyzed the correlations of urinary cytokines with clinical and pathological parameters in IgAN patients. The predictive value of urinary cytokines for adverse renal outcome, which defined as chronic kidney disease (CKD) stage 5 or above at the last follow-up, was also investigated using receiver operating characteristic (ROC) curve analysis

Results: As compared with patients in non-IgAN glomerulonephritis group and normal controls group, patients in the IgAN group showed significant higher urinary cytokines levels of interferon-inducible protein 10 (CXCL10), endocan, growth differentiation factor 15 (GDF15), interferon gamma (IFN-γ), interleukin 6 (IL-6), mannose-binding lectin (MBL), neparin, and transferrin R (TIR) (p < 0.05). The urinary levels of endocan, GDF15, IL-6, and TIR showed significant correlation with estimated glomerular filtration rate (eGFR) (r=0.240, p=0.002; r=0.254, p=0.003 and r=0.386, p=0.001, respectively). Urinary protein excretion was significantly correlated with CXCL10, IL-6, and TfR showed significant correlation with estimated glomerular filtration rate (eGFR) (r=-0.240, p=0.005; r=-0.240, p=0.006; r=-0.254, p=0.003; and r=-0.386, p=0.001, respectively). Protein excretion was significantly correlated with CXCL10, IL-6, and TIR (r=0.205, p=0.002; r=0.210, p=0.017; r=0.165, p=0.040, respectively). ROC curve analyses showed that urinary protein to creatinine ratio, GDF-15, and IL-6 had a moderate predictive value for adverse renal outcome (area under the curve > 0.7).

Conclusions: Urinary cytokines have potential as disease specific biomarkers of IgAN. Further large and prospective studies of extended duration are needed.

PLACX16: A Biomarker Predicts Renal Inflammation and Progression of IgA Nephropathy

Road Luo, Shuwan Ge, Gang Xu, Tongji Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, Wuhan, China.

Background: Noninvasive biomarkers associated with IgAN prognosis are urgently needed for clinical practice. This study was to investigate whether PLACX16 was associated with pathology and renal outcome in IgAN.

Methods: 230 patients with IgAN diagnosed by renal biopsy between 2012 and 2014 at Huazhong University of Science and Technology Tongji hospital, were included in the study. Follow-up time was up to 42.5 months. The renal outcome was defined as composite endpoints, including ESRD and doubling of plasma creatinine. Plasma PLACX16 level was measured by ELISA. Inflammatory cells including CD4+, CD8+, CD20+ and CD68+ cells in renal biopsy tissues and renal CXCL16 expression were detected by immunohistochemistry.

Results: Plasma PLACX16 levels correlated with serum creatinine (p=0.001, r=0.362), estimated glomerular filtration rate (p=0.0001, r=0.411), albumin (p=0.0019, r=0.2068). In renal biopsy specimens, the density of CD8+, CD4+, and CD20+ cells were significantly associated with plasma PLACX16 levels. Mesangial hypercellularity and tubular atrophy/interstitial fibrosis according to the Oxford classification were associated with the plasma levels of PLACX16. ROC curve showed that plasma PLACX16 levels had a predictive value for composite endpoints (cut-off PLACX16=2.968ng/mL, AUC=0.593, sensitivity=0.611, specificity=0.618). Higher plasma PLACX16 levels predicted worse renal outcome during follow-up (Log-rank, p=0.006) by Kaplan-Meier analysis. In multivariate Cox proportional hazard analysis, plasma PLACX16 levels at the time of renal biopsy were found to be an independent predictor of composite endpoints after adjustment for age, gender, mean arterial blood pressure and serum albumin (p=0.012). Immunofluorescence results showed that the receptor CXCR6 was expressed in renal CD8+ T cells, but not in CD4+ T cells. Plasma PLACX16 levels were positively associated with renal CXCL16 expression in tissues (r=0.316, p=0.018). In vitro, IFN-γ promoted PLACX16 expression in HK2 cells through NF-κB pathway. PLACX16 had a chemotactic effect on Jurkat T cells and directly acted on NRK-49F cells to promote fibrosis.

Conclusions: Plasma PLACX16 levels correlate with IgAN pathology and progression. PLACX16 may be a risk factor for progression of IgAN.
TH-PO1013
Influence of Tubular and Interstitial Lesion on Proteinuria Remission and Long-Term Renal Prognosis in IgA Nephropathy with Crescent Lesion Treated with Immunosuppressive Therapy
Takayuki Fujii, Satoshi Suzuki, Junya Koshizaka, Nobuaki Yamauchi, Mayu Morimoto, Noriko Terasaki, Tanaka Hiroaki, Seirii Sakura Citizen Hospital, Sakata, Japan.

Background: Currently, the Oxford classification added crescent (C) score to the conventional membranous hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S), and interstitial fibrosis and tubular atrophy (t) score in IgA nephropathy (IgAN). Although C lesions may be improved with immunosuppressive therapy, renal prognosis with C lesions combined with T lesions remains unclear. We studied proteinuria remission and renal prognosis after steroid therapy in IgAN patients with C lesions in relation to the presence or absence of T lesions.

Methods: This single-center retrospective cohort study included 135 patients with C lesions among 694 patients diagnosed with IgAN and could be followed for at least 1 year or until the restart of renal replacement therapy (RRT) within 1 year. Proteinuria remission and renal prognosis (50% decrease in eGFR or initiation of RRT) after steroid therapy were evaluated in relation to the presence of C lesions with and without T lesions (C1T1 and C1T0, respectively). A similar analysis was conducted in a propensity-matched cohort.

Results: There were 101 patients with C1T0 and 34 with C1T1, and 52 patients in C1T0 and 18 in C1T1 were treated with steroid therapy. The mean observation period was 9.2±7.4 years. Age, mean blood pressure, and daily urinary protein excretion were higher and eGFR was lower in C1T1. Compared to supportive care, steroid therapy caused significant proteinuria remission and renal prognosis improvement in C1T0 (log-rank p<0.01). However, there was no significant difference in renal prognosis between the two groups according to gender. The clinical features at renal biopsy and renal outcomes were evaluated by Cox regression models.

Conclusions: Study of the incidence of C lesions with and without T lesions in IgAN patients with creatinine level T was the effect of steroid therapy on proteinuria remission. Studies on the incidence of C lesions with and without T lesions in patients with C lesions are needed.

TH-PO1014
Examination of the Factor Related to the Prognosis in IgA Nephropathy Patients with Mild Proteinuria at Diagnosis
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Background: The prognosis for patients with IgA nephropathy (IgAN) with urinary protein <0.5 g/day has been considered favorable, but there are few reports on factors that affect their renal prognosis.

Methods: A total of 1171 adult patients who were diagnosed with IgAN by the first renal biopsy between 2002 and 2004 were registered in the Nationwide Retrospective Cohort Study in IgAN from 42 institutes all over Japan. In 394 patients with a baseline urinary protein (U-Prot) <0.5 g/day having sufficient data and observation period, a long-term renal outcome was analyzed. The primary outcome was an increase of more than 50% in serum creatinine levels from the baseline.

Results: Primary outcome was observed in 12 patients (3.0%). Of 394 patients, 330 had U-Prot <0.5 mg/dL and U-Prot <0.5 g/day [Clinical Grade (CG) Ia] and 64 had eGFR <60 ml/min per 1.73 m² and U-Prot <0.5 g/day (CG Ib). There was a significant difference in the incidence of renal outcome between the two groups (log-rank test: p<0.001 between CG Ia and CG Ib). Hazard ratio (HR) in CG Ib vs. CG Ia was 9.2 (95% CI: 3.2-29.3). On univariate analysis using Cox proportional hazards analysis, high uric acid, male, and no remission up to 2 years after renal biopsy were the significant risk factors, whereas older age and lower HDL cholesterol were not significant in renal prognosis between the two groups (p=0.46).

Conclusions: In IgAN patients with C lesions, proteinuria remission is achieved by steroid therapy. However, when there are coexistent T lesions, the effect of steroid therapy in improving renal prognosis is limited.

TH-PO1015
Sex-Related Disparities in IgA Nephropathy Progression
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Background: Sex related disparities in prognosis of CKD has been reported. We investigated the influence of gender on prognosis in immunoglobulin A nephropathy (IgAN) nephropathy.

Methods: This was a multi-center retrospective study. Patients were divided into two groups according to gender. The clinical features at renal biopsy and renal outcomes during the follow-up were collected and analyzed. Renal outcomes were defined as 30% estimated glomerular filtration rate (eGFR) decline from baseline. The prognostic effects of gender were evaluated by Cox regression models.

Results: Total of 238 eligible patients with IgAN nephropathy were enrolled (male: 124, female: 114). Male patients had higher body mass index and HDL cholesterol levels than female patients. There was no statistical difference on other features including age, blood pressure, eGFR and proteinuria. Median follow-up period was 88 (43 - 133) months. In survival analysis, male showed higher hazard ratio (HR) of 30% eGFR decline than female (HR 1.8, 95% confidence interval(CI): 1.1-3.4, p=0.03). Multivariable Cox regression analyses matched BMI and HDL cholesterol revealed that gender was also detected as a prognostic factor (HR 1.4, 95% CI 1.1-2.2, p=0.02). In gender-based survival analysis, eGFR and proteinuria are common risk factors of 30% eGFR decline. In particular, hypertension in men and lower HDL cholesterol in women was gender specific risk factor of 30% eGFR decline.

Conclusions: Sex related disparities in progression of IgAN nephropathy was suggested.

TH-PO1016
Diagnosis, Treatment, and Outcome of IgA Nephropathy with vs. Without Comorbid Diabetes Mellitus
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Background: The U.S. pandemic of diabetes mellitus (DM) has greatly complicated the diagnosis and clinical care of patients with glomerular diseases, such as IgA nephropathy (IgAN), the most common glomerular disease in the world. Our aim was to study the influence of DM on the diagnosis, treatment and clinical outcome of patients with IgAN.

Methods: We conducted a retrospective chart review of patients from the Glomerular Disease Collaborative Network (GDCN) inception cohort of adults with a pathologic diagnosis of IgAN on native biopsies performed between 1/1/1999 - 6/30/2018. GFR was estimated based using the CKD-EPIequation obtained at the time of kidney biopsy. Urine protein:creatinine ratio was measured from a random urine collection.

Results: There was only one patient with type 1 DM and only two patients had histologic diabetic glomerulosclerosis. Indications for kidney biopsy and baseline blood pressure was similar for the two groups. Detailed baseline characteristics, immunosuppressive treatments and clinical outcomes are displayed in Table 1. Conclusions: Patients with IgAN with versus without diabetes do not differ in the severity of proteinuria or eGFR at the time of diagnosis. Despite a reduced use of steroids among patients with IgAN and diabetes, follow-up proteinuria and rate of eGFR decline do not differ from those with IgAN without comorbid diabetes. Larger, long term studies are required to fully understand the relationship between DM and IgAN.

Funding: Clinical Research Support

Sociodemographic and clinical characteristics of Ig A nephropathy patients with versus without comorbid diabetes.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IgAN without DM</th>
<th>IgAN with DM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
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<td>Age, years</td>
<td>49.3±14.5</td>
<td>52.6±14.4</td>
<td>0.0007</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>25 (27)</td>
<td>8 (32)</td>
<td>0.8</td>
</tr>
<tr>
<td>Non-Hispanic white race, N (%)</td>
<td>48 (55)</td>
<td>20 (80)</td>
<td>0.8</td>
</tr>
<tr>
<td>Baseline eGFR, ml/min/1.73 m²</td>
<td>41.7±20.9</td>
<td>37.6±20.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Baseline urine protein:creatinine, g/g</td>
<td>10.1±9.1</td>
<td>4.1±4.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Baseline total body mass index, kg/m²</td>
<td>22.2±2.2</td>
<td>24.9±6.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Duration of follow-up, months</td>
<td>76.3±62.3</td>
<td>76.3±62.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Elevation of proteinuria, N (%)</td>
<td>39 (45)</td>
<td>30 (75)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex-related</td>
<td>10 (13)</td>
<td>6 (16)</td>
<td>0.1</td>
</tr>
<tr>
<td>Malignant features, N (%)</td>
<td>9 (11)</td>
<td>2 (5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Rate of eGFR decline, %/year of follow-up</td>
<td>0.1±1.2</td>
<td>0.1±1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Last available urine protein:creatinine, g/g</td>
<td>0.7±1.2</td>
<td>0.4±1.8</td>
<td>0.4</td>
</tr>
<tr>
<td>New-onset diabetes, N (%)</td>
<td>5 (6)</td>
<td>6 (12)</td>
<td>0.5</td>
</tr>
<tr>
<td>Odds, N (%)</td>
<td>10 (13)</td>
<td>6 (16)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*p-values calculated by Fisher’s exact test for continuous and Wilcoxon two sample test for categorical variables.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underlines represent presenting author.

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TH-PO1017
Characteristics of IgA Nephropathy in the Elderly: Results from a Multicenter, Large-Scale, Long-Term Observational Cohort Study
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Background: Aging of population is a worldwide matter. Especially in Japan, more than 10 years passed after super-aged society had come. Due to increasing number of kidney biopsy underwent for elderly people, the number of aged people who diagnosed IgA nephropathy is also growing. However, little is known about characteristics of IgA nephropathy in the elderly. The indication of corticosteroids or renin-angiotensin system inhibitors is unclear.

Methods: We defined “elderly patients” as patients aged 65 or over at the diagnosis, and “younger patients” as 15-64 years old. Using our multicenter, large-scale, long-term retrospective cohort of elderly people, the number of patients underwent kidney biopsy during 1981-2013, we extracted elderly patients and investigated their cross-sectional clinical characteristics, pathological features, and renal survival compared to younger patients. Survival analysis was performed by Kaplan-Meier method.

Results: The age at kidney biopsy was dramatically increasing during 30 years of registration period. Among 1,924 patients, 151 (7.8%) patients were aged 65 or older. Their median follow-up period was 46 [18-95] month, and their estimated glomerular filtration rate (eGFR, mL/min/1.73m²) was 42.7 [21.7-53.4]. The proportion of CKD stage G1-2 in elderly patients was only 16%, while 60% in younger patients. Amount of urine protein was 1.0 (0.42-2.2) g/gCr. Twenty-five percent of elderly patients had diabetes, while only 5% of younger patients had. The percentage of totally sclerosed glomeruli in elderly patients was higher than that of younger patients. In survival analysis, elderly patients with proteinuria >1 g/g, those having diabetes, and those with global sclerosis in more than half of glomeruli, were significantly associated with poor renal prognosis. Similar to younger patients, corticosteroids were used for 37.7% of elderly patients. However, use of corticosteroids or renin-angiotensin system inhibitors for the elderly patients was not associated with better long-term renal outcome.

Conclusions: Population of IgA nephropathy rapidly aged in Japan. IgA nephropathy in the elderly was characterized by progressed CKD with decreased eGFR and global sclerosis of glomeruli. We need to establish a strategy for treatment for IgA nephropathy in the elderly.

Funding: Government Support - Non-U.S.

TH-PO1018
Analysis of Japanese Histological IgA Classification Using Probabilistic Analysis Associated with the Bayesian Theorem
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Background: Regarding the pathological diagnosis of IgA glomerulonephritis(IgAGN), the Oxford classification is widely used globally, although in Japan, the Japanese Society of Nephrology(JSN) published its original pathological classification. For appropriate classification of the renal biopsies, the Japanese classification requires more than 8 glomeruli, whereas the Japanese classification requires more than 10 glomeruli. However, no study has yet investigated the relationship between the total number of glomeruli and pathological classification by probabilistic analysis. The present study aimed to report how the total number of glomeruli of the “lumped class” as the Japanese histological IgA classification using probabilistic analysis associated with the Bayesian theorem.

Methods: Ninety-nine patients from 2000 to 2009 diagnosed IgAGN by renal biopsy at Oita University Hospital were included. Certified pathologist diagnosed IgAGN using light microscopy and fluorescence microscopy. We used the third edition of IgAGN classification of JSN. We used Bayesian theorem for Probabilistic analysis. We used three models of the prior distribution. First is actual distribution; Second is a similarity of actual distribution by using the beta function, third is no information for the prior distribution.

Results: The median total number of collected glomeruli was 12 [Quartile 7,19]. When the cut-off level was set to less than 60% of the posterior probability, 21 cases (33%) were excluded (7 cases had more than 10 glomeruli, 14 cases had less than 9 glomeruli). When cases with less than 9 glomeruli were excluded before the Bayesian probability test, only 8 cases (12%) showed less than 60% of the posterior probability. However, 19 cases with less than 9 glomeruli showed more than 60% of the posterior probability. Thus, these 19 cases were considered as exclusion cases for classification. The results were the same using the three models of the prior distribution.

Conclusions: It may be better when using the IgA pathological classification of JSN to adopt the probabilistic analysis associated with the Bayesian theorem instead of considering only the total number of obtained glomeruli.

TH-PO1019
Factors Associated with ESRD in an IgA Nephropathy Cohort
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1University of New Mexico, Albuquerque, NM; 2Dialysis Clinic Inc, Albuquerque, NM.

Background: In IgA nephropathy patients, >1 g/day of proteinuria, presence of mesangial hypercellularity, segmental glomerulosclerosis, interstitial fibrosis and tubular atrophy (IFTA) and crescents on kidney biopsy are associated with progression to ESRD. We describe the factors associated with ESRD in an IgA nephropathy cohort with a substantial number of Native Americans and Hispanics.

Methods: We created a cohort of biopsy-proven IgA nephropathy from the UNM kidney biopsy registry which includes biopsies performed between 2002-2016. The demographic and clinical data were abstracted from the electronic medical record. The incidence of ESRD was obtained by chart review until 2016. We used age and sex adjusted Cox proportional hazards models to study the association of the predictor variables (mesangial and endocapillary hypercellularity, segmental glomerulosclerosis, IFTA, and crescents on kidney biopsy in proteinuria) with the incidence of ESRD. Patients were censored upon death or the last follow-up date for the ESRD outcome. We reported hazard ratios for ESRD with 95% confidence intervals (CI).

Results: Of the 66 patients identified with IgA nephropathy, there were 40.9% females, 36.4% Caucasians, 27.2% Hispanics, and 22.2% Native Americans. Mean biopsy age was 35.2 years (SD 16.9). Median creatinine (Cr) and CKD-EPI Cr equation eGFR were 3.1 mg/dl (IQR 2.8), and 23.2 ml/min/1.73m² (IQR 27), respectively. Mean proteinuria was 1.9 g/g (SD 2.7). A total of 45% of patients developed ESRD with a mean follow-up of 4 years. Patients with IFTA involving >50% of the cortical area and those with >50% glomeruli exhibiting global glomerulosclerosis were 4.86 and 2.86 times more likely to develop ESRD than the comparison group, respectively. (Fig 1)

Conclusions: This study demonstrates that significant glomerulosclerosis and IFTA are associated with the development of ESRD in an IgA nephropathy cohort comprising of many Native Americans and Hispanics.

Funding: Private Foundation Support
Conclusions: Hematuria at follow up is an independent predictor of eGFR decline after adjusting for follow-up time, proteinuria, MEST-C score and treatment. This suggests that monitoring the degree of hematuria as well as proteinuria is important for guiding treatment; however, RCTs using a decline in hematuria as a primary surrogate outcome measure are needed.

Funding: Private Foundation Support

TH-PO1021

Application of International Tool for Risk Prediction in IgA Nephropathy in Mexican Patients

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Background: IgA nephropathy is one of the main causes for chronic kidney disease with a progressive deterioration of kidney function with a 10-year risk for end-stage kidney disease ranging from 5-60%. Risk stratification is important for immunosuppressive therapy selection so a risk score was developed called international score tool for risk prediction in IgA nephropathy. The aim is determine the strength of association between the international score tool for risk prediction in IgA nephropathy and the lowering of the glomerular filtration rate at 6 months in Mexican patients with IgA nephropathy.

Methods: The study is a retrospective cohort with descriptive statistics, the international score for risk prediction in IgA nephropathy at the Hospital General de Mexico; a Pearson’s correlation test was performed with a significative p value <0.05 and IC95%.

Results: Twenty patients were included, mean age 35.2±14.06 years, 65% (13) were male, glomerular filtration rate(GFR) at biopsy was 72.93±40.67 ml/min/1.73 m2 CKD-EPI. The correlation between the risk for lowering GFR by 50% at 6 months presented a strong correlation with a statistical significant (Figure 1).

Conclusions: The international score for risk prediction in IgA nephropathy can be used in Mexican patients.

TH-PO1022

Decision Tree Prediction Models for the Development of ESRD in Immunoglobulin A Nephropathy

Xin Han, Yi Tang, Wei Qin. West China Hospital of Sichuan University, Chengdu, Sichuan, China.

Background: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide and up to 40% will develop end-stage renal disease (ESRD) within 20 years.

Methods: The aim of this study was to develop a predictive model to predict the risk of progressing to ESRD by using decision tree algorithm. Data were evaluated from biopsy-proven IgAN patients in West China hospital, Sichuan University in China between 2009 to 2017, 2 final models were selected by Gini index and the area under receiver-operating characteristic (ROC) curve.

Results: Clinical model was developed only by clinical factors, as pathological model was conducted by both clinical and pathological factors. In clinical model (Figure 1), recursive partitioning indicated that the best single predictor of renal deterioration was proteinuria, followed by severe urine acid for patients with severe proteinuria (> 0.98 g/d). Systolic blood pressure (SBP) and estimated glomerular filtration rate (eGFR) were placed in the third tier of the decision tree model. T and S score were put at high levels in pathological model (Figure 2) and followed with eGFR at third level. Proteinuria and SBP were placed at forth level. Nephrotic syndrome was presented at last. The accuracy of clinical and pathological model were 0.85 and 0.86, respectively. The ROC of clinical model was 0.83, compared with pathological model with 0.85.

Conclusions: Decision model can practically predict the risk of incidence of ESRD in IgAN patients. Model with pathological factors can be more accurate.
Conclusions: We derived and validated the risk prediction model at 6 months after renal biopsy including therapeutic options. This model may be useful guide for appropriate treatment in Japan.

Funding: Government Support - Non-U.S.

TH-PO1024

Spontaneous Remission in Asian Patients with IgA Nephropathy Treated with Conservative Therapy

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Background: There are few studies describing IgA nephropathy (IgAN) patients with persistent microscopic hematuria with or without minimal proteinuria. However, spontaneous remissions of hematuria and proteinuria were uncommon.

Methods: 62 adult patients with IgAN who received conservative treatment at least 5years were investigated. We investigated remission rate of hematuria and proteinuria and assessed the period and the decline of renal function. Remission of proteinuria and hematuria were defined as consecutive three times of proteinuria <0.3 g/gCr and urine red blood cells <5 HPF throughout an observation period of at least 6 months respectively.

Results: 38 (61.3%) patients had remission of hematuria, 24 (38.7%) patients had remission of proteinuria, and 19 (30.6%) patients had both remissions. The group with proteinuria <1.0 g/gCr group, the remission rate was 64.2%. The group with proteinuria <0.5 g/gCr group had a higher remission rate than the group with proteinuria ≥0.5 g/gCr group at the time of renal biopsy. The median time to remission of hematuria was 2.8 years (IQR 1.6-4.2), and that of proteinuria was 2.6 years (IQR 1.7-3.4). Patients who showed renal function decline (30% decline of eGFR from baseline) were significantly older, had significantly lower eGFR and higher proteinuria at the time of renal biopsy. Only two patients with normal renal function and normal range of proteinuria at diagnosis showed 30% eGFR decline. The two patients had persistently proteinuria >0.5 g/gCr after five years.

Conclusions: Relative high rate of spontaneous remission were shown. In the proteinuria <0.5 g/gCr group, there is high rate of remission of hematuria and proteinuria and renal function was preserved. In the case of proteinuria <1.0 g/gCr, it may be possible to observe over three years with conservative therapy.

TH-PO1025

Analysis of Appropriate Treatment for IgA Nephropathy with Mild Proteinuria

Shota Nitta. Tokyo Women’s Medical University, Tokyo, Japan.

Background: The 2012 KDIGO clinical practice guidelines recommended the renin angiotensin system inhibitors (RASIs) for the IgA nephropathy (IgAN) patients with mild proteinuria (0.5 to 1 g/day) as treatment. However, in Japan, tonsillectomy and steroid pulse therapy (TSP) was frequently employed in a lot of institutions, even though corticosteroid therapy was recommended only for the patients with persistent proteinuria over 1 g/day, despite of 3-6 months of supportive care, and tonsillectomy was not recommended. Then, we analyzed the appropriate treatment for the IgAN patients with mild proteinuria.

Methods: In this retrospective cohort analysis, 127 patients diagnosed as IgAN by renal biopsy from 1980 to 2015 in our institution, and had mild proteinuria (0.5 – 1.0 g/day) and eGFR ≥60 ml/min/1.73m2 were analyzed. We divided them into three groups: patients treated with TSP (TSP, n=34), with oral prednisolone (oPSL, n=33), and with conservative therapy (CON, n=50). We analyzed the clinical and histological backgrounds at renal biopsy, remission rates of proteinuria (U-P) which met < 0.5 g/g creatinine(Cr), urinary red blood cell (U-RBC) < 5/high power field (HPF), and both of them (clinical remission: CR) for 5 years, and 10-years renal survival rate among three groups.

Results: The clinical and histological backgrounds were similar among three groups (median U-P was around 0.70 g/gCr, median eGFR was around 80.0 ml/min/1.73m2 and mean proteinuria was 1.24g). The use of corticosteroids in addition to ACEI/ARB significantly improve the short-term renal outcome in early-stage IgAN patients.

TH-PO1026

Corticosteroids Improves Renal Survival in Chinese Patients with Early-Stage IgA Nephropathy

Gaiqin Pei,1,2 Yi Tang,3 Wei Qin.1 Division of Nephrology, Department of Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China; 2West China School of Medicine, Sichuan University, Chengdu, Sichuan, China; 3West China Hospital of Sichuan University, Chengdu, China.

Background: The therapy for immunoglobulin A nephropathy(IgAN) patients remains controversial. This study aims to evaluate the effects of corticosteroids and immunosuppressive therapy in Chinese early stage IgAN patients with estimated glomerular filtration rate(eGFR) ≥45mL/min/1.73 m2 and mean proteinuria≥1g/24h.

Methods: Patients with biopsy proven IgAN were retrospectively enrolled from 2007 to 2016. Patients were categorized into supportive care (SC), steroids alone(SC), and steroids plus immunosuppressant(IT) groups. Responses to therapy included complete remission(CR), partial remission(PR), no response(NR)and end stage renal disease(ESRD). The renal outcome was defined as a 50% decline in eGFR and/or ESRD.

Results: 715 patients(Male 47% and Female 53%)were recruited and followed for a mean of 44.6±24.13 months. The rate of CR was 81.8%, 62.7%, 37% in CS, IT, SC, group respectively. Renal outcomes were remarkably better in CS group(4.6%)compared with SC(14.4%)and IT(11.5%)group(p<0.001). Moreover, 36-month and 80-month renal survival was significantly better in CS group (98.3% and 86.4 %)than in the IT(94.2% and 82.4%)and SC(94.0% and 51.6%)group. Early CKD stage disease presented with better kidney survival(p=0.001). Further analysis for CKD stage 1 patients suggested no difference among 3 groups. In CKD stage 2 patients, CS alone or with IT could improve the survival rate when compared with SC alone(p=0.001and 0.007). But, no statistical significant difference could be found between CS and IT groups(p<0.219). For CKD stage 3a patients, renal survival rate in 3 groups were poor(p=0.398). Multivariate model showed that hypertension(HR 1.99, 95% CI 1.16-3.42;p=0.012); serum creatinine (HR 1.02, 95%CI 1.00-1.05;p=0.024); EJ lesion(HR 3.10, 95% CI 1.14-8.42;p=0.027) and T1/T2 lesion (HR 3.34, 95% CI 1.98-6.33;p<0.001)remained as independent predictors of renal survival.

Conclusions: The use of corticosteroids in addition to ACEI/ARB significantly improve the short-term renal outcome in early-stage IgAN patients.

TH-PO1027

Effect of Corticosteroid Therapy for Patients of IgA Nephropathy with Crescents

Mengqin Liang, Jiafan Zhou, Xing Zhang, Zongpei Jiang. The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

Background: Patients with IgA nephropathy (IgAN) presented proteinuria ≥1 g/d and eGFR≤50ml/min/1.73m2 after supportive treatment had been advised 6-month course of corticosteroids therapy. Update of Oxford classification of IgAN had recommended...
crescents be added to the MEST score for which they were predictive of outcome. Whether we should take some more positive therapy for crescents?

Methods: We conducted a single-center, retrospective cohort study enrolling 46 patients from 2017.01 to 2018.06, diagnosed with IgAN by renal biopsy. Eligible patients had proteinuria of 0.5~3.5 g/d, eGFR < 60 and crescent proportion > 20%. Patients were divided into 2 groups. One for classical steroid monotherapy (intravenous methylprednisolone 0.5 g/d for 3 days at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg/d for 6 months, called 1-3-5 Group) and the other assigned an optimized steroid therapy (intravenous methylprednisolone 0.25 g/d for 3 days at the beginning of months 1, 2, and 3, plus oral prednisone as above, called 1-2-3 Group). The primary endpoint was remission of proteinuria, secondary endpoint was deterioration in renal function.

Results: There were 23 patients in each group and no significant differences in age, gender, baseline proteinuria and eGFR between the two groups, except for the proportion of eGFR > 90% in 1-3-5 Group (52.5%) and 13% in 1-3-5 Group vs. 95.7% and 4.3% in 1-2-3 Group respectively, p = 0.001. After 6 months therapy, proteinuria in 1-3-5 Group was 0.5 (0.2, 0.8) g/d (vs. 1.2 (0.8, 2.6) g/d at baseline, p < 0.001) and that in 1-2-3 Group was 0.3 (0.2, 0.6) g/d (vs. 1.5 (0.7, 2.6) g/d at baseline, p = 0.001). 78.3% of patients in 1-3-5 Group had got remission of proteinuria, while 95.7% in 1-2-3 Group (p = 0.187). The slope of eGFR in 1-3-5 Group was 0.7 (1.1, 1.3) ml/min/1.73 m² per month, while that in 1-2-3 Group was 3 (1.2, 5.4) ml/min/1.73 m²/month, p = 0.027. The patients of had met side effects.

Conclusions: Our preliminary results had indicated that optimized steroid therapy had equal effect on reducing proteinuria but more significant advantage to protect against renal function deterioration in IgAN with crescents.

**TH-PO1028**

**Clinical Response to Budesonide in Biopsy-Proven IgA Nephropathy**

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Background: Primary IgA nephropathy is the most prevalent chronic glomerular disease worldwide. STOP-IgAN trial has questioned the benefit of systemic immunosuppression. And significant (24%) mean UFCR reduction from baseline has been concluded from NEFEGAN study. So in this study we aimed at studying the effect of oral controlled release budesonide in biopsy proven IgA nephropathy patients.

Methods: This is an interim analysis of on going study conducted in department of Nephrology, Institute of Nephro-Urology, Bangalore, India from May 2017. A total of 40 patients with biopsy proven IgA nephropathy were included in study. All patients were optimised on RAS inhibitors, Omega 3 fatty acids and budesonide. A decision to start all drugs together was considered as isolated RAS inhibitors will not prevent immunological damage by ongoing IgA deposition. Based on histology (MEST SCORE) patients were stratified into two groups and budesonide was started with oral and IV cyclophosphamide and prednisone followed by budesonide. All patients were regularly followed up every 4 weeks to monitor vitals, Renal function test and Urine PCR. Our primary outcome was mean change from baseline in 24 hr urine protein at the end of 3rd and 6th Month. Clinical response was defined as complete (CR), partial (PR) or non-responders (NR) according to recent definitions.

Results: 22(55%) were males and 18 (45%) were females. Mean age was 48.27 yrs. Mean creatinine at presentation was 3.02 mg/dL Mean proteinuria at presentation was 3.83 g/m L /24 hours.

11(40) had eGFR > 45ml/min/1.7m² And 29(40) had eGFR < 45ml/min/1.7m². All patients were optimised with RAS inhibitors and omega 3 fatty acids and budesonide. A 9 mg dose of ENTOCORT corresponded to 11.7 mg of NEFECON for plasma/serum cortisol suppression. The combined studies indicate that 16 mg of NEFECON for plasma cortisol suppression. The net effect is a lower cortisol suppression per mg dose. A published study has shown that 29 mg of Entocort is equivalent to 20 mg of prednisolone for plasma cortisol suppression. The combined studies indicate that 16 mg of NEFECON is equivalent to 8 mg of prednisolone for plasma cortisol suppression.

Conclusions: Tonsillectomy is an effective treatment option for advanced IgAN patients with persistent hematuria and proteinuria, independent of conventional therapeutic interventions.

**TH-PO1029**

**Systemic GCS Exposure from Nefecon Administration, Estimated from Suppression of Endogenous Cortisol Production**

Markus Jerling,1 Sofia Rendón-Rapp,2 Jens Kristensen.2

1Markus Jerling, School of Medicine, Tokyo, Japan. 2Jens Kristensen.2

Background: Nefecon is a unique two-step release oral formulation for the treatment of Henoch-Schönlein Purpura Nephritis with Hydroxychloroquine (HCQ) is a mild immunosuppressive agent. It has been used clinically as an effective drug in the treatment of rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). We aimed to study the potency of steroids can be assessed by the HPA-axis derived suppression of endogenous cortisol production. A high first-pass metabolism of 90% resulting in limited systemic GCS exposure. The secretory galactose-deficient IgA antibodies. In a phase 2b study once daily oral treatment with NEFECON for 500 mg/day for at least 6 months. Clinical characteristics, including renal function decline, were compared during the same observation periods before and after tonsillectomy.

**Results:** The patient cohort consisted of 5 males and 4 females, with an average age of 49 years. All patients had been treated with RAS inhibitors. Mean serum levels of creatinine were 1.32 mg/dL, with patients waiting an average of 161 months from initial diagnosis to tonsillectomy. Microscopic hematuria (1.10 vs. 0.20 grade, p = 0.003) and total urinary protein excretion (646 vs. 389 mg/day, p = 0.03) decreased significantly after tonsillectomy, relative to those before tonsillectomy. The slope of eGFR > 500 mg/day for at least 6 months. Clinical characteristics, including renal function decline, were compared during the same observation periods before and after tonsillectomy.

Conclusions: Tonsillectomy is an effective treatment option for advanced IgAN patients with persistent hematuria and proteinuria, independent of conventional therapeutic interventions.
The clinical efficacy of hydroxychloroquine in the treatment of Henoch-Schönlein purpura nephritis (HSPN), as well as the occurrence of adverse reactions.

Methods: This was a retrospective cohort study involving 76 HSPP patients. Twenty-two patients who had been treated with hydroxychloroquine were included in the exposure group, while 54 patients in the non-exposure group were treated with ACEI/ARB and/or other immunosuppressive agents instead of hydroxychloroquine. The patients were followed up for 6-34 months (median 14 months). Death, end-stage renal disease or transferring to renal replacement therapy (dialysis or renal transplant), eGFR decreasing more than 30% over baseline within 2 years, serum creatinine doubling from baseline level were considered end points.

Results: There was no significant difference in the remission rate of proteinuria between the exposed group and the non-exposed group. The remission rate of proteinuria in patients treated with hydroxychloroquine alone was 88.89%. At the end of the follow-up period, 30% of patients died or died on dialysis. Both the eGFR of 3 patients in the non-exposed group decreased by more than 30% compared with the baseline (30%, 34% and 41% respectively), while only one patient in the exposed group (54%). No significant adverse events were recorded during HCQ treatment.

Conclusions: Hydroxychloroquine can mildly and safely reduce proteinuria in patients with HSPP.

TH-PO1032
Long-Term Renal Outcomes In Patients with IgA Vasculitis: A Single-Center Retrospective Cohort Study
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Background: IgA vasculitis (IgAV; Henoch Schönlein purpura) is a small vessel vasculitis that most commonly affects children but also occurs in adults. The long term outcome from IgAV in adult patients with renal involvement is not well described, and treatment protocols are variable.

Methods: We conducted a retrospective study of renal outcomes in patients with IgAV with histologically confirmed renal involvement seen previously within our adult renal service. We searched our local renal and pathology databases for those diagnosed between 1990-2018. Demographic data including age, sex, ethnicity and date of presentation were recorded. Clinical data included serum creatinine and albumin, proteinuria (eGFR: creatinine:ratio; UPCR) at presentation and follow up, as well as biopsy findings and treatment.

Results: We identified 59 patients seen within this time period, with median follow up of 6 years (range 0.3-19.7 years). Mean age at diagnosis was 34.5 (±SD 18.4) years. 37 (63%) were male, and 55 (92.8%) were Caucasian. 20 (33.3%) had documentation of a prior skin rash (the remainder presented concurrently), occurring a median of 6 months before, with 11 (18.6%) undergoing a skin biopsy. Median eGFR at diagnosis was 84 (42.3-90) ml/min/1.73m2. Median UPCR at presentation was 120 (21.7-481.7) mg/mmol, with 19 (32.2%) having nephrotic-range proteinuria. Patients with nephrotic-range proteinuria (UPCR >350 mg/mmol) and 8 (13.6%) with nephrotic syndrome (as previous, plus serum albumin ≤ 30 g/L). 24 (40.7%) patients had evidence of crescents on renal biopsy. 16 (28.1%) were treated with prednisolone alone, and 15 (26.3%) combined with another agent, most commonly mycophenolate mofetil. At last follow up, 38 (64.4%) had an eGFR >60 ml/min, and 21 (35.6%) below 8 reached ESRD, at a median of 25 months (2-68.8) months. All had nephrotic-range proteinuria (UPCR >350 mg/mmol) at presentation. When compared to those with similarly severe proteinuria at presentation, patients who reached ESRD were younger, had lower eGFR at presentation and had a higher failure rate in achieving remission from their proteinuria.

Conclusions: Overall, in this cohort, patients with IgAV who achieved proteinuria <1g/d had a good outcome. Those who presented with nephrotic range proteinuria with failure to respond to treatment.

Funding: Government Support - Non-U.S.

TH-PO1033
Incidence of Biopsy-Proven Kidney Disease Among Kaiser Permanente Northern California Patients in 2018
Vivek Chau,1 Maryam Aghighi,2 Jessica B. Lupasiga,2 George Lai,2 Jennifer W. Lin,2 Tracy J. Jonelis,2 Megan L. Troxell,2 Necraja Zheng,1 Sijie Zheng,1 1Pathology, Stanford University School of Medicine, Palo Alto, CA; 2The Permanente Medical Group, Northern California, CA.

Background: Accurate population-level estimates of the incidence of glomerular (G) and primary tubulointerstitial diseases (TI) are lacking. Obtaining such estimates is challenging as accurate diagnosis typically requires a kidney biopsy and lack relevant population-level denominators. Here we provide population-level estimates of biopsy-proven G & TI diseases in a cohort of ~4.3 million at Kaiser Permanente Northern California (KPNC) in 2018.

Methods: We reviewed all KPNC 2018 renal biopsy reports, and categorized patients into study or G & TI disease groups. Incidence rates and associated standard deviations were calculated per 100,000 persons, stratified by age and sex.

Results: 673 native kidney biopsies were performed in 2018, corresponding to 15.8 biopsies/100,000 persons. The incidence of common biopsy-confirmed G & TI diseases are provided in the Table. The commonest diagnosis (40.2%) was minimal changes disease (n=231), followed by focal and segmental glomerulosclerosis (10.7%), diabetic nephropathy (7.9%), and membranous nephropathy (6.8%). 14.5% of patients undergoing kidney biopsy in this cohort had evidence of diabetic nephropathy (n=131), 21.4% of whom had an additional G or TI diagnosis (n=28).

Conclusions: Here we provide incidence estimates of biopsy-confirmed G & TI diseases in a large, racially and ethnically diverse population. Comparison with population-level estimates in other cohorts will help determine the true incidence of these diseases.

TH-PO1034
One Year of the State Registry of CKD in Aguascalientes Mexico: Have We Found a New Hotspot of CKD?
Jose M. Arreola Guerra,1 Centenario Hospital Miguel Hidalgo, Aguascalientes, Mexico.

Background: According to the Institute for Health Metrics and Evaluation, in Mexico the global burden attributed to chronic kidney disease (CKD) is one of the highest worldwide. Unfortunately the country doesn't have any official registry. Since June 2018, the Health Council from Aguascalientes brought together the main health institutions that provide renal replacement therapy, in order to start the registry of CKD in Aguascalientes.

Methods: Describe the results of the first year of data collection of the Aguascalientes CKD registry

Results: Until May 2019, 2,574 patients have been registered, of whom 93 have died and 372 have been transplanted. The estimated prevalence is 1,526 pmp (n= 2,160). The most common causes are CKD: of unknown origin (n= 981, 45.4%), Diabetes Mellitus (n=681, 31.5%), Systemic Arterial Hypertension (n= 326, 15%). The most prevalent modality of renal substitution was hemodialysis (n= 1,365, 63.1%). 39% are men (n= 1,274). The average age of the patients included was 46 years, with a bimodal distribution. The first group between 20 and 39 yo (n=1,107, 51.2%) and the second between 50 and 69 yo (n= 843, 39%). Since January 2012, 389 kidney biopsies have been performed in the state. The main diagnosis was focal and segmental glomerulosclerosis(FSGS) (n= 128, 32.9%), followed by lupus neph (n= 55, 14.1%), IgA neph (n= 48, 12.3%), minimal changes dis (n= 45, 11.5) and membranous neph (n= 22, 5.6%).

Conclusions: In Aguascalientes Mexico, we have a high prevalence of CKD. The main cause is of unknown origin. The main affected group are young adults between 20 and 40 of the most frequent glomerulopathy in this group was FSGS. At this moment a study of screening of CKD in adolescents in the state is being developed which is expected to contribute to the study of the causes of CKD in our population

Characteristics by age groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (20-29 yo)</th>
<th>Group 2 (30-49 yo)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>53 (60.5)</td>
<td>42 (60.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>CKD:Diabetes etiology</td>
<td>74 (80.9)</td>
<td>57 (80.6)</td>
<td>0.60</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>53 (60.5)</td>
<td>57 (80.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>BEN, %</td>
<td>189 (21.4)</td>
<td>138 (20.2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Renal Biopsy</td>
<td>No</td>
<td>135</td>
<td>44</td>
</tr>
<tr>
<td>FSGS, %</td>
<td>18 (20.0)</td>
<td>7 (10.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Lupus, %</td>
<td>19 (21.4)</td>
<td>5 (7.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Other, %</td>
<td>17 (19.5)</td>
<td>9 (13.2)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

FSGS: Focal segmental glomerulosclerosis, HTN: Systemic Hypertension, N: Nephritis

TH-PO1035
Biopsy Proven Diagnosis of CKD in Sub-Saharan Africa: An H3 Africa Cohort Study
Mamuk Mamwen,1,2 Titlaly O. Ilori,1 Oghochuku C. Okoye,2 Rulan S. Parekh,3 Jeffrey B. Hodgin,4 Rasheed A. Gbadegesin,2 Shikhar Kumar,4 Akinolu O. Ojo,5 Dwomoa Adu,6 H3 Africa Kidney Disease Research Network, 1The University of Arizona, Tucson, AZ; 2Medicine, University of Abuja, Abuja, Nigeria; 3Medicine, Delta State University Teaching Hospital, Oghara, Nigeria; 4The Hospital For Sick Children, Toronto, ON, Canada; 5Duke University Medical Center, Durham, NC; 6The University of Michigan, Ann Arbor, MI; 7University of Ghana, Accra, Ghana.

Background: Chronic kidney disease is increasingly prevalent in Sub-Saharan Africa (SSA) and a major factor leading to increased morbidity and mortality. Treatment of CKD, specifically glomerulonephritis (GN) is paramount to reducing CKD progression, morbidity and mortality, however, little is known about the types and incidence of primary glomerulonephritis (GN) nor is pathological diagnosis feasible throughout SSA.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Methods: Among 500 native kidney biopsies performed so far at 10 centers across Africa, we assessed patterns and types of glomerular disease in participants with eGFR greater than 15mL/min/1.73m² enrolled in the H3 Africa Kidney Disease network cohort study from 2017-2019. Biopsies were performed with real time ultrasound guidance and samples were shipped for processing and evaluation of light, immunofluorescence and electron microscopy by 2 US pathologists. We present preliminary results on demographic, clinical and biopsy data obtained.

Results: Demographics and baseline characteristics: The mean age was 30.68 ± 13.12 years, there were 231 males (50.4%), 357 (77.95%) patients were Nigerians, 99 (21.62%) and 94 (20.3%) were females of age ≤ 20 years and > 20 years, respectively. The eGFR was 66.27 ± 37.20. 10 (9.17%) had high blood pressure, 11 (2.43%) had diabetes, 6 (1.32%) were hepatitis B positive and 1 (0.22%) was positive to hepatitis C.

Conclusions: FSGS, membranous nephropathy and minimal change disease were the most frequent primary glomerulonephrites among adults in our region. Lupus Nephritis is a common secondary GN in Sub Saharan Africa.

Funding: NIDDK Support

Types and patterns of biopsy-proven Glomerulonephritis

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**TH-PO1036**

The Spectrum of the Biopsy-Proven Glomerular Disease in Taiwan: A Single-Center Experience

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**Background:** Glomerular diseases are still leading causes of end-stage renal disease. The diagnosis of these disease relies on the interpretation of the renal biopsy. The sonography-guided biopsy is still the major tool to acquire an accurate pathologic diagnosis. The spectrums of the glomerular disease are varied in different regions. Grossly, IgA nephropathy is the leading cause of primary glomerular disease in Asia. To date, there are few articles which report the disease spectrum in Taiwan. This study conducts a retrospective investigation of 19-years cohorts in a single medical center. The trend of disease spectrum was evaluated and analyzed.

**Methods:** This investigation was performed in a tertiary hospital. From 2000-2018 period, totally 2,391 patients first received renal biopsy. After excluding 71 cases of glomerular diseases which are not confirmed by renal biopsy or renal failure patients, 778 cases were fitted. The patients were divided into two groups: the patients were followed until renal biopsy diagnosis or kidney transplantation.

**Results:** Membranous glomerulopathy is the leading category in 2,050 cases (404, 19.7%), followed by IgA nephropathy (560 cases, 14.9%), minimal change nephropathy (243, 13.8%), focal segmental glomerulosclerosis (180, 8.8%). In the secondary disease, lupus nephritis account for 18.4% of the 2050 cases (378), followed by diabetic nephropathy (200, 9.6%), and paraproteinemic renal disease (60, 2.9%). Notably, the incidence of the membranous glomerulopathy is decreasing by year. In contrast, the ratios of IgA nephropathy is increasing gradually.

**Conclusions:** Membranous glomerulopathy is the major category in 19-years cohort of a single medical center, although the incidence is decreasing by year. Further investigation of change of disease spectrum is necessary.

**Funding:** NIDDK Support

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**TH-PO1037**

Positive Family History for CKD in Patients with Primary Glomerular Diseases: Disease Onset and Comorbidities in the CureGN Cohort

Lucrezia Carlassara,1 Maddalena Marasa,1 Rasheed A. Gbadebesin,1 Debbie S. Gipson,2 Matt G. Sampson,3 Bruce A. Julian,3 Simone Sanna-Cerrichi,2 Krzysztof Kuryluk,2 Andrew S. Bombace,2 Ali G. Gharavi,2 1Università degli Studi di Brescia, Vicenza, Italy; 2Columbia University, New York, NY; 3Duke University Medical Center, Durham, NC; 4University of Michigan Mott Children's Hospital, Ann Arbor, MI; 5University of Michigan, Ann Arbor, MI; 6University of Alabama at Birmingham, Birmingham, AL.

**Background:** A positive family history (pFHx) has been associated with worse outcomes for some glomerulonephritides (GNs), but this has not been rigorously examined in a prospective cohort. A pFHx for chronic kidney disease (CKD) can be indicative of Mendelian hereditary diseases, or may reflect a polygenic risk or unmeasured environmental risk factors.

**Methods:** We studied the association of a self-reported pFHx of CKD with renal function at the time of diagnosis and comorbidity burden in the Cure Glomerulopathy Network (CureGN), a prospective multi-center observational study of GN patients (N=2281) with Focal Segmental Glomerulosclerosis (FSGS), Minimal Change Disease (MCD), Membranous Nephropathy (MN), IgA Nephropathy (IgAN), or IgA Vasculitis (IgAV). Comparisons between patients with and without pFHx were analyzed via Chi-square/Fisher and ANOVA/Wilcoxon test.

**Results:** A CKD pFHx was present in 352 (15%) patients: 28% of FSGS, 21% of MN, 15% of IgAN, 13% of MCD, and 9% of IgAV cases. CKD pFHx was associated with lower eGFR at GNs onset in entire cohort (p=0.010), IgAN (p=0.0002), FSGS (p=0.0004), IgAN (p=0.001), and MN (p=0.02) but not MCD patients. CKD pFHx was associated with older age at the GNs onset with adults IgAN (p=0.006) patients. CKD pFHx was significantly associated with a higher prevalence of several comorbidities, even after adjusting for age, sex, ethnicity, race, body mass index, and smoking habit (Table 1).

**Conclusions:** Patients with a CKD pFHx have lower eGFR at presentation and have higher prevalence of certain comorbidities than patients without such family history. The association with allergies, asthma and COPD point to shared biology and environmental factors. Identifying this association may help to elucidate common genetic or environmental causes, shed light on disease pathogenesis, improve GNs management, and ultimately may help develop preventive measures.

**Funding:** NIDDK Support

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**TH-PO1038**

Racial/Ethnic Differences in Socioeconomic Status (SES) and Health-Related Quality of Life (HRQL) Among Children with Glomerular Disease in Cure Glomerulonephropathy (CureGN)

Jian Jason Cai,1 Margaret Sanna,1 Diego H. Aviles,1 Yi Cai,2 Rasheed A. Gbadebesin,3 Keisha L. Gibson,3 Larry A. Greenbaum,4 Guillermo Hidalgo,5 Sangeeta R. Hingorani,5 Sandra Irgorri,5 Myda Khalid,6 Richard A. Lafayette,7 Sherene M. Mason,7 Rulan S. Parekh,12 David T. Selevski,15 Howard Trachtman,13 Katherine R. Tuttle,13 Katherine Twombly,15 Tetyiana L. Vasylyeva,14 Scott E. Wenderfer,15 Michelle M. O’Shaughnessy,15 Stanford Health Care, Redwood City, CA; 14Research Collaborative for Health, Ann Arbor, MI; 15Helen DeVos Children’s Hospital, Grand Rapids, MI; 16Duke University Medical Center, Durham, NC; 17University of North Carolina Kidney Center, Chapel Hill, NC; 18Emory University, Atlanta, GA; 19Eastern Carolina University, Greenville, NC; 20Seattle Children’s Hospital, Seattle, WA; 21Indiana University, Indianapolis, IN; 22Stanford University, Stanford, CA; 23Connecticut Children’s Medical Center, New Haven, CT; 24The Hospital For Sick Children, Toronto, ON, Canada; 25NYU Langone Health, New York, NY; 26University of Washington School of Medicine, Spokane, WA; 27Medical University of South Carolina, Charleston, SC; 28Baylor College of Medicine, Houston, TX; 29LSUHSC, New Orleans, LA; 30University of Oregon, Portland, OR; 31Texas Tech Health Sciences Center, Lubbock, TX.

**Background:** Race/ethnicity, disease severity/duration, and lower SES have been associated with poorer HRQL in children with glomerular disease; however, the relative importance of these factors has not adequately been explored.

**Methods:** CureGN is a 70-center cohort study of patients with MCD, FSGS, MN, or IgAN/IgAV. We compared pediatric patient characteristics (demographics, disease duration/severity, medications, SES) at enrolment across racial/ethnic groups. Multivariable logistic and linear regression models, created using best subsets and backwards selection, were used to examine associations between race/ethnicity and HRQL, as measured by missed school days due to kidney disease and baseline PROMIS questionnaire items.

**Results:** Among 515 White, 146 Black and 74 Hispanic children, Blacks were most likely to have FSGS/MCD and had the lowest eGFR, highest urine protein, lowest serum albumin, and most severe edema. Compared to Whites, Blacks or Hispanics were less likely to have private insurance (59, 35, and 32%, p<0.001), and their parents/guardians were less likely to have completed college (18, 7, and 10% of mothers, and 30, 12, and 12% of fathers, p<0.001). Racial/ethnic differences in HRQL were small (below the Minimal Important Difference of 3) and generally not statistically significant (Table). No differences in missed school days due to kidney disease and baseline PROMIS questionnaire items.

**Conclusions:** Among pediatric CureGN patients, SES varied by minority status such that Black or Hispanic (vs. White) children were less likely to have private insurance and their parents received less formal education. After adjusting for SES and other factors, minority status was not associated with HRQL as measured within this study.

**Funding:** NIDDK Support

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Underline represents presenting author.
TH-PO1039

Racial/Ethnic Differences in Socioeconomic Status (SES) and Health-Related Quality of Life (HRQL) Among Adults with Glomerular Disease in Cure Glomerulonephropathy (CureGN)

Jill Krissberg,1 Margaret Helmuth,2 Salem Almaani,1 Bartosz Foroncweicz,1,3 Guillermo Hidalgo,4 Sangeeet R. Hingorani,5 Michelle A. Hladunewich,3 Koyal Jain,4 Jeffrey B. Kopp,4 Richard A. Lafayettie,6 Barbara Moszczuk,13 Krzysztof Mucha,14 Jordan G. Nestor,10 Rulan S. Parekh,11 Katherine R. Tuttle,12 Tetyana L. Vasylyeva,14 Michelle M. O’Shaughnessy.2

1Stanford Health Care, Redwood City, CA; 2Arbor Research Collaborative for Health, Ann Arbor, MI; 3University of Toronto, Toronto, ON, Canada; 4The Ohio State University Wexner Medical Center, Columbus, OH; 5Seattle Children’s Hospital, Seattle, WA; 6University of North Carolina, Chapel Hill, NC; 7University of North Carolina, Greenville, NC; 8NIDDK, NIH, Bethesda, MD; 9Stanford First Saint Petersburg State Medical University, Saint-Petersburg, Russian Federation.

Background: Recent studies showed that measurement of various biomarkers (BM) can be useful in differential diagnosis of some primary glomerulonephritis (GN) forms. Our aim was to develop an algorithm for differential diagnosis of primary GN based on BM panel using decision tree learning approach.

Methods: 74 patients [39 male, age Me (min; max) = 37.5 (25; 54) years] with biopsy proven primary GN and without AKI, infectious diseases, severe heart failure, respiratory insufficiency, cancer, abnormal thyroid status, treatment with prednisalone more than 10 mg/day were included in the study. Based on the results of kidney biopsy (KB) in 7% of cases minimal change disease (MCD) was diagnosed, in 27% – FSGS, in 27% – membranous nephropathy (MN), in 39% – IgA-nephropathy. BM were measured in the morning on the day of KB: serum creatinine(Scr), albumin(AIb), Cyst(CysC), 24-hour total protein(24hTP), urinary (24-hour collection) cystatin(Ct)(CysC), transferrin(Tr), lgG(lgG), ct1-microglobulin(u1-mg), β2-microglobulin(u2-mg), serum/urine magnesium. The Classification and Regression Trees (CART) learning algorithm with FACT-style direct stopping as pruning criteria was used to create a model for differential diagnosis. Complete machine learning, statistical analysis were performed with Statistica v.12.

Results: A decision tree algorithm was developed including ten predictor variables: age, ct1-mg, trans, 24hTP, ct1-mg, ct1-1mg, EFmg. This algorithm accurately classified patients with MCD in 100% cases (5 out of 5 cases), FSGS - 80% (16/20 cases), MN - 85% (17/20 cases), IgA-nephropathy - 96.6% (28/29 cases) (Figure 1).

Conclusions: A “decision tree” algorithm based on age and few urinary, serum BM can be a powerful diagnostic tool in differential diagnosis of primary GN. Application of this algorithm allows to evaluate patients with high risk progression of CKD, identify treatment targets before or instead of KB.

Funding: Government Support - Non-U.S.

TH-PO1040

A Novel Approach in Differential Diagnosis of Primary Glomerulonephritis Using the Decision Tree Algorithm Model Based on Biomarkers Panel

Elena Saganova, Olga Galkina, Vasilyi Spivovski, Alexey Smirnov, Pavlov First Saint Petersburg State Medical University, Saint-Petersburg, Russian Federation.

Background: Recent studies showed that measurement of various biomarkers (BM) can be useful in differential diagnosis of some primary glomerulonephritis (GN) forms. Our aim was to develop an algorithm for differential diagnosis of primary GN based on BM panel using decision tree learning approach.

Methods: 74 patients [39 male, age Me (min; max) = 37.5 (25; 54) years] with biopsy proven primary GN and without AKI, infectious diseases, severe heart failure, respiratory insufficiency, cancer, abnormal thyroid status, treatment with prednisalone more than 10 mg/day were included in the study. Based on the results of kidney biopsy (KB) in 7% of cases minimal change disease (MCD) was diagnosed, in 27% – FSGS, in 27% – membranous nephropathy (MN), in 39% – IgA-nephropathy. BM were measured in the morning on the day of KB: serum creatinine(Scr), albumin(AIb), Cyst(CysC), 24-hour total protein(24hTP), urinary (24-hour collection) cystatin(Ct)(CysC), transferrin(Tr), lgG(lgG), ct1-microglobulin(u1-mg), β2-microglobulin(u2-mg), serum/urine magnesium. The Classification and Regression Trees (CART) learning algorithm with FACT-style direct stopping as pruning criteria was used to create a model for differential diagnosis. Complete machine learning, statistical analysis were performed with Statistica v.12.

Results: A decision tree algorithm was developed including ten predictor variables: age, ct1-mg, trans, 24hTP, ct1-mg, ct1-1mg, EFmg. This algorithm accurately classified patients with MCD in 100% cases (5 out of 5 cases), FSGS - 80% (16/20 cases), MN - 85% (17/20 cases), IgA-nephropathy - 96.6% (28/29 cases) (Figure 1).

Conclusions: A “decision tree” algorithm based on age and few urinary, serum BM can be a powerful diagnostic tool in differential diagnosis of primary GN. Application of this algorithm allows to evaluate patients with high risk progression of CKD, identify treatment targets before or instead of KB.

Funding: Government Support - Non-U.S.

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Underline represents presenting author.

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**TH-PO1042**

Functional Subclasses of Nephrotic Syndrome Identified Using Consensus Non-Negative Matrix Factorization Clustering of Kidney Tubulointerstitial Tissue Transcriptome

Habib Hamidi,1 Sean Eddy,1 Matthias Kretzler,1 John R. Sedor,2 John F. O'Toole,2 Lawrence B. Holzman,2 Laura H. Mariain.1 1University of Michigan, Ann Arbor, MI; 2Cleveland Clinic, Cleveland, OH; 3University of Pennsylvania, Philadelphia, PA.

**Background:** Interstitial fibrosis and tubular atrophy are common patterns of injury in glomerular diseases, but it is unknown whether multiple mechanisms can result in this pattern of injury and if mechanisms change as disease progresses. Consensus non-negative matrix factorization (NMF) is a clustering approach used with tumor specimen transcriptomics to identify functionally relevant subtypes.

**Methods:** NMF clustering was applied to tubular mRNA expression from kidney biopsies from the NEPTUNE cohort, a prospective cohort of children and adults with nephrotic syndrome enrolled at the time of clinically indicated kidney biopsy. Individual gene expression levels from the tubular compartment were normalized to mean expression to maximize individual patient differences. Cox proportional hazards models were fit for complete proteinuria remission (CR, UPCR <0.3 mg/mg) and ESRD/40% eGFR decline.

**Significance analysis of microarray identified cluster specific differentially expressed genes that were used in pathway enrichment analysis to determine functional relevance.**

**Results:** NMF separated 188 patients into 4 clusters which did not differ age (p=0.46), sex (p=0.77) or UPCR (p=0.46). The clusters did not segregate by disease etiology (Fig). Cluster 2 had lower mean eGFR (56 mL/min vs 83, 66 and 66; p<0.01) and greater UPCR (2.8, p-value <0.01). Pathway enrichment of cluster-specific genes demonstrated unique biological processes (Fig).

**Conclusions:** NMF identified functional subclasses in the tubular kidney tissue mRNA of patients with nephrotic syndrome which crossed traditional diagnostic classifications of FSGS, MCD and MN. Functional analysis revealed both shared and specific pathways associated with the clusters which could help to identify therapeutic targets.

**Funding:** NIDDK Support, Other NIH Support - NCATS

**TH-PO1043**

Elevated Plasma Free Sialic Acid Levels in Individuals with Reduced Glomerular Filtration Rates

Federico Fuentes,1 Marjan Huizing,1 Jodi Blake,2 William Gahl,1 Nuria Carrillo,1 Jeffrey B. Kopp.1 1National Institutes of Health/National Human Genome Research Institute, Bethesda, MD; 2NIDDK, NIH, Bethesda, MD.

**Background:** Sialic acid (SA) is a negatively charged, terminal monosaccharide present on glycoconjugates. They are important contributors to the polyanionic component of the glomerular filtration barrier, which regulates permeability selectivity. Free SA is filtered but not reabsorbed by the human kidney, in contrast to other sugars known to be reabsorbed by tubular cells. We determined plasma free SA levels of subjects with proteinuric diseases and diverse levels of estimated glomerular filtration rate (eGFR) to assess a correlation and emphasize this understudied feature of SA.

**Methods:** Free SA (Neu5Ac) was determined in plasma samples from 16 proteinuric subjects and 22 individuals with normal renal function with a validated LC-MSMS assay.

**Results:** There was a strong inverse relationship between eGFR and plasma SA levels (R2 =0.70, p <0.0001). Plasma SA levels ranged between 114-206 ng/mL in subjects with normal eGFR (>90mL/min/1.73 m²). While in subjects with decreased eGFR (<30 mL/min/1.73 m²), plasma SA levels were at least three-fold higher (431-1260 ng/mL range).

**Conclusions:** It is important to emphasize the often-overlooked feature of renal handling of free SA. If increased plasma SA levels are encountered in subjects, compromised renal function/decreased eGFR should be considered. Of note is that pathologic hyposialylation of glomerular glycoconjugates, associated with podocyte effacement, has recently been implicated in human glomerulopathies. The relation between plasma free SA levels and glomerular hyposialylation remains to be investigated.

**Funding:** NIDDK Support, Other NIH Support - NIGMS

**TH-PO1044**

Urinary Podocalyxin Protein Excretion Is an Early Biomarker in Age-Associated Kidney Disease

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**Background:** Aging is the strongest known risk factor for end-stage kidney disease. Many factors including aging can cause podocyte injury. If the initiating injury causes a critical level of podocyte depletion, it can lead to glomerulosclerosis and progression. Age-associated reduction in podocyte density (increased glomerular volume per podocyte) is associated with podocyte hypertrophic stress and failure that leads to glomerulosclerosis in model systems and humans. Urinary podocyte excretion can be used to monitor glomerular disease activity and progression. This study investigated whether urinary podocyte protein excretion can be used for monitoring age-associated kidney diseases.

**Methods:** From June 2018 to March 2019, spot urine samples were collected from 261 healthy volunteers without diabetes, hypertension and albuminuria during medical checkups by age groups (20–29 years: n=48, 30–39 years: n=53, 40–49 years: n=59, 50–59 years: n=52, ≥60 years: n=49). We investigated the urinary supernatant (U-Poxy) and sediment (Sed-Poxy) podocalyxin protein levels by ELISA to reflect podocyte injury and podocyte detachment, respectively, and urinary albumin/creatinine ratio (U-ACR).

**Results:** There were no significantly different concentrations in systolic blood pressure, fasting blood glucose, and body mass index among the groups. However, estimated glomerular filtration rate significantly decreased with age (20–29 years: 94±1.5 mL/min/1.73 m² vs ≥60 years: 74.5±1.1 mL/min/1.73 m², p=0.01). U-Poxy was also significantly increased in the ≥60 years group (20–29 years: 94±4.57 vs. ≥60 years: 124±6.31 mg/g Cre, p=0.01). U-ACR was also significantly increased in the ≥60 years group (20–29 years: 5.2±4.2 vs. ≥60 years: 8.0±5.6 mg/gCre, p=0.01), but the levels were far lower than the microalbuminuria level. Meanwhile, Sed-Poxy did not differ among the groups.

**Funding:** NIDDK Support, Other NIH Support - NIDDK

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Underline represents presenting author.
Conclusions: U-PCX, but not sed-PCX, was significantly increased the α60 years group without hypertension, diabetes, and microalbuminuria compared with other groups. These results suggest that age per se is a risk factor for podocyte injury and that U-PCX can be used for as an early (prior to overt albuminuria and podocyte detachment) biomarker in age-associated kidney disease.

Funding: Government Support - Non-U.S.

TH-POI045
Exosomal Micro RNA as a Diagnostic Tool in Kidney Biopsy Cohort
Teruhiko Yohei,1 Yohei Hamasaki,1 Yoshifumi Miyamoto,2 Yohei Komaru,3 Keit Doi,4 Jeffrey B. Kopp,5 Masaomi Nangaku,6 NIDDK, National Institutes of Health, Bethesda, MD; 2University of Tokyo, Tokyo, Japan; 3the University of Tokyo Hospital, Tokyo, Japan; 4the University of Tokyo School of Medicine, Tokyo, Japan.

Background: Despite recent advances, clinical renal diagnosis requires pathological examination of a kidney biopsy. Micro RNAs (miRNAs) in exosomes are promising biomarkers for kidney disease diagnosis and management. We sought to identify diagnostic miRNAs in exosomes from blood and urine obtained from subjects with diabetic nephropathy.

Methods: We performed a prospective single-center cohort study, enrolling patients who underwent kidney biopsy at the University of Tokyo Hospital. Blood and urine samples and clinical parameters were obtained at the time of the kidney biopsy. Exosomes were isolated from blood and urine by ultracentrifugation and RNA was extracted. We selected candidate miRNAs by TaqMan array card and measured expression by quantitative PCR. The outcome variable was standardized pathological diagnosis. We confirmed the principal findings by experiments in streptozotocin (STZ)-induced diabetic mice.

Results: The study population consisted of 102 patients who underwent kidney biopsy, including 8 with diabetic nephropathy and 23 with diabetes who had other kidney diseases. For the diagnosis of diabetic nephropathy, a clinical model (diabetic history, retinopathy and hematuria) had moderate accuracy, with AUC [95% CI] 0.65 [0.44-0.81]. Urinary exosomal miR-486 added significant accuracy when combined with the clinical model, showing AUC 0.92 [0.76-0.98] (p < 0.003). In STZ diabetic mice, miR-486 expression was reduced by 94% in urinary exosomes (p < 0.003) and by 40% in laser capture micro-dissected glomeruli (p = 0.02) compared with non-diabetic mice.

Conclusions: Levels of urinary exosomal miRNAs correlate with the histological diagnosis of diabetic nephropathy and may be a promising non-invasive diagnostic tool.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-POI046
Differences in Disease Activity by Sex and Pubertal/Menopausal Status in Primary Glomerulonephropathies
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Background: CKD has been observed to progress more slowly in women than men. However, large studies examining associations between sex, reproductive stage, and disease activity and progression in primary glomerulonephropathies are lacking.

Methods: CureGN is a 70-site prospective cohort study of patients with MCD, FSGS, IgAN/IgAV, or MN. Patients with available eGFR, UPCR, and reproductive stage at enrollment were study. Reproductive stage was categorized as pre-pubertal (Tanner stage I-III), post-pubertal (Tanner stage IV-V, or menarche for females), or post-menopausal (females only). Multivariable mixed linear models adjusted for baseline data at time of enrollment (Table) were fit to examine change in eGFR and UPCR over time.

Results: Median follow-up from enrollment was 2.1 (IQR 1.0-3.1) yrs. Among 1202 patients available enrollment age eGFR, adjusted (Model 3) eGFR slopes amongst females were -0.71, -0.84, and -1.43 ml/min/1.73m2 per year for pre-pubertal, post-pubertal, and post-menopausal women, respectively (Table). For pre-pubertal and post-pubertal males, eGFR slopes were -1.14 and -1.19 ml/min/1.73m2 per year, respectively. Adjusted UPCR slopes by sex and reproductive stage are also shown in the Table.

Conclusions: The protective effect of female sex on eGFR decline was most notable prior to puberty. Of all groups, post-menopausal women had the fastest eGFR decline. Unlike post-pubertal males and females, pre-pubertal participants experienced no significant decrease in UPCR over time, and menopausal status did not seem to impact the rate of UPCR decline seen in post-pubertal females.

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TH-POI047
Development of a Clinician-Reported Outcome Measure for Edema Assessment
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Background: Patients report edema is a high impact manifestation of proteinuric kidney disease. However, evaluation of edema is not standardized and ranges from localized or generalized swelling. Accurate and valid assessment of edema is important for patient care and clinical trials of patients with proteinuric kidney disease. The objective of this study was to develop a clinician reported outcome measure (ClinRO) for edema assessment for use with patients with glomerular disease.

Methods: Semi-structured interviews were conducted with pediatric and internal medicine nephrology clinicians (physicians and advanced practice providers) to elicit physical exam findings of edema manifestations, documentation, and importance. Concepts were derived from these interviews, confirmed with clinicians and then used to create the Edema ClinRO.

Results: 14 clinicians participated in the study, including 7 pediatric and 7 internal medicine experts. Concepts identified included assessment of body regions (periorbital, extremities, trunk and if patient endorsed genitals) and severity rating. The ClinRO was generated (Figure) in an iterative fashion with input from clinician stakeholders. Online training and certification modules were developed for use and a user acceptance testing step was implemented

Conclusions: The Edema ClinRO was developed based upon pediatric and internal medicine clinician input using best practice methods to support implementation of standardized edema assessment in clinical and research contexts. User acceptance testing of the ClinRO has been completed and for the training module is underway. With web-based Edema ClinRO dissemination and data collection, the utility of this measure will be assessed as a future step.

Funding: Commercial Support - Goldfinch Bio

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Time-Updated Systolic Blood Pressure and Progression of CKD in Patients with Glomerulonephritis

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Background: Many guidelines on optimal target of blood pressure in chronic kidney disease are largely based on studies in diabetic and hypertensive patients. However, there is lack of evidence that this blood pressure goal can also be applied to patients with glomerular diseases. The aim of this study was to clarify the longitudinal association between blood pressure and CKD progression in patients with glomerulonephritis.

Methods: We studied 1,016 biopsy-proven patients who were diagnosed with primary glomerular diseases such as IgA nephropathy (n=756 [74.4%]), membranous glomerulonephritis (n=144 [14.2%]), and focal segmental glomerulosclerosis (n=116 [11.4%]) from 2005 to 2017. The main exposure of interest was baseline and time-updated systolic blood pressure (SBP). The primary outcome was a composite of a ≥50% decrease in eGFR from baseline or end-stage kidney disease. We used time-varying cox model and marginal structural model for time-updated SBP.

Results: During 1,607 person-years follow up, the primary outcome occurred in 658 (64.8%) patients. The mean age was 43.6±14.7 years and baseline eGFR was 90.4±28.0 mL/min/1.73 m². 665 (65.5%) patients had the history of previous hypertension. Using time-varying cox model, with compared with SBP of 120 to 129 mmHg, the hazard ratios for the primary outcome were 1.01 (95% CI, 0.84 to 1.22), 1.11 (95% CI, 0.88 to 1.40), 1.36 (95% CI, 1.04 to 1.78), respectively. The marginal structural model also showed consistent results. The corresponding HRs for the noted SBP categories were 1.04 (95% CI, 0.84 to 1.24; p=0.683, 1.14 (95% CI, 1.02 to 1.24; p=0.012, 1.43 (95% CI, 1.08 to 1.89; p=0.01), respectively. This association was consistent regardless of subgroups by age (<60 vs. ≥60), gender, previous hypertension, baseline eGFR (≥45 vs. <45), and proteinuria (≥3g vs. <3g).

Conclusions: Among patients with glomerular diseases, SBP >140 mmHg was significantly associated with higher risk of CKD progression.

Identifying Outcomes Important to Patients with Glomerular Disease and Their Caregivers: A Multinational Nominal Group Technique Study

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Background: Outcomes that are important to patients with glomerular disease remain uncertain and therefore shared-decision making can be challenging. We aimed to identify and prioritize outcomes important to patients and their caregivers, and the reasons for their choices.

Methods: Patients aged 18 years with glomerular disease and their caregivers from Australia, Hong Kong, United Kingdom and United States. Participants identified, ranked and discussed outcomes. Each outcome was ranked using a relative importance score between 0 and 1. Qualitative data were analyzed thematically.

Results: Across 16 focus groups, 132 participants (100 patients, 32 caregivers) identified 58 outcomes. Patients were aged 19 to 85 years (mean 51 years), 47 (47%) were female and 29 (29%) were on dialysis or had received a kidney transplant. Thirty eight (38%) had kidney-limited glomerular disease, 31 (31%) had glomerular disease with systemic features, and 31 (31%) had other or unknown subtypes. The ten highest ranked outcomes were: kidney function (importance score 0.42), mortality (0.39), need for dialysis or transplant (0.22), life participation (0.18), fatigue (0.17), anxiety (0.13), impact on family (0.12), infection and immunity (0.12), ability to work (0.11) and blood pressure (0.11; Figure 1). The top five outcomes were identical for patients and caregivers.

Conclusions: Among patients with glomerular diseases, SBP >140 mmHg was significantly associated with higher risk of CKD progression.
Conclusions: Patients with glomerular disease and their caregivers highly prioritize kidney health and survival, as well as life participation, fatigue, anxiety and the impact on family. Consistent reporting of these outcomes in trials may improve shared decision-making.

Funding: Government Support - Non-U.S.

Methods: NEPTUNE biorepository plasma aliquots (N=150) were obtained (exclusion criteria: anticoagulants or with prior VTE) along with phenotypic data. TGA was performed and endogenous thrombin potential (ETP) calculated as the area under the thrombin activity curve. Plasma albumin levels were also determined.

Results: TGA was undetectable in 3 (2%) of the NEPTUNE samples (excluded). Univariate linear regression on the remaining 147 samples revealed significant relationships with: Age (B=-16), Proteinuria (log-UCP; B=265), Plasma Albumin (B=-657), Total Cholesterol (B=2129), cGFR (B=10), and Steroid (B=853) or RAAS-blockade (B=573) treatment. Histologic NS classification was not significantly associated with ETP. Multivariable modeling revealed an interaction between remission status and proteinuria, such that UPC was independently predictive of ETP in patients with active disease (B=828; P<0.0001; Figure). Age (B=-15; P=0.005) and Total Cholesterol (B=4148; P=0.0001) were also independently predictive. The final multivariable model was highly correlated with ETP (R²=0.35). Similar NS-severity univariate relationships were demonstrated in our local cohort.

Conclusions: Proteinuria and hyperlipidemia were associated with ETP. These data suggest that analysis of these NS severity markers and ETP in relation to thrombotic events in patients with NS may inform their utility as a future guide to anticoagulant prophylaxis.

Funding: NIDDK Support

Figure 1. Relative rankings of outcomes by patients and caregivers

TH-PO1051
Mood, Anxiety, and Hyperactivity Disorders in Patients with Glomerular Disease

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Background: Patients with chronic health conditions are at heightened risk for psychiatric disorders; yet clinical evidence for glomerular disease (GD) little known about presence of mood, anxiety, and hyperactivity disorder or associations with patient and disease characteristics.

Methods: This study included patients with GD enrolled in the Kidney Research Network multisite patient registry. Encounter, diagnosis, medication, lab, and vital sign data are extracted monthly from participants’ electronic health records. ICD9/10 diagnosis codes were used to identify psychiatric disorders, including anxiety and depressive disorders and attention deficit disorder (ADD). Longitudinal GEE models were used to analyze the odds of being diagnosed with a psychiatric disorder. Potential covariates in the models included age at kidney disease onset, sex, race, ethnicity, and time-varying treatment, eGFR and urine protein:creatinine ratio (UPC). Continuous variables are presented as median (IQR).

Results: Data were available for 938 patients with a 51 (IQR: 25-92) month follow-up and kidney disease onset age of 19 (IQR: 5-41) yrs. 202 (21.5%) were diagnosed with a psychiatric disorder at a rate of 4.3 per 100 pt-yrs, with 78 of those having two or more disorders. The most common disorders were anxiety (n=145, 3.1 per 100 pt-yrs), depression (n=101, 2.1 per 100 pt-yrs), and ADD (n=29, 0.6 per 100 pt-yrs). Adolescents vs adults (OR: 2.4, 95% CI: 1.5-4.0), white vs Asian race (OR: 2.7, 95% CI: 1.3-5.6), steroid therapy, higher proteinuria, and white (vs Asian) race. This may be an underrepresentation as data is based on what was documented in participants’ electronic health record. A difference in prevalence by race may suggest a difference in assessment and diagnosis rather than true difference in prevalence. These findings suggest mental health screening may be warranted in patients with GD.

Funding: Private Foundation Support

TH-PO1052
Nephrotic Syndrome Acquired Hypercoagulopathy Is Strongly Associated with Proteinuria and Hyperlipidemia

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Background: Nephrotic syndrome (NS) is complicated by hypercoagulopathy and predictively confers venous thromboembolism (VTE). Routine anticoagulant prophylaxis is controversial. Thrombin generation assay (TGA), a measure of hypercoagulopathy, has known predictive value for VTE in non-NS patients. We have shown that TGA is directly proportional to NS severity in animal NS. We sought to determine if TGA is correlated with human NS severity.

Methods: NEPTUNE biorepository plasma aliquots (N=150) were obtained (exclusion criteria: anticoagulants or with prior VTE) along with phenotypic data. TGA was performed and endogenous thrombin potential (ETP) calculated as the area under the thrombin activity curve. Plasma albumin levels were also determined.

Results: TGA was undetectable in 3 (2%) of the NEPTUNE samples (excluded). Univariate linear regression on the remaining 147 samples revealed significant relationships with: Age (B=-16), Proteinuria (log-UCP; B=265), Plasma Albumin (B=-657), Total Cholesterol (B=2129), cGFR (B=10), and Steroid (B=853) or RAAS-blockade (B=573) treatment. Histologic NS classification was not significantly associated with ETP. Multivariable modeling revealed an interaction between remission status and proteinuria, such that UPC was independently predictive of ETP in patients with active disease (B=828; P<0.0001; Figure). Age (B=-15; P=0.005) and Total Cholesterol (B=4148; P=0.0001) were also independently predictive. The final multivariable model was highly correlated with ETP (R²=0.35). Similar NS-severity univariate relationships were demonstrated in our local cohort.

Conclusions: Proteinuria and hyperlipidemia were associated with ETP. These data suggest that analysis of these NS severity markers and ETP in relation to thrombotic events in patients with NS may inform their utility as a future guide to anticoagulant prophylaxis.

Funding: NIDDK Support

TH-PO1053
Anticoagulation and Anti-Platelet Prescribing in Glomerular Disease: An Observational Study

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Background: Nephrotic syndrome confers thromboembolism (TE) risk. We report frequencies of TE and anticoagulation (AC) and antiplatelet (AP) prescribing in patients with/without nephrotic-range proteinuria enrolled in Nephrop Kidney Research Network (KRN) Registry.

Methods: Patients with glomerular disease (GD) from all KRN sites were included. Encounter, diagnosis, meds, lab, and vital sign data were extracted monthly from patients’ EMRs. Patients were grouped into those with at least one UPC ≥ 3.5 g/g (Nephrotic) vs those with UPCR always <3.5 g/g (Non-nephrotic). TE and AC/AP prescription (Rx) frequencies were determined. Follow-up was censored at ESRD.

Results: Nephrotic (n=568) and Non-nephrotic (n=404) groups were similar in age/sex. Mean eGFR (93 vs 70 ml/min/1.73m2, p<.001) and Total Cholesterol (4.9 vs 853, p<.001) or RAAS-blockade (4.9 vs 828, p<.001) were higher, and serum albumin lower (3.1 vs 3.9 g/dL, p<.001) in Nephrotics vs. Non-nephrotic. Nephrotics and Non-nephrotics had: FSGS/CIQ (59% vs 41%), Minimal change/gMes/GPGN (77% vs 23%), Membranous (79% vs 21%), IgA (28% vs 7%), or other GD (54% vs 46%). 90 Nephrotics and 52 Non-nephrotics had no biopsy (mostly children). Median follow-up for Nephrotics (57 mos) was longer than Non-nephrotics (49 mos). There were 70 TE: 9.2% of Nephrotics (n=52) vs 4.5% of Non-nephrotics (n=18) (p<.005). AC/AP Rxs were more frequent in Nephrotics (203 of 568, 36%) than Non-nephrotics (67 of 404, 17%) (p<.0001). The 203 Nephrotics had AC/AP Rx as follows: heparin, enoxaparin, fondaparinux (64%); aspirin (58%); warfarin (11%); alteplase, urapidil (9%). Factor Xa inhibitors (Xai, 5%); and/or clopidogrel, ticagrelor (4%). Nephrotics (n=67) had heparin, enoxaparin, fondaparinux (46%, p<.0001 vs Nephrotics); aspirin (61%); warfarin (12%); alteplase, urapidil (9%); Xai (6%) and/or clopidogrel, prasugrel, dipyridamole (9%).
Trends of Infection Among Hospitalized Patients with Chronic Glomerulonephritis: A Retrospective Study Spanning 18 Years from a Single Tertiary Hospital

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Background: Infection is one of the most important complications in patients with chronic glomerulonephritis. It confers an additional risk of death. However, its trends over the years in patients with chronic glomerulonephritis have seldom been demonstrated.

Methods: We conducted a retrospective analysis using the database of hospitalization with chronic glomerulonephritis in Peking Union Medical College Hospital (PUMCH), China from 2000 through 2017. The tenth revision from the International Classification of Diseases (ICD-10) codes of discharge diagnosis was used to identify infectious diseases and 6 kinds of glomerulonephritis including lupus nephritis (LN), systemic vasculitis (AAV), Henoch-Schönlein purpura nephritis (HSPN), IgA nephritis (IgAN), idiopathic membranous nephropathy(MN), and minimal change disease(MCD). Cochran-Armitage trend test and Logistic regression were used for analysis.

Results: Between 2000 and 2017, there were 15,714 hospitalizations with aforementioned chronic glomerulonephritis. Their mean age was 51.7±19.8 years and 39.4% were males. The annual prevalence of overall infection increased steadily from 14.7% in 2000 to 33.0% in 2017 among all (p for trend <0.001). We found significant increasing trends of overall infection in LN, AAV, HSPN, IgAN, and MCD, but not in MN.

Conclusions: There was an increasing trend of infection in hospitalized patients with chronic glomerulonephritis except for those with idiopathic membranous nephropathy. Prevalence of infection and infection patterns varied among hospitalized patients with different glomerulonephritides.
Conclusions: Treatment with CCR2 antagonist provides rapid renal protection in the model of FSGS, as measured by improved proteinuria and renal structure. Furthermore, CCR2 blockade protected podocyte integrity, as measured by both SEM and TEM. These results provide further evidence that specific inhibition of CCR2 has therapeutic potential in the treatment of FSGS. CCR2 antagonism thus represents a novel and mechanistically distinct approach for the treatment of FSGS.

TH-PO1060
Knockdown of Podocyte Nephronectin by Glomerular Endothelial Cell-Derived MicroRNA-192 Leads to Alterations in GBM
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Background: Nephronectin (NPNT) is an extracellular matrix protein downregulated by either TGF-β or miR-371a in podocytes. Knockdown of npnt leads to proteinuria, podocyte effacement and splitting of the glomerular basement membrane (GBM) in zebrafish larvae. Here we investigated the regulation of npnt by TGF-β and miR3 as well as GBM phenotype after knockdown of npnt in more detail by using cell culture, zebrafish and mice models.

Methods: By using mouse Smad2/3 knockout podocytes as well as selective inhibitors of the TGF-β pathway we analyzed the TGF-β-NPNT axis more in detail. We overexpressed this miR in zebrafish larvae and analyzed the glomerular phenotype. Finally podocyte specific knockdown of Npnt was investigated in Npnt -/-;Six1-x-cree mice.

Results: TGF-β regulation of NPNT is mediated by the canonical TGF-β pathway in a SMAD-dependent manner. We identified glomerular endothelial cell-derived miR-192 as a regulator of NPNT in podocytes. Transfection of cultured podocytes with a miR-192 mimic down regulated NPNT expression. Overexpression of miR-192 in zebrafish larvae induced edema, proteinuria and GBM thickening similar to the phenotype after morpholino induced npnt knockdown (Fig. 1A). We characterized the phenotype of npnt -/-;Six1-x-cree mice in more detail by using SBF-SEM that allowed a three dimensional view of the zebrafish glomerular filtration barrier in zebrafish (Fig. 1B). The unique GBM pathology was further confirmed in a mouse model with specific knockout of Npnt in podocyte progenitor cells (Npnt -/-;Six1-x-cree mice) (Fig. 1C).

Conclusions: The results confirm the role of podocytic npnt for proper GBM function and suggests its regulation by podocyte- and glomerular endothelial cell-derived miRs.

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a role in albuminuria. Immunofluorescence confirmed binding of HMP1 to glomerular endothelial cells, suggesting a possible cross between these cells. Using β1 integrin activation can occur due to outside-in and inside-out signaling, we investigated the chronicity of events involving endothelial, glomerular basement membrane (GBM) and podocytes. By immunohistochemistry, western blotting and RT-PCR, we found that endothelial and GBM injury preceded β1 integrin activation, nephrin phosphorylation and foot process effacement, suggesting an outside-in β1 integrin activation.

Conclusions: LPS activates β1 integrin on podocytes and leads to FAK and nephrip phosphorylation in vivo. Targeting endothelia/podocyte β1 integrin reduces albuminuria. Changes in glomerular endothelial cells and GBM precede podocyte injury, suggesting that activation of podocyte β1 integrin may be triggered by an outside rather than inside signal in this model of podocyte injury.

TH-PO1062
Podocyte Protective Effects of TRPC5 Inhibitor AC1903 in Human iPSC-Derived Podocytes and Kidney Organoids
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Background: The TRPC5-Rac1 pathway has been shown to induce podocyte injury and loss in two pre-clinical rat models: a transgenic rat FSGS model and a spontaneous hypertensive rat model. The TRPC5 blocker AC1903 protects podocytes in both models. However, less is known about the effect of this compound in rat models that are more relevant to human disease. We aimed to determine the effect of AC1903 in the human podocin (PodC)-null mouse model of FSGS, as well as in the human iPSC-derived podocytes and kidney organoids. Methods: A single i.p. injection of PAN (50mg/kg) was given to wild-type Sprague-Dawley rats (Male, 4-5 weeks, Charles River). AC1903 was administered twice a day for 7 days after PAN injection. 24-hour urine albumin levels were measured on day 7. Human iPSC cells were used to generate podocytes and kidney organoids (according to Subramanian A. et al. 2019 http://dx.doi.org/10.1101/516807). PAN treatment was used to induce human podocyte injury in these in vitro model systems, and the effects of AC1903 were assayed by Western blotting, immunofluorescence and confocal microscopy.

Results: We found that a single i.p. injection of PAN-induced podocyte injury and foot process effacement (FPE) as well as a significant increase in urine albumin levels 7 days after injection. Treatment of proteinuric PAN rats with AC1903 significantly reduced foot process effacement (FPE) and PAN treatment of iPSC-derived podocytes and kidney organoids triggered the TRPC5-Rac1 injury pathway leading to ROS production and cytoskeletal dysregulation. These effects were reversed by AC1903, showing for the first time that TRPC5 inhibition benefits human podocytes and kidney organoids.

Conclusions: Taken together, our results confirmed the relevance of the TRPC5-Rac1 pathway in human kidney tissue thus highlighting the potential of this therapeutic strategy for patients.

Funding: NIDDK Support

TH-PO1063
Pharmacologically Stimulating Nitric Oxide-Soluble Guanylate Cyclase Signalling to Prevent Podocyte Injury
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Background: The effects of nitric oxide (NO) on podocytes are not well known. We hypothesize that NO production by glomerular endothelial cells (GEnC) acts on podocytes as a protective paracrine factor in the glomerulus, thereby preventing podocyte injury. We propose a mechanism in which NO-mediated soluble guanylyl cyclase (sGC) activation results in enhanced cGMP synthesis and reduced expression/activity of the Ca2+-permeable Transient Receptor Potential Channel 6 (TRPC6), thereby inhibiting deleterious podocyte signalling processes. Several market approved drugs for non-renal disorders act on sGC. We aim to investigate glomerular NO-sGC signalling and the potential of repurposing sGC activators to prevent podocyte injury.

Methods: In vitro experiments were performed using conditionally immortalized GEnC and podocytes. NO production was measured by NO-donor SNAP (200 µM) or sGC activators Cinaciguat (2 µM) and Riociguat (20 µM). NO production was visualized using the NO sensitive dye DAF-FM diacetate. Podocyte injury was induced with 0.25 µM iNOS activator NOS (nNOS) was solely expressed by podocytes when injury was induced. All sGC activators were expressed by podocytes. Stimulation of sGC via either SNAP or Riociguat elevated cGMP production in podocytes. Importantly, SNAP, Cinaciguat and Riociguat all significantly fewer foot processes in the aged TRPC6 KO mouse (P=0.046). The GBM thickness was increased (P<0.018) from 0.29±0.02 µm in control to 0.36±0.05 µm in KO animals, demonstrating that old TRPC6−/− mice have morphological changes on the structure of the GBM.

Conclusions: We have demonstrated that in a mouse model, knockout of TRPC6 results in increased glomerular permeability and alterations to the structure of the glomerular filtration barrier in aged mice. This phenotype correlates with disease progression in human patients.

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TH-PO1066
Evaluation of the Human FSGS-Inducing ANLN R431C Variant in CRISPR-Cas9 Mice
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Background: We previously reported that the ANLN R431C variant causes focal segmental glomerulosclerosis (FSGS) and induces endoplasmic reticulum (ER) stress induced apoptosis in cultured human podocyte cells. To further understand the molecular mechanisms underlying disease, we examined the phenotypic effects of this variant in vivo using a CRISPR-Cas9 generated mouse model.

Methods: We generated an orthologous ANLN R431C knock-in point mutation in mice (R246C) using CRISPR-Cas9 technology. ANLN+/+, ANLN431C, and ANLN431C mice were challenged with a sub-therapeutic dose of nephrotoxic antibodies at 22 weeks and evaluated for 5 weeks post injection. Kidney sections were evaluated by two independent pathologists, blinded to genotype, through PAS staining and electron microscopy.

Results: When challenged with nephrotoxic antibodies in a kidney disease resistant genetic background, ANLN431C mice displayed increased proteinuria compared to ANLN+/+ (p=0.049) and ANLN+/- (p=0.0064) mice. Light microscopy evaluation of ANLN431C kidney sections revealed increased protein casts (p<0.0001), as well as larger (p=0.018) and more sclerotic (p=0.0005) glomeruli when compared to wildtype littermates. Semiquantitative analysis using electrot microscope revealed increased podocyte effacement and ER stress including evidence of dilated cisternae, damaged mitochondria, and abnormal autophagy in the ANLN431C mice. Additionally, cultured primary ANLN431C podocytes displayed increased apoptosis compared to ANLN−/− podocytes (p=0.049).

Conclusions: ANLN431C mice display increased susceptibility to glomerular injury when compared to ANLN−/− littermates. Additionally, ANLN431C mouse podocytes displayed similar ER stress and apoptotic phenotypes to cultured ANLN−/− human podocytes, lending further credibility to these results. Further evaluation of this mouse line in a genetic background that is more kidney susceptible to kidney disease should provide a necessary model to evaluate potential therapeutic compounds that have successfully rescued apoptotic phenotypes in cultured ANLN−/− human podocytes.

Funding: NIDDK Support

TH-PO1067
The Drosophila Nephrocyte Model of Podocyte Slit Diaphragm Formation Reveals a Role for the Basal Polarity Complex in Slit Diaphragm Formation
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Background: The podocyte slit diaphragm (SD) plays a key role in glomerular filtration. Mutations in the apical polarity protein Crb2 are present in some cases of steroid-resistant nephrotic syndrome. Animal models indicate an important role for apical polarity proteins in podocyte polarity and SD formation, suggesting cell polarity is a central aspect of podocyte development and function. Surprisingly however, mutations in basal polarity proteins do not cause significant defects in mouse podocytes, even though they express basal polarity proteins. Thus, it is difficult to interpret the relationships between the polarity complexes in podocyte development and SD formation.

Methods: To explore the potential role of the basal polarity proteins in SD formation, I performed a genetic analysis of the basal polarity proteins in SD formation and SD protein localization using the Drosophila nephrocyte, a popular model for podocyte SDs.

Results: I found that all of the canonical basal polarity proteins (Dlg, Scrib, Lgl, and Par-1) play important roles in the localization of nephrocyte SD proteins (Nephrin, Neph1, ZO-1). Loss of Dlg was also associated with dramatically reduced nephrocyte SD number and SD mislocalization. I am currently examining the role of the other basal polarity proteins on SD formation. Loss of Dlg also appears to perturb Crb localization, suggesting the basal and apical polarity complexes function together in nephrocyte SD formation.

Conclusions: Genetic interaction studies suggest the basal proteins work in concert to direct the formation of the nephrocyte SD. Genetic interaction studies also identified an important relationship between the basal polarity proteins and the SD-associated polarity protein Par-3, as well as the SD adapter protein ZO-1.

TH-PO1068
Functional Analysis of a Novel FSGS-Associated ACTN4 Mutation in Podocytes and Drosophila Melanogaster
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Background: The actin cytoskeleton is a central element of podocyte morphology and homeostasis during health and disease. Alpha-actinin4 (ACTN4) has been shown to play an important role in podocyte architecture and function and mutations in the ACTN4 gene are associated with focal segmental glomerulosclerosis (FSGS). Here, in a pediatric patient presenting with steroid resistant nephrotic syndrome (SRNS) and FSGS, gene panel sequencing of genes associated with renal kidney diseases identified an undescribed de novo, potentially disease-causing variant of ACTN4 that was not found in available genome or exome databases. Aim of this study was to characterize this variant and elucidate its pathogenic potential for podocyte homeostasis.

Methods: We analyzed patient-derived primary urinary cells (PUCs) as well as cultured human podocytes that express the novel ACTN4 mutant. Results were obtained using quantitative proteomic analysis as well as cell biology studies in vitro. In order to perform in vivo studies, we exploited Drosophila melanogaster genetics and characterized ActinI loss in nephrocytes, podocyte-like cells of the fruit fly. Here, rescue experiments with human ACTN4 wildtype, other previously described, pathogenic ACTN4 mutations as well as the novel variant will give further insight into its pathogenicity.

Results: Mapping the PUC proteome, we quantified more than 3000 proteins as compared to healthy controls. PUCs of the index patient showed high abundance of DNA-damage response associated proteins, and depletion of the known ACTN4 interactor ZNF385. Cultured human podocytes overexpressing the ACTN4 mutant present with disturbed appearance and localization of the actin cytoskeleton and first experiments suggest the ACTN4 mutant to impact cell viability. Knockdown of Drosophila Actin in nephrocytes leads to a severe functional phenotype, as cells no longer perform proper filtration. Morphologically, we could show that localization of the nephrocyte diaphragm is perturbed, suggesting false architecture of the nephrocyte.

Conclusions: Our results indicate that the identified novel ACTN4 mutation leads to a strong phenotype in vitro, likely making it a disease-causing mutation. The in vivo data underline the importance of actin in nephrocyte architecture and function.

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Linking Polarity Signaling and Mechanotransduction in Drosophila Nephrocytes
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Background: Polarity signaling through the aPKC-Par polarity complex is essential for the development and maintenance of the podocyte architecture and the filtration function of the kidney. Despite its well-established role in aPKC-mediated signaling, neither loss of Par3A nor Par3B causes a glomerular disease phenotype. However, genetic depletion of both, Par3A and Par3B resulted in severe proteinuria and renal failure.

Methods: We utilized Droshophila nephrocytes to study the functional role of Par3 proteins in greater detail. Nephrocytes are the homolog cells of mammalian podocytes and express the Par proteins. We depleted Par3A and Par3B in nephrocytes and monitored the kidney development and function.

Results: Nephrocyte-specific depletion of Bazooka resulted in twisted nephrocyte slit morphology and severe filtration defects, indicating the conservation of this important pathway throughout species. To study the underlying mechanisms, we performed proteomic analysis of Bazooka-depleted nephrocytes and identified an upregulation of focal and cell adhesion proteins, actin-associated proteins and mechanosensors such as Che (Filamin) and Rho (Talin). The putative mechanosensor protein Filamin was identified to be upregulated upon injury in podocytes as well. As podocytes face constant mechanical stress due to blood pressure and filtration, we further investigated the functional role of the mechanosensor protein Cher in nephrocytes. Interestingly, loss of Cher did not cause morphological changes, but resulted in a significantly increased filtration function. Proteome data from Cher depleted nephrocytes revealed an upregulation of ECM associated proteins such as Viking (Col4A) and Mucin and a downregulation of AQP1. The proteinuria phenotype could be rescued by targeting these pathways using Rho inhibitor (C3 transferase), Dynein inhibitor (Cibolinib) or lipid raft sequesterator (Nystatin).

Conclusions: Cher is a key player in regulating the trafficking of nephrocytes and how it is disrupted by FSGS-causing mutations.

Targeting Defective Trafficking of Slt Diaphragm Protein in INF2-Related Podocyteopathy and FSGS
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Background: Focal segmental glomerulosclerosis (FSGS) caused by mutations in INF2 is characterized by mistrafficked nephrin, which comprises the slit diaphragm (SD) of podocytes by its extracellular domain, suggesting INF2 plays an important role in maintaining the surface transport of INF2. This hypothesis is supported by a zebrafish model in which INF2 knockout led to glomerular dysplasia with mistrafficked nephrin, and INF2 R218Q knockin mice which showed defective recycling of nephrin and recovery of the SD following protamine perfusion. This study is to delineate this newly recognized role of INF2 in regulating the trafficking of nephrin, and how it is disrupted by FSGS-causing mutations.

Methods: By employing a yeast 2 hybridization screen, we found the interaction of INF2 with signaling molecules involved in vesicle trafficking pathways. Their interactions with wildtype or FSGS-causing mutants of INF2 were analyzed using yeast mating and co-IP. Podocytes with INF2 knockout or R218Q knockin were treated with antagonists for these pathways, and the trafficking of nephrin was studied by surface biotinylation and fluorescent based trafficking assays, live-cell imaging with analysis using KymographClear, KymographDirect and TrackMate software.

Results: Yeast mating and Co-IP demonstrated the interaction of INF2 with mDia1 (a Rho effector), Dynclin light chain 1 (Dyncl1), Nipsnap3a (a SNARE protein), molecules involved in cytoskeleton regulation and lipid raft-dependent trafficking.

Conclusions: INF2 plays a key role in maintaining the functional trafficking of nephrin by modulating 1) Rho/mDia signaling that halts vesicle movement; 2) Dynclin mediated retrograde transport; 3) Lipid raft dependent vesicle trafficking. INF2 knockout can be disrupted by FSGS-causing mutations, leading to mistrafficked nephrin and disintegration of the SD. The dissection of the dysregulated pathways underlying the mistrafficked nephrin will provide new therapeutic targets for INF2 related podocyteopathy and FSGS.

Defunding: NIDDK Support
TH-PO1074
Sulfatases, in Particular SULF1, Are Important for the Integrity of the Glomerular Filtration Barrier in Zebrafish
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Background: 6-O-endosulfatases (sulfs) are important enzymatic components involved in the regulation of heparan sulfate by altering the sulfation pattern. Specifically in the kidney, sulfs have been implicated in the glomerular podocyte-endothelial cell crosstalk and in the preservation of the glomerular filtration barrier (GFB) in different mouse models. Since it has been shown that in zebrafish larvae, SulfI, Sulf2a, and Sulf2b are expressed in the pronephric kidney we set out to establish if a reduction in sulf expression leads to GFB dysfunction.

Methods: To evaluate the integrity of the GFB, we measured a GFP-tagged vitamin D binding protein derived from Tgflk:flap:eGFP-DBP) zebrafish in the retinal vessel plexus of the zebrafish larvae at 96 hpf. Self-deficiency was induced using different morpholinos. The integrity of the GFB was evaluated by electron microscopy. Paraflin sections of sulf-deficient larvae were analyzed using immunofluorescence microscopy. Dextran microinjections and in vivo confocal imaging of the vasculature using Tg(flk:mcerry) larvae were carried out.

Results: Here, we show that a reduced sulf expression following MO-knockdown in zebrafish larvae promotes damage to the GFB leading to renal plasma protein loss from the circulation. Moreover, a combined knockdown of SulfI, Sulf2a and Sulf2b is associated with severe morphologic changes including narrowing of the fenestration between glomerular endothelial cells as well as thickening of the glomerular basement membrane, and podocyte foot process effacement; suggesting that glomerular damage is an underlying cause of the circulatory protein loss observed after MO injection. Additionally, we show that a decrease in sulf expression reduces the bioavailability of VegfA in the glomerulus of the pronephros, which may contribute to the structural changes observed in the glomeruli of morphant fish. Furthermore, consistent with previous results, knockdown of the sulfs is associated with arteriogenous malformations in particular in the tail region of the larvae.

Conclusions: Overall, taken together our results suggest that 6-O-endosulfatase are important factors in the preservation of GFB integrity and a reduction in their expression levels induces phenotypic changes that are indicative of renal protein loss.

TH-PO1075
Implementation of an Artificial Neural Network for Automated Podometrics in Human Kidney Specimens
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Background: Advanced morphometrics to study podocytes (podometrics) may provide robust readouts for diagnosis, prognosis and management of patients with glomerular diseases. However, their clinical implementation is limited by their time-consuming nature. Thus, artificial neural networks emerge as interesting tools to bring podometrics closer to the bedside.

Methods: Ground truth data was determined in 318 images (144 training, and 174 testing), acquired using immunofluorescence and confocal microscopy. An artificial neural network (U-Net) was implemented, optimised via a systematic grid search and compared to an automatic ImageJ-based segmentation tool. Dice scores (pixel-based), F1 scores (cell-based), and spearman correlations were calculated to validate each method against the ground truth. Model-based stereology podometrics were determined using segmented data.

Results: In nephrectomy samples, U-Net provided higher Dice and F1 scores than those obtained with ImageJ (P<0.0001), with stronger correlation indices for U-Net (R=0.59-0.81, P<0.0001) compared to ImageJ (R=0.61-0.66, P<0.0001). In ANCA-associated glomerulonephritis, Dice and F1 scores were also higher in U-Net (P>0.0001) compared to ImageJ with stronger correlation indices in U-Net (R=0.91-0.94, P<0.0001) compared to ImageJ (R=0.59-0.79, P<0.01).

Conclusions: Our optimised artificial neural network (U-Net) provides readouts that are comparable to manual segmentation and superior to conventional segmentation tools, even in the context of glomerular disease. These findings bring us one step closer to the use of automatic podometrics as a clinical instrument.

TH-PO1076
Single-Cell Transcriptome Profiling of the Mouse and Human Glomerulus
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Background: Though the mouse is widely used to model human glomerular diseases, systematic transcriptome comparison of principal cell types forming the glomerular filtration barrier between two species is lacking. To address this question, we generated single cell RNA sequencing (scRNA-seq) libraries from mouse and human glomerular cells.

Methods: Mouse glomeruli were isolated from 8 wt adult C57BL/6J mice via magnetic bead perfusion. Human healthy glomeruli were purified from 8 donor kidney biopsies via a sieving-coculture. Viable single cells of enriched glomeruli were unbiasedly sorted to 384-well plates and scRNA-seq was performed using the Smart-seq2 protocol. For data comparison between 2 species, we focused on podocytes, glomerular endothelial cells (GEC) and mesangial cells (MC).

Results: In total, 2416 mouse cells and 788 human cells passed quality control. Unsupervised clustering of these cells identified Npsh1+ podocytes, Kdr+ GECs, Pdgfb+ MCs and other cell types such as tubular cells and immune cells. Interestingly, Cdln1+ mouse parietal epithelial cells were captured. Overall comparison showed more genes detected in podocytes than other two cell types. In podocytes, about 70 genes were identified as human-specific, of which half of them showed restricted expression in podocytes. Most human-specific genes have not been implicated in the podocyte function. However, important exceptions were detected, such as PLA2R1 encoding a major autotigogen of human membranous nephropathy, which was absent in mouse podocytes. On the other hand, only 5 genes were identified as mouse-specific. In GEC and MC, < 20 genes showed apparent human-specificity and only 3 genes mouse-specificity. Differential species-specific cell expression patterns for selected genes were validated by analyzing bulk RNA-seq data, qPCR and immunostaining.

Conclusions: Our results highlight differences between mouse and human glomerular molecular signatures that are essential to design and interpret translational studies.

Funding: Commercial Support - AstraZeneca, Government Support - Non-U.S.

TH-PO1077
The Critical Role of Rho Associated Coiled-Coil Containing Protein Kinase 2 for the Enhancement of Actomyosin Contractility in Podocytes
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Background: The highly differentiated podocytes elaborate interdigitated foot processes (FP) to cover the glomerular capillaries and form slit diaphragm (SD) for blood filtration. Therefore, podocytes adhere tightly to glomerular basement membrane (GBM) and generate RhoA/ROCK-mediated contraction force to tolerate the filtration pressure. Two ROCK isoforms, ROCK1 and ROCK2, were identified in mammal. On the other hand, only 5 genes were identified as mouse-specific. In GEC and MC, < 20 genes showed apparent human-specificity and only 3 genes mouse-specificity. Differential species-specific cell expression patterns for selected genes were validated by analyzing bulk RNA-seq data, qPCR and immunostaining.

Results: After temperature switch, the expression of podocyte differentiation marker synaptopodin was increased. The formation of focal adhesions (FA), stress fibers and the

Conclusions: Our optimised artificial neural network to automatically extract the data required for the estimation of podometrics in clinical samples.
Vasohibin 1 Is Essential for the Post-Transcriptional Modification of α-Tubulin on Microtubules in Podocytes
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Background: Microtubules in podocytes are important for maintaining the characteristic cell shape as well as normal intracellular transport and dynamic morphologic alterations. The microtubule functions are affected by various post-transcriptional modifications on tubulin proteins. Recent studies have shown that vasohibin-1 (VASH1), an endothelium-derived angiogenesis inhibitor, has an enzymatic activity that catalyzes the detyrosination of α-tubulin in neurons and cancer cells. In the present study, we examined the roles of VASH1 in the modification of α-tubulin and microtubules in podocytes.

Methods: We used B6 wild-type and flash+/− mice to confirm the localization of detyrosinated (detyr) α-tubulin in the kidney. In addition, 8-week-old female BALB/c wild-type mice received single intravenous injection of 15mg/kg of adriamycin (ADM) or saline to induce podocyte injury and proteinuria. Finally, we cultured immortalized human podocytes, and VASH1 knockdown was performed by siRNA transfection.

Results: In wild-type mice, detyr-α-tubulin was shown to be restricted in podocytes by double immunofluorescence with podocalyxin. The detyr-α-tubulin staining was markedly attenuated in ADM-treated podocytes, indicating decreased α-tubulin detyrosination. Immunoblot analysis demonstrated that detyrosination of α-tubulin in podocytes was decreased by adm. In vitro experiments, immunoblot analysis showed that detyr-α-tubulin knockdown in immortalized human podocytes, and VASH1 knockdown was performed by siRNA transfection.

Conclusions: Our results suggest that VASH2 is critical for the enhancement of actin cytoskeleton architecture for podocyte function.

Funding: Government Support - Non-U.S.

TH-PO1078

Transcriptional Reprogramming by Wilms Tumor 1 and FoxC2 Mediates a Repair Response During Podocyte Injury: Studies in Mice and Human Kidney Organoids
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Background: We previously reported that WT1 is a master regulator of gene expression in podocytes, binding nearly all genes known to be crucial for maintenance of the glomerular filtration barrier. We have now performed ChIP-Seq for FoxC2 transcription factor that also binds nearly all the same target genes as WT1, suggesting that WT1 and FoxC2 mediate transcriptional reprogramming of the glomerular tubulome.

Methods: We used Adramyacin (ADR)-induced podocyte injury as a model for podocyte injury in BALB/c mice to massive albuminuria and decreased detyr-α-tubulin staining in glomeruli compared to the control group, suggesting the detyrosination of α-tubulin could be altered by morphological changes of podocytes. In vitro experiments, immunoblot analysis demonstrated that detyr-α-tubulin knockdown in immortalized human podocytes, and VASH1 knockdown was performed by siRNA transfection.

Results: WT1 and FoxC2 transiently increase after injury, before decreasing to low levels. Immunohistochemistry and quantification of Wt1 to FSGS disease progression. The ephrin signaling pathway was exclusively dysregulated in the proteinuric vs. sclerotic stage of FSGS. Integration of transcriptomics with glomerular Wt1-ChIPseq provided unbiased insight into contribution of Wt1 to FSGS disease progression. The ephrin signaling pathway and specifically EphrinB1 were identified as a differentially expressed in progressed FSGS, affected by proteinuric and sclerotic stages.

Conclusions: Transcriptional profiling of glomerular disease: podocyte biology - I

Funding: Government Support - Non-U.S.

TH-PO1079
Podocyte-specific expression of JAK, STAT, SOCS and PIAS isoforms provides opportunities to develop additional treatments for FSGS.

Funding: NIDDK Support, Veterans Affairs Support, Government Support - Non-U.S.

TH-PO1082

Genetic or Pharmacologic Activation of Nrf2 Worsens Glomerular Injury and Proteinuria


Background: Proteinuric chronic kidney disease (CKD) is a major cause of progressive renal failure. Nrf2 (nuclear factor 2 erythroid 2) is a transcription factor and master regulator of a multitude of target genes with roles in antioxidant protection, electrophile detoxification, and overall cytoprotection. Nrf2-activating compounds such as CDDO-Me (bisdioxolone methyl) and CDDO-Im have been and continue to be explored as treatments for proteinuric CKD in both clinical trials and experimental animal models. The results of some of these studies have suggested that Nrf2 may paradoxically increase proteinuria. To examine this, we tested the effects of genetic or pharmacologic Nrf2 activation on proteinuria.

Methods: Wild type mice and mice with genetic Nrf2 activation (via reduction in the Nrf2 inhibitor Keap1) were compared. Proteinuria was induced experimentally via exposure to 1) adriamycin, 2) angiotensin II, or 3) albumin overload. Injury was assessed with urine albumin excretion, immunohistochemistry, podocyte foot process effacement, and expression of injury genes. Systemic blood pressures were measured with radiotelemetry. We also examined the effect of pharmacologic Nrf2 activation by CDDO-Im in wild type mice during proteinuric injury.

Results: There were no differences in proteinuria at baseline in the wild type and mutant mice. However, genetic Nrf2 activation led to increases in proteinuria in all three proteinuria models, and this was associated with worsened glomerular injury, podocyte foot process effacement, and renal fibrosis. Blood pressures were slightly higher in the mutant mice, due to a lack of dipping during the sleep cycle. In wild type mice, the addition of CDDO-Im to angiotensin-induced injury led to a dramatic increase in proteinuria which could be reversed upon CDDO-Im withdrawal.

Conclusions: Both genetic and pharmacologic Nrf2 activation led to increased proteinuria after injury. This appears to have deleterious effects on the kidney chronically. Increased blood pressures may contribute to this effect. Our results suggest that Nrf2 activation should be used cautiously in proteinuric CKD.

Funding: NIDDK Support, Private Foundation Support

TH-PO1083

Role of Renal PCSK9 in the Rmm2b Mouse Model of Nephrotic Syndrome

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Background: 85% of US chronic disease patient presenting nephrotic syndrome (NS) have mutations of low density lipoprotein receptor (LDL-R), compared to 31.5% in the general population. Proprotein convertase subtilisin/kexin type 9 (PCSK9) was shown to play an important role in the regulation of LDL-c levels in the liver. PCSK9 is expressed in the collecting duct (CD) where it plays a role of chaperon protein for the epithelial sodium channel (ENaC). We studied the expression of PCSK9 in NS in the Rmm2b-/- mouse, a model disease with high levels of low density lipoprotein cholesterol (LDL-c), compared to 31.5% in the general population.

Methods: (1) Rmm2b Control (+/+) and knock-out (-/-) mice were followed weekly under 5.21 ng/ml, P<0.05, and 124.16 ± 10.27 mg/dl, P<0.05, respectively. PCSK9 protein expression was shown by Western blot to increase in the renal cortex from the age of 9 weeks, and decrease in the liver from the age of 7 weeks. By confocal microscopy, PCSK9 was shown to co-localize with Aquaporin-2, indicating expression in the CD where its expression is increased from the age of 7 weeks. When treated with anilomide, Rmm2b mice showed elevated levels of blood PCSK9 and cholesterol compared to mice without treatment. Anilomide blocks ENaC, the CD cells then increase the number of active ENaC present in the plasma membrane and the secretion of PCSK9, initiating hypercholesterolemia.

Conclusions: As Rmm2b mice age and develop NS, PCSK9 protein levels increase in the kidney and serum, and decrease in the liver. Anilomide treatment showed that PCSK9 secreted by CD cells into the circulation induces earlier and higher hypercholesterolemia, CD expressed PCSK9 may play an important role in hypercholesterolemia in NS in the Rmm2b mouse model, as a link between the kidney and the liver.

Funding: NIDDK Support

TH-PO1084

Automated High Content Imaging to Identify New Therapeutics for Podocytopathies


Background: Damage and eventual loss of podocytes is a hallmark of CKD. A key hurdle in the investigation of podocyte loss/damage is the lack of automated relevant cell-based screens. Existing techniques are time consuming and low throughput and cannot be used effectively in drug discovery. Here we describe a novel automated high throughput assay to evaluate and quantify podocytes in animal models of kidney disease.

Methods: Sprague Dawley rat glomeruli were isolated by differential sieving without enzymatic digestion, and plated in 384 well plates. Podocyte quantification was performed using a three immunofluorescence detection of WT1, Nephrin and DAPI using confocal microscopy Opera QHEIS. 3D glomeruli images created by 60X acquisition of 42 planes and quantitative processing were quantified using a customised algorithm using Columbus Analysis System that was developed to exclude artefacts, allow normalisation and ensure unbiased analysis. Tailored readouts include glomeruli number and morphology, podocyte number and nephrin expression.

Conclusions: We successfully developed a tool to allow high throughput automated assessment of podocyte health in isolated glomeruli. This automated 3D-High Content imaging platform enables candidate target validation and drug identification.

Funding: Commercial Support - AstraZeneca PLC

TH-PO1085

Rapid Progression of Glomerulosclerosis due to Concurrent Diabetes and Hypertension Correlates with Podocyte Damage Shown by Expansion Microscopy

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Background: Glomerulosclerosis is a hallmark of diabetes (D) and hypertension (HT) induced kidney failure. Here we studied the combined effect of D-HT on the kidney using expansion microscopy for nanoscale imaging of podocyte foot processes (FP).

Methods: In 6-week-old male double transgenic rats (dTGRNeph-hAT1Rc1rpl1mRen2dF1=mTGR and TGRc1pl1mRen2d (TGR) we induced for 8 weeks with angiotensin (United Kingdom; 2High Content Imaging platform enables candidate target validation and drug identification.

Conclusions: We successfully developed a tool to allow high throughput automated assessment of podocyte health in isolated glomeruli. This automated 3D-High Content imaging platform enables candidate target validation and drug identification.

Funding: NIDDK Support
New Animal Model of Non-HIV Collapsing Glomerulopathy

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Background: Collapsing glomerulopathy, usually classified as a form of focal and segmental glomerulosclerosis (FGS), is the most severe and progressive form of glomerular disease. Most patients end up developing end stage kidney disease that requires dialysis or transplantation. There is presently no specific treatment for non-HIV collapsing glomerulopathy. Absence of animal models of non-HIV form of this disease was a problem in the past.

Methods: Transcriptional factor Zhs2 was overexpressed in rat podocytes under the control of the native human NPHS2 promoter. Two transgenic (TG) rat lines were generated: 142 and 144 which show increased expression of glomerular Zhs2 mRNA by 50.7% and 309.8% respectively. These 2 lines do not have any phenotype at baseline. We induced Adriamycin nephrosis, a model of FSGS, in wild type and heterozygous transgenic rats (7.5 mg of Adriamycin per kg/BW) and assessed for proteinuria and light microscopy at day 3 and 7 after injection. Different doses of Adriamycin (6.5 and 5.0 mg per kg/BW) were also injected in 144 transgenic rats, and studied at day 2, 5 and 9.

Results: TG 144 and TG 142 rats had significantly higher proteinuria than wild type rats following induction of Adriamycin nephrosis (7.5 mg per kg/BW). Renal histology in TG 144 rats on Day 7 revealed extensive glomerular collapse whereas no collapse was noted in TG 142. Injection of 6.5 and 5.0 mg of Adriamycin per kg/BW in TG 144 rats, induced significant proteinuria starting at day 5 and that still continues to rise at day 9. Light microscopy images show classic feature of collapsing glomerulopathy. (Collapsed glomeruli, retraction, prominent VEC…) only in TG 144 rats injected with 6.5 mg; TG 144 rats injected with 5.0 mg dose show classic feature of FSGS.

Conclusions: ZHS2 transgenic rats injected with Adriamycin represent a new animal model of non-HIV collapsing glomerulopathy. Longitudinal glomerular gene expression analysis will be performed to study molecular mechanisms of development of the disease in wild type and ZHs2 144 TG rats at 6.5 mg per kg/BW dose.

Funding: NIDDK Support, Private Foundation Support

Identification of Podocyte Secreted Proteins That Drive Parietal Epithelial Cell Proliferation in a Murine Model of Proliferative Glomerulopathy

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Background: Podocyte injury contributing to parietal epithelial cell (PEC) proliferation is a dominant histologic feature in both rapidly progressive glomerulonephritis and subtypes of focal segmental glomerulosclerosis (FSGS), however factors mediating this cross-talk remain unclear. We recently showed that podocyte-specific loss of Krüppel-like factor 4 (Klf4), a zinc-finger transcription factor, activates STAT3 signaling leading to mitotic catastrophe in podocytes and eventually FSGS, while triggering PEC proliferation in vitro. We utilized this model to identify novel factors secreted by the injured podocyte that drive PEC proliferation.

Methods: Initially, RNA-seq was conducted on glomeruli isolated from mice with podocyte-specific deletion of Klf4 (Klf4 cKO) and controls (Klf4WT). Since our previously reported data demonstrate that conditioned media (CM) isolated from cultured human podocytes with KLF4 knocked down (KLF4-shRNA) triggers PEC proliferation, we performed quantitative mass spectrometry (iTRAQ) on CM from KLF4-shRNA and EV-shRNA cultured human podocytes from day 1 to 3 of differentiation. Subsequent differential expression and pathway enrichment analysis was performed to identify STAT3-dependent and independent secreted factors by the podocyte that drive PEC proliferation.

Results: Pathway analysis revealed that 421 genes were upregulated in Klf4 cKO glomeruli and were related to ECM organization and focal adhesion, whereas 179 identified downregulated genes were enriched for genes critical to podocyte-protein interactions, actin cytoskeleton, and cell differentiation. Proteins upregulated in KLF4-shRNA as compared to EV-shRNA CM were involved in similar pathways. These differentially expressed transcripts from RNA-seq were cross-matched with upregulated proteins identified in iTRAQ to identify factors that drive PEC proliferation. Published ChIP-seq datasets were used to identify top candidates containing STAT3 binding sites (PAI-1 and CYR61) and those without (PRES23 and S100A6). These transcripts were then validated by qPCR in Klf4 cKO-treated with STAT3 inhibitor, S3I-201.

Conclusions: Using a murine proliferative glomerulopathy (podocyte-specific Klf4 knockdown), we identified novel signaling molecules secreted by the injured podocyte that might drive aberrant PEC proliferation.

Funding: NIDDK Support, Veterans Affairs Support

Common Cold-Induced Cytokines Storm Induces Glomerular Disease Relapse in the ZHX2-Deficient State

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Background: Relapse or worsening of glomerular diseases like MCD and FSGS is commonly found after a common cold. Different cytokines and soluble receptors increase at day 9. Light microscopy images show classic feature of collapsing glomerulopathy (Collapsed glomeruli, retraction, prominent VEC…) only in TG 144 rats injected with 6.5 mg; TG 144 rats injected with 5.0 mg dose show classic feature of FSGS.

Methods: A common cold cytokine cocktail (dose X) containing IL-2, IL-4R, IL-6, IL-10, INF-γ, TNF-α and ICAM-1 was injected into control (BALB/c, n=-5) and Zhx2 flox/flox/cre++ mice (n=5). Different doses of the cocktail and the effect of individual cytokines were assessed. Podocyte specific Zhx2 deficient (Zhx2 flox/flox -/cre -) and floxed control mice (Zhx2 flox/flox +/cre +, n=3) and floxed control mice (Zhx2 flox/flox +/cre +, n=3) were injected with 5.0 mg dose show classic feature of FSGS.

Results: Common cold cytokines induced acute albuminuria in BALB/c mice (65.3±24.3 µg per 18h), but not in BALB/c (10.8±1.5 µg per 18h), compared with baseline (BALB/c 5.5±1.1 µg per 18h; BALB/c 6.5±1.1 µg per 18h) (p<0.05), having higher nuclear expression of Zhx1 but not Zhx3. Individually, none of these cytokines which antibodies are in clinical use (IL-4R, IL6, TNF-α) also eliminated albuminuria in BALB/c mice. Cytokine induced albuminuria was also noted in Zhs2 flox/flox/cre- mice, but not in control Zhs2 flox/flox mice. Mice deficient in APA. Mice lacking Ephrin B1 in podocytes did not develop albuminuria. B1. Mma rats had a significant increase in proteinuria (61.5±4.2) from baseline (47±4.1), using a much lower dose (X/50) of the rat “cytokine cocktail”.

Conclusions: These findings suggest that an altered Zhs2 expression and its transcriptional partners predispose to MCD and FSGS relapse following a common cold.

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Reciprocal Regulation Between ANLN and AKT Modules Podeocyte Proliferation

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Background: We previously reported that mutations in anillin (ANLN) cause familial FSGS; however, the physiological functions of ANLN in podocytes remain unknown. ANLN is widely recognized as a driver of cell survival signaling and proliferation through its CD2AP-mediated interactions with the PI-3K/P85/AKT signaling module. We previously showed that ANLN expression is upregulated in proliferating podocytes and described a dynamic modulation of AKT activation with alterations in ANLN expression. Here, we evaluated the reciprocal influence of AKT on ANLN activity and expression in podocytes.

Methods: We established stably expressing ANLN cKO, ANLN cKO/ANLN wild ANLN siRNA, AKTI siRNA, STAT3 siRNA, β-Catenin siRNA and scrambled siRNA podocyte lines and evaluated the lines for proliferation and apoptosis assays and in complimentary biochemical pathway analyses.

Results: ANLN Expression - ANLN expression was markedly reduced with AKT inhibitors and in AKTI knockdown (KD) podocytes. We screened the ANLN promoter to search for transcription factors regulated by AKT and identified multiple candidate binding sequences for β-Catenin and STAT3. ANLN expression was significantly reduced in β-Catenin and STAT3 KD podocyte lines and phosphorylation/activation of β-Catenin was downregulated in AKTI KD podocytes. Conversely, STAT3 phosphorylation was upregulated in AKTI KD podocytes suggesting a compensatory function of STAT3 activation in AKTI KD podocytes. ANLN Phosphorylation - We identified a highly conserved AKT phosphorylation motif (i.e. R-X-S/T-Y) in the ANLN F-actin binding domain. We generated a specific ANLNsiRNA antibody and observed that phosphorylation of ANLN at Ser56 was abrogated in ANLN siRNA expressing podocytes demonstrating the specificity of the antibody. Podocytes expressing ANLNsiRNA exhibited significantly enhanced proliferation relative to ANLN cKO and ANLN cKO/ANLN wild expressing podocytes suggesting that AKT may enhance the activity/stability of ANLN via direct phosphorylation of Ser56.

Conclusions: ANLN and AKT dynamically regulate one another to modulate podocyte proliferation. This study delineates the mechanisms of this reciprocal regulation and highlights potential therapeutic targets for the treatment of ANLN-induced podocyte dysfunctions.

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Deletion of p38 MAPK in Podocytes Aggravates Glomerular Injury by Aldosterone in Podocyte-Specific GC-A Knockout Mice
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Background: Previously, we demonstrated that uninephrectomized aldosterone-infused, high salt-fed podocyte-specific guanylyl cyclase-A (natriuretic peptide receptor 1) conditional KO (pod-GC-A KO) mice exhibited glomerular injury and that pharmacological inhibition of p38 MAPK ameliorates podocyte damage. However, the effects of genetic deletion of p38 MAPK in podocytes of pod-GC-A KO mice have been unknown.

Methods: We generated p38 MAPKfl/fl;Nephrin-Cre (pod-p38 MAPK cKO) mice and p38 MAPKfl/fl;GC-Afl/fl;Nephrin-Cre (pod-p38MAPK/GC-A DKO) mice. For induction of glomerular injury, we treated them with aldosterone and high salt at 2 months of age for 3 weeks without nephrectomy (B-ALDO). In vivo, we examined the effect of p38 MAPK inhibitor in cultured human podocytes transfected with GC-A siRNA.

Results: B-ALDO-treated pod-p38 MAPK/GC-A DKO mice resulted in significant elevation of serum Cr (0.29 ± 0.04 mg/dl), massive albuminuria (42,660 ± 20,200 mg/Cr) and severe foot process effacement in addition to intracellular fibrin thrombi which indicated endothelial damage. Vehicle-treated DKO mice, B-ALDO-treated pod-GC-A KO and non-treated pod-p38 MAPK/GC-A DKO showed normal serum Cr levels (0.14 ± 0.01, 0.18 ± 0.02, 0.20 ± 0.01 mg/dl, respectively), mild increase of albuminuria (223 ± 6.5, 1496 ± 592, 649 ± 303 mg/Cr, respectively) and only segmental foot process effacement. Blood pressure was not elevated in either mutant mice compared with that of B-ALDO control mice. Furthermore, glomerular mRNA expressions of MCP-1, PAI-1, and FN were upregulated and that of VEGF-A was downregulated in DKO mice. Consistent with this, suppression of GC-A mRNA expression by siRNA in combination with p38 MAPK inhibitor downregulated VEGF mRNA in human cultured podocytes.

Conclusions: Genetic p38 MAPK deletion in GC-A-null podocytes exacerbated aldosterone-induced glomerular endothelial cell injury as well as podocytes, and resulted in renal dysfunction, probably through VEGF downregulation. These results suggest p38 MAPK in podocytes is necessary to protect endothelial and epithelial cells from aldosterone-induced injury.

TH-PO1091

ARHGf7 (β-PiX) Protects Podocytes from Cell Apoptosis via Cdc42 Activation
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Background: Rho-family small GTPases (Rho GTPases), including Rac1 and Cdc42, are important for podocyte functions. Rac1 and Cdc42 regulate foot process effacement and podocyte foot processes are involved in the pathogenesis of podocyte injury. ARHGf7 (β-PiX), a guanine nucleotide exchange factors (GEF) that activates Rac1 and Cdc42. Recently, we established that podocyte-specific β-PiX deficient (KO) mice develop progressive proteinuria starting at ~8 weeks of age, and glomerulocystosis and podocyte loss by 13 weeks of age. Here, we investigated the mechanism of podocyte loss induced by β-PiX deficiency, with a particular focus on the pro-survival transcriptional co-activator, Yes-associated protein (Yap), which is known to be activated by Cdc42.

Methods: Cultured mouse podocytes (MP) with β-PiX knockdown (KD) and their controls were established using shRNAs. Rac1/Cdc42 KD activity was assessed by pull-down assay. Rho/Rac/Cdc42 Activator 1 (Cytoskeleton, CN04) and Adriamycin (ADR) were used as a general Rho GTPase activator and a podocyte toxic, respectively. Apoptosis was studied by TUNEL staining and immunoblotting for cleaved caspase 3 (CC3). Nuclear translocation and activity of Yap were assessed by immunostaining and the TEAD domain (TEAD)-luciferase assay. Data are provided as the mean ±SEM.

Results: Cdc42, but not Rac1 activity, was significantly decreased by 34% in isolated glomeruli from 5-week-old β-PiX KO mice, compared with controls (n=7-10, p<0.05). Similarly, Cdc42, but not Rac1, activation in β-PiX KD MP was significantly blunted by 46%, compared with control MP (n=9, p<0.01). At 6 hrs after ADR treatment, KD MP showed ~9.4±2.5 % TUNEL-positive cells, as compared with 3.8±0.7 % in control MP (n=3, p<0.05). CC3 was also increased in KD MP. Correspondingly, there were less adherent KD MP at 8 hrs of ADR treatment, compared with control MP. Control MP showed predominant nuclear localization of Yap, while KD MP exhibited partial cytoplasmic retention (Nuclear/Total Yap ratio; Control: 0.90±0.02; KD: 0.80±0.04, n=4, p<0.05). The TEAD-luciferase activity was significantly lower in KD MP than in control MP (Control: 10.3±1.3, KD: 6.9±0.7 a.u., n=7, p<0.05). mRNA expression of the Yap target gene, cyclin B2, was also decreased in KD MP compared with control MP (n=3, p<0.05).

Conclusions: Loss of β-PiX in podocytes resulted in increased apoptosis and detachment from matrix. This may be mediated by the cytoplasmic retention and decreased transcriptional activity of Yap via decreased Cdc42 activity.

TH-PO1092

Role of Pyruvate Kinase M2-Mediated Metabolic Reprogramming During Podocyte Differentiation
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Background: Podocyte, a type of highly specialized epithelial cells with sophisticated foot processes and unique slit diaphragm, requires substantial levels of energy to maintain its integrity and function, but little is known on the regulation of podocyte’s energetics. Lack of metabolic analysis during podocyte development led to explore the role of cellular metabolism and mitochondrial biology during in vitro differentiation.

Methods: To study the metabolic alterations caused by differentiation, nuclear magnetic resonance (NMR) spectroscopy was performed to analyze the metabolic profiles of GC-A-deficient and wildtype cultured podocytes. A metabolic fingerprinting by Seahorse XF analyzer was performed to analyze the energy expenditure. Mitotracker Red CMXRos and MitoProbe JC-1 Assay Kit were used to identify mitochondrial morphology, mass and membrane potential. PKM2-RNAi-Lentivirus was used to explore the regulating role of PKM2 during podocyte differentiation.

Results: In this study, we observed a huge increase in mitochondrial biogenesis. Changes in mitochondrial mass, morphology and function were correlated with the upregulation of the master regulators of mitochondrial biogenesis, TFAM and PGC-1α. Unexpectedly, concomitant with mitochondrial biogenesis, we observed an increase in glycolysis during podocyte differentiation, which was linked to the overexpression of glycolytic enzymes. Among them, PKM2 was of particular interest. The real-time quantitative PCR and PK activity assay kit showed both pyruvate kinase M2 (PKM2) expression and activity were upregulated. Knockdown of Pkm2 showed dramatic reduction of glycolysis and mitochondrial function, resulting in the defects of podocyte differentiation.

Conclusions: Usually, differentiated cells have repressed glycolysis, as they mostly rely on OXPHOS for energy demand. Our findings here first demonstrate that differentiated podocytes maintain both glycolysis and mitochondrial metabolism to meet their augmented energy demand. We identified PKM2 as a critical regulator of energy metabolism in podocytes. Selective inhibition of PKM2 indicate existence of metabolic checkpoint that need to be satisfied in order to allow podocyte differentiation.

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TH-PO1093

Human Podocyte Modifies Energy Metabolism During Differentiation
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Background: Little is known about the rate of synthesis of mitochondrial proteins or how other components of metabolism, such as the TCA cycle and fatty acid oxidation, change with podocyte differentiation. The goal of this project is to identify metabolic pathways that are required or permissive for podocyte differentiation.

Methods: MTS, ATP abundance, and ATP/ADP ratios were done to ensure human podocyte viability and confirm changes in metabolism during differentiation. Oxygen consumption rate (OCR) and Extracellular Acidification Rate (ECAR) were done by Seahorse at 3, 7, 10, and 14 days of differentiation and compared to undifferentiated cells. The suitability of differentiation was confirmed using staining for VWF/CD31 (all time points) and for differentiated cells (3, 7, 10, 14 days). Mitochondrial mass was measured by seahorse XF analyzer. Mitotracker Red CMXRos and MitoProbe JC-1 staining, and increased mtDNA copy number. With differentiation, we observed an increase in total ATP but a decrease in ATP/ADP ratio. MTS assay showed no significant changes with cell differentiation. Unleaded proteomics abundance showed the greatest increase in OXPHOS (specifically in complex 1 and 5) followed by TCA cycle. We also observed a significant decrease in mitochondrial fission proteins and an increase in mitochondrial fusion with differentiation. The most dynamic proteins with high abundance and high heavy to light (H:L) ratios during differentiation were ATPF8, NDUF56, and OXA1L, reinforcing the importance of OXPHOS with differentiation. The most stable proteins with high abundance and low H:L ratios were involved in TCA cycle, fatty acid degradation, arginine and proline metabolism and valine, leucine and isoleucine degradation pathways (KEGG 2019 Human).

Conclusions: This data shows that podocyte differentiation is dependent on an increase in mitochondrial biogenesis and network with a switch in metabolic programming to oxidative phosphorylation.

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TH-PO1094

Using CRISPR/Cas9 to Generate Second-Generation Cell Lines Used for Detecting Recurrent Focal Segmental Glomerulosclerosis (rFSGS) Patients
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Background: The gold standard for diagnosing glomerular diseases including FSGS requires invasive procedures such as renal biopsy, which may not be safe or feasible to perform in all patients. Recently, we published a cell-based assay for diagnosing FSGS

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
patients, which involved constructing cell lines using the rFSGS responsive genes BML, IL1β, and IGF1BP3. While the assay specifically diagnosed rFSGS patients, the overall assay response was low (~1.5 fold increase over control). To boost the assay response and increase its specificity, a CRISPR/Cas9-based precise genome editing approach was employed, where highly specific and responsive second generation cell lines were created. A total of 8 cell lines are currently under study: 4 LSS AA (Bag3-P209L, Bag3 knock in) and 4 LSS AC (Bag3 expression and characterization). This has led to the identification of Bag3 enrichment in mass-spectrometry data. Further Bag3 expression is regulated by mechanical clues in podocyte cell lines and first interactome results point towards a function at the liquid stress-granula interface. Preliminary analyses of the Bag3 mRNA-targeting mutation Bag3.P209L revealed a mild albuminuria starting at an age of 8-12 weeks in a whole-body overexpression mouse line.

Conclusions: Our findings point towards an important role of Bag3 and chaperone-assisted-selectivity-autophagy in podocytes and their mechanical stress protection. Bag3 expression is regulated by mechanical clues and interacts further corroborates this hypothesis. Further studies based on two podocyte specific mouse lines (Bag3 mutation and conditional knockout) are currently ongoing to understand the role of podocyte-Bag3 in vivo under healthy conditions and in glomerular disease.

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TH-P01097 PAR-CLIP Identification of Cell Type and Context-Specific miRNA/mRNA Interactions
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Background: miRNAs have been implicated as mediators of acute and chronic kidney disease. To identify miRNA:mRNA interactions in human podocytes, we used PAR-CLIP. Moreover, the response was consistent and showed more than 90% specificity in detecting rFSGS patients.

Results: We demonstrate that individuals that carry two LSS mutant variants have defined integration at the “safe harbor locus”. These cell lines are highly responsive in detecting rFSGS patients. Moreover, the response was consistent and showed more than 90% specificity in detecting rFSGS patients.

Conclusions: We present here the development and validation of a second-generation cell lines used for diagnosing rFSGS patients that are superior to conventionally stably transfected cell lines. Unlike the first-generation cell lines, the second-generation cell lines have defined integration at the “safe harbor locus”. These cell lines are highly responsive and demonstrate low variability. Overall, our assay is noninvasive, highly sensitive and specific, and studies are being planned for conducting clinical trials to utilize its full diagnostic potential.

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TH-P01096 Functional APOL1-miR193a Axis (AMA) Prevents Podocyte Injury
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Background: miRNAs have been implicated as mediators of acute and chronic kidney disease. To identify miRNA:mRNA interactions in human podocytes, we used PAR-CLIP. Moreover, the response was consistent and showed more than 90% specificity in detecting rFSGS patients.

Results: We demonstrate that individuals that carry two LSS mutant variants have defined integration at the “safe harbor locus”. These cell lines are highly responsive in detecting rFSGS patients. Moreover, the response was consistent and showed more than 90% specificity in detecting rFSGS patients.

Conclusions: We present here the development and validation of a second-generation cell lines used for diagnosing rFSGS patients that are superior to conventionally stably transfected cell lines. Unlike the first-generation cell lines, the second-generation cell lines have defined integration at the “safe harbor locus”. These cell lines are highly responsive and demonstrate low variability. Overall, our assay is noninvasive, highly sensitive and specific, and studies are being planned for conducting clinical trials to utilize its full diagnostic potential.

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TH-P01096 Bag3 as Potential Mechanoprotector in Renal Podocytes
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Background: Loss of podocytes in the course of glomerular disease leads to glomerulosclerosis and progressive kidney disease. Due to their exposed location on the outside of the glomerular basement membrane podocytes are subjected to extensive mechanical strain by perfusion and filtration. These forces are even higher in disease states such as diabetic nephropathy. Overacting adaptive mechanisms cause podocyte detachment which initially increases the mechanical stress for remaining podocytes. The role of mechanical mechanisms involved in this vicious circle are yet insufficiently defined. Bag3 is an important mechanoprotector protein in mechanically strained tissues. It replaces mechanically unfolded proteins by chaperone-assisted-autophagy (CASSA) and regulates proteins like Familin A and Syntaxin 4 in their role in podocyte biology. Above all Bag3 is an important player in diabetic nephropathy in a mouse model. All this brings Bag3 in a prime position as a candidate mediator of mechanical stress protection in podocytes.

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species (ROS) generation (DCF detection assay), caspase-3 cleavage, and apoptosis (TUNEL assay). Proteins and RNAs were extracted from cells treated under similar conditions (n=6). Protein blots were probed for APO1 and caspase-3; RNAs were assayed for miR193a. Differentiated podocytes (DPCs) were transduced with either empty vector or miR193a plasmid and evaluated for APO1 and caspase-3 expression.

Results: DPCs overexpressing miR193a exhibited reduced levels of APO1 protein and increased APOL1 expression, and attenuated number of TUNEL +ve cells in both Adriamycin and PAN milieus. Both Adriamycin and PAN induced an up-regulation in miR193a and caspase-3 expression in both V-D and G0-DPCs from their baseline. MicroRNA193a inhibitor decreased miR193a levels, increased APO1 expression, and attenuated number of TUNEL +ve cells in both Adriamycin and PAN milieus. Both Adriamycin and PAN increased (P<0.01) ROS generation and a higher (P<0.01) percentage of TUNEL +ve cells in Adriamycin and PAN milieus. DPCs overexpressing miR193a displayed reduced expression of APO1 and enhanced cleavage of caspase-3.

Conclusions: Functional AMA prevents podocyte injury in adverse milieus through down-regulation of miR193.

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TH-PO1099

P2X7 Expressed in Injured Podocytes May Spread the Kidney Injury Through Caspase 3

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Background: We previously generated a mosaic mouse model in which a fraction of podocytes express hCD25 and can be injured by a hCD25-directed immunotoxin, LMB2. After injection with LMB2, kidneys with injured hCD25(+) but not hCD25(-) podocytes were injured along with dramatic induction of P2X7 mRNA in both types of podocytes. P2X7 is a receptor of extracellular ATP and is known to activate inflammation and induce cell death in immune cells. In the present study, we aim to analyze P2X7 protein expression in the mouse model used in our previous study, the protein binding of P2X7 in podocytes.

Methods: Kidneys were harvested from mosaic mice before or 2 weeks after injection with LMB2 (25g/kgBW). Immunofluorescence staining was performed with primary antibodies against P2X7 and cleaved-caspase 3. For functional study, primary cultured mouse podocytes were transiently transfected by electroporation with hCD25 or mock plasmid together with EGFP or tdTomato expression plasmid. Before or 1-2 hours after administration of ATP (0 or 2 mM), the same visual fields were photographed.

Results: No P2X7 staining was observed in the kidney without LMB2. In the kidneys injured by LMB2, hCD25 was expressed in 69.2±6.5% of glomeruli were positive for P2X7 staining. Some P2X7 staining was observed in GFP-labeled hCD25(-) podocytes, which indicated indirect injury activated P2X7 expression. Cleaved-caspase 3 staining was also positive in 12.4±3.1% of glomeruli of LMB2-damaged kidneys, but not in those without LMB2. In in vitro studies, administration of ATP caused leakage of co-introduced EGFP in 51.7±1.4% of P2X7-transfected cells, incorporation of propidium iodide in 18.1±0.9%, and activation of caspase 3 in 17.9±2.8%. However, increase in DH activity in the medium remained minimum, corresponding to only 3.0±1.7% of cell death. These phenomena were not observed in mock-transfected cells treated with ATP or P2X7-transfected cells without ATP administration. Caspase-3 inhibitor significantly attenuated the leakage of EGFP induced by ATP (26.4±2.6 vs. 37.9±3.3%), whereas Caspase-1 inhibitor did not (37.6±3.0%).

Conclusions: These results indicate that injured podocytes express P2X7, which may further augment injury by inducing caspase-3 dependent apoptosis.

TH-PO1100

Expression Profile of the eGAS-STING Pathway in Podocytes: Implications for Glomerular Diseases

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Background: Recent studies suggest that podocytes express elements of the innate immune system which may be involved in the local immune response and contribute to glomerular damage. As part of the innate immune system, the eGAS-STING pathway is involved in the recognition of double-stranded DNA and RNA in innate immune response in disease processes such as systemic lupus erythematosus. Whether or not podocytes express genes in the pathway remains unknown. This study aims to investigate if genes in the cGAS-STING pathway are expressed in murine and human podocytes and the pathway can be activated by CDNs. Activation of the cGAS-STING pathway in mouse models of glomerular disease suggests a possible contribution of this pathway to podocyte injury.

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TH-PO1101

Loss of Ubiquitin-Specific Protease 40 in Podocyte Enhances Kidney Injury

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Background: Although an indispensable role of ubiquitin specific protease-40 (USP40) in podocyte development of zebrafish was revealed, widespread of USP40 function in kidney injury is still unknown. Since there is a close relationship between ubiquitin system and endoplasmic reticulum function, we aimed to explore the protein function of USP40 in the podocyte injury and to determine the interacting partner by focusing on ER resident chaperone.

Methods: USP40-knockout (USP40KO) mice were generated and showed no apparent kidney abnormality. To explore the role of USP40 in podocyte injury, we crossed USP40KO with NEP25 mice, in which selective podocyte injury can be induced by injection with an immunotoxin, LMB2. Urinary protein was analyzed until day 9 after LMB2 injection, and intestinal villi and tight microvascular, immunohistochemistry of p57 and immunofluorescence microscopy of the ER stress marker BIP and calreticulin (CRT).

Results: Both murine and human podocytes showed expression of cGAS-STING. Genes of the cGAS-STING pathway are expressed in murine and human podocytes and the pathway can be activated by CDNs. Activation of the cGAS-STING pathway in mouse models of glomerular disease suggests a possible contribution of this pathway to podocyte injury.

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TH-PO1102

A Urinary Metabolite Constellation to Detect Acute Rejection in Kidney Allografts

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Background: Post-transplant surveillance for acute rejection is mainly based on regular monitoring of serum creatinine levels and transplant biopsies upon functional renal impairment. Recently, we developed a novel method to detect kidney allograft rejection via a characteristic constellation of the urine metabolites alanine, citrulline, lactate, and urea investigated by nuclear magnetic resonance (NMR) spectroscopy (Banaz M et al., Metabolomics 2018).

Methods: Within the prospective, observational UMBRELLA study 986 urine specimens were collected from 109 consecutively enrolled renal transplant recipients and metabolite constellations were analyzed by NMR spectroscopy. A metabolite rejection score was calculated and compared to histopathological results of corresponding allograft biopsies (n=206).

Results: The metabolite constellation was found to be a useful biomarker to non-invasively detect acute allograft rejection (AUC = 0.75; 95% confidence interval (CI) 0.68 to 0.83; based on 46 cases with biopsy-proven rejection and 520 controls). A combination of the metabolite rejection score and the estimated glomerular filtration rate (eGFR) at the time of urine sampling further improved the overall test performance significantly (AUC = 0.84; 95% CI 0.76 to 0.91; based on 42 cases and 468 controls). In a subgroup of patients without rejection episodes the test results remained well below a diagnostic threshold associated with high risk of acute rejection. In other cases a marked increase above this threshold was indicative of an acute allograft rejection already 6-10 days before diagnostic renal biopsies were performed.

Conclusions: In conclusion, a combination of an NMR-based urine metabolite analysis and glomerular filtration rate is promising as a non-invasive test for post-transplant surveillance and to support decision making whether renal allografts need regular monitoring of serum creatinine levels and transplant biopsies upon functional renal impairment.

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TH-PO1103
Plasma Neutrophil Gelatinase Associated Lipocalin (NGAL) Predicts Long-Term Graft Survival in Stable Kidney Transplant Recipients

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Background: Neutrophil gelatinase-associated lipocalin (NGAL) has been evaluated as a biomarker of acute tubular injury in the kidney. The utility of NGAL to predict long-term outcomes in stable kidney transplant recipients (KTR) is unknown.

Methods: We conducted a monocentric, prospective observational study enrolling 709 stable KTR more than two months after renal transplantation. Baseline characteristics, standard laboratory values, and plasma NGAL (pNGAL) levels were determined at the time of inclusion. Patients were followed up for death-censored graft loss, defined by a continued requirement for renal replacement therapy. The utility of pNGAL to predict graft loss was evaluated by Receiver Operating Characteristics (ROC) analyses, Cox regression as well as competing risk analyses and Kaplan-Meier estimates.

Results: During a median follow-up of 58 months, death-censored graft loss occurred in 49 patients. The median pNGAL within the entire cohort was 189 [IQR 130.250] ng/ml. Patients who later experienced graft loss had a pNGAL of 304 [IQR 234.5358] ng/ml (p<0.001). Time-dependent ROC analyses indicated an Area-Under-the-Curve value for pNGAL of 0.79% to predict graft loss within 5 years. pNGAL >230 ng/ml had a sensitivity of 0.82 and a specificity of 0.71. Multivariate Cox regression analyses as well as competing risk analyses showed that pNGAL was an independent predictor of graft loss after adjustment for clinical parameters and kidney function. Patients with serum creatinine (sCrea) values ≥1.75 mg/dl and pNGAL ≥230 ng/ml had an approximately 9.6-fold higher risk of graft loss compared with patients with sCrea 1.75 mg/dl and pNGAL <230 ng/ml (p<0.001).

Conclusions: pNGAL levels in stable KTR may help to predict long-term graft survival.

TH-PO1104
Urinary Biomarkers TIMP-2 and IGFBP7 Are Predictive for Recovery from Ischemia-Reperfusion Injury After Kidney Transplantation

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Background: Conventional clinical markers often fail to predict recovery from ischemia-reperfusion injury in the early phase after kidney transplantation (KTx). Urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), markers for G1 cell cycle arrest, have been identified and validated for the early detection of renal injury in critical ill patients. We evaluated whether post-transplant urinary [TIMP-2]*[IGFBP7] can predict renal recovery early after KTx.

Methods: In a prospective observational multicenter cohort study of renal transplant recipients, urinary [TIMP-2]*[IGFBP7] (NephroCheck®; Astute Medical, San Diego, CA, USA) was evaluated daily from day 1–7 after KTx. Different stages of graft function were defined: immediate graft function (IGF) (decrease ≥10% sCrea within 24 h post KTx); slow graft function (SGF) (decrease ≤10% sCrea within 24 h post KTx) and delayed graft function (DGF) (any dialysis by day 1 week after KTx). Clinical and laboratory parameter were documented.

Results: A total of 186 KTx patients were analyzed, 138 (74%) with a deceased donor, 48 (26%) with a living donor KTx. IGF was observed in 58.6%, SGF in 23.1% and DGF in 18.3% of the cohort. [TIMP-2]*[IGFBP7] was significantly elevated in patients with DGF compared to other groups during the first week of transplant (Fig. 1). Renal function parameters were not able to differentiate between DGF and SGF early after KTx. ROC-Analyses of [TIMP-2]*[IGFBP7] at day 1 posttransplant for event “Non-DGF” revealed a cut-off value of 0.9 (ng/ml)/1000 (sensitivity 87%; specificity 71%). Positive predictive value for non-DGF was 93%.

Conclusions: Early [TIMP-2]*[IGFBP7] measurement can predict recovery from ischemia-reperfusion-injury post KTx. [TIMP-2]*[IGFBP7] is a promising biomarker for clinical decision-making after KTx.

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TH-PO1105
Predicting Transplant Rejection by a Composite Urinary Injury Score

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Background: While sequencing or PCR have been used for quantifying donor-derived cell-free DNA in plasma to detect allograft rejection, they remain expensive and inconvenient for patients and physicians. We assessed the performance of a novel urinary assay measuring nucleic acid, protein, and metabolic markers to provide a quantitative composite risk score without sequencing or PCR to detect kidney transplant (KT) rejection.

Methods: 206 urine samples from 95 KT patients were collected and categorized as stable (n=157) or acute rejection (AR, n=49). Samples were processed for quantification of urinary cDNA and 5 additional protein markers using a custom microowell-based assay, to develop a transplant rejection score. The score from longitudinally collected samples (n=47) from 8 KT patients who were stable and had no evidence of subclinical rejection was correlated with days post-transplant to generate a 95% prediction curve which was used to generate a normalized rejection score for all samples.

Results: The urinary rejection score is significantly increased immediately post-transplant and decreases to a steady baseline by 3 months post-transplant (Figure 1A). The median level of 95% prediction interval-normalized rejection score was significantly higher in AR as compared with stable samples (0.64 vs. -0.71, P < 0.0001) (Figure 1B). The urinary rejection score showed high performance in discriminating the stable and AR samples, with an AUC of 0.9649 (P < 0.0001). At a threshold set at a normalized value of 0, the sensitivity and specificity of the assay was 93.88% and 94.90% respectively (Figure 1C), suggesting that the assay could be used to screen patients at risk of rejection to avoid unnecessary biopsies in the clinical setting.

Conclusions: This novel urinary rejection score enables rapid and accurate discrimination of AR from stable patients without the costs associated with sequencing. As collection of urine requires no training and can be performed as often as needed, this assay can provide inexpensive, accurate, and longitudinal assessment of AR in KT patients.

Funding: NIDDK Support

Figure 1. Determination of rejection score kinetics post-transplantation and discrimination of AR.

TH-PO1106
Utility of a Novel dd-cfDNA Test to Detect Injury in Renal Post-Transplant Patients

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Background: Serum creatinine (SC) and biopsy are the standard of care for detecting renal allograft injury and rejection. SC has poor specificity and sensitivity, and biopsies are costly, invasive, and have attendant complications. We report on the clinical utility of a novel method that measures donor-derived cell-free DNA (dd-cfDNA) using a single SNP-based NGS methodology to diagnose allograft injury/rejection.

Methods: We conducted a randomized controlled trial sampling 154 fellowship-trained nephrologists with two to 40 years of post-residency practice and an active panel
of at least five renal allograft patients. Over two rounds, providers cared for six online, virtual patients—Clinical Performance and Value (CPV) vignettes—validated tool that accurately measures clinical utility and clinical practice. CPV patients were aged 30-75, were 3-24 months post-transplant, and presented in one of three ways: (1) active rejection with moderate SC increase and proteinuria; (2) subclinical rejection with no change in SC; and (3) elevated SC from another nephrotoxic insult but not rejection. Doctors randomized into the intervention arm were given educational materials on the dd-cfDNA test between rounds and dd-cfDNA results before they cared for patients in round 2. The primary outcome determined whether using dd-cfDNA demonstrated clinical utility and improved patient care as manifested by the workup, diagnostic accuracy, and medical management of these patients.

Results: At baseline, providers correctly determined primary diagnosis in only 50% of cases (p=0.853). In round 2, interventional providers improved 32.9 percentage points (p=0.277). In both groups, providers did not improve (p=0.257). Providers in both groups made a correct biopsy or referral decision in 58% of cases at baseline. Intervention improved 30.0 percentage points (p=0.001) while control did not improve in round 2 (p=0.501). Similarly, intervention providers’ medical management improved significantly (+14.3 percentage points, p=0.001) in round 2, while controls’ did not (p=0.485).

Conclusions: Nephrologists shown dd-cfDNA levels were significantly more likely to accurately diagnose, and make better biopsy, referral and medically management decisions for renal transplant patients.

TH-PO1107
Serial AlloSure Testing with Donor-Specific Antibodies in Renal Transplant Recipients Can Avoid Kidney Biopsy
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Background: Donor derived Cell free DNA testing with targeted next gen sequencing assay (AlloSure) has been shown to predict renal allograft rejection at a threshold of 1% having a PPV of 95% for antibody mediated rejection (AMR). We aimed to evaluate the utility of positive AlloSure in the diagnostic algorithm is not well defined and we believe looking at clinical patterns in this subset may shed light on optimal strategy of use.

Methods: A total of 155 patients (pts) transplanted between 2016 - 2019 had 289 AlloSure tests. 40 were tested at predetermined intervals (KIDAR registry) and remaining 115 had for cause testing. Pts with AlloSure levels -1% were assessed for DSA, indication for biopsy, serum creatinine (Cr), rejection, alternate etiology and therapy change.

Results: AlloSure results ranged from detection threshold <0.15% to 13%. 24/155 pts had AlloSure >1%. 4/24 were in KIDAR registry of which 2 had ACR IBM, 1 had AMR, and 1 had AKI 2/2 obstruction. 19/24 underwent AlloSure biopsy. 10/24 had ACR IBM, 3/24 had mixed rejection. 5/24 had no rejection on biopsy 3/10 with AMR and 3/5 with other causes had rise of Cr >0.3mg from baseline at the time of positive result. 5/24 who did not have biopsy had stable Cr with negative/improved DSA. 15/24 had change in therapy, 2 with positive biopsy/AlloSure had stable DSA/Cr with no change in therapy. 2 pts were started on Losartan for AT1 R antibody & AMR. 1/24 pt with initial Cr <12 mg/dl did not recover and declared ESRD. All 15 pts with therapy change stabilized/improved renal function. Median peak AlloSure was 3 and mean peak was 3.09. The lowest positive result was 1.1 and highest was 13, both in pts with ACR IBM.

Conclusions: AlloSure performs well as a test to “rule out” rejection. Serology consistent with DSA and serial trend can safely avoid biopsy. It allows detection of AMR before rise of Cr in the majority of pts. No correlation was found with level of AlloSure and Cr. The mean value was higher than the threshold of a positive result. DSA was stable/negative in all patients with positive renal outcome supporting safety of such an approach. Bar or adding a growing repertoire (AlloSure+) and marker use in kidney transplant.

Study limited by small sample, mixed cohort and non adherence to testing protocol.

TH-PO1108
The Serum CTRP9 Concentration Correlates with Cardiovascular Risk in Renal Allograft Recipients

Background: Cardiovascular disease (CVD) due to atherosclerosis is a major cause of death in renal allograft recipients. Recently, C1q/TNF-related protein-9 (CTRP9), which is a paralog of adiponectin (ADPN), has been suggested to be related to the suppression of atherosclerosis and the occurrence of CVD, but this relationship has not been confirmed in renal allograft recipients. We evaluated the relationships among the serum CTRP9 concentration, serum ADPN concentration, and vascular calcification were investigated in 50 Japanese kidney allograft recipients.

Methods: Calculation of the abdominal aorta was evaluated according to the aortic calcification score (ACS), the percentage of ACI was calculated from CT images. Changes in the serum CTRP9 and ADPN fractions and ACI were examined for 8 years. In addition, the expression of CTRP9 and ADPN and their respective receptors AdipoR1 and R2 in small arteries of the transplanted kidney was examined by immunohistochemistry.

Results: In renal allograft recipients, the serum CTRP9 concentration at the start of the observation was not significant correlated with eGFR or serum high-molecular-weight (HMW)-ADPN concentration (rS=0.009, p=0.950; rS=0.226, p=0.014, respectively). However, the change in the serum CTRP9 concentration was positively correlated with the change in the serum HMW-ADPN concentration (rS=0.315, p=0.016) and negatively correlated with the change in ACI (rS=0.367, p=0.009). Multiple regression analysis revealed that the serum HMW-ADPN concentration was a significant positive factor for the change in the serum CTRP9 concentration. Moreover, for ACI, an increase in the serum CTRP9 concentration was an improving factor, but aging was an exacerbating factor. Furthermore, colocalization of CTRP9 and AdipoR1 was noted in intrarenal arterial endothelial cells.

Conclusions: In renal allograft recipients, CTRP9 and HMW-ADPN were suggested to produce vascular protective effects mediated by AdipoR1 to suppress the progression of aortic calcification.

Funding: Government Support - Non-U.S.

TH-PO1109
Circular RNA in Urine-Liquid Biopsy Biomarker of Acute Rejection in Kidney Transplantation
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Background: Circular RNAs (circRNAs) are long non-coding RNA transcripts with strong gene regulatory function. Their circular structure guarantees stable detection in blood. We hypothesized that circRNAs are detectable in urine as well and serve as a marker of acute T cell-mediated kidney allograft rejection.

Methods: A global urinary circRNA expression analysis was performed in patients with acute rejection compared to patients without rejection. Differentially concentrated circRNAs were validated in patients with acute rejection (n=62), in stable transplant patients (control, n=18) and rejection dependent concentrations were additionally analyzed after successful anti-rejection therapy (n=10). Biomarker specificity was verified in stable transplant patients with urinary tract infection (disease control, n=13).

Results: A distinct urinary circRNA transcriptome signature identified patients with acute rejection. circRNAs hsa_circ_0001334 and hsa_circ_0001475 were strongly altered and thus validated in the whole cohort. Increased hsa_circ_0001334 concentrations were specifically confirmed in patients with acute rejection and returned to base level after anti-rejection therapy. hsa_circ_0001334 showed promising biomarker value and prognostic potential in predicting higher decline of creatinine clearance after one year of transplantation.

Conclusions: In conclusion, a specific urinary circRNA transcriptome signature and circRNA hsa_circ_0001334 was discovered as novel non-invasive diagnostic and prognostic biomarker of acute T cell-mediated kidney allograft rejection. Measurement of concentrations of circRNA in urine might thus serve as novel liquid biopsy in kidney transplant patients.

TH-PO1110
Longitudinal and Cross-Sectional Analysis of Kidney Transplant Urine mRNAs Reveals Glomerular Disease as an Important Driver of Long-Term Graft Loss
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Background: Biopsies from failing allografts (El-Zoghby) and longitudinal protocol biopsies in two studies (Nankivell; Stegal) suggest that glomerular disease (GD) is associated with late graft loss. In a 10yr study Stegal reported GD to be more prevalent than ITA. To understand why kidney transplants fail over time, we utilized neprhon specific specific urine pellet mRNA biomarkers to enable non-invasive analysis of injury patterns

Methods: Longitudinal and cross sectional urine samples covering 20 years post-TP for all donors were collected. Two podocyte markers (podocin, nephrin), a distal tubular/collecting duct marker (aquaporin2) and marker of innate immune/proliferative activity (TGFBeta1) were measured in spot urine samples and normalized to creatinine. Baseline 2kiney (2K) values for 4 markers were obtained from 98 healthy controls and used to derive 1K normal values.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: 380 recipients provided 1997 urine pellets. All markers increased immediately after nephrectomy and remained elevated above 2K control. Downstream tubular injury marker (Agp:CR) remained elevated above 2K level suggesting ongoing TP injury.

Conclusions: Urine pellet mRNA data are compatible with long-term protocol biopsy data suggesting that GD is an important driver of long-term kidney allograft failure.

Funding: NIDDK Support, Other NIH Support - MNORC, Private Foundation Support

TH-PO1113
Biomarker Implementation: Evaluation of the Decision-Making Impact of CXCL10 Testing in a Pediatric Cohort
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Background: Children are at high risk for subclinical rejection and invasive biopsy is currently used for active surveillance. Urinary CXCL10 hold the most promise as a biomarker for post-transplant monitoring of rejection. How it will influence clinical decision has never been tested. As such, our objective was to test whether CXCL10 can improve the clinical decision-making to identify organ rejection risk.

Methods: We first assembled a panel of experts to establish a minimum dataset for standard clinical decision-making for an indication biopsy. Clinical vignettes were then built from 15 prevalent pediatric kidney transplant recipients who had surveillance or indication biopsy and biobanked urine sample. Urine samples were tested for CXCL10 and reported as ratio to creatinine. Pediatric nephrologists were recruited review serial clinical vignettes and A1) predict rejection risk and B) decide to biopsy, without then with urinary CXCL10 result and rejection diagnosis sensitivity/specificity information for different levels. Biopsy decisions were then correlated with the biopsy results. Inter-rater agreement (IRA) was assessed by Fleiss Kappa (K) for binary choice and interclass correlation (ICC) for probabilities.

Results: Eleven pediatric nephrologists were enrolled. IRA for choice to biopsy was fair both before (K=0.48, p<0.01) and after (K=0.43, p<0.01) incorporating CXCL10 data. ICC of probability assessment for rejection was poor before (0.28, p<0.01) and improved to fair (0.48, p<0.01) with addition of chemokine data (p=0.6 for difference). Clinicians did consider the CXCL10 in their decision making process and CXCL10/Cr correlated with urinary CXCL10 result and rejection diagnosis sensitivity/specificity information for different levels. Biopsy decisions were then correlated with the biopsy results.

Conclusions: There is high variability in decision-making on biopsy indication. Urinary CXCL10/Cr improves probability estimates for risk of rejection. However, training may be required to assist nephrologists in using biomarker information for clinical decision-making.

TH-PO1112
Donor Nephrectomy Selectively Increases Proximal Tubular Proteins in Urinary Vesicles
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Background: Donor nephrectomy causes hyperfiltration and hypertrophy occurring in this segment. Accordingly, we hypothesize that human donor nephrectomy increases proximal tubular proteins.

Methods: Nineteen kidney donors were included in this study. Kidney volume was calculated from CT scans prior to donation. Urine was collected prior to and three months after donor nephrectomy. Urinary extracellular vesicles (uEVs) were isolated and used as non-invasive read-out for renal tubular protein abundance. uEVs were quantified using nanoparticle tracking analysis. The following proteins were analyzed in uEVs using ultra-centrifugation and immunoblotting: NHE3, NaPi-IIa and cubilin (proximal tubule), NKCC2 (thick ascending limb), NCC (distal convoluted tubule), and AQP2 (collecting duct). Relative protein abundance was expressed per remaining kidney volume.

Results: Donor nephrectomy reduced kidney volume by 50±10%, creatinine clearance by 34±10%, and uEV excretion by 20%. The relative abundance of proximal tubular proteins in uEVs increased significantly, whereas no change occurred in distal nephron proteins (Figure).

Conclusions: Donor nephrectomy selectively increases proximal tubular proteins in uEVs. This may be due to hyperfiltration and hypertrophy occurring in this segment. It may also explain why a kidney volume reduction of ~50% is accompanied by a decrease in uEV excretion of only ~20%. These results provide insight in the changes after kidney donation and are relevant when analyzing uEVs in kidney donors.

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TH-PO1114

Low Soluble Klotho Levels Are Associated with Renal Function Decline in Kidney Transplantation

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Background: Serum soluble klotho levels have been shown to be associated with renal function in pre-diagnosis patients with chronic kidney disease. However, there are few reports regarding the association between soluble klotho levels and renal function in kidney transplant (KTx) recipients. Thus, we investigated the association of soluble klotho levels of the pre-KTx with renal function decline in living KTx recipients.

Methods: This is a retrospective, observational study of 41 living KTx recipients who received standard immunosuppressive therapy between 2002 and 2017 in our hospital. The serum soluble klotho levels were divided into 2 groups according to the median value: ≥ 456 pg/ml (High group, n=21), or < 456 pg/ml (Low group, n=20). Renal function decline was defined as a 30% or more decrease in estimate glomerular filtration rate (eGFR) compared with that of baseline within 3 months after KTx. A multivariable time-to-event analysis between the groups was performed.

Results: 4.9% of the recipients received preemptive KTx. 75.6% and 19.5% of the recipients were treated with hemodialysis and peritoneal dialysis before KTx, respectively. Median follow-up period was 913 days (IQR: 318-2015 days). KTx recipients in the Low group showed a significant higher incidence of 30% decrease in eGFR than those in the High group (p=0.036). In multivariable Cox models adjusting for patient-age, donor-age, the presence of rejection, and the number of HLA mismatch, the low soluble klotho levels remained to be associated with a higher risk of 30% decrease in eGFR (HR: 2.78, 95% CI: 1.02-8.26).

Conclusions: These results suggest that lower soluble klotho levels of the pre-KTx are associated with increased risk of renal function decline in KTx recipients. Maintenance of higher serum soluble klotho levels before KTx may be preferable for renal function preservation.

TH-PO1115

Increased Delta Neutrophil Index Is Associated with Poor Prognosis in Cadaveric Donor Kidney Transplantation

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Background: Delta Neutrophil Index (DNI) is the fraction of circulating immature granulocytes. In many studies, DNI has been demonstrated as a useful prognostic marker in critical patients. We hypothesized that increased level of DNI in the recipient is associated with poor prognosis in cadaveric donor renal transplantation (CRT).

Methods: We reviewed medical records of a total of 73 patients undergoing CRT from March 2013 to January 2018 retrospectively. The transplant rejection (TR) was assessed using Banff classification, and subclinical rejection was excluded in the study.

Results: Twenty-five (34.2%) patients were diagnosed with TR. Among them, 11 patients were classified as early TR. The post-operative DNI (po-DNI) was higher in the patients with early TR than that of patients without it (1.21 vs. 0.18, p<0.001). In univariate logistic regression test, cold ischemic time, last creatinine level of the donor before transplantation (last-Cr), po-DNI level, and peri-operative infection predicted early TR. In logistic regression test, cold ischemic time, last-Cr, and po-DNI level showed a significant association with early TR (Odds ratio 12.31, 95% CI 1.22-129.82, p=0.034). The c-statistic value of po-DNI in the logistic model was 0.78 (95% CI 0.60-0.95, p=0.004). Multivariable Cox regression analysis showed that last-Cr (Hazard ratio (HR) 2.25, 95% CI 1.26-4.13, p=0.006) and pre-operative DNI (HR 14.02, 95% CI 2.62-75.26, p=0.002) predict renal survival in CRT.

Conclusions: Increased DNI of the recipient in CRT is thought to be a useful marker for predicting early TR and renal survival.

TH-PO1116

Predicting Deceased Donor Kidney Transplant Outcomes: Comparing KDRI/KDPI with Machine Learning

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Background: Kidney transplantation is an effective cure for patients suffering from end-stage renal disease. Kidney transplantation is cost-effective, provides a significant survival benefit, and improves the quality of life for patients. One limitation on kidney transplantation is the appropriate assessment of donor quality, for which several indices have been created.

Methods: Machine learning methods (MLM) were compared to kidney donor risk index (KDRI) and kidney donor profile index (KDPI), for the ability to predict graft failure by 12, 24, and 36 months after deceased donor kidney transplantation (DDKT). The MLM model, an ensemble of thousands of randomly generated decision trees, was trained with the same data initially used to develop KDRI.

Results: An MLM trained with the readily available recipient and donor variables performed significantly better than KDRI/KDPI when predicting graft failure by 12, 24, and 36 months after DDKT. When comparing equal prediction failure rates of 10%, MLM successfully predicted 126% more successful DDKTs (an additional 2,148) than KDRI/KDPI from 1995-2005. Over the entire ROC curve, the MLM performed statistically significantly better c-statistic than KDRI/KDPI in all predictions.

Conclusions: Using MLM, many high-KDRI kidney offers resulted in thousands of successful patient outcomes without increasing risk of predicted graft failure. The MLM provided a significant improvement over KDRI for the assessment of kidney offers and generated professionals an improved basis for making the critical decisions. This work lays the foundation for future MLM in organ transplantation and describes the steps to measure, analyze, and validate future models.

TH-PO1117

Predicting Health Outcomes for Elderly Renal Transplant Recipients with Machine Learning

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Background: Application of machine learning to nephrology research has been scarce. In this study, we demonstrated the use of classification algorithms in predicting all-cause death at three-year among elderly deceased-donor renal transplant recipients.

Methods: This is a retrospective, population-based, cohort study of all cases of deceased-donor renal transplants performed in Ontario, Canada from March 31, 2002 to April 1, 2013. Recipients aged over 70 years were followed up until death or to April 1, 2016. Bootstrap-aggregating classification tree and K-Nearest Neighbors (KNN) were used to train a predictive model for death at three-year post-transplant. Patient-level attributes at the time of transplantation, including demographic characteristics, lab results, transplant information, comorbidities, and pre-transplant health care utilization, were examined as potential determinants of post-transplant death. A ratio of 3.2 was used to construct training and testing sets. Synthetic Minority Oversampling Technique was applied to generate artificial positive cases (death) and under-sample negative cases (alive) in the training set to reduce bias. Models were trained and tuned using ten-fold cross-validation on the training set and tested on the specificity and sensitivity of prediction using the testing set.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Among 275 elderly transplant recipients, the majority (n=271, 98.5%) were transplanted at 71-80 years and four (1.5%) were older than 80 years. Death occurred in 52 (18.9%) cases at three-year post-transplant. Before sampling, classification tree and KNN had test sensitivity of 0.11 (95% confidence interval [CI], 0.01-0.33) and 0.07 (95% CI, 0.01-0.18), respectively, while both achieving 0.95 (95% CI, 0.85-0.98) specificity. After sampling, classification tree and KNN achieved test sensitivity of 0.21 (95% CI, 0.06-0.46) and 0.26 (95% CI, 0.03-0.50), respectively, as well as test specificity of 0.89 (95% CI, 0.81-0.95) and 0.84 (95% CI, 0.74-0.90), respectively.

Conclusions: Our findings add to the growing body of knowledge aimed at improving the performance of risk calculators (e.g., Choose Kidney) that help patients and families to make informed decisions in renal care. Furthermore, our study confirmed the strength of machine learning techniques in population-based nephrology research despite our limited sample size and the rarity of the outcomes assessed.

TH-PO1118
Optimization of Machine Learning Models for Predicting Delayed Graft Function in Renal Allografts
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Background: Delayed graft function (DGF) is associated with worse short- and long-term renal allograft outcomes. Several groups have previously developed models that compute the theoretical risk of DGF for allograft recipients using standard statistical inference methods. In this study, we apply automated computational algorithms to generate tens of thousands of DGF prediction machine learning models based on donor characteristics alone. In this en masse approach, we are able to empirically optimize these machine learning models for the prediction of DGF.

Methods: Deceased donor data available from UNOS for 1,694 renal transplants at our center from 2010-2018 were used in this study, which included various elements of demographics, medical history, and circumstances of death. Cold ischemia time (CIT) and KDPI were included as well. The number of cases was further trimmed randomly to achieve a 50% 50% split in DGF-positive and negative cases, with a final total of 922 cases. These data were used to create 10 runs for each specific parameter combination [each using 90% (n=830) of cases for training phase and 10% (n=92) of cases for model’s validation test] to generate a total of 45,980 unique models within these parameter combinations on 4 distinct machine learning algorithms (logistic regression, k-nearest neighbor, support vector machine, random forest). Models were also produced with fewer donor features, KDPI alone, CIT alone, and KDPI with CIT. The mean accuracy, standard deviation, and area under the curve (AUC) for the best models were calculated.

Results: Of the 45,980 models generated, the best performing models had an accuracy of 74% (5-7) and AUC of 77. A common theme to these optimized models was that they excluded KDPI as a feature but included CIT. KDPI alone performed poorly (accuracy 49-57%; AUC 0.51-0.55). CIT alone was also suboptimal (accuracy 56-62%; AUC 0.46-0.50). Our findings add to the growing body of knowledge aimed at improving the performance of risk calculators (e.g., Choose Kidney) that help patients and families to make informed decisions in renal care. Furthermore, our study confirmed the strength of machine learning techniques in population-based nephrology research despite our limited sample size and the rarity of the outcomes assessed.

TH-PO1119
Factors Impacting the Disparity in Receipt of Live Donor Kidneys by Women vs. Men
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Background: It was noted in the early 2000’s that women received fewer live donor kidneys (LDK) than men. Since that time, more women have entered the workforce, transplantation of highly sensitized individuals has improved and there has been an increase in altruistic donation; factors that might help to increase the LDK rate in women. We examined the rate of LDK transplants in women compared with men since 1998-00, as well as factors that might affect it.

Methods: All 105,729 primary adult living donor kidney transplants reported to UNOS/OPTN between 1998 and 2018 were analyzed. Only adult recipients were included in the analyses. The time period was divided into 3-year intervals to adjust for yearly fluctuations. Logistic regression models were used to assess the odds to receive a LDK for women adjusted for possible risk factors.

Results: Of the 45,980 models generated, the best performing models had an accuracy of 74% (5-7) and AUC of 77. A common theme to these optimized models was that they excluded KDPI as a feature but included CIT. KDPI alone performed poorly (accuracy 49-57%; AUC 0.51-0.55). CIT alone was also suboptimal (accuracy 56-62%; AUC 0.46-0.50). Our findings add to the growing body of knowledge aimed at improving the performance of risk calculators (e.g., Choose Kidney) that help patients and families to make informed decisions in renal care. Furthermore, our study confirmed the strength of machine learning techniques in population-based nephrology research despite our limited sample size and the rarity of the outcomes assessed.

TH-PO1120
Prognostic Value of Standardized Deceased Donor Kidney (DDK) Procurement Biopsies
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Background: Procurement biopsy (PBx) histology is the most common reason for DDK discard but has been shown to be of limited prognostic value. Occasionally DDK are biopsied twice when transported between OPOs, allowing us to assess the standardized approach to performing and interpreting PBx at our OPO.

Methods: We identified 591 DDKs transplanted at our center from 1/2006-12/2016 (imported from 60 OPOs) with an initial PBx (PBx1) that was repeated by our local OPO (PBx2). "Suboptimal histology" was defined as glomerulosclerosis (GS) >10%, interstitial fibrosis/tubular atrophy (IF/TA)>25%, and/or vascular disease (VD) graded as moderate or severe. We calculated kappa coefficients to assess agreement between PBx1 and PBx2 using time-to-event analyses to evaluate the association between suboptimal histology on PBx1 and PBx2 with death-censored allograft survival.

Results: 36% PBx1 and 17% PBx2 were classified as having suboptimal histology. 75% of DDK with suboptimal PBx1 had optimal PBx2. Overall histologic concordance (optimal versus suboptimal) between PBx1 and PBx2 was 65% (k = .013). Categorical agreement was higher for VD (k = .03, 52% concordance) than for IF/TA (k = .008, 67% concordance) or GS (k = .011, 44% concordance). In contrast to PBx1, suboptimal PBx2 histology was associated with death-censored allograft survival in bivariable and multivariable analysis (adjusted hazard ratio 2.17, 95% CI 1.72-3.45, p = .001).

Conclusions: PBx performed at different OPOs were frequently discordant, likely due to variable PBx technique and interpretation between OPOs. Our results suggest that standardization may improve utility and reliability of PBx for assessing DDK quality.

TH-PO1121
Machine Learning-Guided Measurement of Visceral Fat Area in Transplantation: Clinical - Predictors of Outcomes - Biomarkers and Beyond
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Background: Innovative machine learning can be applied to efficiently provide the information on medical imaging and be useful in the prediction model. Accordingly, the present study measured visceral fat area (VFA) with updated machine learning algorithm in kidney transplant recipients and evaluated its correlation with delayed graft function (DGF).

Methods: A total of 287 adult kidney recipients who examined abdominal computed tomography with full range of torso before transplantation were enrolled. VFA in the...
cervical cavity was measured in cubic meters throughout machine learning algorithm. 

Results: The mean age was 47.8 ± 11.3 years and male was 66.2%. The mean body mass index was 24.6 ± 3.5 kg/m². The VFA was 2.88 ± 1.92 m², and the body surface area-adjusted value was 1.59 ± 0.95 m². The adjusted VFA had a linear relationship with the survival time (β = 0.040). The risk of DGF increased depending on an increase of 1 unit in adjusted VFA with an odds ratio of 1.80 (1.07–3.02). However, body mass index was not associated with DGF (odds ratio, 0.99 (0.83–1.19). The area under receiver operating characteristic curve of adjusted VFA was 0.73, which was greater than 0.50 in body mass index (P < 0.02).

Conclusions: Machine learning algorithm may efficiently provide information on VFA of kidney recipients. This issue will improve the predictive capacity of transplant outcomes such as DGF.

TH-PO1122

Construction of a Predictive Model of Delayed Graft Function Using Machine Learning Techniques

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Background: Brazilian studies have been reported incidences of delayed graft function (DGF), 2-3 fold the incidences described by American and European cohorts. The available predictive models of DGF, based on distinct clinical realities, are not validated in our population. The purpose of the study was evaluate the accuracy of the available predictive predictive models and, since none of these models present good accuracy, construct a local prediction model

Methods: Retrospective cohort study including DD KT performed between Jan 2014 and Dec 2017 in two transplant centers (n=443). The predictive DGF models tested were those described by Irish et al., Jeldres et al., Chapal et al., and Zaza et al. For the construction of the new predictive model, machine learning was used

Results: Patients were predominantly men (56.7%), young adults (44.2 ± 14.7 years), mixed race (84.4%), who remained 46.8 ± 45.2 months on dialysis. Donors had a mean age of 31 ± 12.7 years, most of them died from trauma (70.9%), 5.4% were hypertensive (HA), 0.7% were diabetic, and the final creatinine was 1.1 ± 0.6 mg/dL. Only 4.3% were expanded criteria donors. 83.1% of the grafts were perfused with HTK and the mean cold ischemia time (CIT) was 20.9 ± 4.4 hours. The incidence of DGF in this sample was 53%. The predictive models of DGF available presented regular or poor discriminant power: Irish (AUC 0.686), Chapal (AUC 0.638), Jeldres (AUC 0.613), Zaza (AUC 0.591). The three models with the best performance were decision tree, neural networks and support vector machine. In the final model, the variables considered were: from recipients : age, diabetes and time on dialysis; from donors: age, body mass index, HA, serum sodium, creatinine phosphokinase, final creatinine, cause of death, high dose of vasoactive drugs and diuretics; CT. The final model showed excellent discriminant power (AUC 0.942)

Conclusions: The incidence of DGF in the sample was high, despite the predominance of standard criteria donors. In addition to variables classically associated with DGF, variables related to donor management were pointed out in non-linear statistical methodologies. The available predictive models had poor accuracy in predicting DGF in our population. The developed model presented excellent performance.

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TH-PO1123

Patient Survival After Kidney Transplantation: Important Role of Graft-Sustaining Factors as Determined by Predictive Modeling Using Random Survival Forest Analysis

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Background: Identification of the relevant factors for death can improve patient’s individual risk assessment and decision making. A well-documented patient cohort (n=892) in a renal transplant program with protocol biopsies was used to establish robust models for risk assessment at 3 and 12 months posttransplantation by random survival forest analysis.

Methods: Patients transplanted between 2000 and 2007 were observed up to 11 years. Loss to follow-up was negligible (n=15). 2251 protocol biopsies and 1214 biopsies for cause were performed. All rejections and clinical borderline rejections in protocol biopsies were treated.

Results: 10-year patient survival was 78%, with inferior survival of patients with graft loss. Using all pre- and post-transplantation variables until 3 and 12 months (n=63), the obtained models showed good performance to predict death (concordance index: 0.77–0.78). Validation with a separate cohort of patients (n=349) showed a concordance index of 0.76 and good discrimination of risks by the models, despite substantial differences in clinical variables. Random survival forest analysis produced robust models over a wide range of parameter settings. Besides well-established risk factors like age, cardiovascular disease, type 2 diabetes, and graft function, posttransplant urinary tract infection and rejection treatment were important factors. Urinary tract infection and rejection treatment were not specifically associated with death due to infection or malignancy but correlated strongly with inferior graft function and graft loss.

Conclusions: The established models indicate the important areas that need special attention in the care of renal transplant patients, particularly modifiable factors like graft rejection and urinary tract infection.

TH-PO1124

External Validation of Predictive Score for Post-Transplantation Outcome in US Deceased Kidney Transplant Recipients

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Background: We previously published a prediction model (www.transplantscore.com (TS)) for allograft and patient survival, which consisted of only predictors available at the time of kidney transplantation. We aimed to perform external validation to assess the robustness, reliability, and applicability of our model.

Methods: Five hundred eleven patients who underwent first deceased KT in our Institute between 2010 to 2017 were included. We computed the original prediction score for these patients and compared the results with the obtained outcome in terms of the score’s calibration (goodness of fit) and discrimination (AUC: Area Under the Curve). We also assessed the predictive performance in terms of re-classification (NRI: Net Reclassification Improvement) when compared with a binary classifier based on the EPTS raw score.

Results: In the entire cohort, the mean age was 51.2±11.8 years old, 83% were African-American, most of the patients were on hemodialysis (81%) before KT and mean time on dialysis was 5.4 years. The TS-predicted mortality probabilities clearly separate patients as demonstrated in the Kaplan-Meier curves using all available follow-up (Figure panel A). The AUC’s likelihood for TS for 1 and 2-year mortality (panel B) were 0.737 and 0.682, respectively. These were higher than those for the classifier based on the EPTS score (AUC of 0.649 and 0.623 for 1 and 2 year mortality, respectively) and the NRI computed to 0.302 and 0.149 for 1 and 2 year classifications in favor of TS. However, the differences in the AUCs were not statistically significant (p = 0.138 and p = 0.149 for 1 and 2 year comparisons). The Hosmer and Lemeshow goodness of fit test of TS indicated some inadequate fitting (p = 0.015 and 0.038, respectively) apparently especially an overestimation for higher-score patients.

Conclusions: TS appears to broadly correctly classify patients with respect to their 1 and 2 year mortality rate.

TH-PO1125

Development of Donor Kidney Age: A Simple Score Summarising Donated Donor Risk

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Background: Although a number of donor factors are known to affect outcome following deceased donor kidney transplantation, many units have no clear criteria for acceptance. Donor quality scoring systems such as KDR1 are based on historic data sets, performing less well in the modern cadaveric donor pool, and are difficult for patients to understand.

Methods: All deceased-donor kidney offers at a single centre were analysed over a 12 month period in order to develop a patient-friendly scoring system. Donor age is modified and re-estimated in a renal transplant program with protocol biopsies was used to construct multivariable quality scoring systems such as KDRI are based on historic data sets, performing less well in the modern cadaveric donor pool, and are difficult for patients to understand.

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Underline represents presenting author.

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Results: Out of 388 offers, from 301 donors aged 6 - 84, 109 (28%) were accepted and transplanted. 64.4% of recipients were HIV positive. The post-transplantation, recipient GFR over 30 was seen in 80%. Organs were declined due to recipient factors in 26% and donor quality concerns in 46%. Donor Kidney Age was derived incorporating 12 risk factors: donor cardiac death, hypertension, diabetes, vascular disease, baseline kidney function, creatinine rise, oliguria, proteinuria, HLA mismatch, cardiac arrest, use of adrenaline, and duration of hospitalisation before donation. Quintiles of donor risk for all offers were identified using DKA cutoffs: 50, 60, 70, and 80. Increasing DKA quintile was associated with poorer post transplant outcome, with low 3 month GFR (below 30ml/min) in 97, 85, 73, 81 and 38% of patients respectively (p<0.001). In those with functioning grafts (N=105), GFR at 3 months was strongly correlated with DKA (R=0.430, p=0.001) and was seen to reduce across increasing DKA quintiles (61, 52, 41, and 29%) and was seen to reduce across increasing DKA quintiles (61, 52, 41, and 29%).

Conclusions: DKA is a simple score based on donor age, adjusted for 12 donor-related factors, which can help predict post-transplant outcome and is conceptually easy for patients to understand. Prospective evaluation of its influence on deceased donor acceptance decisions will be undertaken.

TH-PO1126

Influence of Donor Characteristics and Delayed Graft Function (DFG) on Renal Function 12 Months After Kidney Transplantation
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Background: The KDPI (Kidney Donor Profile Index) is a score used for donor characteristics used to predict long-term graft survival. Delayed graft function (DFG), a variable included in the KDPI score, is an indicator of a reduced graft survival. We hypothesized that increasing KDPI scores and DGF concurred to reduce renal function 1 and 12 months after kidney transplantation.

Methods: This single center retrospective study included all consecutive deceased donor kidney transplant recipients (n=1221) between January 2014 to December 2015. Analysis was carried out according to deciles of KDPI. Renal function was evaluated by estimated glomerular filtration rate (eGFR, calculated by the MDRDA formula).

Results: The mean cold ischemia time was 25±7 hours and it was similar across the deciles of KDPI. The incidence of DGF increased from 39% to 75% (p<0.001) from 10-90% KDPI deciles. The 1 month eGFRs showed a negative association with KDPI deciles, 59.5 vs. 39.0 ml/min/1.73m2 (p<0.001) for 0-10% and 91-100% KDPI deciles. This trend persisted in the 12 month analysis (64.6 vs. 46.0 ml/min/1.73m2, p<0.001), respectively. DGF was associated with lower 1 month eGFR across all the KDPI deciles (KDPI [0-10%] 67.9 vs. 46.2 ml/min/1.73m2, p=0.029; KDPI [91-100%] 47.7 vs. 36.2 ml/min/1.73m2, p=0.01). In those with functioning grafts (N=105), GFR at 3 months was strongly correlated with DKA (R=0.430, p=0.001) and was seen to reduce across increasing DKA quintiles (61, 52, 41, and 29%).

Conclusions: DKA is a simple score based on donor age, adjusted for 12 donor-related factors, which can help predict post-transplant outcome and is conceptually easy for patients to understand. Prospective evaluation of its influence on deceased donor acceptance decisions will be undertaken.

TH-PO1127

Analysis of Donor Factors for Clinical Prediction of Recipient After Deceased Donor Renal Transplant in a Non-US Transplant System
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Background: There is little data on allograft survival based on deceased donor characteristics outside the United States. Conservative use of deceased donor kidneys despite international deficit of kidney donors. Using South Korea as a model, we analyzed deceased donor characteristics using 1-year creatinine in the recipient as a surrogate marker for long term outcomes.

Methods: We analyzed 2,858 cases contained within the Korean Organ Transplant Registry data which had conducted renal transplant from 2009 to 2017. Univariate, multivariate linear regression analysis and 5-fold cross validation was performed to make a formula for estimating the serum creatinine of the recipient for 1 year after deceased donor kidney transplant.

Results: Univariate analysis indicated a number of different factors were significant in determining outcome, however only donor age, donor serum creatinine and current smoking status without hypertension were statistically significant in a multivariate model for predicting serum creatinine of the recipient after 1 year of transplant (Table 1). We also found that serum creatinine at 1 year predicted 3 year outcomes in a log rank test.

Conclusions: Currently deceased donor kidney transplant outcomes are extremely good in South Korea (despite a much longer period on dialysis prior to transplant) compared to the US. Given differences in culture, economic and racial characteristics compared to the US, the Korean prediction model obtained from analyzing only 3 donor factors, and thus can be obtained relatively quickly and conveniently and yet provides more information to the recipient candidates before transplant. In particular, we also believe this study indicates that there is underutilization of potential decreased donors in Korea and that a wider pool of deceased donors could be used safely.

TH-PO1128

Risk Factors, Prediction, and Outcomes of Delayed Graft Function (DGF): An Analysis from a German Cohort of Extended Criteria Donor Kidneys with Post-Explantation Biopsies
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Background: DGF occurs frequently after transplantation and is associated with worse short- and long-term outcomes and associated with higher rejection rates. Risk factors include both donor and recipient characteristics, although their influence is imprecise. Therefore, we tested known risk factors of DGF and validated the performance of existing risk scores in predicting DGF in recipients of extended criteria donor kidneys with procurement biopsies.

Methods: We retrospectively evaluated the records of 223 consecutive adult cadaver renal transplant recipients with donor procurement biopsies. 135 patients developed DGF (defined as the need for hemodialysis during the first week after transplantation). Clinical donor and recipient characteristics as well as histological features of the biopsy were compared between the two groups and the following risk scores were evaluated regarding their association with observed DGF: Navarro (2011), Ortiz (2004), Balaz (2013), Lopes (2004), Snoeijis (2008), Remuzzi (1999), Nyberg (2003), Rao (2009), Foucher (2009), Schold (2005), Port (2002), Angleichau (2008), Leuven (2013) Irish (2010), KDR/KDPI and EPTS.

Results: Severity of acute kidney injury (similar to AKIN Classification) at ICU stay, last creatinine, proteinuria, macromorphic organ quality, microthrombi by histology, prolonged warm ischemia time, recipient body mass index, and recipient duration of dialysis were significant risk factors for the development of DGF in the recipient in univariable analysis. None of the evaluated scores could accurately predict DGF.

Conclusions: None of the established clinical, histological or combined scores for quality assessment of deceased donor kidneys appeared sufficiently prognostic for DGF in our cohort. We are currently working on a novel combined clinicopathological score better suited for clinical application in the Eurotransplant network.

TH-PO1129

Diffusion MRI Detects an Increase in Interstitial Fibrosis Earlier Than the Decline of Renal Function
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Background: Interstitial fibrosis(IF) is one of the major predicting factors in CKD. Diffusion Weighted Magnetic resonance imaging(DWI-MRI) is a new tool for non-invasive assessment, but its value for follow-up is unknown. We recently adapted a DWI sequence, allowing for the discrimination between the kidney cortex and medulla. The cortico-medullary ADC difference(AAD) was better correlated to IF than absolute ADC. We aimed at analyzing the use of DWI-MRI for the follow up of IF in patients having undergone repeated biopsies in comparison to renal function evolution.

Methods: In this prospective study, we included patients having undergone repeated biopsies for clinical purpose and who agreed to undergo repeated DWI-MRI at the time of biopsy.

Results: 19 kidney allografts patients had repeated biopsies for clinical purposes and parallel MRI examinations. The average interval between the two biopsies was 1.7year. There was no significant correlation between eGFR and IF at baseline(r=0.39,p<0.10), whereas baseline ADC correlated negatively with IF(r=-0.76,p<0.001). Between the two visits, IF as estimated from the biopsy, increased significantly from a fibrosis score of 20% to 32.5%(p=0.03) in individual patients, whereas estimated renal function remained stable(eGFR 54 to 52ml/min/1.73m2;p=0.01). AAD decreased significantly from 30 to 23×10^-3/mm2(Figure A). Considering the difference between the basal and follow-up values, there was a good correlation between the evolution of IF and AAD (r=0.51,p=0.03)(Figure B) but not between the evolution of IF and eGFR (r=0.24,p=0.34).

Conclusions: Thus modifications of AAD derived from DWI-MRI outperformed eGFR to follow IF evolution within a given patient. AAD may be more reliable than eGFR to allow earlier detection of an increase in IF.

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Underline represents presenting author.
TH-PO1130
Donor Kidney Renal Volume Predicts Recipient and Donor Graft Function at 1 Year

Methods: This retrospective cohort study of living donor kidney transplantation (2010-2017) from the National Kidney Transplant Service (NKTS) of Ireland. Renal volume was measured bilaterally in living kidney donors using TenRecon USA. Low eGFR for recipients and donors defined as < 60ml/min 1-year post donation was used in logistic regression modeling with donor volume categorized into tertiles. Donor and recipient characteristics were included in the models as potential confounding variables.

Results: There were 166 living donor kidneys in the study period. Mean donor age was 44.8 years (SD = 10.8). Donor mean BMI was 25.5 (SD = 2.9). Donor kidney volume was measured bilaterally in living kidney donors using TenRecon USA. Low eGFR for recipients and donors defined as < 60ml/min 1-year post donation was used in logistic regression modeling with donor volume categorized into tertiles. Donor and recipient characteristics were included in the models as potential confounding variables.

Conclusions: Donor kidney volume predicts recipient graft function 1-year post transplant but is less conclusive for donor kidney function. Cognizance of donor renal volume may help optimise potential kidney donor selection.

TH-PO1131
Interstitial Fibroblasts in Donor Kidney Predict Late Post-Transplant Anemia
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Background: Post-transplant anemia (PTA) is associated with the progression of kidney disease and mortality in kidney transplant recipients. In general, PTA is categorized into early and late types, commonly appearing during the two years following transplantation. Although the main causes of PTA are recipient factors, donor factors have not been fully investigated. In this study, we investigated the association of donor pathological findings with the incidence of PTA in kidney transplant recipients after 3 y (late PTA).

Methods: We conducted a retrospective cohort study at a single university hospital. A total of 50 consecutive adult recipients and donors were enrolled. To assess the structure of interstitial lesions, immunohistochemical staining of interstitial fibrosis and of fibroblasts were assessed in 0-hr biopsies for quantitative analysis.

Results: The incidence of late PTA in this cohort was 30%. Mean hemoglobin (Hb) was 11.6 ± 0.8 g/dl in patients with late PTA, and 14.3 ± 1.5 g/dl in patients without PTA. An inverse association was observed in biopsies between interstitial fibrosis area and interstitial fibroblast area (P<0.01), and each pathological finding was examined for its association with late PTA incidence after multivariate adjustment. For interstitial fibrosis area, the odds ratio (OR) was 1.94, with a 95% confidence interval (CI) of 1.26 to 2.99; P<0.01. For interstitial fibroblast area, OR was 0.01, 95% CI was 0.00 to 0.16, and P<0.01. Receiver operating characteristic curve analysis indicated that interstitial fibroblast area had high predictive power for the incidence of late PTA.

Conclusions: The presence of interstitial fibroblasts in donor kidney may play an important role in predicting the incidence of late PTA.

TH-PO1132
Presence of Renal Dysfunction Even at the Time of Listing Predicts Risk of ESRD in Isolated Heart Transplant Patients
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Background: Presence of chronic kidney disease (CKD) at the time of heart transplant is an independent predictor of post-transplant ESRD (end stage renal disease) and all-cause mortality. We wished to look at the effect of the presence and severity of CKD at the time of listing on post-heart transplant ESRD and mortality.

Methods: We analyzed 2000-2015 UNOS heart transplant data. Adults receiving first isolated heart transplant, who were not on dialysis were included in study. We divided our cohort into four clinically relevant groups based on their listing eGFR (<30 ml/min, 30-44 ml/min, 45-59 ml/min and ≥60 ml/min). Survival analysis was used to generate Kaplan-Meier curves. Results were adjusted for multiple confounding factors.

Results: We had 27,169 patients in our cohort. In the follow up period there were 7595 deaths and 2335 patients reached ESRD (Table 1). Kaplan-Meier curves for ESRD are shown in Figure 1.

Conclusions: Our findings shows that risk of renal replacement therapy post heart transplant increases with worsening eGFR at listing even after adjusting for multiple confounders with the highest risk in the group with eGFR <30 ml/min. This information may help identify patients for combined heart-kidney transplant in a more reasonable time frame.

Figure 1: Correlation of renal volume and eGFR in donors and recipients at 1 year
Estimated glomerular filtration rate (eGFR) and albuminuria measurements at 1-year posttransplant were used to categorize recipients (eGFR: ≥45 vs. <45 mL/min/1.73 m²; albuminuria: normal vs. mild-heavy). We determined the association between categories of eGFR and albuminuria and posttransplant hemorrhage and venous thrombosis based on diagnostic and procedural codes.

Results: Of 1,284 kidney transplant recipients at 1-year posttransplant, 21% had an eGFR <45 mL/min/1.73 m² and 40% had mild-heavy albuminuria. The mean age of the cohort was 53 years [IQR 41-62]. Previous thrombosis was higher in recipients with lower eGFR, but previous hemorrhage was similar across all groups. Over a median follow-up of 6 years, the age- and sex-adjusted rate of hemorrhage and thrombosis was over 2-fold higher in recipients with lower eGFR and mild-heavy albuminuria compared to recipients with higher eGFR and normal albuminuria (hemorrhage: incidence rate ratio, IRR, 2.6, 95% CI 1.5-4.4, p=0.001; thrombosis: IRR 2.3, 95% CI 1.1-5.0, p=0.046).

Conclusions: Among kidney transplant recipients at 1-year posttransplant, the risk of hemorrhage and venous thrombosis is higher with lower eGFR and mild-heavy albuminuria. Thus, eGFR and degree of albuminuria may help prognosticate kidney transplant recipients long-term.

### TH-PO1133
Kidney Function, Albuminuria, and the Risk of Hemorrhage and Thrombosis After Kidney Transplantation
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Background: Compared to the general population, kidney transplant recipients are at increased risk of hemorrhage and thrombosis. Whether this risk is affected by kidney function and albuminuria is unknown.

Methods: We conducted a retrospective cohort study using linked healthcare databases to identify adult kidney transplant recipients from 2002-2015 in Alberta, Canada. Estimated glomerular filtration rate (eGFR) and albuminuria measurements at 1-year posttransplant were used to categorize recipients (eGFR: ≥45 vs. <45 mL/min/1.73 m²; albuminuria: normal vs. mild-heavy). We determined the association between categories of eGFR and albuminuria and posttransplant hemorrhage and venous thrombosis based on diagnostic and procedural codes.

Results: Of 1,284 kidney transplant recipients at 1-year posttransplant, 21% had an eGFR <45 mL/min/1.73 m² and 40% had mild-heavy albuminuria. The mean age of the cohort was 53 years [IQR 41-62]. Previous thrombosis was higher in recipients with lower eGFR, but previous hemorrhage was similar across all groups. Over a median follow-up of 6 years, the age- and sex-adjusted rate of hemorrhage and thrombosis was over 2-fold higher in recipients with lower eGFR and mild-heavy albuminuria compared to recipients with higher eGFR and normal albuminuria (hemorrhage: incidence rate ratio, IRR, 2.6, 95% CI 1.5-4.4, p=0.001; thrombosis: IRR 2.3, 95% CI 1.1-5.0, p=0.046).

Conclusions: Among kidney transplant recipients at 1-year posttransplant, the risk of hemorrhage and venous thrombosis is higher with lower eGFR and mild-heavy albuminuria. Thus, eGFR and degree of albuminuria may help prognosticate kidney transplant recipients long-term.
Managing High Cardiovascular Risk Patients on Kidney Transplant Waiting List: Costs and Outcome

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Background: High cardiovascular risk patients on the kidney transplant waiting list undergo multiple cardiovascular investigations to ensure fitness for transplant surgery, yet suffering from adverse events. The ideal protocol for managing these patients is unknown. We investigated the benefits of cardorenal multidisciplinary meetings in managing these patients.

Methods: We analysed data from 126 patients discussed between September 1/10/14 and 30/9/17 in biannual multidisciplinary team (MDT) meetings as per protocol, followed up until 11/05/19. We analysed the results of post-MDT cardiac testing and outcomes, including CV events, mortality, and transplantation status. The cost of post MDT cardiac testing was estimated from NHS best practice tariffs.

Results: Clinical characteristics of 126 patients were: age (median 62 years, Inter-quartile range [IQR] 57-67), sex (male 60%), Diabetes Mellitus (58%), Smoker (41%), Hypertension (96%), cholesterol (median 3.8 mmol/L, IQR 3.1-4.8), and PTH (median 33 ng/L, IQR 16-67). The patients were followed-up for a median of 970 days (IQR 584-1334). During the follow up, 44 patients were transplanted. 42 patients had adverse outcomes: 13 patients died, 14 achieved ACS, 5 suffered stroke, 1 suffered TIA, 13 underwent PCI, 7 suffered myocardial infarction, 6 underwent CABG. Diabetic patients were more likely suffer from adverse events (log-rank test p=0.007). Patients with positive stress echocardiogram had worse event rates, but the difference was not statistically significant (log-rank test p = 0.085). There was no difference comparing the group with or without events with respect to age, gender, smoking, hypertension, cholesterol, PTH, phosphate or ferritin levels. The costs of post MDT cardiac tests were as follows: 62 stress echo £1500, 32 Coronary Angiograms £80632, 13 PCIs £53325, and 5 CABG £38350, and total cost = £193897. The approximate cost per patient is £1538, which is approximately £600 per patient per year.

Conclusions: The biannual cardorenal MDT maintained 126 high risk patients on the kidney transplant waitlist for 2.7 years with successful transplants in 35%, adverse events in 33%, and mortality in 13%. A cardio-renal MDT approach for high CV risk patients can ensure successful transplantation one-third patients in 2.7 years with acceptable cost of cardiac testing despite adverse outcomes.

Prevalence of Pulmonary Hypertension in Patients Listed Active for Kidney Transplantation

Sam Kan,1 Christin Iroegbu, Sami Alasfar, Fizza F. Naqvi, Daniel C. Brennan. Nephrology, Johns Hopkins University Hospital, Baltimore, MD.

Background: Pulmonary hypertension (PH) is variably defined, with estimated prevalence in CKD and ESRD of 9% and 19%, respectively. PH at the time of kidney transplantation (KTx) can portend a lower graft survival and the prevalence in wait-listed patients is unknown. We sought to ascertain the prevalence of PH in patients listed active for KTx and characterize based on demographics, comorbidities and ECHO characteristics at our center

Methods: A chart review of EPIC EMR was conducted by assessing problem lists, clinical evaluations and ECHO results for patients listed active for KTx at our institution from 2014-2019. We recorded basic demographics, ESRD cause, type of dialysis access, vintage and modality, listing duration, associated comorbidities and comprehensive ECHO measurements. PH was defined as RSV=P<35 mm Hg on ECHO

Results: Of 634 patients listed active during this period, 104(17%) patients had ECHO evidence of PH. Demographics and ECHO data are shown in Table 1. Mean age of patients was 57 years, with 61% male, 59% African-American and mean BMI of 29.1. Diabetes was the most prevalent cause of ESRD (38%),75% were on HD and 70% had an AVF as dialysis access. Median dialysis vintage was 36 months and listing duration was 20 months; 25% had a history of obstructive sleep apnea (OSA) and 30% had coronary artery disease. The mean RVS was 44.7 mm Hg (SD 8.7, range 35-83), 25% of patients with evidence of PH on ECHO were formally reviewed by a cardiologist, only 3 of whom had PH diagnosed and classified as per WHO criteria. Other ECHO findings showed 57% had HFrEF and 22% had valve abnormalities (moderate-severe)

Conclusions: This is the one of the largest studies to elucidate prevalence, clinical and ECHO characteristics in patients with PH listed active for KTx. PH appears to be under-addressed and efforts should be made to ascertain its cause and direct intervention(e.g. ultrafiltration, improving lung disease, and pulmonary vasculature vasodilators). Future studies could assess the effect of interventions on post KTx outcomes, particularly in groups stratified by PH severity.

Table 1. Demographics and Echocardiogram Characteristics in Patients with PH Listed Active for KTXs

<table>
<thead>
<tr>
<th>Age, mean (SD)</th>
<th>57.3 (15.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>60.0%</td>
</tr>
<tr>
<td>Race</td>
<td>African American, n (%)</td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td>CKD, n (%)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>15 (12.5)</td>
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<tr>
<td>RVSP, mean (SD)</td>
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<td>PHA, n (%)</td>
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<td>PHT, n (%)</td>
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<td>BMI, mean (SD)</td>
<td>29.1 (5.9)</td>
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<tr>
<td>Sex, n (%)</td>
<td>Male, 60%</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>58%</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>41%</td>
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</table>

Table 2. Clinical characteristics in Patients with PH Listed Active for KTXs

<table>
<thead>
<tr>
<th>Age, mean (SD)</th>
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<tr>
<td>Smoker, n (%)</td>
<td>41%</td>
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</table>

Exercise Stress Electrocardiogram for Pretransplant Cardiac Evaluation: A Costly but Generally Useless Effort

Bruno Watschinger, Stefan Scherr, Elias L. Meyer, Katharina Hohenstein-Schefbener. Medical University of Vienna, Vienna, Austria.

Background: There is an ongoing debate on the informative values of cardiac evaluation tests in renal transplant candidates. Exercise stress electrocardiogram (ES-ECG) is advocated and widely used as a non-invasive test to rule out significant coronary artery disease before renal transplantation. The precondition of a test sufficient for interpretation is the achievement of an age adjusted maximal work capacity. We were interested in the fundamental question, whether the test yields meaningful results in transplant candidates at all and how achieved exercise capacities compare to healthy individuals.

Methods: 1319 dialysis patients transplanted at our institution (between 29/02/2000 and 30/09/2017) 453 (mean age 51.2+/=12.6 yrs) underwent cycle-ergometer ES-ECG testing during their pre-transplant work-up. 137 kidney donors (mean age 50.4+/= 9.8 yrs), who were also evaluated by ES-ECG served as control group. We evaluated two endpoints related to the tests meaningfulness and sufficiency: 1) whether study subjects reached maximal work capacity (according to exercise resistance level, measured in Watts or expected heart rate (HR) reached) and 2) whether patients had sufficiently diagnostic test results (i.e. achievement of the maximal work capacity (Watt) or the expected HR or experienced symptoms at lower work intensities. In order to assess test result sufficiency of transplant candidates and kidney donors, absolute and relative frequencies plus 95% CIs for both endpoints were computed and compared by a two-sided two proportion z-Test.

Results: see Table

Conclusions: While maximum exercise capacity (measured in Watt) was achieved by 82 % of healthy kidney donors only a minority of dialysis patients was fit enough to adequately perform during ES-ECC. Consequently meaningful results during ES-ECC were observed in only 37 % of dialysis patients, making Exercise stress electrocardiogram a generally useless, but with regard to time and resources costly effort in the cardiac evaluation of renal transplant candidates.

Table 3. Demographics and Echocardiogram Characteristics in Patients with PH Listed Active for KTXs

<table>
<thead>
<tr>
<th>Age, mean (SD)</th>
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<td>58%</td>
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<td>Smoker, n (%)</td>
<td>41%</td>
</tr>
</tbody>
</table>

* P-values are based on the two-sided two proportion z-Test
Embolization of Polycystic Kidneys as an Alternative to Nephrectomy Before Kidney Transplant

Enric Broseta,1 Francisco Gómez-Palomo,1 Saturnino Luján,1 José Martínez-Rodrigo,2 Daniel Perez-Enguix,2 Raul Garcia-Marcos,2 Jordi Espi,2 Francisco Boronat.1 Kidney Transplant Unit, La Fe University Hospital, Valencia, Spain; 2Interventional Radiology Unit, University Hospital, Valencia, Spain.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is responsible for progressive end-stage renal disease. In case of a massive enlargement of polycystic kidney, renal transplantation surgery may be hindered due to the limited pelvic space. In such cases a radical nephrectomy prior to renal transplantation is warranted. Recently, transcatheter arterial embolization (TAE) has been described as an alternative to nephrectomy. We prospectively evaluated the safety and efficacy on long-term kidney volume reduction of TAE procedures in a group or patients with ADPKD before renal transplantation.

Methods: Between January 2016 and December 2018, 16 patients with end-stage renal disease associated to massive ADPKD were prospectively recruited. Informed consent was obtained from all participants. All procedures were carried out according to the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration. All TAE were performed under local anesthesia and sedation and using cyanoacrylate as embolic agent. A previous CT scan and further CT at 6 and 12 months after TAE were performed. The variables collected were: age, gender, size, renal volume measured by volumetry before and after TAE and score on the visual analog scale (VAS) for pain and complications. A descriptive statistical analysis was made.

Results: A total of 16 patients (9 men and 7 women) were included. The average age was 52.38 (± 9.19) years. The average hospital stay was 3.71 (± 1.32) days. 11 patients presented with mild complications (Clavien-Dindo I). The average score on the VAS scale was 3.38 (± 2.46) points. Only one patient presented a partial embolization of the renal artery, which was resolved by a new TAE with cyanoacrylate and a coil. Before embolization average kidney volume was 2509.08 ± 196.47 cc. Six months later volume was 1303.71 ± 836.2 cc. 6 months after 1089.41 ± 684.9 cc. Within the first 6 months a reduction of 48.05% in renal volume was observed. Of these patients, 9 (56.25%) had a reduction of 48.05% in renal volume.

Conclusions: Our results indicate that TAE is a safe and effective alternative to nephrectomy before renal transplantation in patients with ADPKD.

Liver Biopsy Does Not Change Transplant Candidacy Decisions for Hepatitis B Virus-Positive Living-Donor Kidney Transplant Recipients

Jung a Yoon,1 Keun-hoi Park,2 Hyoang Kim,3 Soon Bae Kim,2 Su-Kil Park,2 Chung Hee Back.1 Nephrology, Asan Medical Center, Seoul, Republic of Korea; 2Asan Medical Center, Seoul, Republic of Korea; 3Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.

Background: Hepatitis B virus (HBV) infection in kidney transplantation (KT) recipients is associated with increased overall mortality, graft loss, and progression of liver disease after KT. Liver biopsy is the gold standard for hepatic diagnosis, but it is an invasive and painful procedure. This study evaluated the necessity of liver biopsy in the decision concerning transplant candidacy among HBV-positive living-donor KT recipients.

Methods: This single-center retrospective study reviewed 3,532 patients who underwent KT from February 1997 to March 2015. Outcomes were analyzed for 144 hepatitis B surface antigen (HBsAg)-positive patients with end-stage renal disease who underwent liver biopsy. To compare clinical characteristics, we divided the patients into two groups according to the degree of fibrosis based on META VIR score. Pathologic findings without fibrosis (F0) were found in 65 (49.6%) cases, and 79 (50.4%) patients were included in the fibrosis group (fibrosis score F1 to F4).

Results: There was no significant difference in age, sex, mode of dialysis before KT, proportion of deceased-donor KT, aspartic acid transaminase levels, total bilirubin, albumin levels, and prothrombin time between non-fibrosis patients and fibrosis patients. The Child–Pugh scores were similar between patients with or without fibrosis (p = 0.155). There was no liver failure after KT in non-fibrosis patients, and five (6.3%) fibrosis patients progressed to liver failure (p = 0.064). Hepatocellular carcinoma was diagnosed in 2 (13.1%) non-fibrosis patients and 6 (7.6%) fibrosis patients (p = 0.294). Biopsy-confirmed acute rejection occurred in 12 (18.5%) non-fibrosis patients and 22 (27.8%) fibrosis patients (p = 0.187). The 5-year graft survival rate was 96.9% in non-fibrosis patients and 94.6% in fibrosis patients. There were no significant differences in graft and patient survival between patients with or without fibrosis (p = 0.381 and p = 0.113, respectively).

Conclusions: The graft and patient survival were not affected by fibrosis detected by pre-KT liver biopsy. Additionally, fibrosis status did not significantly affect liver-related morbidity among HBsAg-positive recipients. In the new antiviral era, liver biopsy findings might not be helpful for guiding the management of HBsAg-positive KT candidates.
TH-PO1142
Non-Candidacy for Kidney Transplant: An Experience from Rural Eastern North Carolina
Debargha Basu,1 Geetha Samuel,1 Hsiao L. Lai,1 Samuel Dadzie.2 1East Carolina University, Greenville, NC; 2ECU Nephrology & Hypertension, Greenville, NC.

Background: Kidney transplant is the optimal therapy for the end-stage renal disease patients in order to improve the expectancy and quality of life. Recently there are many studies investigating how to improve the referral process to improve the access to kidney transplantation. However, there is not much data looking into the rate and causes disapproval of these referred patients by the transplant program to be activated in the waiting list. Thus it is important to study the disapproved population so that we can identify the barriers and intervene to improve kidney transplant rates.

Methods: The electronic health records of 309 ESRD patients undergoing dialysis by one major dialysis practice, East Carolina University were accessed manually to obtain information about the referral by the nephrologists for a transplant and the decision of the transplant selection committee. Disapproved rate for transplant was calculated by percent, and any disparities in disapproval was measured based on gender and race of the patients. Statistical analysis was conducted with t-test and a p<0.05 was considered significant.

Results: Our preliminary data shows although all ESRD patients were referred for transplant within 1 year of initiation of dialysis, about 63 percent of the referred ESRD patients were initially disapproved for further evaluation for a transplant. 40 percent of these patients were disapproved because of modifiable factors like smoking, alcohol abuse, overweight, not completing age appropriate screening tests. Only 40% of these patients were able to successfully modify the risk factors and were accepted as transplant candidates in following transplant evaluation visits. Interestingly, 83% of the disapproved patients were African-Americans, and 41% were females.

Conclusions: Our reports shows that there are major barriers to transplant in ESRD patients in eastern North Carolina even after patients have been referred early. Majority of the disapproved patients were African-Americans and only less than half of the patients with modifiable risk factors were able to be enlisted for transplant after proper intervention. More quality improvement endeavors are required to reduce the disparity in race and to support ESRD patients to overcome modifiable barriers to improve transplant rates in this population.

TH-PO1144
Utilizing the Estimated Post-Transplant Survival Score (EPTS) to Assess Dialysis Facility Referral for Pre-Transplant Evaluation
Antonia Harford, S. Payne, Huan Jiang, Ronald Sanders, Ambren Gul, Phillip Zager. Dialysis Clinic Inc, Albuquerque, NM.

Background: Although transplant (txp) is the optimal treatment for End Stage Kidney Disease (ESKD), only ~15% of prevalent patients (pts) are waitlisted annually. It is estimated that approximately half of ESKD pts would have a survival advantage from txp. The 4-factor (age, vintage, diabetes, & prior txp) EPTS in conjunction with the Kidney Donor Profile Index maximizes the use of donor kidneys with the highest predicted survival by allocating them to potential recipients with the highest predicted post txp survival. Lower EPTS is associated with higher projected longevity. With the exception of diabetes, the 4 factor EPTS does not include comorbidities. We calculated EPTS for incident ESKD pts cared for in outpatient dialysis facilities operated by a nonprofit provider, to determine if pts with a favorable prognosis were being appropriately referred for evaluation.

Methods: We studied 14,043 hemodialysis (HD) & 2,739 peritoneal dialysis (PD) pts, 18-71 years who started dialysis between 2009-2018 & were followed for 1 year unless transplanted. SAS & R statistical packages were utilized for data analysis.

Results: EPTS distributions in HD & PD pts differed (see figure). The median (IQR) scores were 36 (19-54) & 29 (14-46) in HD & PD pts, respectively. Overall, 47.9% of HD & 71.0% of PD pts were evaluated in the first year. The % pts in the lowest EPTS quintile was higher among PD (36.7%) vs. HD (27.9%) pts. Among pts with the best predicted longevity by EPTS, 41.3% HD vs. 20.9% PD pts were not evaluated in the first year.

Conclusions: Overall, the present referral practices within this nonprofit dialysis provider demonstrate that pts are being actively referred for pre-txp evaluation. Better referral rates & EPTS scores among PD vs. HD pts likely reflect the overall health of those pts selected for home dialysis. EPTS use in conjunction with an incident comorbidity review will allow dialysis facilities to optimize transplant referral practices.

Funding: Commercial Support - Dialysis Clinic, Inc.

TH-PO1143
Longer Distance from Dialysis Facility to Transplant Center Is Associated with Lower Access to Transplantation
Aditya Whelan,1 Kirsten L. Johansen,1 Deborah B. Asey,1 Garrett R. Roll,1 Salpi Sylwah1, Elaine Ku.1 1University of California, San Francisco, CA; 2Hennepin Healthcare, Minneapolis, MN.

Background: The distance between patients’ residence and their kidney transplant center is not associated with access to transplantation. However, distance from the dialysis facility to the transplant center (DFTC distance) may be important for access to transplantation, as dialysis providers closer to the transplant center may maintain better dialysis facility to the transplant center (DFTC distance) may be important for access to transplantation. As the dialysis facility to the transplant center (DFTC distance) may be important for access to transplantation as the dialysis providers closer to the transplant center may maintain better performance of lab tests, that longer DFTC distance would associate with longer time to transplantation.

Methods: The electronic health records of 309 ESRD patients undergoing dialysis by one major dialysis practice, East Carolina University were accessed manually to obtain information about the referral by the nephrologists for a transplant and the decision of the transplant selection committee. Disapproved rate for transplant was calculated by percent, and any disparities in disapproval was measured based on gender and race of the patients. Statistical analysis was conducted with t-test and a p<0.05 was considered significant.

Results: Our preliminary data shows although all ESRD patients were referred for transplant within 1 year of initiation of dialysis, about 63 percent of the referred ESRD patients were initially disapproved for further evaluation for a transplant. 40 percent of these patients were disapproved because of modifiable factors like smoking, alcohol abuse, overweight, not completing age appropriate screening tests. Only 40% of these patients were able to successfully modify the risk factors and were accepted as transplant candidates in following transplant evaluation visits. Interestingly, 83% of the disapproved patients were African-Americans, and 41% were females.

Conclusions: Our reports shows that there are major barriers to transplant in ESRD patients in eastern North Carolina even after patients have been referred early. Majority of the disapproved patients were African-Americans and only less than half of the patients with modifiable risk factors were able to be enlisted for transplant after proper intervention. More quality improvement endeavors are required to reduce the disparity in race and to support ESRD patients to overcome modifiable barriers to improve transplant rates in this population.

TH-PO1145
Accessibility and Graft Outcome According to Economic Inequality in South Korea: A Widening Gap After Expansion of Insurance Coverage
Sehoon Yon Su,1 S. Chang,1 S. Chong,1 H. Kang,1 S. Lee,1 M. Kim,1 J. Yoon,1 J. Joo,1 Yoon,2 Joo Su Kim,1 Hajeong Lee.1 Seoul National University Hospital, Seoul, Republic of Korea.

Background: Disparity in accessibility to and prognosis of kidney transplantation according to wealth inequality has been an important issue.

Methods: We performed a nationwide, population-based cohort study using the national renal registry database of Korea in which nationwide health insurance is provided. End-stage renal disease (ESRD) patients from 2007 to 2015 were included. As their wealth status was identifiable annually, the financial states were collected and stratified into five subgroups in each year. Time-trends of incidence proportion of kidney transplantation among ESRD patients in each year was initially assessed. Risk of graft failure was analyzed as prognostic outcome within the transplant recipients.

Results: Significant disparity in kidney transplantation accessibility was present and it was further widening, particularly from the year 2009 in which the national health insurance service started to cover desensitized kidney transplantation. Desensitized or preemptive transplantation was less common in the poorest group who were more frequently receiving transplantation after 5 years of dialysis in the recent periods. The prognosis of kidney transplantation was significantly worse in the poorer people, and this disparity also worsened during the study period.

Conclusions: Prominent disparity regarding accessibility to and prognosis of kidney transplantation presented in Korea according to wealth inequality and was further worsening. Worsening pressure of donor shortage was less severe in the richer people who were preferentially benefited from the recent expansion of donor pool.
It's Now or Never: A Retrospective Audit of Patients Suspended from the Deceased Donor Transplant List

**Background:** The primary purpose was to evaluate the outcomes of patients suspended from the deceased donor renal transplantation list in Northern Ireland. A three year follow-up period was used from October 2015 to December 2018. The primary outcomes measures were to assess the proportion of patients who were alive and had been transplanted by December 2018. Secondary outcomes were to measure the duration patients were suspended, the reasons for this and to examine the relationship between duration and reason for suspension and likelihood of transplantation.

**Methods:** A list of patients suspended from the deceased donor transplant list on 28th October 2015 was obtained from the regional transplant centre in Belfast City Hospital. Regional medical databases were used to extract data on the date of initial listing on the active list, dates of suspensions, reasons for suspensions and outcomes. The end of follow-up period was 10th December 2018.

**Results:** 56 patients were identified on the initial deceased donor renal transplant list. 41 patients (73%) were alive at the end of follow-up, 14 (25%) were deceased and 1 (2%) unknown (moved out of region). 30 patients (53%) had received a renal transplant, 25 patients (45%) had not, with 1 (2%) unknown outcome. The three most common causes for suspension were: the patient was medically unfit to undergo transplant surgery, the patient was awaiting a specialist opinion or investigation and suspension on patient request. Mean time suspended was 645 days and from original listing to transplantation was 807 days. In patients suspended for under one year, 11 of 14 patients were transplanted (79%), however patients suspended for over one year, only 13 of 34 patients were transplanted (38%). Patients suspended as they were medically unfit had the lowest rate of transplantation (6/20). All patients suspended on patient request, awaiting radiological investigation or were transplanted (12 patients).

**Conclusions:** In a three year follow-up period, most patients who had been suspended in October 2015 were alive and had undergone renal transplantation. The fitness of recipients was the most common reason for suspension from the list and is associated with poorer outcomes. Patients suspended for over one year had a significantly lower rate of transplantation. Regular multi-disciplinary review is required to try to minimise the duration of suspensions.
search results for identifying transplant centers that treat patients like them. We used this feedback to develop a new website.

**Results:** A website based decision aid informed subjects about transplant center’s use of high KDPI organs and PHS increased risk organs. It also informed subjects about transplant centers that perform transplants in candidates with age over 70 and other comorbidities such as high BMI. [figure1] [figure2]

**Conclusions:** Patient-specific information using SRTR data can be provided to patients using an interactive web-based decision tool.

**Funding:** Other U.S. Government Support
after multivariate adjustment. DCD recipients demonstrated a higher risk of delayed graft function (adjusted OR: 3.2; 95% CI: 2.1 – 4.7; p < 0.001).

**Conclusions:** Although DCD recipients are at higher risk of delayed graft function, we found no difference in 5-year patient or graft survival between DCD and matched non-DCD recipients.

### Demographic and baseline characteristics of donors and recipients

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<td>15.4 (4.6)</td>
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### TH-PO1152

**Use of Expanded Criteria Donors for Pediatric Kidney Transplantation in the United States**

Sarah J. Kizilbash, Scott T. McEwen, Michael D. Evans, Blanche M. Chavers.

University of Minnesota, Minneapolis, MN.

**Background:** The use of marginal kidneys for transplantation has increased in the recent years to expand the deceased donor pool. Transplant outcomes associated with the use of expanded criteria donors (ECD) in children are unknown.

**Methods:** We used the Scientific Registry of Transplant Recipients to identify all pediatric (<18 years at transplant) deceased donor kidney transplants that were performed in the US using ECD (donors older than 60 years or older than 50 years with comorbidities) between 1987-2017.

**Results:** Our final cohort included 96 ECD and 375 non-ECD recipients. The demographic and baseline characteristics of donors and recipients are presented in table 1. ECD donors were older (58.4 vs. 25.1 years; p < 0.001), and less likely to be males (33.3 vs. 64.2%; p=0.001). Compared with non-ECD recipients, ECD recipients were at significantly higher risk of delayed graft function (aOR: 3.2; 95% CI: 1.8 5.6; p < 0.001), graft failure (aHR: 1.6; 95% CI: 1.2 2.2; p < 0.01) and mortality (aHR: 1.6; 95% CI: 1.02–3.3; p < 0.01). Five-year acute rejection free survival tended to be lower in ECD vs. non-ECD recipients (24.3 vs. 34.4%; p=0.06).

**Conclusions:** ECD kidney transplants in children are associated with higher risks of delayed graft function, graft failure and mortality compared with matched non-ECD recipients. We recommend that kidneys from ECD donors not be considered for pediatric candidates.

### TH-PO1154

**Is Age Just a Number? Outcomes of Older Living Donors for Pediatric Kidney Transplant Recipients**

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**Background:** Living donor kidney transplantation is encouraged in the pediatric population due to better long term allograft survival compared to deceased donor kidney transplantation. Often, pediatric recipients are listed inactive while awaiting evaluation of their living donors. However, there are limited data addressing the impact of age on allograft survival from living donor. We therefore examined the association of living donor-recipient age combinations with allograft survival in children.

**Methods:** Using the Scientific Registry of Transplant Recipients (SRTR), we analyzed graft survival among living donor kidney transplant pediatric recipients from older living donors (≥50 years old) compared to younger donors (<50 years old) between 1993 - 2017. Statistical analysis was performed using STATA and a p value of <0.05 was considered to be significant.

**Results:** The age of the younger living donors was 35.4 ± 7.6 years while that of the older living donors was 53.4 ± 3.6 years (p < 0.005). The pre-operative creatinine for the younger donors was 0.86 ± 0.34 mg/dL vs. 0.89 ± 0.19 mg/dL for the older donors (p=NS). The average post-operative creatinine for the younger donors was 1.2 and 2.8 for the older donors while that of the older donors was 1.34 ± 0.30 mg/dL (p < 0.05). The BMI, presence or absence of hypertension or diabetes, and cigarette use were not significantly different between the two groups. The HL mismatch in younger donors was 2.6 ± 1.1 and 2.8 ± 1.3 in the older donors (p < 0.05). The allograft survival from younger living donors were superior compared to those from older donors (Figure 1) (p < 0.05).

**Conclusions:** Allograft survival from younger living donors is superior at ten years compared to older living donors. In potential pediatric kidney transplant recipients on the wait-list, deceased donor kidney transplant consideration is beneficial if these individuals have older living donors.

### TH-PO1153

**The Pediatric Renal Transplant Experience: Reflecting Through Photographs**

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**Background:** Poor self-management contributes to reduced renal allograft survival during adolescence and young adulthood. For many pediatric patients and their families, the symptoms, complications, and natural history related to ESRD and its treatments are unfamiliar. These unmet information needs lead to uncertainty, interfere with goal setting and result in ineffective self-management. Providing patients with self-reflection tools to help explore the question “Is my experience normal?” may help mitigate these challenges. We present data from a pilot study exploring how photo-elicitation, a qualitative method where images are used to prompt individuals to talk about their personal experiences and values, engages pediatric transplant recipients and their families to generate insight into their experiences living with kidney disease.

**Methods:** Pediatric renal transplant recipients from a single center, along with one family member, were invited to participate. All participants were asked to submit 5 photographs telling their transplant story. No restrictions were placed on what photos individuals could submit. During interviews, participants were asked to tell their story utilizing the photos as prompts. Interviews were recorded, transcribed and analyzed using an inductive grounded theory approach to identify common themes.

**Results:** 13 individuals (7 patients: ages 9 - 19, 6 >1 year post transplant, and 6 parents) completed the study. The photographs generated conversations on four emergent themes: (1) feeling different/isolated from their peers; (2) importance of peer support, including those with and without kidney disease; (3) fear about transitioning to self-care; and (4) the need to create a “normal” child/adolescent experience. Finally, subjects reported significant value in the self-reflection that took place during the photo elicitation process and wanted to share their photos with their clinicians to provide additional insight into their personal experiences.

**Conclusions:** Photo elicitation generated a rich dataset describing a range of pediatric renal transplant experiences, showing potential as a clinical intervention to support patient and family self-reflection. Finally, the process of self-reflection and sharing visual stories with peers and clinicians can result in greater empathy from caregivers and medical professionals, ultimately improving self-management.

**Funding:** NIDDK Support
TH-PO1155

Kidneys from African American Donors Are Associated with Accelerated Podocyte Detachment After Kidney Transplantation
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Background: Kidneys from AA donors have reduced survival compared to kidneys from non- AA donors. Longitudinal histological data to better delineate the relationship of donor race, post-transplant histology and outcomes is lacking. We used urine nephrin segment specific mRNA markers to understand whether kidneys from AA donors have different injury patterns than non-AA donors. We tested the hypothesis that high prevalence of glomerular disease in AA donors would be associated with differences in urine podocyte markers.

Methods: We used a published cohort (Naik AS, et al, NDT, 2018) with linear mixed model with random intercept (pt. level) and slope (time post-transplant) with Urine Podocin mRNA:Urine creatinine ratio (UPod:CR) as the dependent variable. The model was adjusted for age, race, and the change in eGFR by 14 days post donation.

Results: 534 urine samples from 125 recipients were analyzed. 14 recipients received kidneys from AA donors contributing to 59 urine samples. AA donors were younger (34 vs.41,p<0.04). Other characteristics were well balanced. One-year surveillance biopsy revealed no difference in burden of observable glomerular disease between AA and non-AA groups (p=0.21). There was no difference in proteinuria by donor race. Although at time of TP there was no difference in nephrin expression, by 1yr post-TP nephrin expression was significantly down-regulated in AA vs. non-AAs groups. Figure 1 demonstrates factors associated with podocyte detachment.

Conclusions: These data are compatible with AA donors developing podocyte injury and loss that is observable prior to development of proteinuria or glomerular disease on surveillance biopsies. Further studies expanding the current cohort and assessing relationships of accelerated podocyte loss with APOL1 genotype are ongoing.

Funding: NIDDK, Support, Other NIH Support - MNRRC

TH-PO1156

Early Post-Donation Hyperfiltration Is Associated with Accelerated Podocyte Detachment
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Background: Living kidney donation is associated with increased long-term risk of CKD/ESRD post-donation. Diabetes and hypertension are reported to be associated with ESRD. The remaining kidney is rarely biopsied and thus mechanisms behind progression remain unproven. Parallel data from uni-nephrectomized rat models shows podocyte hypertrophic stress, detachment and depletion, progressive proteinuria and FSGS. While proteinuria is common among donors vs. matched non-donors, it is often low grade.

Methods: We used urine podocyte nephrin segment specific mRNA markers expressed per creatinine to understand biology of the remaining kidney early post-donation. Donor urine samples were divided by time of collection. Group 0, before donation; Group 1, 1-2days post donation; Group 2, 10-14days and Group 3, 6-12months post donation. Linear mixed model clustering for patients was used to assess trends across two podocyte specific markers (podocin, nephrin), a distal collecting duct marker (Aqp2) and a marker of innate immunity/proliferotic activity (TGFbeta1) and proteinuria.

Results: 72 donors provided 178 urine samples for the analysis. Figure 1 reveals that proteinuria and podocin, Aqp2 and TGFbeta1 mRNAs were increased immediately post donation (referenced to Group 0) but normalized by 2weeks post-donation. Nephrin remained significantly increased over the first year.

Conclusions: All markers showed evidence for hypertrophic kidney stress immediately post-TP. Sustained increased urinary nephrin mRNA in living donors after TP may represent hypertrophic adaptation to the single kidney state requiring up-regulation of nephrin to maintain increased filtration slit length. Whether higher level nephrin mRNA expression is related to future risk of progressive kidney disease remains to be tested.

Funding: NIDDK Support

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TH-PO1158

Clinical Significance of AKI and Kidney Donor Profile Index on Clinical Outcomes in Deceased Donor Kidney Transplantation: A Multicenter Cohort Study

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Background: It is important to evaluate the donor quality before allocation in deceased donor kidney transplantation (DDKT). Kidney Donor Profile Index (KDPI) is an effective tool, but the association with acute kidney injury (AKI) is uncertain. The aim of this study was to investigate the clinical significance of AKI and KDPI on clinical outcomes in DDKT.

Methods: Four transplant centers enrolled 657 kidney transplant recipients (KTRs) from 526 deceased donors (DDs). We divided the high KDPI and low KDPI by the median of 65%, and each group was divided into AKI-KT and non-AKI-KT subgroups according to DDs with AKI.

Results: There was no significant difference in the incidence of delayed graft function between high KDPI-KT and low KDPI-KT groups, but AKI-KT subgroup showed significantly higher incidence of delayed graft function compared with non-AKI subgroup in the two groups (P=0.001, P=0.001). There was no significant difference in the incidence of biopsy-proven acute rejection between high KDPI-KT and low KDPI-KT groups regardless of DDs with AKI. Death-censored graft survival rate was significantly lower in the high KDPI-KT group compared with the low KDPI-KT group (P=0.005), but there was no significant difference in the death-censored graft survival rate between AKI-KT and non-AKI-KT subgroups in each group. Only in the high KDPI-KT group, the KT group from DDs with AKI stage 3 was lower in death-censored graft survival rate compared with that from DDs with non-AKI, AKI stage 1, or 2.

Conclusions: KTs from DDs with AKI showed an adverse effect on the allograft outcome, especially from DDs with AKI stage 3 in the high KDPI-KT group. Therefore, close observation and prevention of severe AKI will be required, especially for KTs from DDs with high KDPI.

Figure 1. Death-censored graft survival according to AKI stage in high KDPI group.

TH-PO1159

Kidney Transplantation from Small Pediatric Donors May Be Feasible to Those Who Developed Chronic Refractory Dialysis Hypotension: A Single-Center Experience

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Background: Chronic refractory dialysis hypotension (CRDH) is a serious issue in dialysis patients waiting for transplants. CRDH leads to fatal clinical outcomes and disqualification from kidney transplantation. Kidney transplantation from small pediatric donors to adult patients with lower blood pressure (BP) may be an option. To our knowledge, there has been no report on the benefit of transplantation from pediatric donors to CRDH recipients.

Methods: Ten single-kidney transplantations from five small pediatric donors after cardiac death in our center between August 2016 and April 2018 were analyzed. Half of the recipients were CRDH (group A) and each of them was matched with no-CRDH patient (control, group B) from same deceased pediatric donor. The operation method of vascular anastomosis and ureterocystoneostomy was the same as that of adult donors. Clinical characteristics, post-operative treatment and outcomes were retrieved. Postoperative BP, graft function and size were compared between the two groups. The follow-up time was up to April 2019.

Results: There were no acute rejection, graft loss or death in CRDH patients after kidney transplantation. The postoperative systolic BP in four recipients in group A was above 100mmHg persistently. Their renal function was recovered despite three transient delayed graft function (2 in group A and 1 in group B). There was no significant difference in serum creatinine or graft size (P=0.84, 0.94) after transplantation between two groups.

Conclusions: In conclusion, kidney transplantation from small pediatric donors may be feasible to CRDH patients and their BP may return to normal after transplantation.

TH-PO1160

Donor Source of Kidney Transplantation in New Zealand by Ethnicity: A Longitudinal Cohort Study

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Background: Marked disparity is present in access to kidney transplantation based on ethnicity. We explored whether donor source for kidney transplantation in New Zealand was associated with recipient ethnicity adjusting for socioeconomic and clinical factors.

Methods: We performed a longitudinal cohort study in patients a18 years with ESKD who commenced replacement therapy in New Zealand between 2006-2015, using ANZDATA. Deprivation score and treating centre were obtained by data linkage with the National Health Index. Primary outcomes were time to receiving first transplant (live and deceased donor) and proportion who received a pre-emptive kidney transplant. Poisson regression was performed for pre-emptive and competing risks regression for live and deceased donor transplantation (accounting for competing risks of death and alternate donor source) with 95% confidence intervals. Estimates were adjusted age, sex, smoking, deprivation, BMI, late referral, treating centre, diabetes, and coronary artery disease.

Results: Among the 5106 participants, 822 received a kidney only transplant (479 living and 343 deceased donor). Māori and Pacific patients were younger, more frequently had diabetes and referred late to specialist care, and lived in more socioeconomically deprived areas than Europeans. In European patients, 65% received a live donor kidney transplant, while the proportion was smaller for Asian (44%), Māori (44%), and Pacific (39%) patient groups. Compared to European participants, those who identified as Māori, Pacific and Asian were markedly less likely to receive a pre-emptive and live donor kidney transplant even after adjustment for socioeconomic factors, comorbidity, and referral practices (Table 1). The difference in transplantation rates between participant groups was less marked for deceased donor kidney transplantation and was not evident in Māori and Asian groups after adjustment.

Conclusions: Transplantation rates for pre-emptive and live donor transplantation but not deceased donor transplantation vary with ethnicity, socioeconomic factors and late referral to specialist services within New Zealand, after adjustment for comorbidity.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Association of Perceived Information and Knowledge with Pursuit of Live Donor Kidney Transplants (LDKTs) Among African Americans

Ashley N. Cabacungan, Matthew J. Ellis, Debra Sudan, Cheri Changu, A. Davenport, Patti Ephraim, Tara S. Strigo, Iris Pouli, Aviel N. Alkon, Dinushika Mohottige, Nicole DePasquale, Sarah B. Peskoe, Jane F. Pendergast, Clarissa J. Diamantidis, Jennifer St. Clair Russell, L. Ebony Boulware, Duke University School of Medicine, Durham, NC; National Kidney Foundation, Washington, DC; Duke University, Durham, NC; Johns Hopkins University, Baltimore, MD.

Background: It is unknown whether African Americans’ (AA) pursuit of LDKT is related to their perceived information or knowledge about LDKT.

Methods: We conducted a cross-sectional analysis among AA kidney transplant candidates enrolled in the Talking about Living Kidney Donation Support (TALKS) trial. We quantified associations between participants’ perceived sufficiency of LDKT information and knowledge with pursuit of LDKT or the occurrence of live donor inquiries. We asked: “How well informed do you feel you are about live donor kidney transplantation?” and “How much knowledge do you feel you have now about live donor kidney transplant?” We characterized pursuit of LDKT by self-reported behaviors reflecting low (no family/friends LDKT discussion, no donor), moderate (family/friends LDKT discussion, no donor) or high (family/friends LDKT discussion and potential donor identified) activation toward LDKT. In adjusted logistic regression models, we quantified the association between perceived sufficiency of LDKT information and knowledge with LDKT activation or live donor inquiries.

Results: Among 300 AA, the mean age was 52 (SD 11), 56% were male, 61% had a greater than high school education, and 50% had below 9th grade-level health literacy. The median time on the waitlist was 292 (IQR 81, 697) days. A total of 117 (39%) felt “very” or “extremely” well informed about LDKT and 114 (38%) reported “a great deal” of LDKT knowledge (3.05 [1.24, 8.08]). Those who received (vs. did not) LDKT information from health professionals had 4-fold higher odds of high LDKT knowledge (adjusted OR [95% CI]: 4.01: [1.49, 12.18], while those who received (vs. did not) LDKT information or their sharing of LDKT knowledge was associated with access to LDKT. Yet, little is known about factors associated with LDKT knowledge or receipt of information about LDKT.

Conclusions: Fewer than half of African Americans on the deceased donor kidney waiting list felt well informed or very knowledgeable about LDKT. Efforts to increase African American potential recipients’ perceived LDKT information and knowledge could enhance their access to LDKT.

Funding: NIDDK Support

Use of Opioids and Nonsteroidal Anti-Inflammatory Drugs in Living Kidney Donors: Clinical Correlates and Early Outcomes

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Background: Limited data are available on pain medication use in living kidney donors (LKD). While there is growing national concern related to opioids, there is also concern over non-steroidal anti-inflammatory (NSAID) use due to potential nephrotoxicity.

Methods: We examined a novel database wherein national LKD registry identifiers were linked to records from a large U.S. pharmaceutical claims warehouse (2007 to 2017 fills). We selected LKD with 1 year of postdonation pharmaceutical fill records. Associations of baseline demographic and clinical factors with opioid and NSAID use (adjusted odds ratio, 95% LCL aHR 95% UCL) were quantified by multivariable logistic regression.

Results: Among 23,564 eligible LKD, opioid use declined postdonation: 36.6%, mos. >0-0.5; 14.7%, mos. 0.6-6; 12.6%, mos. 7-12. NSAID use was uncommon, but increased: 0.5%, 0.5; 14.7%, mos. 0.6-6; 12.6%, mos. 7-12. NSAID use was uncommon, but increased: 0.5%, 0.5; 14.7%, mos. 0.6-6; 12.6%, mos. 7-12. NSAID use was uncommon, but increased: 0.5%.

Conclusions: Improved provision of LDKT information to patients with advanced CKD and involvement of family members or friends could aid efforts to improve LDKT rates.

Funding: NIDDK Support, Other U.S. Government Support
Living Kidney Donors with Metabolic Risk Increased in South Korea

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Background: Living donor kidney transplantation is the best treatment option with regard to patients’ prognosis for end-stage renal disease(ESRD) if only donor safety is secured. Hence, it is worthwhile to review of epidemiology of living kidney donors nationwide and living kidney donors with higher risk including metabolic syndrome.

Methods: Living kidney donors in 4 national university hospital of South Korea were enrolled. Demographic and laboratory data were collected. Hyperuricemia was defined as uric acid greater than 7 mg/dL. Underweight, overweight and obesity were defined as body mass index (BMI) <18.5, 25-29.9 and ≥30 kg/m², respectively. The era of the transplant was classified into 4 groups with quartiles of the number of donors as follows: 1982-2001, 2002-2009, 2010-2014, and 2015-2019.

Results: A total of 2,002 living kidney donors were enrolled and the number of living kidney transplants increased rapidly from 109 in the 1980s to 987 in the 2010s. Mean age were 42.6±11.5 years and 45.9± years were male. The most common donor-recipient relationship was parent-child (39.5%), followed by sibling (30.6%), and husband-wife (21.5%). The proportion of donors with IGT, dyslipidemia, and overweight/obesity tended to increase across the era of transplant from 2015-2019. Mean estimated glomerular filtration rate(eGFR) was 90.9±20.5 and 98.8±16.3 mL/min/1.73m² by MDRD and CKD-EPI equation, respectively. The baseline eGFR were increased in course of time. Patients with diabetes and imputed glucose tolerance (IGT) were 90.25% and 37 (1.85%), respectively. The proportion of donors with IGT, dyslipidemia, and overweight/obesity tended to increase over time.

Conclusions: The results related to metabolic syndrome generally tended to increase in kidney donor over time, and living kidney transplants between couples increased. Whether the donors’ metabolic syndrome affect post-donation morbidity or not should be further evaluated.

Funding: Government Support - Non-U.S.

Financial Strain and Pursuit of Live Donor Kidney Transplants Among African Americans on the Kidney Transplant Waiting List

Ashley N. Cabacungan,1 Matthew J. Ellis,1 Debra Sudan,4 Clementina A. Davenport,1 Patti Ephraim,1 Tara S. Strigo,1 Iris Pounds,1 Avil N. Alkon,1 Dinushika Mohottige,1 Nicole DePasquale,1 Sarah B. Pescoe,1 Jane F. Pendergast,1 Clarissa J. Diamantidis,1 Jennifer St. Clair Russell,1 L. Ebony Boulware.1 Duke University, Durham, NC; 2Duke University School of Medicine, Durham, NC; 3National Kidney Foundation, Washington, DC; 4Duke University Medical Center, Durham, NC; 5Johns Hopkins University, Baltimore, MD.

Background: The extent to which financial strain may influence African American’s (AA) pursuit of LDKT is unclear.

Methods: We studied cross-sectional associations between financial strain and LDKT activation or live donor inquiries to the transplant center among AAs on the kidney transplant wait-list. We measured financial strain using the InCharge Financial Distress/Frugal Well-being 8-item Scale (IFDFWS—responses ranging from 1 (high) to 10 (low/no distress). We measured LDKT activation as participants’ self-reported behaviors reflecting low (no family/friends LDKT discussion, no donor identified), moderate (family/friends LDKT discussion and donor identified) or high (family/friends LDKT discussion and donor identified) activation. In logistic regression models, we quantified the association between financial strain and LDKT activation or inquiries.

Results: Among 300 participants, the median time on the wait list was 292 (IQR 81.7, 708) days. The mean age was 52 (SD 11), 56% were male, 50% were retired due to disability, 43% had household income < $40,000 and 25% were near or below poverty. The mean (SD) IFDFWS score was 6.2 (2), indicating moderate financial distress. Subscale mean (SD) scores were 4.7 (2.8) for current and 4.7 (2.8) general financial stress; 4.5 (2.9) for financial concern; 5.4 (2.7) satisfaction and 5.6 (2.6) comfort, 6 (3.2) for confidence to afford recreational activities. Overall financial distress was not associated with LDKT activation (OR: 1.04, 95% CI 0.91, 1.19) or donor inquiries (OR: 1.08, 95% CI 0.95, 1.22). However, participants with greater (versus less) confidence in obtaining emergency funds had statistically significantly greater odds of having a donor inquiry (OR: 1.14, 95% CI 1.04, 1.24).

Conclusions: Financial confidence may be associated with access to LDKT, including the receipt of live donor inquiries. The impact of financial strain on pursuit of LDKT among African American transplant candidates requires further study.

Funding: NIDDK Support
Conclusions: In the present analysis, patients with higher proteinuria were more likely to have persistent proteinuria and a higher risk of developing CKD. This result is consistent with previous studies, indicating that proteinuria is an important risk factor for the progression of CKD.

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TH-POI172
Are We There Yet? Meeting the Goal of Improved Utility Under the New Kidney Allocation System
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Background: The Kidney Allocation System (KAS) was designed to improve limitations of the previous deceased donor kidney transplant (DDKT) allocation algorithm in the United States. A key feature in the KAS is a scoring system that matches longest recipient life expectancy with longest donor graft survival expectancy, trading fairness for utility by prioritizing the best kidneys to the healthiest candidates. This study compared outcomes between patients aged 50 years and younger (<50) versus patients aged 51 and older (≥50), the patient groups specifically impacted by the longevity matching scores.

Methods: This study used patient-level data from the Scientific Registry of Transplant Recipients. Relative risk of DDKT and waitlist mortality or removal from the waitlist due to deteriorating health was estimated in the pre- versus post-KAS eras with logistic regression models including fixed effects for organ supply and several patient clinical and demographic characteristics. The post-KAS era was divided into four distinct periods (0-6 months, 6-12 months, 12-24 months, 24-36 months) to assess trends over time. Survival benefit of transplant compared to remaining on the waitlist by KAS era and age group was estimated with a Cox proportional hazard regression model.

Results: This study included 239,265 incident and prevalent adult candidates on the kidney transplant waitlist between December 4, 2011 and December 3, 2017. Relative risk of DDKT for younger candidates versus older candidates was greatest in the first six months post-KAS compared to the pre-KAS era (1.17 95% CI 1.11-1.23). Candidates aged ≥50 years and >30 years had 1.15 (95% CI 1.06-1.30) and 1.19 (95% CI 1.07-1.30) times the risk of mortality on the waitlist or removal due to deteriorating condition in the third year post-KAS compared to the pre-KAS era, respectively. There was no difference in relative risk of mortality within age group in the first two years post KAS compared to the pre-KAS era. The survival benefit of DDKT compared to remaining on the waitlist was greater in the post-KAS era compared to the pre-KAS era among both age groups.

Conclusions: This study suggests the KAS is at least partly meeting the goal of improved utility in DDKT in the first years of implementation; however, inefficiencies in DDKT exist. Continual evaluation is needed to assess the sustained benefit of the KAS.

Funding: Other U.S. Government Support

TH-POI173
Contraindications to Transplant and Home Dialysis: Variation in Nephrologist Practices
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Background: There is notable variation in ESRD patients’ transplant waitlisting rates and home dialysis use across care providers. This variation persists after controlling for differences in patients’ clinical need and community factors. It is unclear how much variation there is in nephrologists’ decisions about whether a given patient is eligible for transplant or home dialysis.

Methods: We are administering a new and innovative survey—the Transplant and Home Dialysis Recommendations Survey of Nephrologists, or THRoNe—in a nationally representative sample of n=120 nephrologists (non-pediatric). The THRoNe, which we have pre-tested and validated rigorously using a modified Delphi approach with 12 representative sample of n=120 nephrologists (non-pediatric). The THRoNe includes 192 questions. An initial analysis of THRoNe data is needed to assess the sustained benefit of the KAS.

Results: This study was completed on August 16, 2018. The survey was completed by 118 of 120 nephrologists (98%). The response rate was 85%.

Conclusions: This study suggests the KAS is at least partly meeting the goal of improved utility in DDKT in the first years of implementation; however, inefficiencies in DDKT exist. Continual evaluation is needed to assess the sustained benefit of the KAS.

Funding: Other U.S. Government Support

TH-POI174
Kinetic Estimated Glomerular Filtration Rate (KeGFR), a New Tool to Predict Delayed Graft Function (DGF)?
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Background: Delayed graft function (DGF) is a common clinical problem in pediatric patients and in deceased donor kidney transplantation. Early prediction of DGF could be beneficial. It could improve the adjustment of nephrotoxic drugs, such as CNI and antibiotics are routinely used as prophylaxis.

Methods: A retrospective study was carried out, from June 2016 to August 2018, which included 145 kidney transplant patients, either living or deceased kidney donor transplantation, in the immediate postoperative period, in a hospital in Western Mexico. Creatinine was measured at the time of reperfusion (hour 0), and 10 and 18 hours after kidney reperfusion. The Kinetic Estimated Glomerular Filtration Rate (KeGFR) was calculated were sCr110 constituted both the baseline creatinine and creatine at first point, and sCr18 was used as creatinine at second point. The primary outcome was DGF, defined as need for dialysis (according to the nephrologist consideration) during the first time of transplantation.

Results: 157 patients, between 17 and 69 years old, received a kidney transplant during that period, 113 males (71.9%) and 44 females (28.02%); in most of the patients (146/92.9%) the etiology of CKD was unknown. 108 patients (68.7%) received a kidney from a related living donor, 32 patients (20.3%) from a non-related living donor, and 17 (10.8%) patients from a deceased donor. 20 patients presented DGF (12.7%), with a mean GFR estimated with creatinine kinetics (KeGFR) of 5.09 ml/min, while 17 patients (89.4%) had present DGF and had a mean KeGFR of 14.9 ml/min, with a statistically significant difference and a p value of 0.000. When establishing a KeGFR threshold value of 7 ml/min, it had a sensitivity of 70% and a specificity of 81% to predict DGF, with an area under the curve of 0.759.

Conclusions: An eGFR was determined using unstable creatinine values. Our goal was to evaluate the KeGFR using serum creatinine values at 10 and 18 hours after reperfusion of the kidney, which is the time the blood samples are routinely taken in our center. When establishing a KeGFR threshold value of 7 ml/min, we could predict DGF with a sensitivity of 70%, a specificity of 81%, and an AUC of 0.759.

TH-POI175
Changes in Kidney Function After Live Donor Nephrectomy
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Background: Better understanding the decline in kidney function after live donor nephrectomy and how this differs by donor characteristics can inform counselling, selection, and follow-up care.

Methods: We conducted a retrospective matched cohort study of living kidney donors in Alberta, Canada between 2002 and 2016 using linked healthcare administrative databases. We matched 604 donors to 2,414 healthy non-donors from the general population based on age, sex, year of cohort entry, urban residence, and estimated glomerular filtration rate (eGFR) before cohort entry (nephrectomy date for donors and randomly assigned date for non-donors). The primary outcome was rate of eGFR change over time (median follow-up 7 years, maximum 15 years).

Results: The median age was 43 years, 64% were women, and the baseline (predonation) eGFR was 100 ml/min/1.73 m2. Overall, from 6 weeks onwards, the eGFR increased by +0.32 ml/min/1.73 m2 per year (95% CI +0.17 to +0.46) in donors and decreased by −0.88 ml/min/1.73 m2 per year (95% CI +0.96 to −0.79) in non-donors (p<0.001). The change in eGFR between 6 weeks to 2 years, 2 to 5 years, and >5 years onwards in donors was +1.05, +0.61, and +0.09 ml/min/1.73 m2 per year, respectively. The change in eGFR over time in donors varied by sex, percent decline in eGFR within the first 6 weeks, and eGFR category at 1 year, but not by age category at donation, predonation hypertension, or predonation eGFR category.

Conclusions: The function in the remaining kidney of a living donor initially increased by +0.32 ml/min/1.73 m2 per year due to hyperfiltration; however, this begins to plateau by 5 years postdonation. In contrast, non-donors experience a more steady decline of 1 ml/min/1.73 m2 per year.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Mean estimated glomerular filtration rate (eGFR) over time in living kidney donors (solid line) and matched, healthy non-donor controls (dotted line).

TH-PO1176
Survival Benefit of HLA-Incompatible Living Donor Kidney Transplantation Compared with Deceased Donor Kidney Transplantation or Dialysis in Korea
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Background: HLA-incompatible (HLAI) living donor (LD) kidney transplantation (KT) is one of efforts to increase KT opportunity for sensitized ESRD patients. Although removing anti-HLA antibodies may be high risk, to find a compatible LD or wait for a deceased donor (DD) may be long. Recently, there are controversies for outcomes of HLAI KT. US data showed better outcomes of HLAI LDKT compared to HLA-compatible (HLAC) DDKT or dialysis, whereas UK data demonstrated that waiting for HLAC DDKT or HLAC LD KT by donor exchange has good outcomes comparable to obtain LD KT. Therefore, we tried to compare outcomes of HLAI LD KT with those of DD KT or dialysis in Korea.

Methods: One hundred eighty-nine patients underwent HLAI LD KT after desensitization that consisted of rituximab, plasmapheresis, and intravenous immunoglobulin between 2002 and 2018 in Seoul National University Hospital and Severance Hospital. Indications of desensitization were positive cytotoxicity cross-match, positive flow-cytometric cross-match, and positive donor-specific antibodies with negative cross-match. We compared outcomes among HLAI LD KT patients, DD KT patients (HLAC-DDKT group, n=930), wait-listed patients who had continued to undergo dialysis (dialysis-only group, n=930), or patients who underwent either dialysis or DD KT (dialysis-or-DDKT group, n=930) using propensity score matching.

Results: In the HLAI LD KT group, patient survival rates were 98% at 5-year and 96% at 7-years post-KT. Patient survival rates at 5- and 7-years in the HLAC-DDKT group were 92%, and 91%, respectively, those in the dialysis-only group were 90%, and 85%, respectively, and those in the dialysis-or-DDKT group were 91%, and 88%, respectively. HLAI LD KT group showed significantly better patient survival rate compared to HLAC-DDKT group, dialysis-only group and dialysis-or-DDKT group. And there was no significant difference in the graft survival rates between HLAI LD KT and HLAC-DDKT group in multivariate analysis, waiting or DD KT was a significant risk factor for mortality (HR, 3.93; 95% CI, 1.44-10.74) independently of old age, diabetes and blood type O.

Conclusions: In conclusion, patients undergoing HLAI LD KT has a survival benefit as compared with patients who were still on the waitlist for HLAC DD KT or received HLAC DD KT in Korea that has longer waiting time for DD KT than Western countries.

TH-PO1177
Low Nephron Numbers and Larger Glomerular Size Are the Predictors of Long-Term Kidney Function in Kidney Donors
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Background: Microstructural findings of larger nephron size and nephrosclerosis on kidney biopsy are predictive of kidney function after donation at short-term follow up. Our hypothesis is that kidney structural findings also predict long-term kidney function after donation.

Methods: We contacted living kidney donors who were at least 5 years post-donation to obtain information on blood pressure and kidney function test results. Microstructural (biopsy) and macrostructural (contrast CT scan) findings of the kidney at the time of donation were assessed as predictors of estimated glomerular filtration rate (eGFR), proteinuria, and hypertension with adjustment for years since donation and baseline clinical characteristics.

Results: Among 1687 donors contacted, 807 (48%) participated a mean 10.5 years after donation. At follow-up, 6.4% had developed an eGFR <45 ml/min/1.73 m², the mean residual eGFR ratio (post-/pre-donation eGFR) was 75%, proteinuria (self-reported) occurred in 5.1%, and new onset hypertension occurred in 19% (119/653). An eGFR <45 ml/min/1.73 m² was predicted by larger glomerular volume per SD (OR=1.48, p=0.01) and low nephron number (below age-specific 5th percentile) (OR=3.40, p=0.01). Residual eGFR ratio was predicted by low nephron number (-6.1%, p=0.004) and cortical volume per BSA (1.3%, p=0.03). Proteinuria was predicted by glomerular volume per SD (OR=1.42, p=0.01). Hypertension was not predicted by any structural finding. Nephrosclerosis (glomerulosclerosis, interstitial fibrosis, or arteriosclerosis) did not predict any outcome.

Conclusions: Lower nephron numbers and large glomeruli appear to be the most important structural determinants of long term kidney dysfunction after donation.

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TH-PO1178
Non-Simultaneous Kidney Exchange Cycles in Resource-Restricted Countries Without Nondirected Donation
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Background: Recent reports suggest that bridge donor renage is rare (1.5%) as part of non-simultaneous kidney exchange chains. In developing countries, surgical space and resources limit the number of simultaneous kidney exchange transplant surgeries.

Methods: The aim of this study was to evaluate the bridge donor renage rate during non-simultaneous kidney exchange cycles in a prospective single center cohort study (n=44). We describe the protocol to prepare donor-recipient pairs for non-simultaneous surgeries designed to reduce the renage rate. We propose using standard criteria deceased donor kidneys in the event of a bridge donor renage to protect vulnerable recipients.

Results: We report 12 successful non-simultaneous kidney exchange cycles resulting in 44 living donor kidney transplants. These cycles involved 16 bridge donors who were trusted to donate after their incompatible recipient was transplanted, placing 15 recipients at risk (two were at risk from two bridge donors), and no donor renaged. We propose that non-simultaneous kidney exchange cycles could increase living donor kidney transplantation, especially for difficult to match sensitized patients (17 of 44), in countries with limited transplantation resources.

Conclusions: Our study confirms that non-simultaneous kidney exchange cycles can be safely performed with careful patient-donor selection and non-anonymous kidney exchange.

TH-PO1179
Glomerular Filtration Rate Measurement by Iohexol Plasma Clearance in an Ethnically Diverse Living Donor Population
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Background: Iohexol is a good agent for measurement of GFR (mGFR) due to its low extrarenal excretion, tubular secretion or reabsorption, and protein binding affinity. We compared mGFR by plasma clearance of iohexol with serum creatinine (sCr) based GFR estimations in our living kidney donor candidates and investigated the association between GFR and donor demographic characteristics.

Methods: All potential living donors with GFR measurement by iohexol plasma clearance at our center between 10/2016 – 4/2019 were included. Linear regression was performed for comparison of mGFR by ethnicity, sex, age, and BMI. Medical records were reviewed for age, BMI, ethnicity, and sCr to calculate GFR by CKD-EPI and MDRD.

Results: Of 407 potential living donors evaluated, 35% were men and the mean age was 42. Racial distribution: 47% Caucasian, 29% Hispanic, 28% Asian, 4% Black. Median mGFR was 102 ml/min/1.73m2. Median mGFR was higher for Hispanics (106) and Asians (108) compared to Caucasians (96) [Figure1]. Women > 50yrs had faster mGFR decline than men the same age. Correlation between mGFR and sCr based GFR showed that CKD-EPI had a closer correlation (slope=0.42, R = 0.27) than MDRD (slope=0.37, R =0.25) [Figure 2]. Compared with Caucasians, Hispanics had higher mGFR than eGFR by CKD-EPI. Both Hispanics and Asians had higher mGFR compared to eGFR by MDRD. 

Conclusions: Hispanic and Asian ethnicities have higher mGFR compared to Caucasians in our potential living donor population, which is an important finding that requires further delineation. CKD-EPI and MDRD eGFR calculations may also underestimate mGFR when used in these ethnicities.
Background: Prioritization of highly sensitized (HS) candidates under the Kidney Allocation System (KAS) and expansion of kidney-paired donation (KPD) have broadened the transplant options available to HS candidates.

Methods: To quantify temporal trends in utilization of these differing transplant modalities, we used national SRTR registry data from 2009-2017 to study 45,759 adult HS (cPRA ≥80%) waitlisted candidates and 19,003 HS transplant recipients. We used competing risks regression to quantify temporal trends in likelihood of deceased donor kidney transplantation (DDKT), KPD, and non-KPD living donor kidney transplantation (LDKT) for HS candidates over time (Era 1: 1/1/2009-12/31/2011; Era 2: 1/1/2012 – 12/31/2013; Era 3: 12/3/2014 – 12/31/2017).

Results: Although the likelihood of DDKT and KPD increased over time for all HS candidates (adjusted subhazard ratio [aSHR] for Era 3 vs. 1 for DDKT: 1.72, 95% CI 1.71-1.72, p<0.001; aSHR for KPD: 1.57, 95% CI 1.57-1.57, p<0.001), the likelihood of LDKT decreased over time (aSHR for Era 3 vs. 1: 0.82, 95% CI 0.82-0.83, p<0.001). However, these changes affected HS recipients differently depending on their cPRA. For example, an increased proportion of cPRA 80-99% recipients were transplanted with DDKT over time (aSHR for Era 3 vs. 1: 0.82, 95% CI 0.82-0.83, p<0.001), whereas DDKT was used for fewer recipients (80.1% in Era 3 vs. 86.2% in Era 1) and LDKT was used for more recipients (1.9% in Era 3 vs. 30.9% in Era 1 for cPRA 99.9%+, p<0.001), at the expense of fewer recipients being transplanted with either DDKT (96.2% in Era 3 vs. 59.1% in Era 1 for cPRA 99.9%+) or KPD (2.0% in Era 3 vs. 3.8% in Era 1, p<0.001), whereas DDKT was used for more recipients (80.1% in Era 3 vs. 86.2% in Era 1) and LDKT was used for fewer recipients (1.9% in Era 3 vs. 30.9% in Era 1 for cPRA 99.9%+) or KPD (2.0% in Era 3 vs. 10.0% in Era 1 for cPRA 99.9%+). Conclusion: HS candidates had an increased likelihood of KPD and LDKT over time, although the effect of this varied across cPRA. In the KAS era, the most HS candidates (cPRA 98%-99%) have seen significant declines in use of KPD and LDKT.

Funding: NIDDK Support

Table 1. Event rates and hazard ratios

Table 2. Changes in the transplant modalities used for HS recipients by cPRA categories by use of transplantantes.
**FR-PO001**

**Significant Numbers of Hospitalized Patients with AKI Are Seen in Primary Care Before Admission, Representing Opportunities for Early Intervention**

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**Background:** Acute kidney injury (AKI) confers increased morbidity and mortality and e-errals are evenly distributed between hospital and community settings (Holmes et al, CJASN, 2016). Primary care physicians (PCPs) are well-placed to enact sick-care interface is required to effectively manage these patients (Thomson & Tomlinson, CJASN, 2019 and Clark et al, Heart, 2019). We sought to determine the proportion of patients with AKI, who might benefit from advice in primary care.

**Methods:** Retrospective data were collected on hospitalized patients (Nov 2018-May 2019) identified by elevated serum creatinine results (as per national AKI reporting guidance). In ligation procedure codes to identify in-hospital acute kidney injury and evaluate their outcomes over a twelve year period in Taiwan.

**Results:** In total, 1116 patients treated with CRRT were included in the registry. The mean age of patients was 57.9 (14.2) years, 58.5% were male, mean (SD) APLACHE II and SOFA score were 28.8 (7.3) and 13.8 (3.9), respectively, 81.2% of patients were mechanically ventilated and 83.0% required vasopressor support. The most common admission diagnosis was respiratory failure (20.1%), followed by sepsis (16.2%), cardiovascular emergency (14.3%) and acute liver failure (6.0%). Mean serum creatinine at ICU admission was 3.13 (256.7) umol/L. The most common triggers for CRRT initiation were volume overload (47.8%), oligo-anuria (27.5%) hyperkalemia (5.7%), metabolic acidosis (3.7%) and uremia (1.9%). 46.9% of patients survived the ICU stay and 43.6% survived to hospital discharge. 34.2% of patients had complete renal recovery, 19.5% of patients had partial renal recovery while 46.4% had ongoing need for RRT. Mean ICU and hospital lengths of stay were 20.5 (26.2) and 43.2 (44.4) days, respectively.

**Conclusions:** In this large multi-centre prospective registry of critically ill patients treated with CRRT the most common etiology of AKI requiring CRRT was sepsis and the most common specific indication was volume overload.

**Funding:** Private Foundation Support

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**Table 1. Demographics and waitlist outcome of 7017 patients waitlisted for kidney transplant with previous history of cancer**

**FR-PO002**

**Underreporting of In-Hospital AKI in Taiwan: A Nationwide Study**

Jinn-Yang Chen, Taipei Veterans General Hospital, Taipei, Taiwan.

**Background:** Hospital-acquired AKI is associated with high morbidity and mortality. We used ICD-9 CM code and Taiwanese National Health Insurance (NHI) dialysis procedure codes to identify in-hospital acute kidney injury and evaluate their outcomes over a twelve year period in Taiwan.

**Methods:** In a nationwide retrospective study based on the NHI Database, we identified all adult patients requiring the first in-hospital dialysis, or with ICD-9 code 584 between 2003 and 2014. We excluded patients with previous renal transplantation or chronic dialysis from 2000 to 2002.

**Results:** A total of 628,120 in-hospital AKI episodes were identified, and 203,064 episodes were dialysis-requiring AKI. Among 203,064 dialysis-requiring AKI episodes, 22,746 patients (11.2%) had advanced chronic kidney disease (CKD), 121,054 patients (59.6%) had history of CKD, 59,271 patients (29.2%) received dialysis during admission without documenting CKD. Among patients without pre-existing CKD, 46.7% had sepsis; 6.6% were related to cardiac surgery; 91.2% had been admitted to ICU and 42.5% received CRRT. Patients without pre-existing CKD showed the highest in-hospital mortality (71.1%). Time trend analysis showed that there were decreased trends of in-hospital mortality and increasing trends of long-term dialysis from 2003 to 2014. For those who was discharged without receiving regular dialysis, 25% and 12% of patients died within 1 and 2 years after discharge.

**Conclusions:** We found in-hospital AKI was severely under-reported and was associated with high mortality. Strategies to increase the accuracy of discharge diagnosis is required to improve patient safety.

**Funding:** Government Support - Non-U.S.

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**FR-PO003**

**Epidemiology of Patients Receiving Continuous Renal Replacement Therapy: The Multicenter CRRTNet Study**

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**Background:** There have been limited studies evaluating key performance metrics of patients undergoing continuous renal replacement therapy (CRRT). Our aim was to assess the case-mix, acuity, diagnosis, clinical course and outcomes of patients undergoing CRRT.

**Methods:** CRRTNet is an international multicenter data registry of adult patients undergoing CRRT to assess the variations in CRRT prescription and delivery across quality domains and to develop and benchmark CRRT specific key performance indicators. We evaluated the demographic criteria of adult critically ill patients undergoing CRRT.

**Results:** In total, 1116 patients treated with CRRT were included in the registry. The mean age of patients was 57.9 (14.2) years, 58.5% were male, mean (SD) APLACHE II and SOFA score were 28.8 (7.3) and 13.8 (3.9), respectively, 81.2% of patients were mechanically ventilated and 83.0% required vasopressor support. The most common admission diagnosis was respiratory failure (20.1%), followed by sepsis (16.2%), cardiovascular emergency (14.3%) and acute liver failure (6.0%). Mean serum creatinine at ICU admission was 3.13 (256.7) umol/L. The most common triggers for CRRT initiation were volume overload (47.8%), oligo-anuria (27.5%) hyperkalemia (5.7%), metabolic acidosis (3.7%) and uremia (1.9%). 46.9% of patients survived the ICU stay and 43.6% survived to hospital discharge. 34.2% of patients had complete renal recovery, 19.5% of patients had partial renal recovery while 46.4% had ongoing need for RRT. Mean ICU and hospital lengths of stay were 20.5 (26.2) and 43.2 (44.4) days, respectively.

**Conclusions:** In this large multi-centre prospective registry of critically ill patients treated with CRRT the most common etiology of AKI requiring CRRT was sepsis and the most common specific indication was volume overload.

**Funding:** Private Foundation Support

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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**AKI risk factors by stage**

- **AKI Stage 1**
  - (n=396)
  - Age (years): 52
  - Weight (kg): 75
  - Albumin (g/dL): 3.5

- **AKI Stage 2**
  - (n=269)
  - Age (years): 56
  - Weight (kg): 78
  - Albumin (g/dL): 3.0

- **AKI Stage 3**
  - (n=131)
  - Age (years): 60
  - Weight (kg): 80
  - Albumin (g/dL): 2.5

- **All AKI**
  - (n=836)
  - Age (years): 55
  - Weight (kg): 77
  - Albumin (g/dL): 3.3

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**AKI: Epidemiology, Risk Factors, Prevention - II**
**FR-PO004**

**Dialysis Initiation in AKI: An Evaluation of the Wait and See Approach**

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**Background:** The optimal timing of RRT initiation in critically ill patients has been an area of intense investigation. Recent trials have suggested that dialysis may be avoided in patients with severe AKI by waiting to initiate therapy unless there are life-threatening complications requiring emergent intervention. We evaluated the outcomes of this “wait and see approach” (WSA) in comparison to elective intervention based on the severity of AKI and non-emergent indications. We hypothesized that the WS approach would be associated with higher mortality and resource utilization.

**Methods:** We conducted a retrospective multinational cohort study of critically ill adult patients admitted to four centers in Germany, UK and USA between Jan2014 and Dec2017. We excluded patients with ESRD, kidney transplant and those who stayed <72hrs. in the ICU. Need for dialysis was classified as emergent, defined as AKI Stg2 and higher, in the presence of any one of the criteria 1) arterial blood gas pH<7.15, 2) K+≥ 6.5 Meq/L, 3) BUN>112 mg/dl or 4) PO2/FO2≤150 with cumulative fluid balance from admission ≥ 15% and urgent hospitalization. Urgent initiation was considered if patients had AKI Stg3 and none of the emergency criteria, and elective for the rest of the indications. The primary outcome was ICU and hospital mortality.

**Results:** Of 20,560 eligible patients, 9712 (47.2%) developed AKI (2,156;10.5) receiving dialysis (D); of whom 438(2) at dialysis initiation were at Stg1, 124(5) Stg2, 380(17) Stg3 and 953(44) no AKI. They were categorized as elective (2156;76), urgent (252;11) and emergent (252;11). Among 18404 non-dialyzed (ND) patients, 253(1.4%) met the urgent and 127(0.7%) the emergent criteria. Dialyzed patients had higher SOFA scores, vasoactive index, mechanical ventilation, and cumulative fluid balance. Hospital mortality in D patients was almost 2 fold higher as compared to urgent and elective groups, and in the ND patients hospital mortality was > 2 fold higher when urgent and 4.5 fold higher when emergent criteria were present. D and ND patients had similar mortality in emergent category.

**Conclusions:** Reaching emergency criteria was associated with higher ICU and hospital mortality in dialyzed and non-dialyzed patients. Further studies are needed to identify appropriate criteria for initiating dialysis in ICU patients.

**Funding:** NIDDK Support, Veterans Affairs Support, Other U.S. Government Support

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**FR-PO005**

**Outpatient Dialysis for AKI: A Non-Profit Provider Experience**

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**Background:** Medicare approved reimbursement of outpatient hemodialysis (HD) for patients with acute kidney injury (AKI) in 2017. Lack of national data hinders a consensus on optimal management. We describe the experience of a multi-state non-profit dialysis provider.

**Methods:** We reviewed electronic medical records of all patients treated for AKI between 1/1/17 and 12/31/18 with follow-up until 3/31/19. We identified 6515 new AKI patients. Patients were categorized as elective (2156;76), urgent (252;11) and emergent (252;11). We excluded patients with ESRD, kidney transplant and those who stayed <72hrs in the ICU. Need for dialysis was classified as emergent, defined as AKI Stg2 and higher, in the presence of any one of the criteria 1) arterial blood gas pH<7.15, 2) K+≥ 6.5 Meq/L, 3) BUN>112 mg/dl or 4) PO2/FO2≤150 with cumulative fluid balance from admission ≥ 15% and urgent hospitalization. Urgent initiation was considered if patients had AKI Stg3 and none of the emergency criteria, and elective for the rest of the indications. The primary outcome was ICU and hospital mortality.

**Results:** Of 20,560 eligible patients, 9712 (47.2%) developed AKI (2,156;10.5) receiving dialysis (D); of whom 438(2) at dialysis initiation were at Stg1, 124(5) Stg2, 380(17) Stg3 and 953(44) no AKI. They were categorized as elective (2156;76), urgent (252;11) and emergent (252;11). Among 18404 non-dialyzed (ND) patients, 253(1.4%) met the urgent and 127(0.7%) the emergent criteria. Dialyzed patients had higher SOFA scores, vasoactive index, mechanical ventilation, and cumulative fluid balance. Hospital mortality in D patients was almost 2 fold higher as compared to urgent and elective groups, and in the ND patients hospital mortality was > 2 fold higher when urgent and 4.5 fold higher when emergent criteria were present. D and ND patients had similar mortality in emergent category.

**Conclusions:** Reaching emergency criteria was associated with higher ICU and hospital mortality in dialyzed and non-dialyzed patients. Further studies are needed to identify appropriate criteria for initiating dialysis in ICU patients.

**Funding:** NIDDK Support, Veterans Affairs Support, Other U.S. Government Support

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**FR-PO007**

**Epidemiology of Hospitalization Preceding Initiation of Outpatient Dialysis for AKI Among Medicare Beneficiaries**

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**Background:** Little is known about hospital admissions preceding initiation of outpatient (OP) dialysis for acute kidney injury requiring dialysis (AKI-D), which would represent transitions of renal-care management, presumably represent transitions of AKI-D care from inpatient to outpatient settings. We examined Medicare claims to assess hospitalizations preceding the initiation of OP dialysis for AKI-D.

**Methods:** We analyzed the 100% sample of institutional claims in 2014–2017 Medicare Limited Data Sets. To identify initiation of OP dialysis for AKI-D, we located the first OP dialysis facility claim in 2017 with condition code 84 and Healthcare Common Procedure Coding System code G0491. We excluded any patients with Medicare claims history of OP dialysis indicated for end-stage kidney disease, dating to January 1, 2014. We retained the subset of patients with Medicare coverage during the 6 calendar months preceding the month of initiation of OP dialysis for AKI-D. We then analyzed hospitalization claims, including ICD-10 diagnosis codes.

**Results:** The cohort comprised 8500 patients. Mean age was 70.5 ± 11.0 years, 77% were white, and 44% were female. During the 6 months preceding the initiation of OP dialysis for AKI-D, 8209 (97%) patients were hospitalized, with cumulative totals of 1.9 admissions and 273 hospitalized days. Regarding the last hospitalization preceding initiation of OP dialysis for AKI-D, mean (median) length of stay was 20 (15) days; 29% were discharged home under self-care, 25% to home health care, 42% to a skilled nursing facility, and 3% to intermediate care settings. The number of days between hospital discharge and initiation of OP dialysis for AKI-D was ≤ 1 in 34% of patients, 2–3 in 52%, 4–7 in 8%, and >7 in 6%. During the last hospitalization preceding initiation of OP dialysis for AKI-D, chronic kidney disease (CKD) was documented in 86% of admissions, diabetes in 59%, heart failure in 53%, and atrial fibrillation in 34%. Clinical events included acute respiratory failure in 29% of admissions and sepsis in 20%.

**Conclusions:** In Medicare beneficiaries, hospitalizations preceding initiation of OP dialysis for AKI-D are typically long and often complex, with 1 in 5 experiencing sepsis and 1 in 3 acute respiratory failure. CKD is common in this population, as is skilled nursing care in a skilled nursing facility at initiation of OP dialysis for AKI-D.
FR-PO008
Predictors of Recovery of Kidney Function and Transition to ESKD in Patients on Outpatient Dialysis for AKI
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Background: Most patients initiating outpatient hemodialysis (OP HD) for acute kidney injury requiring dialysis (AKI-D) recover function or transition to end-stage kidney disease (ESKD) within 3 months. Identifying factors predictive of OP HD outcome may improve clinical care processes. We assessed associations of baseline patient characteristics and biochemistry at initiation of OP HD for AKI-D with competing risks of recovery of kidney function and transition to ESKD.

Methods: We analyzed patients initiating OP HD for AKI-D in a Fresenius Kidney Care (FKC) dialysis facility between May 1, 2017, and December 31, 2018, excluding those discharged from FKC facilities within 7 days of initiation of OP HD or with incomplete biochemical data. We followed patients to the earliest of recovery of kidney function, transition to ESKD, death, or loss to follow-up (typically, transfer to another dialysis provider), with end of follow-up on March 31, 2019. We used Fine-Gray regression to model subdistribution hazards of recovery of function and transition to ESKD, as a function of age, sex, and biochemistry measured within 7 days of initiation of OP HD; death was classified as a competing risk.

Results: The cohort comprised 12,221 patients. During follow-up, 4,786 (39%) recovered kidney function, 5,066 (46%) transitioned to ESKD, and 1,136 (9%) died. Adjusted hazard ratios of recovery of function and transition to ESKD per standard deviation (SD) of each factor are displayed in the table.

Conclusions: Younger age, female sex, lower serum creatinine, lower serum potassium, higher serum phosphorus, and lower serum parathyroid hormone are most strongly associated with recovery of kidney function after initiation of OP HD for AKI-D, whereas higher serum creatinine is most strongly associated with transition to ESKD.

FR-PO009
The Relationship Between Intra-Parenchymal Renal Resistant Index Variation and Renal Functional Reserve Under Physiologic and Pathologic Conditions
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Background: The assessment of renal functional reserve (RFR), which is increased of glomerular filtration rate after a protein load, has been proposed for the risk stratification of patients undergoing potentially nephrotoxic procedures. In previous studies, we described a bedside ultrasound/BUS test (intra-parenchymal renal resistive index variation, RRV test) to identify the presence of RFR. The aim of this study is to externally validate IRRIV test in a validation cohort of healthy subjects and preliminary explore the correlation between IRRIV and RFR under pathologic conditions.

Methods: We enrolled a group of healthy subjects and a group of patients scheduled for cardiac surgery. Each underwent protein loading test and IRRIV test. It relies on a mechanical abdominal stress consisting of compressing renal vessels through an externally applied weight on the abdomen (fluid-bag 10% of subject’s body weight) which reduces blood flow and activates the autoregulation mechanism. This leads to apparent vasoconstriction which can be measured by a fall in RRI. Pearson and logistic regression analyses were used to assess the correlation between IRRIV and RFR in both groups.

Results: In 47 healthy subjects, Pearson correlation coefficient between RFR and IRRIV is 0.83, CRIV50(0.71-0.90), p<0.01. Among these, concordance between RFR and IRRIV is described in 45 subjects (95.7%). IRRIV predicts RFR with a ROC-AUC of 0.86, CRIV50[0.68-1.0]. In 31 cardiac surgery patients, Pearson correlation coefficient between RFR and IRRIV is 0.81, CRIV50[0.63-0.90], p<0.01. Among these, concordance between RFR and IRRIV is described in 27 (87.1%) patients. IRRIV predicts RFR with a ROC-AUC of 0.87, CRIV50[0.66-0.96].

Conclusions: IRRIV test is a feasible BUS test that significantly predicts the presence of RFR in healthy subjects. Correlation between IRRIV and RFR seems to be also maintained in pathologic conditions.

FR-PO010
Pathological Characteristics and Prognosis of Community-Acquired AKI: Risk Factors of AKI to CKD Transition
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Background: Community-acquired acute kidney injury (CA-AKI) wins more attentions from society. Underlying pathological damages are regraded as major determinants to AKI to CKD transition. In this study, we clarified the pathological characteristics of CA-AKI and evaluated the influence of morphologic changes in the renal biopsy on the rapid loss of renal function and AKI-CKD transition.

Methods: This single-centered cohort study enrolled CA-AKI patients with renal biopsy examination from January 1, 2010 to September 30, 2017 admitted to Shanghai Changzheng Hospital. All patients were followed up for 90 days after diagnosis. The demographic characteristics, pathological lesions and outcomes were recorded and analyzed. Cox proportional hazard models were used to evaluate the risk factors for all-cause mortality and renal replacement therapy requirement after diagnosis. Logistic regression analyses were used to identify the risk factors associated with progression to CKD or maintained dialysis, and renal recovery as well.

Results: A total of 251 eligible CA-AKI patients were recruited into the cohort, of whom 148 (57.4%) were male and age ranged from 18 to 85 years old (median 53). Our results showed that pathological lesions played critical role in AKI-CKD progression and renal recovery. With regard to progression on 90th day, segmental glomerulosclerosis (Relative Ratio (RR) 6.64; 95% CI, 2.05 to 20.38, p<0.002), severe vascular lesion (RR 14.92; 95% CI, 2.35 to 94.80, p=0.004), and crescent index (RR 3.50; 95% CI, 2.07 to 5.91; p=0.037) were significantly associated with progression to maintained dialysis. Over 50% area of Interstitial inflammation (RR 8.09; 95% CI 2.54 to 25.77, p<0.001) and crescent index (RR 3.30; 95% CI 1.78 to 6.12, p<0.001) were risk factors for progression to CKD. Moreover, interstitial fibrosis and crescent were risk factors for partial renal recovery. While, renal morphologic changes showed little impact on in-hospital all-cause mortality and RRT requirement by Cox proportional hazard modeling analysis.

Conclusions: Pathological damages played a part in the rapid loss of renal function and AKI-CKD transition of CA-AKI patients in a short term, affected renal recovery as well. Whereas, it did not interfere with severity of AKI; all-cause mortality and RRT requirement.

Funding: Government Support - Non-U.S.
FR-PO012

Underordered AKI in Pediatric Intensive Care: Incidence, Risk Factors, and Outcomes
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Background: Acute kidney injury (AKI) is increasingly recognized in critically ill pediatric patients. AKI is frequently underreported leading to the potential for increased morbidity and mortality associated with this disorder. Our study seeks to identify the incidence, risk factors, and outcomes of patients with undocumented AKI in the pediatric critical care population.

Methods: We conducted a retrospective chart review of patients admitted to the PICU at Comer Children’s Hospital between January 1, 2017-December 31, 2017. Patients with a rise in serum creatinine (SCr) levels consistent with the KDIGO AKI criteria were considered to have AKI. Patients with a physician note in their electronic medical record (EMR) containing the terms “AKI”, “Acute Kidney Injury” or “Acute Renal Failure” were considered to have AKI. Our primary outcome of interest was a comparison between AKI patients with and without EMR documentation of disease. All statistical analyses were performed using STATA software with a p-value of < 0.05 considered statistically significant.

Results: AKI was identified in 8.3% of the total population, with 71% of these patients not having any documentation of AKI in the EMR. There was a significant increase in the documentation of AKI in patients with oliguria, nephrotic medication and inotropic/vasopressor exposure. Patients with documented AKI had a statistically significant increase in their median length of PICU admission (13.5 days vs 2 days, p=0.000) and median length of mechanical ventilation (12.94 days vs 6.84 days, p=0.034). Anaphylaxis consultation was placed in 2.2% of patients with undocumented AKI.

Conclusions: Our data shows that a substantial number of all AKI diagnosis were not documented in the EMR. Of note, this does not indicate that the provider failed to recognize AKI, but it does represent a deficiency to convey to the medical team the occurrence of this disorder. There were also a significant number of patients with AKI that did not receive a nephrology consultation, an intervention that has been shown to reduce morbidity and mortality of AKI.

Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Documented AKI (n=35)</th>
<th>Undocumented AKI (n=85)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (Within 90 days)</td>
<td>0 (9.0%)</td>
<td>6 (9.2%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Length of PICU Admission, Median (IQR)</td>
<td>13.5 (12.1, 20)</td>
<td>2 (1, 8)</td>
<td>0.00</td>
</tr>
<tr>
<td>Length of Mechanical Ventilation, Median (IQR)</td>
<td>12.34 (11.54, 15.44)</td>
<td>6.54 (6, 9.86)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

FR-PO013

Burden and Outcomes of Drug-Induced AKI
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Background: Acute kidney injury (AKI) affects up to third of all hospitalizations. Although drug induced AKI (DI-AKI) is reported to be frequent, limited data exists in determining its true burden, and description of associated risk factors and outcomes.

Methods: All AKI consults (defined by KDIGO guidelines) across an academic health system were retrospectively recorded in an approved electronic registry. Of the available 500 cases of AKI (January to June 2018), 321 were studied (exclusion: kidney transplants, end stage renal disease, transfers on dialysis). AKI was classified by etiology on the day of consult as either nephro toxic, biologic, or multifactorial; multifactorial was then scored (1 to 10 scale) based on contribution of the drug class. Drug induced (DI-AKI) was defined as either nephro toxic or those with a multifactorial score > 5, and others as

Biol-AKI. AKI was also classified as community acquired (CA-AKI), < 2 days or 2 or more days after admission (hospital acquired, HA-AKI). The composite outcome mortality of death, hospice discharge, dialysis dependence at discharge or 1.5 times median length of stay. Chi-square tests, and logistic regression were used for covariate adjustment (demographic, co-morbidities, and admission details).

Results: Of the 321 AKI cases (62% Male, 29% Black, median age 59 years, median baseline creatinine 1.3 mg/dl) DI-AKI occurred in 88 cases (27%). DI-AKI cases were more likely to be Black (40% vs 25%, p=0.01). Compared to Biol-AKI, DI-AKI admissions were mostly Medical (91% vs 78%, p=0.008). The most common drug classes associated with DI-AKI were diuretics 48%, antimicrobials 42%, renin-angiotensin system inhibitors 39%, contrast agents 30%, chemotherapy 7%. Most common source of DI-AKI was community acquired (64%). Need for dialysis was similar across two groups (DI-AKI 22% vs Biol-AKI 34%). Overall, 50% of cases met the primary composite outcome (DI-AKI – 38% vs Biol-AKI – 54%, p=0.008); risk-adjusted odds ratio (OR) 0.52 (95% CI, 0.31 – 0.86).

Conclusions: Almost 1-in-3 AKI consults are drug induced, and attributable to commonly prescribed agents. Although Biol-AKI cases had a greater risk of composite outcome, DI-AKI cases continue to face devastating consequences, including similar risk of dialysis dependence. Strategies to mitigate drug induced AKI could improve clinical outcomes.

FR-PO014

Drug-Induced AKI: Can We Prevent It?
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Background: Acute kidney injury (AKI) can affect 1-in-3 hospitalizations, with an adverse impact on both patients and health systems. AKI is far too commonly drug induced (DI-AKI). Limited data exists in identifying whether DI-AKI can be prevented, and whether patient or provider interventions could improve kidney safety.

Methods: We studied all inpatient nephrology consults with AKI (defined by KDIGO guidelines) at two centers across our academic health system between January and June of 2018. Based on a prior quality improvement program, AKI cases were retrospectively adjudicated to be Biologic (Biol-AKI) or Drug Induced (DI-AKI). We further identified DI-AKI as Preventable (Prv-AKI) when the use of the culprit drug(s) was not considered to be of life-saving value for diagnosis or treatment. Source of AKI was defined as community acquired (CA_AKI – AKI criteria met < 2 days of admission) or hospital acquired (HA_AKI). A composite outcome was hospital death, discharge to hospice or dialysis dependence on discharge. Chi-square tests were used for comparison.

Results: Of the 500 AKI consults, 321 were studied (exclusion: kidney transplants, end stage renal disease, transfers on dialysis). DI-AKI occurred in 27% (88/321), and was deemed preventable (Prv_AKI) in 24/28 (27%) of cases. Prv_AKI cases were 63% Men, 54% Black (median age 60.5 years; median baseline creatinine 1.3 mg/dl) Prv_AKI predominantly occurred in Medical settings (96%), and admissions for sepsis or cardiovascular causes comprised 50% of all cases. The top two drug classes associated with Prv_AKI were diuretics (63%) and Renin-Angiotensin System (RAS) blockers (54%). For non-Prv_AKI cases, anti-microbial use (50%) and diuretics (42%) were the top two offending drug classes. Contrast agents were third common class for both groups. Source of AKI in the Prv_AKI group was CA_AKI 54% vs HA_AKI 46% and not significantly different from non-Prv_AKI group (p=0.62). The composite outcome was similar in Prv_AKI (38%) and non-Prv_AKI (38%) groups.

Conclusions: Almost third of drug induced AKI can be preventable, and the majority of these AKI cases manifest within 2 days of admission. Preventable AKI cases faced the same devastating outcome as their counterparts. These findings suggest that patient or provider education about medication safety could improve clinical outcomes in AKI.

Funding: Clinical Revenue Support
renal function compared with non-user of RAS blockers (31.4% vs 10.9%, p = 0.002). In subgroup analysis, patients with chronic kidney disease have statistically significant risk of acute kidney injury by fenofibrate (47.1% vs 21.1%, p = 0.017). Mean estimated glomerular filtration rate (eGFR) by MDRD was each 28.4 ± 12.1 mL/min/1.73m² in chronic kidney disease group and 66.2 ± 20.3 mL/min/1.73m² in non-chronic kidney disease group.

Diabetes mellitus, hypertension, and concomitant use of RAS blocker have a statistically significant association with acute kidney injury by fenofibrate in our study. And patients with chronic kidney disease have greater risk in acute kidney injury by fenofibrate.

FR-PO016
The Incidence, Risk Factors, and Clinical Outcomes of Rhabdomyolysis Associated with Fenoverine Prescription: A Retrospective Study in South Korea (1999–2014)

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Background: Fenoverine is a spasmylic drug that has been used to treat abdominal pain. Although sporadic case reports of rhabdomyolysis associated with fenoverine have been published, there are no studies evaluating the correlation of this drug with rhabdomyolysis.

Methods: We retrospectively reviewed the medical records of 22 patients admitted with rhabdomyolysis associated with fenoverine from January 1999 to December 2014, while excluding other well-known risk factors of rhabdomyolysis. This period was subdivided into two periods, January 1999–December 2007 and January 2008–December 2014. We analyzed the clinical and laboratory characteristics, and the prognosis of fenoverine associated with rhabdomyolysis for these time periods.

Results: The incidence of rhabdomyolysis associated with fenoverine was 0.27% during the period (22/8257), 0.34% in the first period (18/5298), and 0.14% in the second period (4/2959) (p < 0.001). Rhabdomyolysis occurred in 22 liver cirrhosis (LC) patients (2.03%), whereas only 3 cases (0.04%) occurred in non-LC patients (p = 0.001). Drug duration, total dose, muscle enzymes, and clinical characteristics were not different between the LC and non-LC groups. Acute renal failure (ARF) occurred in 5 patients in the LC group and 2 patients in the non-LC group (p = 0.270). Severity of hepatic derangement according to the Child-Pugh classification was not different between the ARF group and non-ARF group (p = 0.270). Four patients died, having complications of oliguric ARF (p = 0.005) and underlying severe LC (p = 0.017). Higher serum lactate dehydrogenase, blood urea nitrogen, creatinine, and potassium levels but lower serum sodium levels were found in the group that died (p = 0.001).

Conclusions: Physicians should not use fenoverine in patients with LC because of a high incidence of rhabdomyolysis and its poor prognosis.

FR-PO017
Postoperative AKI and Intraoperative Mean Arterial Pressure Variability: A Multi-Cohort Observational Study

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Background: Clinical evidence for the association between intraoperative mean arterial pressure (MAP) variability and the risk of postoperative acute kidney injury (PO-AKI) in non-cardiac surgeries is rare.

Methods: This study included three distinct cohorts in Korea with different time intervals for recording blood pressure during surgery. Non-overlapping first surgery cases were included, excluding those without creatinine measurements or with preexisting renal failure. The main study outcome was PO-AKI, defined by KDIGO serum creatinine criterion cutoffs, and critical AKI, which merged stage 2 KDIGO PO-AKI and post-AKI death or dialysis within 90 days. Standard deviation, coefficient of variation, variation independent of mean, and average real variability were calculated with measured MAP values.

Results: We analyzed 45,575/3,182,502, 29,724/1,354,820, and 7,435/48,923,796 patients/measured MAP values from the three cohorts, respectively. On discovery analysis, the variability parameters were significantly associated with the risk of the studied AKI outcomes, even after adjusted for duration of significant intraoperative hypotension (MAP < 65 mmHg). An increment of 10 mmHg average difference between the measured MAPs, which were measured at a median interval of 2 minutes, was associated with higher risks of PO-AKI [adjusted OR 1.549 (1.307–1.820)] and critical AKI [adjusted OR 1.566 (1.098–2.211)] events. The above results were similar in the other two validation cohorts, and the average real variability was the most significant variability parameter.

Conclusions: High intraoperative MAP variability is an independent risk factor for the risk of PO-AKI and associated patient-outcome in non-cardiac surgeries.

FR-PO018
Influence of Perioperative Statin Use on Risk of AKI Following Cardiac and Noncardiac Major Surgery: A Nationwide Population-Based Cohort Study

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Background: Postoperative acute kidney injury (AKI) is independent associated with high morbidity and mortality following surgery. The effects of perioperative statin use on the occurrence of AKI are not well understood. The present study investigated the association between perioperative statin use and AKI following cardiac and non-cardiac major surgery in the Korean population.

Methods: All patients aged 30 years and over who underwent cardiac or non-cardiac major surgery between 2013 and 2015 were included in this nationwide population-based cohort study (n = 382,198). The primary outcome was defined as the occurrence of AKI after surgery. Four patterns of statin use were analyzed in this study according to peroperative and/or previous statin use. The generalized logit model was used to evaluate the association between statin use and the risk of AKI. Subgroup analysis was conducted to investigate the differences in the effect sizes of statin use patterns.

Results: Perioperative statin use was associated with an increased risk of AKI after surgery in patients who were naïve to statin prior to both cardiac and non-cardiac surgery (OR 1.35, 95% CI 1.11–1.64; OR 1.20, 95% CI 1.01–1.44, respectively). Non-cardiac patients who underwent perioperative statin therapy and who had previously taken statins had a higher risk of AKI following surgery, whereas withdrawal of statins led to a significant reduction in the occurrence of AKI in these patients (OR 0.82, 95% CI 0.76–0.87).

Conclusions: The results presented here demonstrate the association between perioperative statin use and the increased incidence of AKI following major surgery. Our findings reveal that the risk of AKI of non-cardiac major surgery is reduced when statin treatment is withdrawn at the time of surgery.

FR-PO019
Preoperative Medication Use and Development of Postoperative AKI
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Background: The use of medications such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and proton pump inhibitors (PPI) has been associated with acute kidney injury (AKI), whereas animal data suggest that aldosterone antagonists (AA) may be protective. The aim of this study was to examine the relationship between the preoperative use of these medications and development of postoperative AKI.
Methods: This was a retrospective study of adult patients (excluding those with CKD status) undergoing CABG, valvular, or orthopedic surgery at the University Hospital in Reykjavik in 2006-2015. Clinical data and disease diagnoses were retrieved from electronic medical records. AKI was defined based on serum creatinine (SCr) according to the KDIGO criteria. Information on medication use was obtained from the National Prescription Drug Database of the Directorate of Health and patients were considered to be using a medication if they had filled a prescription within six months prior to surgery. A daily defined dose (DDD) was determined for all patients. Risk of AKI was assessed using multivariable logistic regression analysis.

Results: Abdominal, cardiac, thoracic, vascular or orthopedic surgeries were performed on 28,418 patients during the study period. Pre- and postoperative SCr was available for 19,279 cases. Postoperative AKI occurred in 1,455 (7.5%) cases. A total of 6,568 (34%) patients filled a prescription for a PPI prior to surgery, 547 (8.3%), of whom developed AKI. Of 9,217 (35%) patients who received ACEi, ARB or AA before surgery, 724 (10.8%) developed AKI. In adjusted analysis, the odds ratio (95% CI) for AKI was 1.00 (0.89-1.13) for PPI, 1.07 (0.93-1.23) for ACEi, 1.30 (1.15-1.48) for ARB and 0.83 (0.62-1.09) for AA. When DDD examination was performed, there was no evidence of a dose-response relationship between medication use and postoperative AKI.

Conclusions: In this surgical cohort, we found that preoperative use of ARB associated with postoperative AKI. However, no such a risk was evident for PPI and a protective effect of AA was not observed.

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FR-PO020
AKI After Lung Transplantation: A Meta-Analysis
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Background: Lung transplantation has been increasingly performed worldwide and considered as an effective therapy for patients with various end-stage lung diseases. We performed this meta-analysis to evaluate the incidence and impact of acute kidney injury (AKI) in patients after lung transplantation.

Methods: A literature search was conducted utilizing MEDLINE, EMBASE and Cochran Database from inception through April 2019. We included studies that evaluated the incidence of AKI, severe AKI requiring renal replacement therapy (RRT), and impact of AKI among patients after lung transplantation. Pooled incidence and odds ratios (OR) with 95% confidence interval (CI) were calculated using random effects meta-analysis.

Results: 3 progression cohorts with a total of 40,293 patients after lung transplantation were enrolled. Overall, the pooled estimated incidence rates of AKI (by standard AKI definitions) and severe AKI requiring RRT following lung transplantation were 52.1% (95% CI: 45.9%-59.1%) and 9.5% (95% CI: 7.7%-11.8%). Meta-regression analysis showed that year of study did not significantly affect the incidence of AKI (p=0.11) and severe AKI requiring RRT (p=0.54). The pooled OR of hospital mortality among patients after lung transplantation with AKI and severe AKI requiring RRT were 2.75 (95% CI, 1.18-6.41) and 10.89 (95% CI, 5.03-23.58). At 5 year, the pooled OR of mortality among patients after lung transplantation with AKI and severe AKI requiring RRT were 1.47 (95% CI, 1.11-1.94) and 4.79 (95% CI, 3.58-6.40), respectively.

Conclusions: The overall estimated incidence rates of AKI and severe AKI requiring RRT in patients after lung transplantation are 52% and 9.5%, respectively. Despite advances in intensive care medicine, incidence of AKI in patients after lung transplantation does not seem to decrease over time. In addition, AKI after lung transplantation is significantly associated with reduced short-term and long-term survival.

FR-PO021
The Association of AKI with Hospital Readmission or Death After Pediatric Cardiac Surgery
Sophia Nunes,1 Jason H. Greenberg,2 Chirag R. Parikh,1 Jeremiah R. Brown,4 Heather Thiesen Phillbrook,3 Prasad Devarajan,3 Ana Palijan,1 Michael Zappitelli,7 TRIBE-AKI 1The Hospital for Sick Children, Toronto, ON, Canada; 2Yale University, Woodbridge, CT; 3Johns Hopkins University, Newton, MA; 4The Dartmouth Institute, Lebanon, NH; 5Cincinnati Children’s Hospital, Cincinnati, OH; 6McGill University Health Centre, Montreal, QC, Canada; 7Toronto Hospital for Sick Children, University of Toronto, Toronto, ON, Canada.

Background: AKI in children undergoing cardiac surgery (CS) is strongly associated with increased hospital morbidity, however post-discharge AKI outcomes are less studied. Hypotheses: In children undergoing CS with cardiopulmonary bypass (CPB), (a) AKI is associated with increased risk for readmission or death within 30 days and 1 year of CS discharge and (b) the association of AKI is modified by surgical severity and cyanotic heart disease.

Methods: Prospective 3-centre cohort study of children surviving to hospital discharge after CS with CPB. Main exposure: AKI during index CS admission defined by KDIGO. Comparator: no AKI in patients after lung transplantation does not seem to decrease over time. In addition, AKI after lung transplantation is significantly associated with reduced short-term and long-term survival.

Results: Of the 360 participants included (mean age 4.0±4.6 years, 155 [43%] AKI, 47 [13%] stage 2 AKI, 4 (1.1%) and 6 (1.7%) died and 30 (8.3%) and 99 (27.5%) were readmitted within 30 days and 1 year post-discharge, respectively. Figure illustrates a graded increase in the risk of the composite outcome with increasing AKI stage. AKI and aStage 2 AKI were associated with time to outcome within 30 days (adjusted HR 3 [95%CI 1.08-5.27], respectively) but not within 1 year of CS discharge. RACHS-1 and cyanotic heart disease did not modify these relationships (interaction p value<0.1).

Conclusions: Children with AKI post-CS were more likely to be readmitted or die within 30 days of CS discharge, compared to children without AKI. Future research should evaluate measures to reduce short-term morbidity and mortality risk in children who develop AKI after CS.

Funding: NIDDK Support

FR-PO022
Correlation Between Incidence and Attributable Mortality Fraction of AKI: A Systematic Review
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Background: The incidence and mortality of acute kidney injury (AKI) has extremely varied even after the introduction of RIFLE, AKIN and KDIGO criteria. The quality of AKI diagnosis and management may also be influential. The present study aimed to investigate the association between AKI incidence and mortality of each cohort. We also investigated the effect of publication year and economic index on AKI mortality.

Methods: Our study aggregated the incidence and mortality of AKI through a systematic review of manuscripts on AKI patients diagnosed by Kidney Disease: Improving Global Outcomes (KDIGO)-equivalent criteria from 2004 to May, 2018. The search was conducted in MEDLINE, EMBASE, and Cochrane Library. We investigated the correlation between AKI incidence, mortality, and AKI attributable fraction of mortality. AKI attributable fraction of mortality in each cohort was calculated as follows: (mortality of AKI patients)-(mortality of patients without AKI) / (mortality of AKI patients). The impact of publication year and gross domestic product (GDP) on the mortality were also studied.

Results: The systematic review screened total 4149 manuscripts, and finally yielded 287 eligible cohorts (adults: 203 cohorts consisted of 7067545 patients; children: 84 cohorts of 69677 patients). In the adult cohorts, the mortality of AKI patients became higher (R2=0.13, β=-0.12, P=0.033) but the attributable fraction of mortality otherwise decreased (R2=0.27, β=-0.43, P<0.001), as incidence of AKI augmented. Although the crude mortality of AKI patients decreased in more recent publications and in reports from higher GDP countries, the AKI attributable fraction did not decline in the same settings.

Conclusions: The AKI attributable fraction of mortality in the cohorts with high AKI incidence was relatively low, which possibly indicated the advantage of more experience in AKI diagnosis and management.
FR-PO023
The Value of Plasma Inflammatory Biomarkers in Sepsis-Associated AKI
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Background: Sepsis-associated acute kidney injury (SA-AKI) may be mediated by inflammation. We evaluated the association of plasma inflammatory biomarkers with SA-AKI beyond traditional AKI risk factors and markers of structural damage (nGAL and UACR).

Methods: We included 453 adults with sepsis (SIRS and adjudicated infection) with collected samples within 24 hours of ICU admission. Admission AKI risk factors were adjudicated into the following categories: hypotension, hypovolemia, neprotoxins, obstruction and other (e.g. rhabdomyolysis). AKI was defined by a 50% serum creatinine (SCr) rise within 7 days from preadmission SCr or nadir SCr if the former was missing. Plasma and urine biomarkers were log-transformed. We evaluated the relationship between plasma biomarkers and AKI using univariate and multivariable logistic models with and without backwards stepwise selection (p=0.05). Analysis was repeated for severe AKI (KIDGO stage 2-3).

Results: 275 subjects (60%) had AKI, 100 (22%) had severe AKI, 42 (9%) required dialysis and 140 (31%) died-in-hospital. A model with demographics and clinical variables (Table 1) had AUC of 0.68 for AKI. The addition of structural damage markers improved the AUC to 0.71, and all plasma biomarkers further increased the AUC to 0.73 (p<0.01). No plasma biomarkers remained after backwards selection for AKI. Findings were replicated for severe AKI. Inclusion of all plasma biomarkers improved the AUC from 0.75 to 0.79 (p<0.03). Only ICAM remained during backwards selection.

Conclusions: Inflammatory biomarkers only modestly improve SA-AKI prediction. Inflammation and structural damage are likely to have occurred before ICU admission. Efforts targeting systemic inflammation to prevent SA-AKI in the ICU may be limited.

Funding: NIDDK Support

FR-PO024
Renin-Angiotensin System Blockade After AKI and Risk of Recurrent AKI
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Background: How to best medically manage patients who survived hospitalized acute kidney injury (AKI) is unclear. These patients are at higher risk of further loss of renal function so angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) may be renoprotective. However, recurrent AKI is common and use of ACE-I/ARB in this setting may increase risk of diuretic resistant AKI.

Methods: This is a retrospective cohort study of 10,242 members of an integrated healthcare delivery system in Northern California who experienced AKI and survived a hospitalization between January 1, 2006 and December 31, 2013. All study participants did not have a prior heart failure or previous use of ACE-I or ARB therapy up to five years prior. New receipt of ACE-I/ARB was identified based on dispensed prescriptions found in outpatient health plan pharmacy databases. The primary outcome of interest was subsequent episode of hospitalized AKI after discharge from an initial index hospitalization complicated by AKI. Recurrent AKI episode was defined using acute changes in serum creatinine concentrations. Marginal structural models (MSM) were used to adjust for baseline and potential time-dependent confounders.

Results: During follow-up, we observed 220 episodes of recurrent AKI/100 person-years while taking ACE-I/ARB (95% CI: 20.5 to 23.6 episodes per 100 person-years) compared to 14.1 episodes/100 person-years while not receiving ACE-I/ARB (95% CI: 13.7 to 14.5 episodes per 100 person-years). However, in MSM causal inference models that adjusted for baseline and potential time-dependent confounders, exposure to ACE-I or ARB use was not associated with higher incidence of recurrent AKI (adjusted odds ratio 0.71, 95% CI: 0.45 to 1.12).

Conclusions: Our study provided reassuring data about the safety of initiating ACE-I or ARB after an episode of AKI.

Funding: NIDDK Support

FR-PO025
Hospitalized AKI Among Black and White Individuals with CKD: The CRIC Study
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Background: Although black race and APOL1 high-risk genotypes are risk factors for various forms of kidney disease, few studies have rigorously examined whether an independent association of black race and APOL1 genotypes exists for occurrence of hospitalized AKI. Prior studies have not accounted for baseline eGFR and proteinuria levels near the time of AKI and have relied only on diagnostic codes to define AKI.

Methods: We studied black and white participants enrolled in the CRIC Study, a multicenter prospective cohort study of CKD, who had an annual in-person study visit between July 2012-June 2013. The primary outcome was hospitalized AKI in the subsequent 2 years (defined as a ≥50% increase from nadir to peak inpatient serum creatinine). We evaluated the association of race, APOL1 genotype and AKI using multivariable logistic regression.

Results: Among 1,162 eligible CRIC participants, 481 were black with 86 (18%) having a high-risk APOL1 genotype. The overall mean (SD) eGFR was 47 (16) mL/min/1.73m² and neither eGFR or proteinuria significantly differed by APOL1 risk status (Table). The crude risk of AKI was similar between black and white patients (5.2% vs. 5.3%). After adjusting for eGFR and urine-protein-to-creatinine ratio, age, sex, educational attainment, blood pressure, prevalent cardiovascular disease, diabetes and receipt of ACE-I/ARB, there was no significant association of race or APOL1 status with AKI (Table).

Conclusions: Among black and white participants with similar baseline eGFR, neither black race nor APOL1 genotype is significantly associated with subsequent hospitalized AKI.

Funding: NIDDK Support

Baseline characteristics and risk of AKI among CRIC participants by APOL1 status.

Funding: NIDDK Support

FR-PO026
Renal Outcomes and Recovery in a Large Cohort of Critically Ill Patients Requiring Venoarterial or Venoovenous Extracorporeal Membrane Oxygenation and CRRT
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Background: The development of acute kidney injury in adult patients requiring venoarterial or venoovenous ECMO is very common. Many of these patients will require renal replacement therapy. Despite an extremely high mortality in such a patient population, centers are reporting improving outcomes with respect to survival. Little is known about the renal outcomes and renal recovery rate of those who required renal replacement therapy patients who survive to discharge.

Methods: Over the last 6 years, we have performed over 600 cannulations for VA or VV ECMO at our institution. Of these patients, 268 of them required renal replacement therapy for acute kidney injury. We have collected demographic and epidemiologic data as well as outcome data on those that have survived.

Results: Of the survivors, the cohort of patients most likely to recover renal function were patients with no prior known renal dysfunction who were on venoarterial ECMO. The patients most likely to require ongoing hemodialysis at the time of discharge were patients with heart failure who were on venoarterial ECMO. Diabetes seemed to be a major risk factor in overall renal recovery, as did preadmission creatinine levels. The patients most likely to require renal replacement therapy patients who survive to discharge.

Conclusions: Many of the traditional predictive measures for renal recovery after critical illness apply to the ECMO population. Despite having a large cohort of ECMO patients requiring renal replacement therapy, there is no clear pathway to being able to predict renal recovery.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Initial Lactate Level and Lactate Clearance on Renal Outcomes in Critically Ill Patients with Sepsis
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Background: Lactate and lactate clearance have been implicated as predictors of mortality in patients with sepsis. However, their roles for renal outcomes remain uncertain.

Methods: We retrospectively reviewed a total of 151 adult patients with sepsis who met the Sepsis-3 definition. Serum lactate levels were measured at initial and 24 hours from the intensive care unit admission. Among patients with initial lactate level ≥2 mmol/L, the lactate clearance was calculated as (initial lactate−24-hour lactate)/initial lactate × 100, then, they were divided as those with lactate clearance <20% and ≥20%.

Results: AKI occurred in 52 (68.4%) patients with initial lactate level <2 mmol/L and 69 (92.0%) in those with initial lactate level ≥2 mmol/L (P=0.001). In addition, patients with initial lactate level ≥2 mmol/L had higher probabilities of renal replacement therapy than those with its level <2 mmol/L, independent of age, sex, and the sequential organ failure assessment (SOFA) score. However, the lactate clearance was not related with AKI occurrence and renal replacement therapy use (OR=1.000 and 0.295). The lactate clearance <20% was associated with 28-day mortality, independent of age, sex, and the SOFA score (HR 3.8, 95% CI 1.5–9.7, P=0.005), but Initial lactate level was not (P=0.164).

Conclusions: In critically ill patients with sepsis, initial lactate level can predict the AKI occurrence and renal replacement therapy need, however, lactate clearance cannot. In addition, renal function recovery may be associated with neither initial lactate level nor lactate clearance.

Diastolic and Systolic Dysfunction on Renal Outcomes in Critically Ill Patients with Sepsis
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Background: Diastolic and systolic dysfunction have been regarded as predictors of mortality in patients with severe sepsis and septic shock. Myocardial dysfunction may contribute to hemodynamic instability and may result in organ failure, but their impacts on renal outcomes remain uncertain. In this study, we investigated the impacts of diastolic and systolic dysfunction on renal outcomes in critically ill patients with sepsis.

Methods: We retrospectively reviewed a total of 164 adult patients with sepsis who met the Sepsis-3 definition. Left ventricular (LV) function was assessed using echocardiography and 39 patients (24%) were excluded from the initial left ventricular unit admission. Systolic dysfunction was defined as an ejection fraction <50%, and diastolic dysfunction was defined as the septal E/e' ratio >15 among patients with ejection fraction ≥50%. Acute kidney injury (AKI) was defined using the KDIGO guideline.

Results: LV e' were 36 (22.6%) with normal LV function, 37 (22.6%) with diastolic dysfunction and 41 (25.0%) with systolic dysfunction. The incidence rate of AKI was 68.6%, 83.8% and 87.8% in the respective groups (P=0.029). Patients with diastolic and systolic dysfunction had more highly required renal replacement therapy than those with normal LV function, and these results persisted after the adjustment for age, sex, and the SOFA score (OR 3.4, 95% CI 1.4–8.5, P=0.045). Moreover, systolic dysfunction predicted 28-day mortality, independent of age, sex, and the SOFA score (HR 3.3, 95% CI 1.1–9.9, P=0.033), but systolic dysfunction did not (P=0.094 in multivariate analysis).

Conclusions: Both diastolic and systolic dysfunction could predict the AKI occurrence and renal replacement therapy need in critically ill patients with sepsis. More studies are needed to investigate individualized approaches according to LV function in this disease population.
AKI: After developing AKI, 30/67 (44.8%) children receiving NSAIDs and 10/16 (62.5%) children receiving angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers continued receiving them (Figure)

Conclusions: We identified gaps in provider adherence to AKI management guidelines in hospitalized children. We recommend establishing electronic health record-integrated best practice bundles to improve care for children with AKI

Funding: NIDDK Support

Percentage of patients continued on nephrotic medications after developing AKI

FR-PO032
Pediatric Kidney Stone-Associated AKI
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Background: Rates of stone AKI in children may be as high as 30%. Retrospective review examined children for AKI at emergency department (ED) visits for renal colic.

Methods: Retrospective: 1-26 years Akron Childrens Hospital 1/08-1/17. ICD code and radiographic evidence of stones or documentation by nephrologist. ED visits with + imaging for stones or physician documentation. Anthropometric, lab and management data were collected. AKI defined by Kidney Disease: Improving Global Outcomes, Acute Kidney Injury Network and Pediatric Risk Injury Failure End Stage criteria.

Results: 399 patients with 589 visits. 39% unique patients had data to assess AKI, with 33% AKI+. 36% visits had data to assess AKI with 27.7% +AKI. Data was not sufficient to assess for AKI in 65.6% of patients and 63.8% visits. Among AKI patients, 15% had documentation of AKI; 22% with Cr in lab documentation, but no mention of abnormal cr assessment/plan. 55.9% of AKI+ visits, patients were treated with NSAID in the ED. 47% of AKI+ visits were discharged home with NSAIDs.

Conclusions: Pediatric AKI due to stones is under recognized. 27.7% of ED stone visits AKI+. Only 64% of visits had data to assess AKI. Only 15% of AKI+ had documentation of AKI by physician of AKI, and 55% of AKI patients received NSAIDs. Concerning given known association of stones with chronic kidney disease.

FR-PO033
The Incidence and Frequency of Diagnosing AKI in Non-Critically Ill Pediatric Patients
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Background: Acute kidney injury (AKI) is commonly seen among hospitalized pediatric patients. Most studies have focused on critically ill patients and the incidence in non-critically ill (NCI) patients is less well studied. There has been only one study, McGregor et al (2016), that has looked at the incidence of AKI in this population and no studies evaluating the frequency of AKI diagnosis during NCI admissions. McGregor et al found that the rate of AKI among NCI patients to be 5%. The purpose of our study is to validate the finding of McGregor et al and to assess the frequency of provider diagnosis of AKI in NCI patients during admission.

Methods: We performed a retrospective cohort study on all patients admitted to the NCI hospitalist service at our tertiary care pediatric hospital between July 1 2017 and June 31 2018. Patients included in the study were between the ages of 2 weeks and 18 years without history of chronic kidney disease or intensive care unit admission at any time of their hospitalization, and who had 2 or more serum creatinine values. We used the KDIGO criteria, defined as serum creatinine increase by ≥0.3mg/dl within 48 hours or increase by a 1.5 times the baseline within 7 days, to identify patients with AKI. Of those identified with AKI, we reviewed the chart to assess whether providers had identified the AKI during the admission.

Results: Of the 14,495 patients admitted, 1,223 (8%) patients were included in the study. 132 (10.8 %) patients met the KDIGO criteria for AKI. Of these 132 patients, only 51 (37.8%) were identified to have AKI by providers during their admission.

Conclusions: Our study suggests that the incidence of AKI in the NCI setting is higher than previously reported; 10.8% of NCI patients in our institution had AKI, compared to the 5% reported by McGregor et al. Since we were only able to analyze 8% of the total patients admitted, due in part to lack of data, it is possible that the rate of AKI is even higher. This shows the limitations of applying the KDIGO criteria in diagnosing AKI in the clinical setting. We also found the frequency of identifying AKI was low at 37.8%. As prompt identification of AKI is crucial in preserving kidney function, new strategies are needed to help providers identify these patients.

FR-PO034
Use of Tramadol and Reduced Risk of AKI in Hospitalized Children
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Background: Various interventions have been reported to prevent the development of AKI, but only few have been validated in children. This study is aimed to investigate the potential renoprotective effect of tramadol on the risk of pediatric AKI.

Methods: We conducted a multicenter retrospective cohort study in hospitalized children aged 1 month to 18 years from 25 tertiary hospitals across China during 2013-2015. Patient-level data were obtained from the electronic hospitalization information system. The outcome was hospital-acquired (HA-)AKI. AKI was defined and staged by Kidney Disease Improving Global Outcomes criteria. Patients who developed AKI after two days of admission were identified as having HA-AKI. We used a cox proportional hazards model to estimate the risk of HA-AKI, in which exposure to tramadol was modeled as a time-varying variable.
Results: Among 46295 children analyzed, 1779 (3.8%) used tramadol and 3555 (7.6%) had HA-AKI events during hospitalization. Most of tramadol (53.18%) was prescribed for postoperative analgesia. After adjusting for demographics status, prevalent comorbidities and concomitant use of medications, use of tramadol was associated with a significantly reduced risk of HA-AKI compared with non-users (HR 0.20; 95% CI, 0.15-0.27). The results were consistent in subgroups and multiple sensitivity analysis. An increasing cumulative dosage of tramadol use was associated with a graded lower risk of HA-AKI.

Conclusions: Tramadol was associated with a reduced risk of HA-AKI in hospitalized children. Future intervention study should evaluate whether tramadol use could prevent AKI in high risk patients.

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FR-PO035
Prevalence, Risk Factors, and Prognosis of AKI in Pediatric Nephrotic Syndrome
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Background: Children with nephrotic syndrome (NS) are at an increased risk of severe infection, thrombosis, and acute kidney injury (AKI). In NS patients, AKI was associated with an increased risk of chronic kidney injury, and its incidence is increasing. Despite this, there is limited data regarding the epidemiology and risk factors of AKI in pediatric NS patients. Thus, the aim of this study was to investigate the incidence, clinical profiles, and risk factors of AKI in pediatric NS patients.

Methods: This was a retrospective multicenter study involving 14 pediatric nephrology centers. From 2013 to 2017, a total of 814 patients with idiopathic NS were reviewed, and 487 patients hospitalized for NS were analyzed.

Results: Among 363 children, 574 hospitalizations occurred. AKI occurred in 10.9% (89 patients) of the 814 children with NS and 16.2% of the 363 children who were hospitalized. Among the 588 cases of hospitalization, AKI was found in 93 (16.2%) cases:

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

FR-PO036
Rhabdomyolysis in Young Adults
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Background: Rhabdomyolysis is a clinical entity that directly causes AKI and is associated with a subsequent increase in patient mortality. The primary means of diagnosis is via clinical suspicion from patient history, clinician knowledge of risk factors, and laboratory testing such as the utilization of CK for diagnosis. However, patient risk factors are dependent upon age and if not adequately assessed can lead to a missed diagnosis. Furthermore, other serum markers can potentially be used to aid in prognosis. Our study seeks to describe the risk factors for rhabdomyolysis in adults younger than 50 years. It explores etiology and demographic characteristics in relation to several important outcomes of stay, and short-term outcomes. Finally, it indicates the accuracy of NLR as a prognostic tool.

Methods: A single-center retrospective cohort study was completed to evaluate patients admitted to hospital for primary diagnosis of rhabdomyolysis. NLR was calculated and compared to AKI levels to determine association and assistance with diagnosis.

Results: 331 rhabdomyolysis patients were included in the study. Data were stratified into 3 groups based on CK level (1500-5000, 5000-50000, >50000 IU/L). 34.83% of cases were due to illicit drugs with 80% attributed to Heroin and/or Cocaine use. Drug use was also the major etiology (28.1%) when CK level was 1500 - 50000 IU/L. The second leading cause of rhabdomyolysis was exercise-induced (16.47%). Exercise was the major etiology (40%) in subjects with CK levels above 50000 IU/L. Subjects with exercise-induced rhabdomyolysis had a median serum CK (8,840) more than twice the median for the entire group (4,012), but their median length of stay (2 days) was half the entire group’s median (4 days). On the other hand, there was a statistically significant positive correlation between the NLR (4.79, 5.61, and 10.19 respectively) and the length of stay (4.58, 6.59, 7.8 days respectively) (p<0.001; Spearman correlation 0.22).

Conclusions: Illicit drug use was the major cause of rhabdomyolysis in adults < 50 years old. Exercise was the second leading cause of rhabdomyolysis with a higher median serum CK but lower than the median length of stay indicating that AKI is not an accurate prognostic indicator. NLR has a positive correlation to serum CK and the total length of stay suggesting it is an important prognostic biomarker. Larger studies in different patient populations are warranted to validate findings.

FR-PO037
Change in Right Ventricular Systolic Function After CRRT Initiation and Renal Recovery

Background: Echocardiographic parameters have been associated with outcomes in patients on continuous renal replacement therapy (CRRT). We investigate the impact of CRRT on echocardiographic parameters and the association between improvement of these parameters with renal recovery and mortality.

Methods: This is a retrospective analysis of patients admitted to the intensive care units (ICU) at a tertiary care hospital from December 2006 through November 2015 who underwent CRRT and had an echocardiogram available within 4 weeks from CRRT initiation. The primary outcome was Major Adverse Kidney Events at day 90 (MAKE90). Multivariable logistic regression was performed to identify independent predictors ofMAKE90. Secondary outcome included mortality at 30 days.

Results: The cohort included 303 patients with acute kidney injury (AKI). The median age was 62 (IQR 52-71) years with 130 (43%) female and median SOFA on the day of CRRT initiation 12 (IQR 10-14). Overall 110 (36.5%) patients on CRRT had improvement in RV systolic function (43% vs. 67%), or had 20% reduction in RVSP (35% vs 59%), p<0.05 for both. On multivariate logistic regression, the improvement in RV systolic function (adjusted OR 23.07; 95% CI, 12.06-44.21) and 20% reduction in RVSP (OR 23.17; 95% CI, 12.06-44.21), p<0.05 were associated with lower MAKE90 after adjusting for age, SOFA score, fluid balance before CRRT initiation and baseline serum creatinine. For 30-day mortality, adjusted hazard ratio (HR) for improvement in RV systolic function was 0.48 (95%CI: 0.24-0.93, p<0.031). Patients who had an improvement in their RV systolic function were in negative fluid balance leading to the day of repeat echocardiogram -2.1L vs. +0.22L, p=0.026.
FR-PO038
Net Ultrafiltration Rate and Its Impact on Mortality in Patients with AKI Receiving CRRT
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Background: Fluid overload, a critical consequence of acute kidney injury (AKI), is associated with worse outcomes. The optimal volume of fluid removed per day during continuous renal replacement therapy (CRRT) is unknown. The purpose of this study is to evaluate the impact of ultrafiltration rate on mortality in critically ill patients with AKI receiving CRRT.

Methods: We retrospectively reviewed 1,398 patients with AKI who received CRRT between December 2006 and November 2015 at Mayo Clinic, Rochester, MN. The net ultrafiltration rate (UFi) was categorized into low- and high-intensity groups (< 35 and ≥ 35 ml/kg/day, respectively). The impact of different UFi intensities on 30-day mortality was assessed using logistic regression after adjusting for age, sex, body mass index, fluid balance from ICU admission to CRRT initiation, APACHE III and SOFA scores, baseline serum creatinine, ICU day at CRRT initiation, Charlson comorbidity index, and need for mechanical ventilation.

Results: The mean age was 62±15 years, 82% (594) were male. There were 969 patients (68.5%) in low- and 58.5% in high-intensity groups. Thirty-day mortality was 755 (54%). There were 420 (64%) deaths in low- and 335 (48%) in high-intensity group (p<0.001). UFi≥35 was 77±35 ml/kg/day remained independently associated with lower 30-day mortality (adjusted odds ratio (aOR): 0.49; 95% CI: 0.39-0.63, p<0.001) compared to <35 ml/kg/day.

Conclusions: More intensive fluid removal, UFi≥35 > 35 ml/kg/day among AKI patients receiving CRRT is associated with lower mortality. Future prospective studies are required to confirm such a finding.

FR-PO039
CKD and AKI Outcomes After Left Ventricular Assist Device Implantation
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Background: Left ventricular assist devices (LVAD) are used as a bridge to heart transplant or destination therapy for patients with end-stage heart failure. Acute kidney injury (AKI) or need for renal replacement therapy (RRT) post LVAD implant can lead to poor outcomes. Identifying risk factors of AKI post LVAD can help stratify LVAD candidates.

Methods: A retrospective study of all patients who received continuous-flow LVAD at our institution from January 2015 until August 2017. We calculated incidence of AKI and need for RRT post LVAD implant, rate of renal recovery and survival rates at 30 days and 1-year post implant. Presence of Chronic kidney disease (CKD) with staging and proteinuria was assessed and a prior kidney ultrasound (KU) was reviewed for all patients if available. CKD was present if eGFR<60 ml/min per 1.73m2 for >3 months preceding LVAD implant and/or proteinuria≥20mg/dl on 2 or more urine analysis prior to implant and/or an abnormal KU with increased echogenicity or small size <9 cm. AKI was defined per KDIGO guidelines.

Results: A total of 137 patients received LVAD. 112 males and 25 females with mean age of 59±2 years. Race: 64 Caucasians, 38 Africans, 30 Hispanics and 5 Asians. Incidence of AKI and need for RRT during hospitalization post LVAD implant were calculated in all patients and in sub-groups based on the presence of CKD, underlying CKD stage, proteinuria and KU findings. See table. 30 day and 1-year mortality rates post LVAD implant were 4.3% and 21.1%, respectively. Out of the 27 patients requiring RRT, 9 (33.3%) were off RRT at 1 year. Compared to eGFR on day of LVAD implant, eGFR at 30 days LVAD showed 57% patients with higher and 42% with lower eGFR. At 1 year, eGFR was higher in 32% and lower in 67% patients.

Conclusions: Incidence of AKI and need for RRT post LVAD implant are very high. Of all patients, 2 out of 3 patients had a lower eGFR at 1-year post implant and only 1 out of 3 patients requiring RRT recovered at 1-year post implant. Presence of CKD, advanced CKD stage and abnormal KU are statistically significant (P<0.05) risk factors of AKI post LVAD and/or need for RRT.

FR-PO040
The Influence of Left Ventricular Assist Device Implantation on Short-Term and Long-Term Renal Functions in End-Stage Heart Failure Patients
Anar Sadigov,1 EmreDemir,2 Sanem Nalbantgil,2 Cenk Demirci,1 Cagatay Engin,1 Tahsin Yadig,2 Pelin Ozturk,2 Mustafa Ozbaran,3 Meltem Sezis Demirci,1 Ege University,1 Fresenius Medical Care, Izmir, Turkey; 2Ege University Medical Faculty, Izmir, Turkey.

Background: Left Ventricular Assist Devices(LVAD) are used as an interventional treatment method for patients with decompensated heart failure(HF). The aim of this study is to retrospectively evaluate the short and long-term effects of LVAD implantation on renal function and survival in patients with end-stage HF.

Methods: 329 patients with LVAD were investigated. Basal and follow-up GFR(KDIGO-Ep) values were calculated retrospectively. Patients were divided into three groups based to baseline GFR; group 1(GFR<60), group 2(GFR 60-90) and group 3(GFR>90). SPSS 22.0 software was used for all statistical analyses.

Results: The mean age of the patients was 50.8±13.2, 86% was male, mean basal GFR was 77.6±25.7 ml/min, 29.5% patients had DM, 34.1% had HT. Mean follow-up time was 22.6±17.9(0.2-71.6) months. There was a significant increase in mean GFR values of all patients in the postop first month(p<0.01). In group 1, there was a significant increase in GFR at 1, 12, 24 months after implantation compared to baseline(p<0.001), but this increase was not significant at 36 months(p=0.08). One-year transplantation-censored survival was 81.9%, 70.3% for 2-year, 55.8% for 4 and 5-years. The survival rate at first year was 87.9% in group 3, 81.9% in group 2 and 76.2% in group 1. Patients with postoperation first month GFR increase≥227, 2-year survival rate was 73%, 4-year was 58% and patients with not increase GFR≥69, 2-year survival rate was 56% and 4-year was 38%(p<0.01).

Conclusions: In patients with LVAD, short- and long-term results are quite good in terms of renal function. Even though GFR was low before, we observed that there was a significant improvement in GFR after LVAD implantation and this improvement continued for the first 3 years.

FR-PO041
Safety and Efficacy of In-Series Continuous Renal Replacement Therapy in Patients on Venoarterial and Venovenous Extracorporeal Membrane Oxygenation
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Background: There is no standardization or consensus on performing continuous renal replacement therapy in patients on extracorporeal membrane oxygenation in the adult population. Given the limited access points available for patients on extracorporeal membrane oxygenation, it has been the practice at our institution to run CRRT in line with ECMO and then transition to a tunneled dialysis catheter at the time of ECMO decannulation.

Methods: We have performed over 600 ECMO cannulations, 268 of which have required dialysis for renal failure and metabolic clearance or primarily for ultrafiltration and volume removal. Of these 268, we performed CRRT in series on 265 of them using the Nxtstage System One with both the Maquet Rotaflow as well as Cardiohelp ECMO systems. There are two separate connections used on the rotaflow ECMO circuit, and a single connection in the Cardi helped system detailed in the images attached.

Results: In 265 patients, we successfully performed well over 1000 dialysis days of treatments in series with ECMO with virtually no complications. Efficacy was determined by adequate control of acid/base abnormalities as well as overall clearance of urea. Volume removal was typically determine by the overall hemodynamics of the patient, but there were no machine or circuit imitations regarding ultrafiltration.

Conclusions: We have found and demonstrated safety and efficacy of in series CRRT with ECMO in the adult population in a large cohort of patients.
FR-PO042

Use of Nesiritide in Total Artificial Heart to Rescue From Dialysis Dependence
Christophbert Hebert, Kidney and Hypertension Associates of Dallas, Dallas, TX.

Introduction: It is well described in the literature that patients with total artificial heart implantation as a bridge to transplant have low atrial natriuretic peptide levels. Patients post ventriculotomy may lose the ability to produce urine in some cases as a consequence to having low AINP levels.

Case Description: We present a 56yo man who underwent total artificial heart implantation. Post operatively, he developed severe shock and was placed on VA ECMO as well as CRRT. He was initially on nesiritide post operatively but after a relatively quick decannulation and cessation of nesiritide in 48 hours, he became anuric and required ongoing hemodialysis. After 10 days of hemodialysis, it was decided to restart nesiritide as a trial to see if we could promote some urine production. On day 1, he made a liter of urine and by day 6 his creatinine had gone from 6 to 1.3 and he no longer required dialysis. He was discharged home and received a heart transplant a month later. To date, he remains off dialysis with creatinine level of 1.0

Discussion: There are a few case reports detailing such a response to nesiritide. This particular case was an extreme example of a patient going from an anuric state on hemodialysis with really no ability to discharge him from the hospital, to making ample urine and recovering renal function.

FR-PO043

The Role of Perioperative Renal Replacement Therapy in Heart Transplantation
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Background: Heart transplantation (HT) is the treatment of choice for patients with end-stage heart failure. Although several studies had reports about association with acute kidney injury (AKI) and HT, little is known about the impact of perioperative renal replacement therapy (RRT) on clinical outcomes of HT. We compared the clinical characteristics and outcome of patients according to RRT at the time of HT.

Methods: A total of 23 patients were underwent heart transplantation from January 1995 to May 2019 at Seoul St. Mary's hospital and Eunpyeong St. Mary’s hospital. The most recent patient was excluded because of the short follow-up duration. We reviewed data including the cause of heart failure, cardiac function and renal function based on electronic medical records. The patients were divided as heart transplant recipients (HTRs) who underwent perioperative RRT (RRT group, n=9) and HTRs who did not receive RRT (non-RRT group, n=14). Renal function was analyzed at baseline, 1 month, 3 months, 6 months and 12 months after HT.

Results: The most common cause of HT was dilated cardiomyopathy (n=11, 50%), then followed by ischemic cardiomyopathy (n=8, 36%). The LVEF before HT in the RRT group was significantly lower than that of the non-RRT group (LVEF 15.2 % vs 24.8%, P=0.014, respectively). In the RRT group, six patients (27.6%) underwent RRT before HT including with five patients of continuous renal replacement therapy (CRRRT) and a patient of peritoneal dialysis. Finally, eight patients (36.4%) received RRT before and after HT, including five patients who initiated RRT prior to transplantation. After 1 month and 6 months post-transplantation, the renal function of RRT group were significantly worse than that of non-RRT patients (eGFR 40.95 vs 63.48 ml/min/1.73m²; p=0.031, after 1 month; 39.40 vs 71.01 ml/min/1.73m²; p=0.011, after 6 months). However, after 12 months post-transplantation, there was no significant difference of renal function between RRT group and non-RRT groups (eGFR 54.98 vs 68.30 ml/min/1.73m²; p=0.294). All the patients in the RRT group were tolerated without dialysis after HT.

Conclusions: RRT at the perioperative period in the heart transplant recipients will be a good bridge therapy for recovery of renal function in the cases with a high risk of cardiorenal AKI with low LVEF.

FR-PO044

Impact of Intermittent Online Hemodiafiltration vs. High-Flux Hemodialysis on Markers of Inflammation and Fluid Status Assessed by Bioimpedance Analysis in Septic AKI Patients: A Randomized Trial
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Background: In sepsis, fluid status is a widely accepted challenge. Traditional approaches such as CRRT have limited utility. Bioimpedance (BI) has been used in CKD patients for dry weight assessment and studies have shown cardiovascular benefits when BI was utilised for fluid status assessment. We aimed at comparing impact of two modes of clearance i.e online HDF and high flux HDF on fluid status and inflammation markers as assessed by BI analysis.

Methods: This pilot study was conducted in PGIMER, India between Sep 2017 to Sep 2018. Non critically ill septic AKI patients requiring dialysis were included. Patients in ICU and those requiring more than one ionotrope and/or mechanical ventilation were excluded. All patients underwent either HDF or CRRT. BI was assessed with BIOMED-3 system at specified intervals i.e before commencement of RRT, alternate day for 1 week, weekly till discharge and during 1st and 3rd monthly visits. All patients were followed for a period of 3 months from discharge. Plasma cytokine (IL6, ak TFN alpha) levels were assessed before and after one week of RRT initiation.

Results: 80 patients were randomized in each RRT arm. Baseline characteristics and sepsis parameters were comparable. Phase angle (PA), body cell mass (BCM), extracellular water (ECW) and Total body water (TBW) at baseline were comparable. No significant improvement in BCM and PA were noted at 1 month however significant improvement seen at 3rd month. Mean PA at initiation of RRT and at 1 month after discharge was 6.05 and 10.5 respectively (P=0.0628). Likewise, no difference in plasma cytokine clearance was noted between the arms. At 3 months overall change in PA within the arms was significant (p=0.003), with no difference across the arms. BI and PA correlation was assessed at 3 months. Mean of diRRT at day 37 was 37.28 ml/min and 30 day mortality was 12.5%.

Conclusions: Phase angle and body cell mass correlated with other traditional markers of sepsis. There was no differential impact of convective and diffusive clearance on PA and BCM when applied intermittently.

Funding: Government Support - Non-U.S.

FR-PO045

Mortality in Patients with Sepsis and Non-Sepsis AKI Requiring CRRT: A Retrospective Single-Center Experience
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Background: Short term and long term renal and survival outcomes of pts who undergo CRRT is highly variable in published literature. We have done a retrospective analysis on patients who have required CRRT at our institution over a 3 year period and have analyzed their survival outcomes based on their reason for initiation of CRRT.

Methods: Single center retrospective analysis on all patients who underwent CRRT between January 2015 and December 2017 were included for the analysis. Patients who expired within 12 hours after initiation of CRRT were excluded. All the patients underwent CRRT (CVVHDF) using the Prismaflex machine. Patients were grouped under sepsis (sepsis group) vs other etiologies (non-sepsis group) based on the reason for initiation of CRRT. Baseline characteristics and overall outcomes were analyzed between the 2 groups across multiple variables including comorbidities. Comparisons were made using T-test and correlations on primary outcomes based on need for CRRT was done using Pearson’s test. Each variable was independently correlated with etiology of CRRT using logistic multiple regression analysis.

Results: Sepsis was the underlying etiology for initiating CRRT in 64% of pts. Cardiogenic shock was the most common cause for the rest. Patient groups were comparable across all variables analyzed. There was 51% mortality in the patients who needed CRRT in the study population. Mortality was 55% in patients in the sepsis group and 48% in non-sepsis group (p=0.4). Mean duration of CRRT in patients with sepsis who were alive at the end of 1 month was 7.1 (5.5) days and 3.2 (2.8) days in pts who were in non-sepsis group (p=0.001).

Conclusions: Hemodynamically unstable patients who were initiated on CRRT irrespective of sepsis or non-sepsis etiology had a significantly high mortality at the end of 30 days. Patients initiated for CRRT due to sepsis had more than patients in the non-sepsis group. However randomized clinical trials are needed to compare the need and efficacy of CRRT on renal and survival outcomes in patients requiring continuous slow dialysis.

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FR-PO046

Outcomes with Implementing CRRT in a Community Hospital

Maggie Kim, Dae joong Park, Sung Jun Yoo, Seok Hoon Hwang, Min Soo Oh, Jang Jin Park, Jung eun Lee, Soo Young Park, Dae jeong Kim, Hye Ryoun Jang, Young Ho Kim, Young Bae Kim, Ki Seok Park, Yun Young Yoon, Kun Young Kwon, Jang Ho Lee, Sung Min Lee, Young Tae Kim, Seung Min Park, Chang Su Lee, Soo Hyun Bae, Boon Sung Yoon, Yeon Soo Shim, Jin Young Park, Jun Young Kim, Sung Joon Park, Sung Jin Park, Young Min Lee, Jang Gun Choi, Sung Min Park, Jun Hyuk Kim, Jang Soo Kim, Yong Jin Park, Jang Hyun Park, Soo Young Park, Jee Hang Ahn,根 92% were Caucasian with a male predominance (62%). The prevalence of Hypertension was 75%, Anemia 70%, CKD 47%, Multisorgan Failure 79%, Mechanical Ventilation 73% and ECMO 12%. Our mean duration of CRRT days was 3.84 in 2016, 2.53 in 2017, and 2.2 in 2018. The average direct total cost of hospitalization was $82,858. Our mortality rate was 51%. Patient dispositions: home 21%, LTAC 11%, Rehab 9%, SNF 8%, Hospice 6% and Decedent 45%.

Conclusions: Our community hospital implementation of CRRT over a two year period had a mortality rate of 50.9%, which was better than mortality rates found in the literature of ~62%. CRRT in our community setting was associated with similar to better outcomes than reported in literature. We attribute this to a common CRRT EMR order set, limited settings in which CRRT is utilized (medical and surgical ICU) and intuition of CRRT limited to nephrologists.

FR-PO047

Continuous Renal Replacement Therapy with AN69ST Membrane Reduces Plasma IL-8 in Sepsis Patients

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Background: Polyethyleneimine-coated polycrylonitrile (AN69ST) membrane has a hydrogel structure, which enables adsorption and thereby exhibits an increased capacity for cytokine removal in continuous renal replacement therapy (CRRT). This capability is expected to improve the outcomes of severe sepsis and septic shock. IL-8 is a chemokine with a molecular weight of 8000 MW and is known as a neutrophil chemotactic factor in sepsis.

Methods: APACHE II scores after ICU admission were evaluated for 23 sepsis patients. Patients with sepsis underwent CRRT using the AN69ST membrane. Plasma IL-8 was measured at the start of CRRT and 24 hours after the start of CRRT. At the start of CRRT, plasma IL-8 was measured pre AN69ST membrane and post. Patients were divided into two groups: survival group and death group.

Results: There were 11 cases in the survival group and 11 cases in the death group. The APACHE II score was 25.0 (20.5-30.0). Plasma IL-8 at the start of CRRT was 87.3 (28.1-182.8) pg/mL and was significantly reduced to 35.9 (19.6-62.0) pg/mL 24 hours after initiation of CRRT (P < 0.01). At the start of CRRT, plasma IL-8 was significantly reduced to 31.2 (13.1-65.9) pg/mL downstream of the AN69ST membrane (P < 0.01). Logistic analysis for death was associated with age (1.15, 95%CI:1.02-1.49, P = 0.02), and plasma IL-8 reduction rates at 24 hours after CRRT initiation (0.89, 95%CI:0.74-0.96, P < 0.01).

Conclusions: CRRT with the AN69ST membrane reduces plasma IL-8 in sepsis patients. Our results suggest that plasma IL-8 reduction rate 24 hours after initiation of CRRT is an independent contributing factor to death.

FR-PO048

Effects of a Novel CRRT Fluid Protocol on Electrolyte Stability

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Background: Continuous renal replacement therapy (CRRT) is the standard treatment for critically ill patients with acute kidney injury. During CRRT, electrolyte disturbance such as hypokalemia or hypophosphatemia frequently occurs unless dialysate and replacement solutions are adequately adjusted. Samsung Medical Center CRRT team developed a new protocol to prevent electrolyte disturbance by adjusting dialysate and replacement fluids depending on serial changes in serum potassium and phosphorus levels. We evaluated the impact of the new CRRT fluid protocol on electrolyte stability.

Methods: Adult patients who received CRRT for 3 days or more during the previous two years (2013 to 2014; pre-protocol group) and the last two years (2016 to 2017; protocol group) following the development of the fluid protocol were compared. Individual coefficient of variation (CV) and the number of abnormal measurements for electrolytes during CRRT were analyzed. The frequency of potassium, phosphorus, or magnesium replacement therapy was also compared. The Wilcoxon rank sum test was used for analysis.

Results: A total of 1456 patients were included. There were no significant differences in age, gender, and CRRT duration between the two groups. The CRVOsferum potassium was lower in the protocol group (pre-protocol group vs. protocol group, 0.113 [0.066 - 0.160] vs. 0.092 [0.052 - 0.132], p = 0.0001). The CV of serum phosphorus was also lower in the protocol group (pre-protocol group vs. protocol group, 0.292 [0.173 - 0.411] vs. 0.248 [0.140 - 0.356], p < 0.0001). The event rates of abnormal potassium levels (pre-protocol group vs. protocol group, 0.205 [0.199 - 0.211] vs. 0.083 [0.079 - 0.087], p < 0.0001) and abnormal phosphorus levels (pre-protocol group vs. protocol group, 0.406 [0.398 - 0.415] vs. 0.280 [0.273 - 0.286], p = 0.0001) were lower in the protocol group. The CV of serum magnesium, sodium, and ionized calcium was also lower in the protocol group. The frequency of potassium, phosphorus, and magnesium replacement was significantly reduced after application of our new CRRT fluid protocol (p < 0.0001).

Conclusions: Our novel CRRT fluid protocol significantly increased electrolyte stability and consequently prevented electrolyte disturbance during CRRT.

Figure 1: Temporal distribution of hypotensive events between higher intensity and standard intensity CRRT treatment groups in the ATN trial

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO050

The Effect of Therapeutic Hypothermia on Urine Output After Cardio-pulmonary Resuscitation

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Background: Therapeutic temperature management (TTM) is strongly recommended by the 2015 International Liaison Committee on Resuscitation as a component of post-resuscitation care. It has been known to be effective in improving the survival rate and neurologic functional outcome of patients after cardiac arrest. While commonly described cold diuresis, renal tubular function is diminished in the induction and maintenance phase of TTM, few studies have characterized cold-induced diuresis or warm anti-diuresis during TTM. In this study, we sought to characterize urine output changes during postcardiac arrest therapeutic hypothermia.

Methods: We conducted retrospective cohort study to determine urine output changes during TTM of the postcardiac arrest patients. We analyzed 104 patients who underwent all phase TTM for 3 years from Jan 1, 2012 to Dec 31, 2014. We calculated the hourly IV fluid input and urine output rates for each TTM phase. We fit a generalized linear mixed model with each TTM phase as a categorical variable to compare the urine output at each phase of analysis.

Results: Four-fifths of the patients suffered out-of-hospital arrest. Approximately 70% survived to hospital discharge. Urine output rate was highest at 249 ± 255.7 mL/hr in the hypothermia induction phase but lowest at 96 ± 6.53 mL/hr during re-warming phase even though total I/O showed the most positive balance during the re-warming phase.

Conclusions: We observed modest increases in urine output during induction phase of TTM. This has important implications for fluid management in patients undergoing therapeutic hypothermia. We will collaborate with the statistics team to analyze changes in continuous urine output and overall I / O data rather than average data of the larger number of patients.

FR-PO051

A Study of Severe Tropical AKI Requiring Renal Replacement Therapy in a Tertiary Care Hospital in South India

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Background: The etiology of tropical AKI can be divided into infections, toxins, poisons and miscellaneous causes like heat stroke and obstetric AKI etc. Acute tubular injury occurring secondary to community acquired infections remains the commonest cause of tropical AKI. Through this study we attempt to study the causes and factors associated with mortality and morbidity of severe AKI requiring RRT in southern India

Methods: This is a retrospective observational study done in Narayana Medical College, Nellore. Patients admitted in the ICU with AKI within a period of 3 years (2016-2018) were screened. Patients with non-tropical causes of AKI and AKI not requiring RRT were excluded from the study. The baseline eGFR was calculated according to the MDRD 75 formula. All patients eGFR was calculated 3 months after discharge to look for recovery or classify as CKD. Complete recovery was defined as improvement in the eGFR to more than the calculated baseline eGFR, at the end of 3 months after discharge.

Results: A total of 130 patients were studied with the mean age of presentation being 42.7 years and 62.3% (n=81) of the patients were males. The mean duration of stay in the hospital was 12.35 days. 8.4% (n=11) patients received peritoneal dialysis and 91.5% (n=119) received hemodialysis (HD). The most common etiology of AKI was acute gastroenteritis (40.7%) followed by snake bite (15.3%), hair dye poisoning (11.5%), malaria (9.2%), obstetric AKI (6.9%), Dengue (5.3%), leptospirosis (3.8%), scrub typhus (3.0%), rhodamolysis (1.3%), parquat poisoning (0.7%) and petrol products consumption (0.7%). 96.9% patients presented with KDIGO stage 3 of AKI with average eGFR of 9.72. The average eGFR after 3 months of discharge was 40.93. Out of 130 patients 18.4% recovered completely, 14.6% (n=19) expired and 66.92% progressed to CKD. Snake bite, dengue fever, thrombocytopenia, presence of diabetes mellitus, hypertension and coronary artery disease were independently associated with progression towards to CKD. Parquat poisoning and petrol product ingestion were independently associated with death.

Conclusions: Severe tropical AKI requiring RRT holds a poor prognosis with majority of patients progressing to CKD.

FR-PO052

The Interactive Effects of Input and Output on Managing Fluid Balance in Patients with AKI Requiring Continuous Renal Replacement Therapy

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Background: Fluid balance is a key factor for better survival rate in patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT). However, appropriate regulation of input and output to achieve optimal fluid balance is not well elucidated yet. This study aimed to evaluate the effect of fluid components on morbidity and mortality of severe AKI requiring CRRT.

Methods: A total of 258 patients who were in the intensive care units of Ewha Womans University Hospital and who required CRRT were enrolled (from 2016 to 2018). The amounts of fluid input and output were assessed by electronic medical charts with 24-hr and 72-hr intervals immediate after initiation of CRRT. The study endpoints were 7-, 14-, and 28-days all-cause mortality.

Results: The mean age of study subjects were 64.7 ± 15.8 years and 165 (64.0%) were male. The 28-day mortality was observed 118 (53.9%) cases during the follow-up. The amounts of cumulative fluid balance and cumulative input were higher and cumulative output was lower in non-survivors compared to survivors during 72-hr after CRRT initiation. A positive value of both 24-hr and 72-hr assessed cumulative fluid balance was associated with increased risk for 7-, 14-, and 28-days mortality. When the subjects were classified according to tertiles of total fluid output or input, the increasing amount of cumulative fluid balance assessed with 24-hr and 72-hr was associated with the increased risk for mortality irrespective of tertiles of total input. However, increasing amount of cumulative fluid balance was not associated with the mortality risk according to tertiles of output.

Conclusions: The impact of CBF on mortality might be more dependent on cumulative output. The physicians need to decrease the CBF of CRRT patients as much as possible and consider increasing patient removal.

Funding: Government Support - Non-U.S.

FR-PO053

Fluid Balance After Continuous Renal Replacement Therapy: Is a Predictor of Mortality

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Background: Higher cumulative fluid balance in critically ill patients was associated with hospital mortality. Inbody, impedance body fat analyzer, can measure body water, and segmental water values. In this study, we examined the fluid balance by time using bioimpedance analysis (inbody), and investigated the association of fluid balance with clinical outcomes in the CRRT patients.

Methods: Among the patients who started CRRT at multi-center from May 2017 to March 2018, Inbody was measured at D0, D1, D2, and D7. Fluid overload was defined when either of the following two conditions is met; at day 7, TBW/height was more than 13 L/m² or the change of body weight more than 5%. Reaching euvolemia was defined when either of the following two conditions is met; at day 7, TBW/height was less than 13 L/m² or the change during 7 days was less than -2.1 L/m². The association with 60-days mortality was investigated.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: 72% patients showed fluid overload. These patients were younger and had lower urine amount during 2 hours before CRRT, and started CRRT later compared to those without fluid overload. The change of body weight and TBW/height² at CRRT initiation were much more than those without fluid overload. There is no statistical significance; however, the patients with fluid overload at CRRT initiation were shown to have a higher risk for mortality. Among the patients with fluid overload, 36 patients reached euvolemia at 7 days after CRRT initiation. Comparing with patients who failed to reach euvolemia, TBW/height² at each time point and delta value during 7 days were significantly lower in the patients who reached euvolemia. Failing to reach euvolemia was a risk factor of 60-day mortality. After adjusted for age, gender, BMI, Charlson comorbidity index, APACHE II, and SOFA score, failing to reach euvolemia were closely correlated with 60-day mortality, doubling the risk of mortality.

Conclusions: Fluid overload at CRRT initiation, defined based on the change of body weight and TBW/height², was associated with the 60-day mortality. Based on the definition using TBW/height² measured by InBody6, patients who failed to reach euvolemic status within 7 days after CRRT initiation showed a higher mortality rate, compared to those who reached euvoletic status.

FR-PO054
The Use of Machine Learning to Predict the Renal Replacement Therapy-Free Survival in Patients Who Require Continuous Renal Replacement Therapy
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Background: AKI in critically ill patients is common and continuous renal replacement therapy (CRRT) is the preferential mode of renal replacement therapy patients who are hemodynamically unstable. Prior studies have yielded conflicting results for predictors of CRRT discontinuation and mortality. Therefore, we tested machine learning algorithms for predicting renal replacement therapy-free survival (RRTFS) in patients who required CRRT.

Methods: We used the Medical Information Mart for Intensive Care III database to identify patients ≥18 years old, and who had AKI requiring CRRT for ≥24 hours. ESRD patients were excluded. RRTFS was defined as patients who were discharged alive and did not require RRT 7 days prior to hospital discharge. Five machine learning algorithms: the multi-layer perceptron neural network (MLP), random forest (RF), support-vector machine (SVM), logistic least absolute shrinkage and selection operator (LASSO) and logistic regression were trained. We evaluated model performance using area under the receiver operating characteristic curves (AUCs) from original scoring systems and the machine learning-based mortality-prediction may be needed when starting CRRT.

Funding: NIDDK, Support

Figure 1 The receiver operating characteristic curves and the area under the receiver operating characteristic (AUROC) for predicting the RRT-free survival after CRRT using machine learning algorithms the multi-layer perceptron neural network (MLP), random forest, support-vector machine (SVM), logistic least absolute shrinkage and selection operator (LASSO) and logistic regression

FR-PO055
Machine Learning Algorithm to Predict Mortality in Patients Undergoing Continuous Renal Replacement Therapy
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Background: Many scoring systems such as the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) and the Sequential Organ Failure Assessment (SOFA) have been used in predicting outcomes in patients admitted to the intensive care unit (ICU), but these original systems show poor predictability in the subset of patients undergoing continuous renal replacement therapy (CRRT). Accordingly, this study developed the machine learning model to improve the predictability in this subset.

Methods: 1,571 adult patients undergoing CRRT were reviewed from 2010 to 2016 years: 70% and 30% of patients were randomly assigned into training and testing set. The primary outcome was mortality in the ICU or hospital admission. To develop the machine learning model, several algorithms were used. (logistic regression, linear discriminant analysis, k-nearest neighbors, support vector machine, multivariate adaptive regression spline, random forest, extreme gradient boosting and neural networks model). Area under the receiver operating characteristic curves (AUCs) from original scoring systems and the machine learning models were compared using the DeLong test.

Results: Among the machine learning models for ICU mortality, the linear support vector machine showed the highest AUC (0.733), and logistic regression and linear discriminant analysis were the second (0.730 in both). The AUCs of APACHE II and SOFA scores were 0.611 and 0.677, respectively. The support vector machine showed greater predictability than the original systems (P<0.05). The machine learning models for in-hospital mortality had a similar trend.

Conclusions: Machine learning models show a better performance in predicting mortality of CRRT patients than the original scoring systems. Accordingly, incorporating the machine learning-based mortality-prediction may be needed when starting CRRT.

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7 (3.5-17.1) days. 41% patients discontinued dialysis prior to discharge and 38% died. Higher volume of fluid resuscitation in the first 3 hours (HR 1.07; CI 1.01-1.14; p = 0.03) and diabetes (HR 1.75; CI 1.17-2.61; p = 0.006) were associated with kidney recovery.

Conclusions: Among septic shock patients who initiated kidney replacement therapy in MICU, 41% recovered kidney function prior to hospital discharge. A higher initial fluid resuscitation volume was associated with recovery, and interestingly, patients with diabetes had a higher chance of recovery.

Kidney recovery stratified by A Fluid in 1st 3 hrs; B Diabetes

FR-PO057
Clinical Usefulness of Contrast-Enhanced Computed Tomography in Patients with Nonobstructive Acute Pyelonephritis-Associated AKI
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Background: The aim of this study is to investigate the clinical utility of contrast-enhanced computed tomography (CE-CT) in patient with non-obstructive acute pyelonephritis (APN).

Methods: From 2007 to 2013, 537 APN patients who underwent a CE-CT scan within 24 hours after hospital admission were enrolled. We divided these patients into greater (50% or greater involvement, n=143) and lesser (less than 50% involvement, n=394) group based on renal parenchymal involvement in CE-CT examination. We compared clinical characteristics between two groups and analyzed the clinical value of CE-CT scan as a reliable marker for predicting clinical severity and disease course in patient with non-obstructive APN.

Results: The mean age of these patients was 55.2±17.9 years and 93.9% were women. The mean estimated glomerular filtration rate was 70.6±25.5 ml/min/1.73 m2. Compared with patients in lesser group, the patients in greater group had lower serum albumin levels (3.5±0.5 vs 3.8±0.6, p=0.01) and longer hospital stay (10.4±4.7 vs 8.8±4.5, p<0.05). In addition, AKI (23.1% vs 11.4%, p<0.005) and bacteremia (36.4% vs 26.8%, p=0.02) were frequently developed in greater group, respectively. The overall incidence of AKI was 14.8%, of which 93.5%, 4.9% and 0.6% were classified as risk, injury and failure, respectively, according to RIFLE criteria. In a multivariable logistic regression analysis for predicting AKI, age, presence of diabetes mellitus and the presence of renal parenchymal involvement of greater than 50% in CE-CT were significant predictors of AKI.

Conclusions: The CE-CT scan could be useful to predict the clinical severity and course including AKI in non-obstructive APN patients with preserved renal function.

FR-PO058
Early High-Dose Thiamine Supplementation for Dialysis-Requiring Septic AKI: A Nationwide Inpatient Database Study
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Background: Recent studies have reported that high dose thiamine supplementation potentially reduces mortality and progression of acute kidney injury (AKI). However, these studies have small sample size and the impact of thiamine is still controversial. Therefore, we investigated the association of early thiamine supplementation with mortality and short-term non-recovery from renal replacement therapy (RRT), using a propensity-score inverse probability of treatment weighting to adjust for measured confounders. Primary outcome was 28-day mortality and secondary outcome included in-hospital mortality and major adverse kidney events (MAKE), which was defined as death and RRT dependence at discharge.

Methods: In this retrospective observational study using the Japanese nationwide Diagnosis Procedure Combination inpatient database during a period between April 2010 and March 2017, we identified patients with septic AKI who required continuous renal replacement therapy within 2 days of admission. Patients were divided into those who received high dose (100 mg or more) thiamine supplementation within 2 days of admission (thiamine group) and those who did not (control group). We performed propensity-score inverse probability of treatment weighting to adjust for measured confounders. Primary outcome was 28-day mortality and secondary outcome included in-hospital mortality and major adverse kidney events (MAKE), which was defined as death and RRT dependence at discharge. Conclusions: A total of 9,927 patients (2,809 in thiamine group and 7,118 in control group) were eligible. The 28-day mortality was 31.5% (884/2809) in thiamine group and 39.5% (2,168/7118) in control group. After adjustment for confounders (a total of 49 covariates, including comorbidities and co-interventions by inverse probability of treatment weighting, there were no significant differences in 28-day mortality between the two groups (adjusted risk difference, 0.2%; 95% adjusted confidence interval [CI], -2.0% to 2.3%). There were no significant differences in in-hospital mortality (95% CI -1.2% to 0.8%, p=0.04), in MAKE (adjusted risk difference, -0.4%; 2.8% to 2.0%), nor in RRT dependence at discharge (adjusted risk difference, -0.4%; -1.5% to 0.7%).

Conclusions: Early high dose thiamine supplementation was not associated with decrease in mortality or MAKE, in patients with septic dialysis-requiring AKI.

FR-PO059
Short-Term Dietary Restriction for Prevention of Contrast-Induced AKI in Patients at Risk Undergoing Percutaneous Coronary Angiography: A Randomized Controlled Pilot Trial
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Background: Short-term dietary restriction (DR) has been proven effective to prevent acute organ damage from ischemic or toxic insults in animal models but clear evidence for effectiveness in humans is missing. Contrast media-induced acute kidney injury (CI-AKI) represents a leading cause of hospital-acquired acute kidney injury and both, ischemia and cytotoxic effects contribute to its pathophysiology. The objective of this trial was to determine the effectiveness of a 4-day dietary restriction for the prevention of CI-AKI in patients undergoing percutaneous coronary intervention (PCI).

Methods: Patients scheduled for PCI were randomized to receive either a formula diet containing 60% of calculated daily energy requirement (DR group, n=40) or ad-libitum food (control group, n=40) in the 4-day interval before PCI. Primary endpoint was the change of serum creatinine 48h after PCI (Acetaminone). Further exploratory analyses included various renal function parameters, incidence of CI-AKI, and safety evaluation.

Results: With a median ±100ml of contrast agent (DR group 803 (93.1) ml vs. control group 803 (93.1) ml, p=0.92) no difference in the DR group vs. 0.09 (-0.03,0.22) mg/dl in the control group there was no difference in the primary endpoint (p=0.97). Subgroup analyses revealed a significant beneficial impact of DR in patients who received >100ml of contrast agent (DR n=26. Acetaminone -0.03 (-0.20,0.08) mg/dl vs. control n=24. Acetaminone 0.10 (-0.08,0.24) mg/dl, p=0.041) and in patients with ≥2 risk factors for CI-AKI (DR n=27; Acetaminone 0.01(-0.18,0.07) mg/dl vs. control n=31; Acetaminone 0.09 (-0.03,0.16) mg/dl; p=0.030). Most patients in the experimental group reported a good physical condition (59.4%) with respect to DR and only 5.6% reported a profound sensation of hunger.

Conclusions: Although the primary endpoint was not met, the results of this trial suggest a beneficial impact of DR in low-to-moderate risk patients. Moreover, in this setting DR appears safe and feasible. Further investigations are needed in order to optimize DR protocols and to exploit its therapeutic potential.

Funding: Government Support - Non-U.S.

FR-PO060
Timing of Initiation of Renal Replacement Therapy in Critically Ill Patients with AKI: A Systematic Review and Meta-Analysis
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Background: Acute Kidney Injury is common in critically ill patients and has been associated with increased morbidity and mortality. The timing of initiation of renal replacement therapy (RRT) has been controversial in Acute Kidney Injury with no guidelines to help physicians make this decision. We aimed to analyze the prospective randomized clinical trials (RCTs) addressing this question and synthesize the evidence to guide clinical decision making for acutely ill patients who suffer from acute renal failure (ARF).

Methods: We performed a literature search using PubMed, Embase, clinicaltrials.gov, National Kidney Foundation and American Society of Nephrology meeting abstracts for 5 years. We identified RCTs involving critically ill patients and initiation strategies for renal replacement therapy. We then performed a meta-analysis, using Review Manager version 5.3. The outcome of interest included mortality, dialysis dependence, length of stay (LOS) in the hospital and in the intensive care unit (ICU).

Results: We identified 13 randomized control trials. The pooled estimates did not show a mortality difference between “early RRT” versus “Late RRT” with a RR of 1.01 (95% CI 0.99-1.10, p=0.88). We did not find a significant difference in the dialysis dependence at 90 days with a RR of 0.77 (95% CI 0.40-1.48, p=0.44). There was a decreased ICU LOS with a mean difference of 1.52 days (95% CI 0.6-2.44, p = 0.001) and hospital LOS with a mean difference of 6.2 days (95% CI 4.97-7.56, p<0.001) in the early RRT versus late RRT. Early RRT was associated with decreased hyperkalemia with RR of 0.57 (95% CI 0.34-0.97, p=0.04) and respiratory complications with RR of 0.86 (95% CI 0.77 – 0.97, p=0.01).

Conclusions: Early initiation of RRT in ARF in critically ill patients does not seem to alter mortality or the dependence on long term dialysis. However, it does shorten the ICU and hospital LOS, and is associated with decreased hyperkalemia and respiratory complications.
Incidence and Clinical Outcomes of Outpatient Hemodialysis for AKI in a Large Dialysis Organization

Eric D. Weinhandl,1,2 Lorien S. Dalrymple,1 Yeping Sun,1 Norma J. Ofsthun,1 Jeffrey L. Hymes,1 Franklin W. Maddux,1 Fresenius Medical Care North America, Waltham, MA; 2University of Minnesota, Minneapolis, MN.

Background: Little is known about patients undergoing outpatient hemodialysis (OP HD) for acute kidney injury requiring dialysis (AKI-D) in the US. We examined the incidence and clinical outcomes of such patients in a large dialysis organization.

Methods: We examined patients initiating OP HD for AKI-D in a Fresenius Kidney Care (FKC) dialysis facility between May 1, 2017, and December 31, 2018; we excluded those discharged from FKC facilities within 7 days of initiation of OP HD. Patients were followed from initiation until the earliest of recovery of kidney function, transition to end-stage kidney disease (ESKD), death, or loss to follow-up (typically, transfer to another dialysis provider), with end of follow-up on March 31, 2019.

Results: The cohort comprised 15,606 patients with AKI-D; monthly counts increased from approximately 650 during mid-2017 to 850 during late 2018. Mean age was 63.6 ± 14.6 years and 41% were female. The vast majority (97%) were prescribed thrice-weekly HD, with mean session duration of 223 ± 26 minutes. During follow-up, 6028 (39%) recovered kidney function, 7104 (46%) transitioned to ESKD, and 1550 (10%) died. Cumulative incidence of these events is displayed. At 1 month after initiation of OP HD for AKI-D, 18% had recovered function, 9% had transitioned to ESKD, and 5% had died; at 3 months, percentages were 38%, 44%, and 10%. In 14,682 patients who reached any endpoint, mean (median) days between first and last OP HD sessions was 50 (45).

Conclusions: During 2017 and 2018, an increasing number of patients underwent OP HD for AKI-D in one large dialysis organization. Within 3 months after initiation of OP HD, approximately 40% of patients recovered enough kidney function to discontinue dialysis and 45% transitioned to ESKD.

Unresolving Renal Failure After Treatment of UTI

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Introduction: Malakoplakia is a rare granulomatous inflammation. Most of the patients had the history of previous urinary tract infection and around one-third were immunocompromised hosts. The most common pathogen is Escherichia Coli. Pathogenesis postulated by inadequate lysosomal enzyme in the bactericidal process of macrophages resulting in the specific histological finding of Michaelis-Gutmann bodies. Due to lack of specific radiological morphology, histological diagnosis is mandatory.

Case Description: A 46-year-old alcoholic woman has presented with prolonged fever without any specific organ symptoms after UTI treatment. Laboratory showed Hb 9.6 g%, WBC 11,990 cell/μL, N 92%, Platelet 46,000 cell/μL, CR 12 mg/dL, UA: RBC 200-2000 HP, WBC 30-50 HP, few bacteria. Hemoculture was E. coli. After 2 weeks of ATB, she still had septic shock and high creatinine with persistent pyuria. CT scan showed RT kidney 11x7 cm. and Lt kidney 14x10.6 cm. with heterogeneous density without demarcation of cortex and medulla. Kidney pathology showed 23 glomeruli infiltrated with cells described in tubulointerstitial area into Bowman space. The interstitium showed massive infiltration of cells with granular eosinophilic cytoplasm (PAS, PASD resistant). These cells were marked with CD68, a histiocytic marker. There were a few round basophilic lamellated bodies identified as Michaelis-Gutmann bodies. AFB and GMS stains were negative. She was continuing antibiotic and surgical drainage of pus. Due to oliguric AKI with pulmonary edema, she was transiently done hemodialysis. Her clinical was improved and kidney function was recovered with 6 weeks of ATB.

Discussion: Un-resolving renal failure and persistent pyuria after proper antibiotic treatment of UTI in immunocompromised host (alcoholism) with E.Coli sepsis and enlarged heterogeneity kidney introduced the differential diagnosis of complication of UTI such as abscess, malakoplakia, and xanthogranulomatous pyelonephritis or otherwise kidney mass. Due to unexplained cause of kidney injury in our patient, kidney biopsy should be considered. Typical Michaelis-Gutmann bodies in cytoplasm of histiocytes were found. Treatment of renal malakoplakia is prolonged ATB and surgical drainage or resection depend on the severity of kidney damage. Therefore, prompt diagnosis and proper treatment are essential to keep the kidney tissues and function in renal malakoplakia.
FR-PO064
Postoperative AKI in Noncardiac Surgery and Long-Term Renal Outcome
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Background: It is well known that acute kidney injury (AKI) is an independent predictor of long-term renal dysfunction. As a result, the KDIGO guideline recommended evaluation of renal function 3 months after AKI. However, there has been no data to support the recommendation.

Methods: This is a retrospective cohort study on adult patients who underwent non-cardiac surgery under general anesthesia from 2007 to 2011 at Nara Medical University. Exclusion criteria were pre-operative dialysis, urologic, obstetric surgery, or missing creatinine levels pre- and post-operatively. Postoperative AKI (within 1 week from surgery) was determined by the KDIGO criteria. Association between AKI and renal outcome (development of end-stage renal disease or doubling of creatinine) was analyzed using Cox regression and time course of renal function between those with and without AKI was compared by a mixed effects model.

Results: Among 6,692 patients, 445 developed AKI. During a median follow-up of 1.4 years, 493 renal outcomes were observed. Postoperative AKI was an independent predictor of the renal outcome (adjusted HR 3.18 [2.38-4.25]). Decline of estimated glomerular filtration rate (eGFR) was faster among those with AKI (P=0.001). The eGFR declined at 6 months postoperatively. Even when analysis was limited to those with eGFR≥60 at baseline and 3 months, AKI was significantly associated with development of incident chronic kidney disease (eGFR<60) (HR 1.81 [1.09-3.03]).

Conclusions: AKI after non-cardiac surgery was an independent predictor of renal outcomes. Decline in renal function was more prominent more than 6 months after AKI. Those with preserved renal function at 3 months after AKI have higher risk of progressive renal dysfunction compared with those without AKI. Longer follow-up than KDIGO recommendation is necessary.

FR-PO065
Quality of Life and Long-Term Survival After Persistent AKI in Sepsis Patients
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Background: Acute kidney injury (AKI) is one of the most common complications among hospitalized patients. It is important to consider the duration of renal recovery in order to characterize the natural history of this complex condition and its effect on kidney health and long term functional status. We have determined the epidemiology of persistent AKI and its effect on long-term functional status and survival in sepsis patients.

Methods: In the prospective observational study of 245 sepsis patients, AKI types were adjudicated using KDIGO criteria and ADQI recommendations. In contrast to rapidly reversed AKI, persistent AKI is characterized by the persistence of KDIGO creatinine beyond 48 hours of the onset. The Zubrod Scale has been used to measure and compare the performance status of a patient’s ambulatory nature and Zubrod score of 0 indicated that patients were fully active. One-year survival was compared using log-rank test and Cox proportional hazards model was fit to examine association between AKI type and long-term mortality.

Results: Two percent (6/245) had preexisting end-stage renal disease (ESRD) and 15% (36/245) had pre-existing chronic kidney disease (CKD). Sixty-two percent of the study population developed AKI. Only one third of AKI episodes rapidly reversed within 48 hours and had sustained renal recovery at discharge while the remaining 68% had persistent AKI. Prevalence of 1 year mortality in patients with persistent AKI (44%) was significantly higher than patients with rapidly reversed AKI (11%) and patients who did not develop AKI (9%). Percentage of those who were fully active and able to carry out activities without restrictions at 1 year of sepsis onset were only 8% among for patients with persistent AKI, whereas it was 29% for both patients who had rapidly reversed AKI and those who did not develop AKI. Hazard rate (HR) was about five-fold for persistent AKI group (HR 5.38, 95% confidence interval 2.74-11.80) compared to patients who did not develop AKI, while there was no evidence of significant difference in hazard ratios of those with rapidly reversed AKI and no AKI.

Conclusions: Among critically ill septic patients, persistent AKI is a significant risk factor for reduced functionality and increased long-term mortality.

FR-PO066
Clinical Outcomes of Patients Admitted to the ICU with AKI in a Jordanian Tertiary Hospital
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Background: Despite advances in medical technologies, therapeutic options, acute kidney injury (AKI) still a major contributor of death in intensive care units (ICU) regardless of renal replacement therapy used to treat severe AKI

Methods: We retrospectively reviewed electronic patient records for all patients admitted to our ICU. We used acute kidney injury network (AKIN) classification to define and stage AKI, For continuous variables; mean, standard deviation, minimum and maximum were used, and for differences between normally distributed values we used t test. Percentages used for categorical variables. Pearson Chi-square test was used to test categorical variables. Univariate and multivariate regression analyses were performed to determine the independent predictors of AKI.

Results: We evaluated 1500 patient electronic records who were admitted to our ICU between 2014 - 2015 with at least one year follow up. Using univariate analysis age was a predictor of AKI, Serum albumin at admission was a strong predictor of AKI, mean serum albumin for the AKI group 30.1 g/dl (SD 9.4), and 33.5 g/dl (SD 8.9) for the non AKI group, P=0.001, also admission Hb predicted AKI, mean Hb for the AKI was 10.9 (SD 3.1) vs. 11.4 (SD 2.9), P=0.0004. The incidence of AKI was 35.6%, most of them were with stage 1 AKI. Mean serum creatinine was 150.7 mmol/l (SD 147.7) for patients with AKI vs. 118.2 mmol/l (SD 135.3) for the other group, P=0.001. Out of the patients who developed AKI, 52.2% (82 patients) started on dialysis for different reasons (Hyperkalemia 15%, fluid overload 46.6%, combination of both 38.4%), of whom 22 patients continued dialysis as outpatients. Renal recovery (defined as return to baseline creatinine) at discharge was 17.2% (51 patients), Mortality by the time of discharge was 4.3% (62 patients).

Conclusions: AKI incidence in Jordan is comparable to worldwide incidence with significant effect on long term survival after discharge, correttable factors should be addressed to decrease incidence in the future.

FR-PO067
Three-Year Outcomes After AKI in a Prospective Cohort: Effects on CKD, Survival, and Cardiovascular Events
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Background: Acute Kidney Injury (AKI) is associated with adverse long-term outcomes. There is a need for prospective studies to identify those at highest risk and to improve understanding of the effect size across different outcomes and patient groups. Here we report three-year outcomes from a large prospective parallel group cohort study.

Methods: In a single UK centre, hospitalised patients who sustained AKI were recruited and matched 1:1 with controls (hospitalised patients without AKI) for age, gender, and comorbidities. AKI was defined as an increase in serum creatinine of > 0.3 mg/dl or a need for renal replacement therapy. Three-year outcomes included mortality, renal replacement, and cardiovascular events.

Results: Among 6,692 patients, 445 developed AKI. During a median follow-up of 1.4 years, 493 renal outcomes were observed. Postoperative AKI was an independent predictor of the renal outcome (adjusted HR 3.18 [2.38-4.25]). Decline of estimated glomerular filtration rate (eGFR) was faster among those with AKI (P=0.001). The eGFR declined at 6 months postoperatively. Even when analysis was limited to those with eGFR≥60 at baseline and 3 months, AKI was significantly associated with development of incident chronic kidney disease (eGFR<60) (HR 1.81 [1.09-3.03]).

Conclusions: AKI after non-cardiac surgery was an independent predictor of renal outcomes. Decline in renal function was more prominent more than 6 months after AKI. Those with preserved renal function at 3 months after AKI have higher risk of progressive renal dysfunction compared with those without AKI. Longer follow-up than KDIGO recommendation is necessary.
baseline eGFR stage and diabetes. Biochemical parameters including renal function and proteinuria were measured at 3 months, 1 year and 3 years following index hospitalisation. CKD progression was defined as ≥25% decline in eGFR with decline in eGFR stage, and a composite renal endpoint as a doubling of serum creatinine, eGFR<15ml/min or initiation of renal replacement therapy.

Results: 1125 patients were recruited of whom 866 were successfully matched. There was no difference between AKI and control groups in age (71 yrs (IQR 14) vs. 71 yrs (IQR 13), p=0.7) or baseline eGFR (70.3±20ml/min vs 69.6±20ml/min, p=0.58). Two-thirds of AKI episodes were stage 1 with median duration 3 days (IQR 3). Mean eGFR was lower at all-time points in AKI group. At 3 years, eGFR was 61±20ml/min in AKI group versus 70±20ml/min in controls (p<0.001), and CKD progression occurred in 26.7% of the AKI group, as compared to 6.6% in the control group (p<0.001). The greatest odds of CKD progression rates were seen at three months, with progressive attenuation over time. Proteinuria was also more common and more severe in the AKI group at each time point. The composite renal endpoint occurred in 3% of AKI group versus 0.7% of controls (OR 4.4, 95% CI 1.3-15.7, p=0.012). Mortality rates were also significantly higher in the AKI group (15.7% versus 9.7%, p=0.008), as were heart failure events. Binary logistic regression demonstrated that presence of AKI and non-recovery by 90 days had independent associations with CKD progression.

Conclusions: AKI is associated with long term renal dysfunction, proteinuria, higher rates of ESKD and increased mortality. This is true even in a general hospitalised population in which a majority of patients had AKI stage 1. Non-recovery of renal function by 90 days is an important predictor of subsequent CKD.

Funding: Private Foundation Support

FR-PO068
Comparison of Outcomes of Early vs. Delayed Renal Replacement Therapy in Critically Ill Patients: A Meta-Analysis of Randomized Controlled Trials
Ajai S. Rajabalan, Satyanarayana V. Vaidya, Niraj Karki, Jonathan J. Suarez, Jason Cobb, James L. Bailey, Emory University School of Medicine, Atlanta, GA.

Background: The question of optimal timing of Renal Replacement Therapy (RRT) initiation in Acute Kidney Injury (AKI) remains unanswered. We collected data from available randomized controlled trials (RCTs) comparing the early RRT (ERRT) with delayed RRT (DRRT) and performed a meta-analysis of outcomes.

Methods: A literature search was done using electronic databases from Pubmed, Cochrane and Embase from inception until April 2019 for RCTs comparing early RRT with delayed RRT. The relevant data was extracted and statistical analysis was done using RevMan 5.3.

Results: A total of 12 RCTs comparing ERRT vs DRRT in patients older than 18 years were included, yielding 2267 patients of which 1143 were in early RRT group and 1124 were in delayed RRT group. Mortality at 30 days (8 RCT) [OR 0.95, 95%CI (0.77, 1.17), p=0.64, I²=49%] did not show any difference between the 2 groups. There was no significant difference between the 2 groups in dependence on RRT at 90 days (5 RCTs) [OR 0.80, 95%CI (0.57, 1.12), p=0.25, I²=69%]. There was no significant difference between the 2 groups in incidence of arrythmias (5 RCTs) [OR 1.34, 95%CI (0.96,1.87), p=0.10, I²=47%]. Two-thirds of AKI episodes were stage 1 with median duration 3 days (IQR 3). Mean eGFR was 61±20ml/min in AKI group versus 70±20ml/min in controls (p<0.001), and CKD progression occurred in 26.7% of the AKI group, as compared to 6.6% in the control group (p<0.001). The greatest odds of CKD progression rates were seen at three months, with progressive attenuation over time. Proteinuria was also more common and more severe in the AKI group at each time point. The composite renal endpoint occurred in 3% of AKI group versus 0.7% of controls (OR 4.4, 95% CI 1.3-15.7, p=0.012). Mortality rates were also significantly higher in the AKI group (15.7% versus 9.7%, p=0.008), as were heart failure events. Binary logistic regression demonstrated that presence of AKI and non-recovery by 90 days had independent associations with CKD progression.

Conclusions: ERRT did not show any benefit in mortality, dependence on RRT or arrythmias. However, ERRT did show increased rates of catheter related complications. This suggests that DRRT may not offer benefits in mortality or renal outcomes, but may lead to less vascular access related complications. More data is needed to better elucidate the cause of less catheter related complications in the DRRT group.

FR-PO069
Myoglobin Clearance in Acute Rhabdomyolysis: Theralive and Theranova
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Background: Rhabdomyolysis is a cause of acute kidney injury (AKI) in a large number of cases where traumatic or non-traumatic causes induce muscle cell disruption. Although the rationale for a quick and effective removal of myoglobin in acute rhabdomyolysis would be strong and logical, the practical results obtained with extracorporeal therapies are modest. Theralive2100 and Theranova400 (Baxter) are new generation membranes designed to increase the removal of larger middle molecules like myoglobin. While Theralive takes advantage of the membrane high cut-off (HCO), the high retention onset (HRO) and internal filtration are the peculiarities of Theranova. We report a critically ill patient case to describe and compare two novel strategies for extracorporeal elimination of myoglobin in rhabdomyolysis-associated AKI with Theranova and Theralive continuous venovenous hemodialysis (CVVHD).
Methods: The treatment included 22 hours of HRO-CVVHD (Qh 200 ml/min, Qd 4000 ml/h, Quf 150 ml/h), followed by 6 hours of HCO-CVVHD (Qh2000 ml/min, Qd 4000 ml/h, Quf 0 ml/h). Samples were collected from arterial, venous, and effluent lines in two timepoints: t1 (30 minutes after starting each session) and t2 (before changing hemodialyzer). Plasmatic clearance for myoglobin (Km) was calculated at t1 and t2 to evaluate the efficiency in myoglobin removal. The intensity (Km, x hours of treatment) was estimated using the mean value of calculated Km.

Results: During CVVHD the Km in t1 and t2 were 37.99 and 16.88 ml/min and 66.05 and 46.68 ml/min, using HRO and HCO respectively (Fig 1). The blood volume cleared of myoglobin after the entire treatment was 36.221 and 28.291 for twenty-two hours of HRO-CRRT and six hours of HCO-CRRT, respectively (Fig 2).

Conclusions: Theranova-CVVHD guaranteed quick and efficient removal of myoglobin. Theranova-CVVHD might be considered as efficient for longer treatment and even more when an adjunctive convective mechanism is desirable, customizing the prescription on the basis of the patient clinical status.

FR-PO070

Standardization of a Furosemide Stress Test in the Pediatric Intensive Care Unit

Jean-Philippe Roy, Kelli A. Kralman, Ranjit S. Chima, Alexandra Schmerge, Bradley S. Gerhardt, Lin Fei, Stuart Goldstein. Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Early prediction of patients (pt) at risk of severe acute kidney injury (sAKI) and need for renal replacement therapy (CRRT) in pediatric intensive care unit (PICU) is a desired strategy for early intervention. Functional assessment of tubular reserve with diuretic, furosemide stress test (FST), has been validated in acutely ill adults with promising prediction for sAKI and CRRT requirement but has not been evaluated in critically ill children.

Methods: Prospective observational study. All PICU admissions have an automated renal angina index (RAI) calculated 12h after admission. RAI positive pt (a, RAI+) are assessed with a urine NGAL to improve risk prediction. RAI+/NGAL+ (>15mg/mL, NGAL>+) pt are assessed for the FST. The FST include a standard dose of furosemide (1mg/kg if naïve or 1.5mg/kg if exposed within 24h) and hourly urine output (OUP) monitoring 6 hours prior and after the dose administration. Increase in (iOUP) at 2 and 6h were calculated by subtracting the mean hourly OUP per kilogram using the same time length before and after administration. FST was considered positive (FST-responder) if the iOUP met a certain threshold at either one of the time marks.

Results: From 7/1/2018 to 2/28/2019, 1730 pt were admitted, 15 had a FST done, 3 (20%) of which required CRRT. Incremental hourly iOUP cutoff from 1 to 10ml/kg/h show an excellent AUC of 0.847 for CRRT prediction. 5mL/kg/h iOUP had the best Youden’s J index at 0.58 but a 4mL/kg/h cutoff, with second best index, was deemed more clinically relevant due to a better specificity. At this cutoff, 2/4 (50%) FST non-responder vs 1/10 (10%) FST responder required CRRT (p=0.15) (see table).

Conclusions: FST seems applicable in acutely ill children to predict CRRT requirement but with an increase threshold of iOUP. However this prospective cohort will need more FST pt to make any definitive conclusions.

Funding: NIDDK. Support

Table - CRRT need prediction with variable iOUP threshold after an FST

| iOUP (ml/kg/h) | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value | Youden
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FR-PO071

Effect of CME on Nephrologists’ Knowledge and Confidence Related to Management of Hepatorenal Syndrome Type 1

Amy Larkin, Donald Blathewick, George Boutsalis, Juan Carlos Q. Velez.

Medicine Education, Nicholsonville, KY; Medscape, Medford, NJ; Ochsner Clinic Foundation, New Orleans, LA.

Background: As emerging therapies hold promise to improve management of hepatorenal syndrome type 1 (HRS-1), clinicians are in need of improved understanding of the therapies and the current management of HRS. We sought to determine if online continuing medical education (CME) could improve the clinical knowledge and confidence of nephrologist in HRS.

Methods: The online CME activity consisted of a video-based roundtable discussion with a leading faculty in the area of HRS-1. The educational effects were assessed using a repeated pairs pre-assessment/post-assessment study design, where individual participants served as his/her own control. For all questions combined, the chi-squared test assessed whether there was improvement in the proportion of participants who answered questions correctly at post as compared to pre. P values < .05 are statistically significant. Cramer’s V was used to calculate the effect size (0.05-0.15 is a noticeable effect, 0.16-0.26 considerable, and ≥0.26 extensive). The activities launched between December 4, 2018 and data were collected through February 14, 2019.

Results: Improved knowledge and confidence was demonstrated among nephrologists: Overall, the effect of the education was considerable (V=0.153, P<.001, N=115) 21% demonstrated improved identification of predictors of death or renal replacement therapy in patients with liver disease and stage 3 acute kidney injury (P<0.05, V=139) 21% demonstrated improved related to timing of dosage adjustment of terlipressin (P=0.072, V=0.118) 36% demonstrated improved recognition of the goal of initial vasopressor therapy in HRS-1 (P<0.001, V=0.330) 38% reported increased confidence in their ability to appropriately diagnose HRS-1 Persistent knowledge/competence gaps remain: 46% incorrectly identified predictors of death or renal replacement therapy in patients with liver disease and stage 3 acute kidney injury. 30% did not understand timing of dosage adjustment of terlipressin 23% failed to recognize the goal of initial vasopressor therapy in HRS-1.

Conclusions: This study demonstrates the success of an online, video-based CME activity on improving knowledge and confidence of nephrologists related to current and emerging treatment for HRS-1. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Developed through an independent educational grant from Mallinckrodt.

FR-PO072


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Background: Clinical decision support (CDS) initiatives can be effective strategies for enhancing healthcare delivery and improving patient outcomes. However, such interventions for acute kidney injury (AKI) have reported variable effectiveness. Involved of end-users in the development and implementation may help optimize accessibility and uptake of CDS systems for AKI. Evaluation of healthcare providers’ experiences can inform the process.

Methods: We used a multi-phase approach involving healthcare providers, decision-makers, and implementation leaders to deploy an electronic CDS system on surgery units in Calgary, Alberta. The system consisted of: AKI stage alerts, Adverse medication alerts, AKI clinical summary display, and AKI order set. Implementation included usability testing of tools, co-development of tailored strategies for using the tools, education programs for staff, and audit and feedback of AKI quality indicators. The perceptions and experiences of end-users were evaluated using surveys and interviews; the latter were analyzed using a qualitative descriptive approach.

Results: During the initial 12 month post-implementation period, 318 AKI alerts and 48 adverse medication alerts were generated on the units. 104 clinical end-users have completed surveys and 10 have participated in interviews. Overall 88% of physicians and 98% of nursing staff stated it was important to improve AKI care on their hospital units. There was variable uptake of the specific tools with interview responses indicating that the AKI stage alerts and flagged medications were most valuable for the users. Interviews identified themes related to CDS implementation; 1) culture of increased AKI awareness, 2) credibility around communicating about AKI within an interdisciplinary team, 3) system barriers for recognition and timely AKI management.

Conclusions: End-user engagement in the process of developing and implementing CDS tools for AKI can enhance the acceptability and perceived value of tools by care providers outside the discipline of nephrology. Further strategies may be needed to address system-wide barriers to early management for AKI and to evaluate whether this degree of intensive end-user engagement enhances the impact of CDS interventions on processes of care and outcomes of AKI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
FR-PO073
Chloride-Liberal vs. Chloride-Restrictive Intravenous Fluids to Prevent Contrast-Induced AKI
Felix S. Seibert, Timm H. Westhoff. University Hospital Marien Hospital Herne, Herne, Germany.

Background: For decades plasma expansion by intravenous volume application constituted the central cornerstone in the prevention of contrast-induced acute kidney injury (CI-AKI) for patients with preexisting chronic kidney disease (CKD). The recent AMACING study challenged this approach and showed no benefit by isotonic saline solution. Consequently, several institutions have stopped prophylactic fluid application in CKD. Based on considerations regarding the tubuloglomerular feedback there are increasing data from intensive care and emergency room settings showing that chloride restrictive fluids might be superior to isotonic saline in the prevention of AKI.

Methods: Based on the above mentioned data, we changed our standard operating procedure for the management of CKD patients with contrast media enhanced computed tomography scans from periprocedural infusion of chloride-liberal to chloride-restrictive solutions. The present work compares the CI-AKI rates of the first n=100 CKD patients with Ringerlacrat (Cl concentration 112 mmol/l) or Jonosteril (Cl concentration 110 mmol/l) to a historical cohort of 100 subjects with 0.9% saline solution as periprocedural fluid application (11 before and 11 after contrast application in each group). CI-AKI was defined as a ≥0.3 mg/dl increase of serum creatinine concentration from baseline to day 2-3 after radio contrast application.

Results: CI-AKI occurred in 14 subjects of the overall cohort (7%). The incidence of CI-AKI was 44% lower in those subjects receiving chloride-restrictive fluids (n=5, incidence 9%) than in those ones with isotonic saline application (n=9, incidence 9%) without reaching statistical significance (chi-squared p=0.27). In multiple logistic regression analysis, use of diuretics turned out to be an important risk factor for a periprocedural decrease of eGFR (B=7.5). In contrast, the effects of congestive heart failure, diabetes, and use of inhibitors of the ren angiotensin system were below significance level.

Conclusions: The present analysis compares the potency of chloride-liberal vs. chloride-restrictive fluid application in the prevention of CI-AKI for the first time. It revealed no change to a lower incidence of CI-AKI using chloride-restrictive fluid application and may thereby constitute a rationale for a sufficiently powered randomized prospective trial.

FR-PO075
Adherence to Best-Practice Guidelines in Severe AKI: A Multicenter Study
Tatiana Arora,1 Dennis G. Moledana,1 Yu Yamamotob,2 Aditya Biswas,2 Kyle Carey,2 Matthew M. Churpek,2 Sherry Mansour,3 Jay L. Koyner,3 Francis P. Wilson.1 1Yale School of Medicine, New Haven, CT; 2Yale University, New Haven, CT; 3University of Chicago, Chicago, IL.

Background: In the absence of a specific therapy for acute kidney injury(AKI), consensus guidelines recommend certain supportive measures to improve patient outcomes. We quantified adherence to those measures in patients with severe AKI.

Methods: We reviewed the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for recommended diagnostic and therapeutic interventions after AKI. We quantified rates of adherence to 22 best practice measures at 3 hospitals within 2 health systems for patients with severe AKI (KDIGO stage 2 or higher).

Results: We identified 13,039 patients with severe AKI. The cohort was 52% women, 34% black and had a mean age of 63 years. Baseline creatinine ranged between 0.9-1.0mg/dl. Of this cohort, 42% were surgical patients and 62% were in the ICU. Among the 22 best practice measures, we found a low rate of discontinuation of nephrotoxic agents. Of patients on ACEI/ARBs 24 hours before AKI, 51% continued to use this drug up to 24hours after AKI. Similarly, 38% of patients were continued on Aminoglycosides and 42% on NSAIDs. We also observed inadequate maintenance of some hemodynamic metrics (61% of patients still had a mean arterial pressure >65mmHg up to 24hours post AKI) in patients with severe AKI (Figure).

Conclusions: We noted a low rate of adherence to certain best practice measures, particularly a failure to discontinue nephrotoxic agents in patients with severe AKI. Future research could attempt to improve adherence to best practice guidelines using electronic health record-based alerts.

Funding: NIDDK Support

FR-PO076
A Simplified, Weight-Based CVVHDF-RCA Prescribing Algorithm That Works Regardless of Citrate Metabolism Is Verified in Ex Vivo Simulations
Halasz Szamosfalvi, Lenar T. Yessayan. University of Michigan, Ann Arbor, MI.

Background: In practice great variations in CRRT-RCA protocols exist with many centers avoiding RCA in severe shock and liver failure patients and most small intensive care units avoiding RCA completely. Complications of hypercalcemia and hypernatremia, hypo- or hyperpyrexia, and metabolic-alkalosis or acidosis are reported with most protocols. We present a new, simplified approach to CRRT-RCA prescribing and demonstrate in an ex vivo simulation system devoid of citrate metabolism that all electrolyte complications due to CRRT-RCA can be avoided by careful protocol design.

Methods: We used a recently FDA-approved CRRT system to deliver CVVHDF-RCA in an ex vivo system (Figure 1). IV pumps delivered infusions of urea/citrate, ACDA and calcium. PRBCs and plasma filled the CRRT circuit and reservoir to target Hct. We tested QB 20, 40, 60 ml/min and Hct 45, 33, 21. Commercial 140Na, 4K, 35HCO3, 1.5Mg, 5Ca, 5.5mMGlu CRRT fluid spiked to phosphate 4.2 mg/dL (1.5 mM) was used. A 136 mM CaC2 solution was prepared in 0.9% saline. Dosing weight (DW) = round(weight+10) if patient weight (Kg) ≤100 otherwise round (weight*(weight+20) (kg). QB (ml/min) = 0.5*DW. ACDA (ml/h) = 2.5*QB, QDialysate (ml/h) = 30*QB, QReplacement (ml/h) = 10*QB and QCa (ml/h) about 0.7*QB and Orea (ml/h) = QB. Blood and fluid samples were collected and analyzed by I-stat and in the laboratory.

Results: We had no CRRT alarms. The reservoir iCa was 1.1-1.5 mM. All circuit iCa was < 0.25 mM. Reservoir Na was 135-140 and other major electrolytes were at physiologic values. Single pass citrate removal was 80-90%. Effluent dose was 25-35 ml/hour.

Conclusions: We showed that a simple approach to CVVHDF-RCA prescribing using commercially available equipment achieved target effluent dose, below 0.25 iCa in the CRRT circuit and normal iCa and systemic electrolytes in the patient without any concern for citrate metabolism.

Funding: Private Foundation Support, Clinical Revenue Support
Design of the 1128-CL-0201 Study: A Phase 2 Proof of Concept, Double-Blind, Randomized, Placebo-Controlled Study of ASP1128 in Patients at Risk for AKI After Cardiac Surgery

Olivier Van till,1 Ronny Renfurn,1 George Mulligan,1 Effie Tozzo,1 Chisato Kameska,1 Bruce A. Molitoris,1 Andrew Shaw,1 Daniel Engelman,1 John A. Kellum,1 Astellas Pharma Inc., Tokyo, Japan; 2none, Rotterdam, Netherlands; 3Mitobridge, an Astellas company, Cambridge, MA; 4University of Pittsburgh, Pittsburgh, PA; 5Mitobridge Inc., Cambridge, MA; 6Indiana University School of Medicine, Indianapolis, IN; 7Baystate Medical Center; Springfield, MA; 8University of Alberta, Edmonton, AB, Canada.

Background: AKI occurs in approximately 20-30% of cardiac surgery patients, but can reach 70% in high risk or biomarker-defined populations. No treatments are approved to treat AKI. ASP1128 is a peripherally active selective modulator of PPARδ that improves mitochondrial and metabolic function. In AKI animal models, ASP1128 ameliorated renal function, histopathology, and injury biomarkers. It was shown to be safe in healthy human volunteers.

Methods: This is a randomized, double-blind, placebo-controlled, proof-of-concept, phase IIa study, to be conducted in patients at risk for AKI following cardiac surgery. A maximum of 220 patients will be randomized at ~40 sites in North America. The study comprises three parts: 1) pre-surgery screening period, 2) CABG and/or valve surgery, and 3) post-surgery double-blind treatment period with a 90-day follow-up. To evaluate patient outcomes, patients with moderate/severe risk of AKI (based on urinary biomarkers TIMP-3) post-surgery double-blind treatment period with a 90-day follow-up. To evaluate patient outcomes, patients will be followed-up as an observational standard-of-care cohort. Randomized treatment for AKI to improve patient outcomes following cardiac surgery. The study results are expected in the second half of 2020.

Conclusions: The Aim of this study is to develop a short-term early intervention treatment for AKI to improve patient outcomes following cardiac surgery. The study will provide insight into the role of mitochondrial injury and fatty-acid oxygenation in propagating AKI.

Funding: Commercial Support - Astellas Pharma Inc.

FR-PO079

Glucose, Citrate, Calcium, Na, HCO3-, and Phosphate Mass Balance Studies in Ex Vivo Simulations of a Simplified CVVHDF-RCA Protocol That Works Regardless of Citrate Metabolism

Lenar T. Yessayan, Balazs Szamosfalvi. University of Michigan, Ann Arbor, MI.

Background: We developed a new, simplified approach to CRRT-RCA prescribing with commercially available equipment and CRRT fluids. It is important to study the mass balance of glucose (Glu), citrate, Ca, Na, HCO3-, and phosphate in an ex vivo system to demonstrate that a new CRRT protocol will approximate physiologic values of these solutes in the patient even in the absence of citrate metabolism.

Methods: We used a recently FDA-approved CRRT machine to deliver CVVHDF-RCA in an ex vivo system (Figure 1). IV pumps delivered infusions of urea/citrate, ACDA and calcium. Human PRBCs and plasma filled the CRRT circuit and reservoir to target Hct. Commercial CRRT fluids were spiked to 140Na, 4K, 35HCO3, 1.5Mg, 0Ca, 1.5mMPhos with 0 or 5.5mMGlu. A 136 mM CaCl2 solution in D50.9% or 0.9% saline was paired with 0 or 5.5mM Glu CRRT fluid, respectively. We tested QB 20, 40, 60 ml/min and Hct 45, 33, 21. ACDA (ml/h) = 2.5* QB, QDialysate (ml/h) = 30 * QB, ACDA and calcium. Human PRBCs and plasma filled the CRRT circuit and reservoir to target Hct. Commercial CRRT fluids were spiked to 140Na, 4K, 35HCO3, 1.5Mg, 0Ca, 1.5mMPhos with 0 or 5.5mMGlu. A 136 mM CaCl2 solution in D50.9% or 0.9% saline was paired with 0 or 5.5mM Glu CRRT fluid, respectively. We tested QB 20, 40, 60 ml/min and Hct 45, 33, 21. ACDA (ml/h) = 2.5* QB, QDialysate (ml/h) = 30 * QB, QReplacement (ml/h) = 10 * QB, QCa (ml/h) about 0.7 * QB and Qurea (ml/h) = QB. Blood and fluid samples were collected and analyzed by I-Stat point-of-care device and in the laboratory.

Results: The reservoir iCa was 1-1.3 mm. All circuit iCa was < 0.25 mM. Reservoir Na was 135-140 and other major electrolytes were around physiologic values. The reservoir glucose remained in the 70-150 mg/dl range with either CRRT fluid/Ca-infusion pair and glucose dialysis was 80-90% of CRRT circuit plasma flow. Single pass citrate removal on the filter was 80-95% and clinically significant citrate accumulation in the reservoir was avoided.

Conclusions: Ex vivo simulation suggests that the new CVVHDF-RCA protocol will approximate normal systemic solute levels without citrate metabolism. I-stat bedside glucose dialysis may be used in a clinical study to indirectly monitor plasma citrate- and Ca-clearance.

Funding: Private Foundation Support, Clinical Revenue Support

FR-PO078

Clinical Efficacy of Intraoperative Hemodialysis During Open-Heart Surgery with CKD Stage G4 and G5

Takahiro Inoue,1 Hiroshi Kuki,1 Kanako Nagaoka,1 Takafumi Akamasa,1 Munakata Yu,2 Yoshishiko Watanabe,3 Junko Fukuda,1 Mamiko Ohara,1 Tomo Suzuki,1 Department of Nephrology, Kameda Medical Center 2Kameda Medical Center; Kamogawa, Japan; 3Munakata Clinic, Chiba, Japan.

Background: Severe acute kidney injury after cardiac surgery frequently requires renal replacement therapy (RRT) and moreover increases mortality rates and a prolonged length of hospital stay. Recently, we performed intraoperative hemodialysis (IHD) during open-heart surgery for the patients with chronic kidney disease (CKD) to prevent postoperative RRT. However, the clinical implication is unclear, therefore we investigated the efficacy of IHD.

Methods: This is a single-center cohort study with patients undergoing non-emergency cardiac surgeries between Jan, 2008 to Dec, 2018 in our hospital. The subjects were 61 patients classified as CKD G4 or G5 without chronic dialysis and post-transplant. Until Aug 2013, patients underwent surgery without IHD. Since Sep, 2013, patients were dialyzed intraoperatively. We evaluated the efficacy of IHD, comparing an IHD group (IHD) with a non IHD group (non-IHD).

Results: Comparing IHD and non-IHD, the patient number was 19 vs. 28 (CKD G4) and 9 vs. 5 (CKD G5). Preoperative eGFR (CKD G4) was 19.1±5.6 vs. 22.0±5.2 ml/min/1.73m² (p = 0.039), and 19.1±5.6 vs. 22.0±5.2 (CKD G5). Diabetic mellitus accounted for 35.7% vs. 42.4% (p=0.384), and operative duration 331±99 vs. 295±65 min (p = 0.16). Clinical characteristics and preoperative renal function were similar between two groups. Ninety-day mortality, hospital days, duration of postoperative intubation, renal function at discharge were not significantly different between IHD and non-IHD. Regarding CKD G4, the rate of RRT within 30 days after surgery (30-day RRT) was significant lower in IHD. Conclusions: IHD had lower incidence of 30-day RRT than non-IHD in patients with CKD G4 prior to surgery.

Clinical features and Outcome between IHD group and non IHD group

<table>
<thead>
<tr>
<th>Patient undergoing cardiac surgery (N = 61)</th>
<th>IHD (N = 28)</th>
<th>non-IHD (N = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs.</td>
<td>74±5.77</td>
<td>72.6±9.4</td>
<td>0.744</td>
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<tr>
<td>Male, n (%)</td>
<td>73/106</td>
<td>76/60</td>
<td>0.530</td>
</tr>
<tr>
<td>Preoperative eGFR (G4/m³/min/1.73m²)</td>
<td>22±5.5</td>
<td>23±6.3</td>
<td>0.723</td>
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<tr>
<td>170±15.6</td>
<td>18.1±5.6</td>
<td>20±15.9</td>
<td>0.166</td>
</tr>
<tr>
<td>CKD G4, n (%)</td>
<td>19</td>
<td>28</td>
<td>0.116</td>
</tr>
<tr>
<td>90-day mortality (%)</td>
<td>7.1</td>
<td>8.8</td>
<td>0.582</td>
</tr>
<tr>
<td>30-day ICU days, n (%)</td>
<td>0.05</td>
<td>(2.5±0.3)</td>
<td>0.933</td>
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<tr>
<td>G3, n (%)</td>
<td>5/125.6</td>
<td>1/120.0</td>
<td>-</td>
</tr>
</tbody>
</table>

| FR-PO077

FR-PO079

AKI: Clinical Outcomes, Trials

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
FR-PO080

Crossover Study Comparing Bioavailability of Captisol-Enabled (CE) Iohexol Injection with Reference Iohexol Injection in Healthy Subjects

Keith Marschke,1 Vincent Antle,2 Eric G. Vajda,1 Lin Zhu,1 Daniel Cushings,1 James Pipkin.1 Ligand Pharmaceuticals Incorporated, San Diego, CA; 1Medical and Regulatory Affairs, Phoenixville, PA.

Background: Inodated contrast agents may place patients with certain risk factors at an increased risk for acute kidney injury during cardiac imaging procedures.1 Studies in renovascular-compromised mice and rats demonstrated that the addition of sulfobutylether β-cyclodextrin (Captisol®) to a clinically administered dose of iohexol significantly reduced renal pathology scores, and increased survival in rats from 50% to 88%.2 A Phase 1, single-center, randomized, double-blind, two-period crossover study was conducted to determine relative bioavailability of CE-Iohexol and a reference Iohexol injection (OMNIPAQUE™) after intravenous (IV) administration in healthy adults.

Methods: A total of 24 subjects were enrolled in the study as 2 groups of 12 subjects in 2 treatment periods. Subjects received each of the following treatments as a single IV dose (80 ml infused over 20 seconds): CE-Iohexol -755 mg/mL iohexol (350 mgI/mL);50 mg CAPTISOL/mL; OMNIPAQUE - 755 mg/mL iohexol (350 mgI/mL). Serial blood samples were collected for Iohexol plasma concentration determination, and safety was assessed during the 48 hours following each dose. Subjects were discharged on day 3.

Results: 22 subjects completed the study; 2 subjects were withdrawn for technical reasons. Bioequivalence was demonstrated by calculation of geometric mean ratios (GMR) between CE-Iohexol and OMNIPAQUE for key pharmacokinetic parameters. GMR of the area under the concentration-time curve for time 0-infinity (AUC(0-∞)) was 1.00 (90% confidence interval [CI], 0.98-1.02). GMR of the maximum concentration (Cmax) was 1.00 (90% CI, 0.95-1.06). Other PK parameters, including time to maximum observed concentration (Tmax), half-life (t1/2) and elimination rate constant (K) were similar between treatments. All treatment-emergent adverse events during the study were mild to moderate in severity. No subject had a serious adverse event or discontinued from the study due to an adverse event.

Conclusions: The observed PK profile supports clinical development of CE-Iohexol as a next-generation contrast agent with a reduced risk of renal toxicity (NCT03669983).

Funding: Commercial Support - Ligand Pharmaceuticals Incorporated

FR-PO081

Membrane Therapeutic Plasma Exchange (mTPE) with Citrate Regional Anticoagulation: A Single-Center Experience

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Background: Membrane Therapeutic Plasma Exchange (mTPE) is an extracorporeal blood therapy that uses convection through pressure applied upon a semi permeable membrane to remove from plasma elements such as antibodies, cytokines, lipids and viral particles. Usually, the anti coagulation method utilized is systemic unfractionated heparin (UFH). Coagulation components loss in mTPE in association with UFH enhances bleeding risk. Considering that risk, our center proposed the use of regional citrate anticoagulation as a safe option in patients undergoing mTPE. Below, we describe 12 sequential sessions performed using our citrate protocol.

Methods: mTPE was performed on the Prismaflex with TPE 2000 membrane. We used 4% Sodium Citrate with a target concentration of 3mmol/L of treated blood. We delivered 1.5% Calcium chloride to the patient at 3=0.1mmol/L of effluent flow. A Solution 5% Albumin plus 10% Magnesium sulfate (1mmol/L) was used as replacement fluid. Within 2 hours of treatment we measured ionized calcium in the extracorporeal circuit, systemic ionized calcium and systemic magnesium.

Results: No changes were observed on serum concentrations of magnesium in all treatments. Median systemic ionized calcium concentration was 1.24mmol/L. No symptoms of hypocalcemia, arrhythmias or bleeding were reported. Median ionized calcium in the extracorporeal circuit was 0.36mmol/L. No sessions were interrupted due to system clotting. The median time of therapies was 170 minutes with similar costs to our center.

Conclusions: mTPE using regional citrate anticoagulation can be used by the nephrologist to provide a safe and cost effective option of plasma exchange. This modality of anticoagulation is an option for patients at risk or with active bleeding.

Funding: Private Foundation Support

FR-PO082

Effect of Remote Ischemic Preconditioning to Prevent CI-AKI in CKD Patients Undergoing Contrast-Enhanced Computed Tomography: A Randomized Controlled Trial

PINEDRATI Goyadollya, Bancha Satirapoaj, Pamia Tanasanives, Narittaya Varothai, Theerasak Tangwonglert, Naowanit Nata, Oupphathum Supasyndh, Amanrat Chairaisrat. Phramongkutklao Hospital, Bangkok, Thailand.

Background: Chronic kidney disease (CKD) is an important risk factor of contrast-induced acute kidney injury (CI-AKI). Remote ischemic preconditioning (RIPC) transient ischemia followed by reperfusion of the extremity may subsequently protect against ischemia-induced injury in the other organs. Whether RIPC can prevent CI-AKI after contrast-enhanced computed tomography (CT) is not known.

Methods: We conducted a randomized controlled trial in CKD patients, glomerular filtration rate (GFR) less than 60 mL/min/1.73m2, who underwent contrast-enhanced CT during July 2018 to January 2019 at Phramongkutklao Hospital. All patients received standard protocol to prevent CI-AKI. Patients were allocated in 1:1 ratio to receive RIPC (not control) by using block of 4 randomization. RIPC consisted 4 cycles of 5 minutes of cuff to induce arm ischemia with 5 minutes of reperfusion before undergoing contrast-enhanced CT. All patients were closely monitored for possible complications.

Results: A total of 70 CKD patients (35 in the RIPC group, 35 in the control group) were enrolled. Mean age was 73.4±9.9 years and baseline GFR was 45.3±12.2 mL/min/1.73m2. Forty-two (60%) patients were male. The incidence of CI-AKI is lower in the RIPC group than the control group (8.57% vs 0%), p-value = 0.07. Changes of serum creatinine from baseline to 48-hour and from 24-hour to 48-hour were better in the RIPC group than the control group; -0.09±0.16 vs -0.02±0.20 mg/dL, p-value = 0.13 and 0.00±0.12 vs 0.08±0.17 mg/dL, p-value = 0.03, respectively. Change of GFR from 24-hour to 48-hour was also better in the RIPC group than the control group; -0.0±0.54 vs -2.4±1.6 mL/min/1.73m2. In the RIPC group, 25 (71.4%) patients had local numbness. Eighteen (51.4%) patients experienced arm pain, mean pain score 3.1±1.2 out of 10, which immediately resolved after the procedure. No serious complication was observed.

Conclusions: RIPC may decrease the risk of CI-AKI in CKD patient undergoing contrast-enhanced CT, without any serious side effect.

Funding: Private Foundation Support

FR-PO083

Mind the Gap: Achieving Less Than Prescribed Net Ultrafiltration with CRRT Associates with Mortality

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Background: Management of fluid overload (FO) via ultrafiltration (UF) is an important goal of continuous renal replacement therapy (CRRT). Clinicians carefully assess volume status, recommending individualized UF goals. Unfortunately, UF goals are not always met, which may worsen FO. As FO is associated with poor outcomes, we hypothesize that failing to achieve UF goals will also be detrimental.

Methods: Prospective cohort study of 66 ICUs from patients requiring CRRT admitted to the University of Kentucky Hospital from 08/2017 to 04/2019. We excluded
CRRT was 5 [3-9] days. Hospital mortality rate was 59.5%. Time from ICU admission to CRRT initiation and prescribed net UF were not different between survivors and non-survivors. However, total fluid removal rate (ml/kg/day) was higher in survivors vs non-survivors (median 27 vs 21, p<0.001) while FO% per CRRT day was lower in survivors vs non-survivors (median -0.5% vs 0.6%, p<0.001). UF goal achieved was higher in survivors vs non-survivors (median, IQR, 44%, -40 to 83 vs 4.3%, -115 to 54, p<0.001). In fully adjusted models, every unit decrease in UF net goal achieved was independently associated with hospital mortality. (HR, 95% CI: 1.003, 1.001-1.006, p=0.018).

Conclusions: Our study examined UF net goal achievement, a CRRT deliverable that requires closer attention. We found that UF goal underachievement was independently associated with higher mortality. Our study reinforces the value of optimizing fluid management with CRRT. Future work should focus on closing this net UF prescribed vs achieved gap by developing better tools for assessing UF goals and monitoring patient response to fluid removal.

FR-PO084
Fluid Overload, AKI, and Mortality in Influenza Patients: Our Two-Year Experience
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Background: Influenza virus, especially A/H1N1, has been associated with high mortality in critically ill patients who develop Acute Distress Respiratory Syndrome (ADRS). ARDS is considered a septic condition and one of the cornerstones for its treatment is an adequate fluid resuscitation. Fluid overload (FO) is now recognized as a cause of acute kidney injury (AKI), and its association with mortality in critically ill patients has been well documented. The impact of FO in mortality of ARDS influenza patients has not been well described.

Methods: This is a retrospective 2-year study of patients admitted to the ICU with A/RE and suspicion of influenza infection during the Influenza seasons 2016-2017 and 2017-2018. FO was defined as the net UF prescribed vs achieved. We calculated the FO as the algebraic sum of the inputs and outputs during the ICU stay divided by the patient’s weight at admission and expressed as a %. We divided patients in groups: A) < 10% FO and B) > 10% FO and compared mortality and AKI incidence among both groups.

Results: 40 records met the inclusion criteria. Mean age in our cohort was 43.5yrs, 60% were male. Influenza was confirmed in 55% of the patients; 22.7% with A/H1N1. Mortality among A/H1N1 patients was 100%. AKI was diagnosed in 24 patients (60%) with 12.5%, 7.5% and 40% of KDIGO stages 1-3 respectively. RRT was initiated in 13 (32%) of AKI patients. Among groups A and B AKI was diagnosed in 52% and 73% of patients respectively p=0.182. ICU mortality was 55% among the whole cohort. Median fluid balance (FB) among survivors was 3.813mL (2.131-7.284) and among non-survivors -3.870mL (4.477-16.502) p<0.008. Mortality in group A was 40% and in group B was 42% (p=0.736). In multivariate analysis, FO was associated with mortality (HR, 0.545; 95% CI, 0.400-0.742; p < 0.001, respectively). The effects were also consistent in matched cohort (HR, 0.527; 95% CI, 0.333-0.834; p=0.006). But, there was no significant difference in the risk of 1 year survival after surgery between groups in matched cohort (HR, 0.836; 95% CI, 0.413-1.697; p=0.618). Its reduction in risk for postoperative AKI in the LS group was also consistent with subgroup analysis including all groups of age, sex and BMI. And, the effect of reducing the incidence of postoperative AKI in the LS group was remarkable in the lower preoperative Hb, ASA score, and cancer stage.

Conclusions: Our findings suggest that postoperative AKI with stomach cancer after gastrectomy has been attenuated in the LS group, especially in the subgroup including low ASA score, low hemoglobin, small tumor size, low grade cancer stage and smoking.

FR-PO086
Preceding High-Phosphate Diet Exacerbates AKI in Rats
Yousuke Nakagawa,1 Hirokata Komaba,2 Hiroaki Ishida,3 Naoto Hamano,2 Kaichiro Sawada,2 Abul Fajol,1 Takehiko Wada,2 Michio Nakamura,2 Masafumi Fukagawa.2 Interactive Translational Research Center for Kidney Diseases, Tokai University School of Medicine, Isehara, Japan; 3Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan; 2Department of Transplant Surgery, Tokai University School of Medicine, Isehara, Japan.

Background: Animal studies and epidemiological studies suggest that high phosphate diet accelerates the progression of chronic kidney disease. However, little is known whether high dietary phosphate intake affects the severity of acute kidney injury (AKI).

Methods: Six-week-old male rats were subjected to 35-min bilateral ischemia reperfusion injury (IRI) or sham surgery. For 1 week preceding the surgery, the rats were fed either standard diet (0.9% calcium and 0.8% phosphate) or high phosphate diet (0.9% calcium and 1.2% phosphate). After surgery, all rats were placed on standard diet. We evaluated the time course of changes in renal function and mineral metabolism for 3 days following IRI.

Results: Compared to rats on standard diet, rats fed high phosphate diet for 1 week showed normal renal function, normophosphatemia, non-significant increases in FGF23 and PTH, and markedly increased urinary phosphate excretion. In rats kept on standard diet, IRI led to a 10-fold increase in blood urea nitrogen on day 1, which were accompanied by a 1.7-fold increase in serum phosphorus, a 2.4-fold increase in PTH, an 8-fold increase in FGF23, and a 2-fold decrease in 1,25-dihydroxyvitamin D. Rats fed high phosphate diet for 1 week prior to IRI showed more severe kidney injury and alterations in mineral metabolism. The renal and metabolic changes following IRI started to regress by day 3 in rats kept on standard diet, but persisted for 3 days in rats fed high phosphate diet prior to surgery.

Conclusions: We show that high phosphate diet exacerbates AKI in rats even if they are switched to standard diet at onset. Our results suggest the need for routine dietary phosphate restriction in individuals who are at high risk for AKI.

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Role of Macrophages in Human AKI
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Background: Macrophages are an important player in the injury and repair of experimental ischemia/reperfusion injury (IRI). While M1 macrophage contribute to IRI, phenotypic shift from pro-inflammatory M1 to anti-inflammatory M2 macrophages is important for repair. However, emerging evidence also show persistence of M2 macrophages is associated with fibrosis. The purpose of this study is to examine the role of macrophages in human acute kidney injury (AKI).

Methods: We retrospectively reviewed the medical records of 72 patients with biopsy-proven acute tubular necrosis (ATN) without chronic lesions, including 29 cases of native kidneys and 43 cases of deceased donors. M1 and M2 macrophage infiltration was determined by immunohistochemistry of CD68 and CD163 respectively. Healthy kidney sections obtained from nephrectomy was used as control.

Results: CD163+ macrophage outnumbered CD68+ cells in control kidneys and both of these macrophage subtypes increased significantly in ATN. The number of CD68+ M1 macrophage was significantly higher in stage 3 AKI compared to stage 1 or 2. However, there was no difference in the number of CD163+ M2 macrophages according to different stages of AKI. The mean follow up period of 35.4 ± 30.9 months, 72.2% showed renal functional recovery defined as eGFRa60±ml/min.1.73m². In contrast to CD68+ M1 macrophage that showed no association with renal recovery, the number of CD163+ M2 macrophage was significantly lower in patients with renal recovery (3.34 ± 2.3 vs 5.23 ± 2.92 cells/HFP, P<0.005). This association was evident especially in native kidney ATN; more advanced stage AKI and also in late biopsy groups. The number of CD168+ M2 macrophage was found to be an independent predictor of no recovery of renal function at 3 months in advanced stage AKI.

Conclusions: This is a first human study demonstrating the possible important role of macrophages with heterogeneous phenotypes in injury and repair of AKI.

Kidney-Resident Macrophages Exist in Unique Subsets and Demonstrate Subsets-Specific Responses to AKI

Background: Myeloid cell-mediated inflammation plays a key role in AKI. Kidney resident macrophages (KMs) are embryonically derived, self-renewing, and are a distinct lineage from infiltrative macrophages. The means by which these cells differentiate and facilitate these events is unknown. Our objectives were to define KRM subsets using single cell RNA-sequencing (scRNAseq), identify subsets that are responsive to AKI, and facilitate these events is unknown. Our objectives were to define KRM subsets using single cell RNA-sequencing (scRNAseq), identify subsets that are responsive to AKI, and determine target genes for treatment.

Methods: C57BL/6J mice were subjected to 20 min bilateral ischemia-reperfusion injury (n=3) under ketamine/xylazine anesthesia. At 6 d post-injury, KMRs (F4/80+/CD11b+) were isolated by FACS and subjected to scRNAseq using the Chromium 10X immune response p=2.9x10-12, leukocyte differentiation p=1.6x10 -11. There are 2 potential decision points during that transition. Gene ontology analysis suggests produced by the Monocle algorithm (V2.3.6), which constructs a “trajectory” of cellular states. Six transcriptionally unique KRM subsets exist and demonstrate subsets-specific responses to AKI.

Results: Underline represents presenting author.
Results: PX24R knockout mice were protected against renal IR injury with decreased plasma creatinine (1.33 ± 0.17 mg/dL), blood urea nitrogen (91.4 ± 8.6 mg/dL), and NGAL mRNA (395.3 ± 74.4 fold increase over sham) compared to wild type mice (P< 0.01 mg/dL, BUN = 115.1 ± 4.1 mg/dL, and NGAL mRNA = 1194.2 ± 169.2 fold increase over sham, N=4 for all groups). In addition, PX24R knockout mice had lower necrotic (H&E score of 31 ± 5.6%) and apoptotic (reduced TUNEL positive cells by 78.2 ± 1.5%) tubular cells compared to wild type mice. PX24R knockout mice were also protected against renal inflammation with lower pro-inflammatory cytokine/chemokine mRNA induction after renal IR (monocyte chemoattractant protein-1 [MCP-1] = 2.2 ± 0.2 fold increase over sham) compared to wild type mice (MCP-1 = 11.1 ± 1.7, MIP-2 = 206 ± 65.2, IL-6 = 123.5 ± 29.6 and ICAM-1 = 3.7 ± 0.4 fold increase over sham) after renal IR injury. Consistent with this, kidney neutrophil infiltration was reduced by 49.3 ± 5.7% (N=4) in PX24R knockout mice compared to wild type mice after renal IR injury.

Conclusions: Taken together, our studies suggest that PX24R activation exacerbates ischemic AKI by promoting renal tubular inflammation and apoptosis after renal IR injury. Our studies provide a novel insight into the pathophysiology of PX24R in ischemic AKI, suggesting a potential therapy for ischemic AKI.

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FR-PO092
A Novel Noncoding RNA (LRNA9884) Promotes AKI via Maintaining Mincle-Dependent M1 Macrophage Phenotype
Yingying Zhang1, Chen Yu1. Shanghai Tongji Hospital, Shanghai, China; Shanghai Tongji Hospital, Shanghai, China.

Background: Macrophages are key inflammatory cells and play a critical role in renal inflammation in acute kidney injury (AKI). M1 inflammatory macrophage and M2 anti-inflammatory macrophage act reverse role. Phenotype of macrophages in kidney-infiltrating T cells upon T cell receptor-mediated stimulation. All of these functions VISTA functioned as a scavenger of apoptotic cells and served as a checkpoint to control all of these functions. When these kidney-resident cells within the normal organ environment remains unresolved.

Methods: Expression level and pattern of LRNA9884 were examined in cisplatin-induced AKI mice. The regulatory mechanisms of LRNA9884 was investigated in cultured bone marrow–derived macrophages (BMDMs) in vitro by silencing or overexpressing of LRNA9884. Flow Cytometer, fluorescence in situ hybridization (FISH) and other multiple molecular biological techniques were applied to figure out the role of LRNA9884 under acute kidney injury.

Results: LRNA9884 was significantly upregulated in the kidney of cisplatin-induced mice and was associated with the progression of the renal inflammation by using RT-PCR and ISH assay. FISH assay with IF co-staining detected that LRNA9884 was largely expressed in the nucleus of macrophage in cisplatin-induced mice kidney compared with the sham group at day 1 after AKI injury. LRNA9884 was remarkably induced by TNF-α (10ng/ml) in BMDMs as time- and dose-dependent. Western blot and RT-PCR showed that silencing of LRNA9884 effectively inhibited upregulated of macrophage-inducible C-type lectin (Mincle) and iNOS induced by TNF-α. More importantly, we identified that LRNA9884 maintained M1 macrophages phenotype by triggering mincle production at transcriptional level as evidenced by CHIP assay.

Conclusions: LRNA9884 is a mincle-dependent lncRNA that highly-expressed in macrophages under AKI development. Targeting of LRNA9884 effectively blocked the inflammatory macrophage phenotype and thus might promote repair after injury. Through single-cell trajectory analysis on integrated datas, MHC-II- Gpx3 high kidney resident macrophage was the major populations on day 3, which had a strong ability of proliferation. Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2high macrophage and Gdf15high macrophage mainly existed in the chronic phase (day 17).

FR-PO094
Single-Cell Deconvolution of Macrophage Heterogeneity in Mouse Ischemia-Reperfusion Kidney Injury
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Background: Acute kidney injury (AKI) is a clinically critical illness without effective treatment. It has been known that macrophage plays important roles in the repair and fibrosis after acute injury, whereas its heterogeneity in subtypes and the related pathophysiological functions during the progression of AKI have not been well established.

Methods: Unilateral ischemia reperfusion (uIRI) acute kidney injury model was set up in C57BL/6J male mice (37°C for 45minutes). Macrophages were collected from the injured kidney on day 1, 3,10,17 post surgery by flowcytometry cell sorting through co-culturing with F4/80 and Cd11b. Meanwhile, monocytes co-culturing with Ly6c and Cd11b were sorted from peripheral blood and spleen respectively. Single cell transcriptome sequencing was performed through 10X genomics method.

Results: Altogether eleven clusters of macrophages were discovered in the kidney. There were three subclusters of kidney resident macrophages in normal kidney and they almost disappeared after injury. On day 1 post uIR injury, S100a4+ and S100a8+ macrophages took the majority of macrophage subtypes in the kidney, while Stmn1+ macrophage was the major populations on day 3, which had a strong ability of proliferation. Cxcl2+ macrophage and Gdf15+ macrophage mainly existed in the chronic phase (day 17). According to Gene Oncology analysis, Cxcl2+ macrophage exhibited inflammatory response and TNF signaling pathway activation, while Gdf15+ macrophage had more related genes and thus might promote repair after injury. Through single-cell trajectory analysis on integrated datas, MHC-II+ Gpx3+ kidney resident macrophage developed into S100a4+ macrophage through Stmn1+ macrophage and S100a8+ macrophage mainly derived from spleen in the acute phase. In the chronic phase, MHC-II+ MMP13+ and MHC-II+ Fli1+ kidney resident macrophage developed into Cxcl2+ macrophage while Stmn1+ macrophage proliferate and different into Hspa1a+ macrophage and Gdf15+ macrophage.

Conclusions: Macrophages have strong heterogeneity in AKI. S100a4+ and S100a8+ macrophages might contribute to inflammation during acute injury phase. Gdf15+ macrophage was likely to promote repair, while Cxcl2+ macrophage could be involved in the chronic inflammation and fibrosis processes. Kidney resident macrophages and monocytes derived from spleen might play important role in AKI.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO095
Increased Expression of the Ca2+ Channel Orail and IL-17 in Blood CD4+ Cells in Critically Ill Patients with AKI
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Background: Acute kidney injury (AKI) affects up to 50% of critically ill patients and is associated with high mortality rates approaching 60%. In surviving patients, reduced kidney function is irreversible for over AKI. AKI increases the risk developing of chronic kidney disease (CKD). IL-17, a pro-inflammatory cytokine secreted by CD4+ T cells (Th17 cells), has been linked to the activation of the store-operated calcium channel, Orail. Th17 cells, have been associated with various autoimmune diseases such as psoriasis and SLE and also in delayed graft function. In rodent models of kidney injury, Th17 cells have been shown to enhance the severity of AKI and AKI-to-CKD transition. However, no direct evaluation of Th17 cells has been conducted in AKI patients.

Methods: Prospective, case-control study of critically ill patients with AKI (KDIGO stage 2, n=9) and ICU matched-controls without AKI (n=8). Matching criteria included age, gender and baseline eGFR. Venous blood was collected 12-24 hours post diagnosis and 12-24 h ICU admission and analyzed for expression of CD4+/IL17+ cells and the expression and activity of Orail.

Results: The percent of CD4+IL-17+ was significantly higher in AKI patients (0.98%±0.11) vs ICU controls (0.15%±0.06, p<0.05). In addition, there was an enhancement in the expression of Orail, from 3.5% in ICU controls vs 30% in the AKI group. To determine if the increase in Orail expression was in mediating IL17 activity, we isolated CD4+ cells and stimulated in vitro for ~12 hours with either extracellular sodium (170mM) and/or AngII (10^{-7} M), which was previously shown to enhanced IL17 production in kidney T cells of post-AKI rats. In blood from AKI patients, there was significant increase in IL17 producing CD4+ in response to in vitro stimulation (from 2.3%±0.07 to 9.1%±0.07, p<0.05). Moreover, the increased IL17 response from blood of AKI patients was completely blocked by the inclusion of the Orail/ISOCE inhibitor YM58483 (p=0.05 vs. stimulated). Interestingly, there was no IL17 response in CD4+ cells from ICU controls without AKI.

Conclusions: These results suggest that circulating Th17 cells are activated early in critically ill patients with AKI vs ICU controls without AKI. Th17 cells and/or IL17 may represent a target as a potential early biomarker of AKI in the ICU, and Orail may represent a therapeutic target.

Funding: NIDDK Support

FR-PO096
Regulatory Innate Lymphoid Cells Suppress Innate Immunity and Reduce Renal Ischemia-Reperfusion Injury
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Background: Innate lymphoid cells (ILC) are a recently recognized group of immune cells with critical roles in tissue homeostasis and inflammation. Regulatory innate lymphoid cells (ILCregs) are a newly identified subset of ILCs, which play a suppressive role in the innate immune response, favoring the resolution of intestinal inflammation. However, the expression and role of ILCregs in kidney has not been reported.

Methods: ILCregs were assessed by flow cytometry in human and mouse kidney. Mouse ILCregs isolated from IL-10-GFP mice were used for phenotypic and functional analysis. Bilateral renal ischemia was imposed in C57BL/6 or Rag-/- mice. Adoptive transfer of ILCregs into mice with ischemia/reperfusion injury (IRI) was used to assess their in vivo functions. IL-2/IL-7/2Aβ complexes (ILC-2C) were generated by 3 consecutive daily injections prior to IRI operation to inducing expansion of ILCregs in vivo. Results: Here, we show that ILCregs are present in both human and mouse kidney. Human and mouse renal ILCregs expressed similar surface markers and formed a similar proportion of total kidney ILCs. ILCregs from kidney were expanded in vivo and in vitro with a combination of IL-2, IL-7 and TGF-β. The expanded ILCregs exhibited immunosuppressive effects on innate immune cells, such as ILC1 and macrophages, via secretion of IL-10 and TGF-β. Adoptive transfer of ex vivo expanded ILCregs improved renal function and attenuated histologic damage when administered before or after induction of IRI, in association with reduction of neutrophil infiltration and induction of M2 macrophages in kidney. Moreover, treatment with IL-2C promoted expansion of ILCregs in vivo, and prevented renal IRI in Rag-/- mice. Depletion of ILCregs with anti-CD25 Ab abolished the beneficial effects of IL-2C in Rag-/- mice.

Conclusions: This study shows that ILCreg are effective against renal IRI through suppressing innate immune inflammation. This demonstrates a novel strategy of manipulating ILCregs to treat disease.

Funding: Government Support - Non-U.S.

FR-PO097
Ex Vivo Gene Editing and Pharmacologic Modification of T Cell Keap1/ Nrf2 Towards Immunotherapy for Experimental AKI
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Background: Adoptive transfer of Keap1 deficient T cells with enhanced Nrf2 activity has been shown to lead to significant protection from IR-induced AKI in mice (JASN 2013), and gene editing of Keap1 in human T cells enhances Nrf2 products (J Immunol 2018). Pre-clinical studies in mice with Keap1/Nrf2 gene editing and pharmacologic manipulation in AKI are needed to set the stage for the human cell-based therapies.

Methods: Primary mouse CD4+ or CD8 T cells were-isolated from B6 WT spleen with negative selection using Dynabeads. Nrf2 activity was modulated either by treating T cells with different concentrations (10nM, 20nM and 50M) of the pharmacologic Nrf2 activator CDDO-Im or using CRISPR/Cas9 system to edit Keap1 gene. The efficiency of gene editing was assessed by using ATTO 550-labeled tracrRNA. Various T cell culture conditions were tested and viable cells were enriched using flow-sorting. Viable cells were detected by 4′-6-diamidino-2-phenylindole (DAPI). Functional effects of ex vivo Nrf2 activation and Keap1 editing were assessed on Nrf2 dependent antioxidant genes NADPH dehydrogenase quinone 1 (NQO1), heme oxygenase 1 (HO-1) and Glycyl-histidyl-tyrosine conjugate (GCLC) expression using quantitative real-time PCR.

Results: Ex-vivo marine CD4+ T cell CDDO-Im treatment resulted in a dose dependent response in Nrf2 target gene expression. The higher dosage of 50nM CDDO-Im had the highest impact on NQO1 (~16.4-fold), HO-1 (~3.6-fold) and GCLC (~2.8-fold). Pre-clinical studies in mice with Keap1/Nrf2 gene editing and pharmacologic modification in AKI are needed to set the stage for human cell-based therapies.

Conclusions: Pharmacologic and gene editing techniques increased murine T cell Nrf2 target genes ex vivo for inhibition in studies to prevent AKI and accelerate repair in human kidney. These studies set the stage for immunotherapy treatment for AKI and other immune mediated kidney diseases.

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FR-PO098
Ischemia-Reperfusion Injury Affects Co-Signaling Molecules TIGIT/CD226 in Kidney T Cells
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Background: T-cells play important roles in AKI pathogenesis and repair processes, but current immunotherapies are not successful. Unbiased cell specific RNAseq is a powerful tool to discover new therapeutic targets, and led to the discovery of AKI stimulated kidney CD4 cell co-inhibitory molecule, T-cell immunoreceptor with Ig and ITIM domain (TIGIT) and its co-stimulatory counterpart CD226.

Methods: 8-week-old male C57BL6/J wild type (WT) mice underwent bilateral IR surgeries to induce AKI. CD4 T-cells from post ischemic and control kidney were flow sorted 24 hours after inducing AKI and RNA sequencing (RNA-seq) performed. Flow cytometric analysis was performed to validate RNA-seq findings in T-cells from post secondary kidney, and to determine proportion of pre and post-clamp human kidney samples of renal cell carcinoma nephrectomies.

Results: RNA-seq analysis showed significant increase in TIGIT expression (63.0±2.6 fold vs 21.8±2.6; p<0.05) in CD4 T-cells from post IR mouse kidneys compared to control. TIGIT protein expression was not different in CD4 and CD8 T-cell isolated from post IR and control kidneys, however, double negative T-cells (CD3+CD4+CD8-; DN) showed significantly reduced (17.1±6.8 vs 56.3±10.2; p<0.0002) expression in post IR kidneys. Human kidney assessment showed significant increase in absolute number of TIGIT positive CD8 (4.0±2.3 vs 1.8±0.9; p<0.04) T-cells from post IR kidneys compared to control. Control CD226 protein expression was not different in CD4 and CD8 T-cell isolated from post IR and control kidneys, however, double negative T-cells (CD3+CD4+CD8-; DN) showed significantly reduced (17.1±6.8 vs 56.3±10.2; p<0.0002) expression in post IR kidneys. Human kidney assessment showed significant increase in absolute number of TIGIT positive CD8 (4.0±2.3 vs 1.8±0.9; p<0.04) T-cells from post IR kidneys compared to control.

Conclusions: These data demonstrate that ischemia reperfusion leads to marked upregulation of TIGIT and CD226 in mouse and human kidney T-cells. Given the effectiveness as well as renal side effects of traditional anti CTLA4 and anti PD1 therapies, TIGIT/ CD226 may be a novel target for developing next generation check point inhibitor therapies for AKI and other kidney diseases.

Funding: NIDDK Support
FR-PO099
Multifaceted Role of ST2/IL-33 Axis During Kidney Injury
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Background: Renal diseases are a major cause of morbidity and mortality. Inflammation elicited by variety of cytokines and chemokines are a major player in initiation and progression of the disease. Interleukin 33 (IL-33) belongs to IL-1 family of cytokines, which was identified for eliciting T helper-2 (Th2) cytokines. IL-33 acts as an ‘alarmin’ that regulates the immune response during injury. IL-33 acts in an autocrine/paracrine manner on the ST2 membrane receptor IL33R or Il1rl1, triggering innate and adaptive immune responses. ST2 is widely expressed in immune cells playing regulatory role in T cells (Tregs). Importance of ST2/IL-33 signaling in Tregs has been demonstrated in multiple inflammatory conditions. However, cell specific contribution of ST2/IL33 signaling is not understood. Here, we investigated the cell specific ST2/IL33 signaling activity using murine renal injury models.

Methods: Murine ischemia-reperfusion injury (IRI) model was used to investigate cell specific ST2/IL-33 signaling using Il1rl1−/− and cell specific Pepsin, Foxp3 and Foxp3−/− mice to delete ST2 expression in proximal tubular cells (PTC), pericytes and Tregs respectively. The structure and function of the kidney were probed using flow cytometry, histology, immunohistochemistry, qRT-PCR and biochemical analysis.

Results: In vivo experimental data indicated that deletion of ST2 in PTC and pericytes attenuated renal injury suggesting that activation of ST2/IL-33 signaling in these cells leads to impaired renal function following IRI, leading to fibrosis. On the contrary, elimination of ST2/IL33 signaling from Tregs resulted in greater renal injury to the indicating that activation of ST2/IL33 signaling in Tregs mediate renal protection during inflammation and injury.

Conclusions: This study addresses the cell specific role of ST2/IL33 signaling in immune-regulation, fibrosis and repair. Our findings try to delineate the multifaceted role of ST2/IL33 axis in renal injury. We conclude modulation of ST2/IL33 signaling as a promising therapeutic option.

Funding: NIDDK Support

FR-PO100
CC-Chemokine Receptor 7 Deficient Mice Are Resistant to Renal Ischemia-Reperfusion Injury
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Background: One of the most prominent chemokine receptors in the adaptive immune system is CC-chemokine receptor 7 (CCR7), which has been established as an important component of lymphocyte-driven immune function. CCR7 promotes homing of T cells and antigen presenting cells to areas of lymphoid tissues where T cell priming occurs. Apart from chemotaxis, CCR7 defines a precursor for natural killer T (NKT) cells in the thymus and periphery. Manipulation of the CCR7 axis has either protective or deleterious role in mouse kidney injury models. We sought to clarify the role of CCR7 in the pathogenesis of renal injury after ischemia reperfusion injury (IRI).

Methods: Experiment (Exp.) 1: CCR7 deficient mice (KO) or wild-type mice (WT) underwent IRI. Mice were euthanized at 1, 3 or 7 days after the surgery. Kidney & serum were collected for biochemical analysis & histological evaluation. Exp. 2: KO or WT were injected intravenously with alpha-galactosylceramide: a specific ligand for NKT cells. NKT cells were isolated from spleen 24 hours later, and cytokine profiles were assessed by qPCR. Exp. 3: Prior to IR surgery on Day 0, KO mice were injected intraperitoneally with IFNγ or vehicle on Days −3, −2, −1, 0 and 1. Kidney & serum were harvested on Day 1.

Results: Exp. 1: Blood urea nitrogen & creatinine levels in KO were lower than WT throughout experimental periods. Similarly, KO developed milder tubulointerstitial injuries than WT. Exp. 2: Serum IFNγ concentration & IFNγ mRNA expression in isolated NKT cells were lower in KO than WT. Exp. 3: KO injected with IFNγ showed similar kidney damage to KO injected with vehicle.

Conclusions: CCR7 KO mice are resistant to IRI. KO mice show blunted production of IFNγ. We speculate that less production of IFNγ in KO induces insufficient development of an effector T cell response and reduces kidney damage. However, supplementation of IFNγ was not sufficient to increase the susceptibility to IRI in KO mice. Although we need further investigation to resolve the mechanism(s), intervention of CCR7 axis could have therapeutic potential for AKI, especially IRI.

Funding: NIDDK Support

FR-PO101
Superagonistic CD28 Protects Against Renal Ischemia Injury-Induced Fibrosis Through a Regulatory T Cell Expansion Dependent Mechanism
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Background: To investigate the potential protective effect of superagonistic CD28 (CD28sα) on the chronic outcome post acute kidney ischemia injury and related mechanisms.

Methods: Male C57BL/6/N mice were treated with CD28sα via peritoneal injection 6 days before the induction of ischemia renal injury (IRI), IRI was induced by bilateral clamping of renal pedicles for 35 min following reperfusion. 7, 14 and 28 days after the surgery, IRI mice were euthanized and specimens were harvested. The role of regulatory T cells (Tregs) expansion in the renal protection conferred by CD28sα treatment was examined using an anti-CD25 antibody (PC61) to partially deplete Tregs. The chronic pathological outcome of mice renal was identified by Masson staining, Sirius Red staining and renal fibrosis related extracellular matrix immunohistochemistry (IHC) staining.

Results: CD28sα treatment significantly promoted the percentage of Tregs in the spleen, kidney and peripheral blood 24 h after the IRI. Serum creatinine level was remitted by CD28sα administration in a short term (7 days). Histological analysis indicated that CD28sα attenuated renal tubular damage. CD28sα also attenuated the extracellular matrix deposition in the renal medulla site 28 days after IRI. Immunoblot showed that Collagen IV expression of kidney was lowered by CD28sα administration 28 days after IRI. IRI cells in kidneys from CD28sα pre-treated IRI mice were characterized by an increased percentage of Tregs and MHCII/CD11c dendritic cells, significantly decreased Th17 cells and also increased secretion of Tregs effect cytokine IL-10. CD28sα pretreatment also resulted in less cells apoptosis and less oxidative stress of reals marked by less TUNEL and 8-OHdG positive stained cells. On the other hand, the renal protection bestowed by CD28sα was abolished by PC61 administration.

Conclusions: CD28sα alleviated chronic outcome after the acute ischemic injury, probably associated with the incoheate up-regulation of Treg cells.

Funding: Government Support - Non-U.S.

FR-PO102
Enhancement of Tregs with IL23s Hybrid Cytokine Rescues Kidney Function in Aristolochic Acid-Induced Nephropathy
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Background: Aristolochic acid (AA) is used as a “traditional medicine” to induce labor, promote the treatment of inflammation and intoxication. The Balkan nephropathy is supposedly caused by chronic dietary consumption of AA and genetic predisposition. However, recent studies showed that consumption of AA leads to tubular epithelial cell (TEC) injury and inflammation, which triggers acute and chronic renal dysfunction. Our current study was to investigate the role of Tregulatory cells (Tregs) and susceptibility of TEC in experimental AA nephropathy.

Methods: We induced renal injury in male C57Bl/6 mice with AA injection (i.p.) and evaluated the progression of acute nephropathy for 4 weeks. Additionally, PC61 (anti-CD25 Ab to deplete Tregs) and IL23s (a novel Treg-enhancing hybrid cytokine bearing the activities of IL-2 and IL-33) were applied to evaluate the progression of nephropathy. Sera samples were collected and used for plasma creatinine (PCr) and blood urea nitrogen (BUN) assessment with the commercially available kits. Tubular necrosis in the kidneys was assessed on H&E sections. Kim-1 and NGAL were used for kidney injury markers. Flow cytometry was used to evaluate inflammatory cells and cytokine profile in kidneys, spleen and blood. The effect of IL23s on PC61 and IL-33R (ST2) KO mice in AA nephropathy was also studied to understand the underlying mechanisms. All animal procedures and personnel were approved by institutional animal care and committee care.

Results: Mice treated with AA developed severe renal dysfunction, inflammation and tubular necrosis. Immune cells were elevated alongside renal inflammation. Administration of anti-CD25 mAb PC61 worsened renal dysfunction in AA-treated mice, increased the susceptibility of mice to AA-induced nephrotoxicity, suggesting a role of Tregs. Treatment of mice with IL23s (a Treg-enhancing hybrid cytokine containing IL-2 and IL-33), after the onset of injury suppressed inflammation, renal dysfunction and injury, evident by the reduced levels of plasma creatinine, BUN and in these animals, whereas PC61 mAb together with IL23s mediated protection indicating Tregs as primary immune cells rendering protection.

Conclusions: IL23s protect from AA induced nephrotoxicity in a Treg-dependent manner with a role for ST2 and PD-1, and bears therapeutic potential.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

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Acute kidney injury (AKI) due to cisplatin is a significant problem that limits its use as an effective chemotherapeutic agent. TCR+CD4-CD8- (double-negative - DN) T cells constitute a major T cell population in human and mouse kidney and protect from ischemic AKI. However the pathophysiologic roles of DN T cells in cisplatin-induced AKI are unknown.

Methods: Mice were treated with cisplatin (30mg/kg) or vehicle and effect on kidney DN T cell numbers and function assessed using flow cytometry. In vitro studies evaluated effects of kidney DN T cells on cisplatin-induced apoptosis and PD ligand 1 (PD-L1) in renal epithelial cells. In vivo adoptive transfer studies assessed role of DN T cells on kidney structure and function during cisplatin-induced AKI.

Results: Kidney DN T cell population increased (p=0.01) at 24 hours and declined (p<0.01) by 72 hours after cisplatin treatment. Cisplatin increased kidney DN T cell proliferation (p<0.05), apoptosis, CD69 (p<0.05) and IL10 (p<0.01) expression whereas CD26L (p<0.03), CD44, IL-17A, IFN-α (p<0.05) downregulated. Cisplatin decreased both kidney DN T cell PD1 (p<0.05) and NK1.1 (p<0.05) subsets with pronounced effect on PD1 subset. In vitro kidney DN T cells co-culture decreased cisplatin-induced apoptosis (p<0.05) in kidney proximal tubular epithelial cells (PTECs), increased expression of Bcl-2 (p<0.05) decreased cleaved caspase 3 (p<0.05), and attenuated PTEC PD-L1 expression (p<0.05). Adoptive transfer of DN T cells attenuated kidney dysfunction (p<0.05) and structural damage (p<0.05) from cisplatin-induced AKI.

Conclusions: These results demonstrate that kidney DN T cells respond rapidly and play a protective role during cisplatin-induced AKI. DN T cells may have important translational implications for humans undergoing cisplatin and immune checkpoint inhibitor therapy for cancer.

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FR-PO104

B Cells Are Associated with Renal Recovery After AKI
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Background: The mechanisms associated with renal recovery after an episode of Acute Kidney Injury (AKI) are still poorly understood but immune factors seem to play a role. We aim to determine the association between the urinary immune profile of AKI patients and renal recovery.

Methods: Adult patients with AKI ≥stage 2 by KDIGO and sterile leukocyturia at admission in 2 Intensive Care Units (ICUs) of a Portuguese tertiary Hospital were prospectively included in a consecutive way. Anuria, CKD > stage 3, dialysis one week previous admission and absence of informed consent were exclusion criteria. Urinary flow prospectively included in a consecutive way. Anuria, CKD > stage 3, dialysis one week previous admission and absence of informed consent were exclusion criteria. Urinary flow

Results: From January to September 2018, a total of 552 patients were admitted in both ICUs, 108 with AKI ≥stage 2 by KDIGO at admission. Of these, 18 had sterile leukocyturia and no exclusion criteria. Median baseline serum creatinine was 1.45mg/dl. APACHE II score was 15, 66.7% medical and 33.3% surgical admissions. AKI: Mechanisms - Inflammation/Sepsis/Remote Injury

Conclusions: Immune mechanisms seem to play a role in renal regeneration and recovery after an episode of AKI. In our critically ill population, urinary B Cells were statistically significantly associated with renal recovery at 7 days after AKI at ICU admission.
Methods: Male C57BL/6 mice were treated with 1xM of MS417 for 7 days before unilateral ischemia was performed followed by reperfusion for 24 hours. Kidney tissue, blood and bone marrow was collected for neutrophil analysis using a custom flow cytometry panel. For in vitro studies, freshly isolated neutrophils from healthy volunteers were labeled with Calcein AM and incubated with MS417 media for 1 hour. HUVEC were activated by TNFα and then incubated with neutrophils and allowed to adhere for 30 minutes. Non-adherent cells were removed and neutrophil adhesion was quantified using a fluorescent plate reader.

Results: Absolute neutrophil counts increased in the bone marrow (p<0.0001 vs sham) and blood (p<0.0001 vs sham) 24 hrs after injury, indicating a significant trend toward neutrophil mobilization from bone marrow into the circulation following IRI. BRD4 inhibition may represent a therapeutic strategy to limit neutrophil recruitment to the kidney, following IRI.

Conclusion: BRD4 inhibition blocked neutrophil upregulation of the adhesion receptor, CD66α, neutrophil adhesion to activated endothelial cells, and recruitment of neutrophils to the kidney, following IRI. BRD4 inhibition may represent a therapeutic approach to limiting IRI in the kidney.

FR-PO107

The HMGB1-IL17A Axis Promotes Neutrophil Infiltration in Renal Ischemia-Reperfusion Injury

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Background: Renal ischemia/reperfusion (IR) injury is the leading cause of acute kidney injury (AKI), which is associated with increased morbidity and mortality. Neutrophils are the first leukocyte to be recruited to the site of inflammation and also play a central role in the inflammatory cascade. We previously reported that inhibition of HMGB1 release ameliorated IR-induced neutrophil infiltration in mice. However, it is poorly understood whether HMGB1 was involved in regulating and activating the IL23/IL17 axis in renal IR injury. In this study, we aim to delineate whether the HMGB1/TLR4 signaling promotes the Th17 responses and contribute to the renal IR injury.

Methods: C57BL/6 mice were subjected to 60 min clamping of the left renal pedicle and followed by right nephrectomy and up to 24 h of reperfusion. The involvement of HMGB1 and IL17A was assessed in functional assays by neutralizing HMGB1, IL-23 or IL-17A antibody, and recombinant HMGB1 (rHMGB1), IL-23 or IL-17A (rIL-17A), respectively. Urea nitrogen, creatinine and lactate dehydrogenase levels were measured. Renal histopathological changes and neutrophil infiltration were assessed by immunohistochemistry. The expression of HMGB1, TLR4, IL-23, IL-17A were assessed by western blot analysis and mRNA expression. The levels of MCP-1, IL-8 and RANTES were assessed by ELISA.

Results: IL-23, IL-17A and neutrophil infiltration were increased after renal IR injury in mice. HMGB1 antibody significantly ameliorated IR-induced neutrophils infiltration, recruitment and IL-23 expression. IL-17A-/- mice following renal IR injury were treated with HMGB1 significantly reduced the expression of IL-23, IL-17A and neutrophil infiltration. Furthermore, IL-23 or IL-17A antibody significantly inhibited IR induced neutrophils infiltration. Moreover, HMGB1 or IL-17A antibody remarkably decreased production of neutrophil chemotactic MCP-1, IL-8 and RANTES, whereas rHMGB1 or rIL-17A may promote production of them.

Conclusion: These results suggested that HMGB1 facilitated the injury effect of the IL-23/IL-17 axis, which contributed to neutrophils infiltration in renal IR injury.

Funding: Government Support - Non-U.S. scientific community

FR-PO108

Dexamethasone Pretreatment Prevented Chemotherapy-Induced Acute Renal Failure by Inducing Polymorphonuclear Myeloid-Derived Suppressor Cells

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Background: Chemotherapy for cancer patients leads to renal toxicity which was the main cause for chemotherapy discontinuation. Current preventive measures failed to be successful. Previous studies indicated dexamethasone cured renal diseases. The present study is designed to explore the efficacy and mechanism of dexamethasone in preventing chemotherapy induced renal toxicity.

Methods: Cisplatin was utilized to build acute renal failure mice model. Th17, Treg, polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC) and monocytic MDSC (M-MDSC) was tested in injured kidney. Dexamethasone pretreatment was used to relieve renal failure with the immune mechanism investigated.

Results: Cisplatin induced acute liver failure confirmed by increased serum creatinine. Th17 cells were increased in injured kidney, with increased PMN-MDSC and decreased Treg cells. Dexamethasone pretreatment decreased serum creatinine and induced PMN-MDSC and Treg in kidney and increased Th17 cells. Gr-1 antibody was utilized to eliminate PMN-MDSC after dexamethasone pretreatment. PMN-MDSC depletion eliminated the efficacy of dexamethasone in relieving renal failure. Dexamethasone induced PMN-MDSC was transferred to mice before cisplatin administration, which decreased serum creatinine. Dexamethasone induced PMN-MDSC suppressed T cell proliferation through reactive oxygen species (ROS) pathway.

Conclusion: Dexamethasone pretreatment relieved chemotherapy induced renal failure by inducing PMN-MDSC, which suppressed Th17 cells and induced Treg cells.

FR-PO109

Sepsis Alters Renal Tubular Epithelial Phenotype and Disrupts Intercellular Communication

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Background: The success of sepsis therapy requires an understanding of time and cell-specific responses to infection. Such knowledge will allow accurate staging of septic patients to precise spatial and temporal therapy. We recently showed that the renal response to endotoxin (LPS) involves the sequential activation of inflammation, antiviral signaling and translation shutdown leading to organ failure. This propagation of injury was mediated in part by tubular epithelial and macrophage cross-talk. However, the kidney is composed of over twenty cell populations including epithelial, endothelial, immune and stromal cells. We therefore hypothesize that many of these cell types have precise roles in injury propagation along the sepsis timeline. To address this hypothesis, we used single cell RNAseq to dissect each cell subpopulation’s contribution to endotxin injury over time.

Methods: We harvested single cell suspensions from murine kidneys at time points spanning the injury and recovery phases of sepsis. Cells were processed via 10x Chromium RNA sequencing platform and analyzed with Seurat R package.

Results: We identified 26 clusters representative of major renal cell populations defined by known canonical markers. Endothelial cells and macrophages showed early transcriptional changes but opposite metabolic profiles. Interestingly, the pericyte also showed early signaling activation that persisted well into the recovery phase. In contrast, layered, cell-specific approach to the pathophysiology of sepsis may reveal biomarkers that allow the accurate staging of septic patients and identify temporally and spatially precise therapeutic targets.

Funding: Other NIH Support - Research included was supported by NIH awards: T32HL091816, RO1DK107623

FR-PO110

Photoacoustic Microscopy Reveals Early Decrease in Peritubular Capillary (PC) O2 Tension Associated with Temporal Changes in Cell Metabolism and Injury Despite Unimpaired PC Flow in Sepsis-Induced AKI

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Background: The ability to monitor dynamic changes in the renal metabolic rate of oxygen (MRO2) is critical to understanding the time course of changes in local tissue. Micron scale spatial factors that influence renal injury such as AKI acute kidney injury. These observations have impinged in vivo measurement of three key hemodynamic parameters—total hemoglobin concentration (CtHb), oxygen saturation of hemoglobin (SO2) and peritubular capillary blood flow (PCBF) at the microscopic level. To address this, we have developed a new technique - intravital multi-parametric photoacoustic microscopy (PAM).

Methods: To validate our system C57BL/6 mice were subjected to 1) hypoxia or 2) LPS-induced sepsis (5 mg/kg LPS, ip). The new intravital PAM platform uses nanosecond-pulsed lasers (532 and 558 nm) for dual-wavelength excitation-based spectroscopic measurement of ox. In vivo PAM imaging was performed over time on kidneys at depths of up to 200 μm. Plasma and kidneys were collected for measurement of creatinine, Kim1, NGAL, ATP, and various injury markers.

Results: In vivo PAM performed in mice challenged with 12 or 100% oxygen showed a strong correlation between ΔSt and inhaled oxygen concentration. After LPS, time-dependent changes in hemodynamic parameters and injury markers were observed. PCBF increased within 10 min but returned to and remained normal from 20-200 min. PC SO2 declined to below 15% at 40 min and increased in Kawin (~20-fold) and Ngal (~300-fold) and decreases (~80%) in Ne2 mRNA were observed at 12 hr. Creatinine increased at 24 hrs. Taf4 and Myd88 mRNA increased at 12 hr.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Conclusions: In vivo PAM enables dynamic monitoring of renal MRO, in AKI. The time-lapse description of PAM in AKI disease showed decreased maintained yet so, was limiting and produced marked temporal changes in biochemical parameters of cell metabolism and injury. This technical innovation lays the foundation for dynamic monitoring of renal oxygen metabolism in AKI, as well as chronic kidney disease, providing a new tool for AKI and CKD studies. (Zheng & Sun are co-first authors and contributed equally.)

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FR-PO111

BAM15, A New Mitochondrial Uncoupler, Improves Sepsis AKI

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Background: (2-fluorophenyl)-[6-(2-fluorophenyl)aminol]-[1,2,5-oxadiazolo[3,4-e]pyrazin-5-yl]amine (BAM15) is a new mitochondrial uncoupler protects mitochondria with more specificity and less cytotoxicity than other uncouplers. Kenwood et al. (Mol. Metab. 2013) demonstrated that BAM15 treatment improved renal outcomes after renal ischemia/reperfusion injury. We evaluated the therapeutic potential of BAM15 for sepsis AKI.

Methods: Cecal ligation and puncture (CLP) was performed to 10-week-old CD-1 mouse to induce sepsis. BAM15 (5mg/kg, i.p.) was injected 0 hours after CLP. We also evaluated kidney injury and systemic organ damage and inflammation 18 hours after CLP. A survival study was conducted with both (0hrs) and delayed (6hrs) BAM15 treatment.

Results: BAM15 treatment at the time of CLP surgery improved both survival (fifteen of twenty of non-treatment group and five of twenty of treatment group were died in 7days: P<0.05) and kidney function at 18 hours along with reduced tubular histological damage; tubular hypoxia, systemic inflammation (e.g. IL-6 and IL-10) and splenic apoptosis (a marker of late immunosuppression), but did not improve other organs (e.g. liver and muscle). Furthermore, delayed treatment of BAM15 (6 hours after CLP) also improved survival (seventeen of twenty of non-treatment group and ten of eighteen of treatment group were died in 7days: P<0.05) and kidney dysfunction after sepsis.

Conclusions: Sepsis increased mitochondrial damage, tubular hypoxia, renal histological damage and, accelerated splenic apoptosis and systemic inflammation resulting in AKI and death. BAM15 significantly attenuated these processes, improved survival, and selectively improved septic AKI.

Funding: NIDDK Support

FR-PO112

Circulating Peroxiredoxin 1 Is a Novel DAMP and Aggravates Acute Kidney Induced by Lipopolysaccharide via Promoting Inflammation

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Background: Damage-associated molecular patterns (DAMPs) are initiators of sterile inflammation and are important in the pathogenesis of both acute and chronic kidney diseases. Peroxiredoxin 1 (Prdx1) was identified as a new DAMP and plays a role in the development of kidney injury. However, the current knowledge on those DAMPs that activate renal inflammation under AKI remains incomplete. Peroxiredoxin-1 (Prdx1) is a small protein in the Peroxiredoxin family, which are ubiquitous expressed enzymes reducing peroxide levels. Interestingly, recent studies indicated that intracellular Prdx1 could be released to extracellular space under certain stimuli and extracellular Prdx1 has been recently identified as a novel DAMP due to its pro-inflammatory property by binding to Toll-like receptor (TLR) 2/4. However, the crucial role of Prdx1 in AKI remains unclear.

Methods: Prdx1 deficient mice and patients with AKI were used to determine its function in AKI, potential mechanisms and human relevance.

Results: Intraperitoneal injection of lipopolysaccharide (LPS) elicited a progressive course of AKI in mice developed from 12 to 24-hour post injection along with renal inflammation evident by macrophage infiltration and upregulation of cytokines (IL-1β, IL-6); these alterations were concurrently occurred with a robust and progressive production of serum Prdx1. Similar observations were also obtained in ischemia-reperfusion-induced AKI mouse model in mice. Removal of the source of serum Prdx1 protected mice deficient in Prdx1 from LPS-induced liver injury, and decreased macrophage infiltration, IL-1β and IL-6 production. As a result, Prdx1 +/- mice were strongly protected from LPS-induced death that was likely progressed from AKI. Additionally, intravenous re-introduction of recombinant Prdx1 (Prdx1 +/− mice) reduced or reversed all the above events, demonstrating an important contribution of circulating Prdx1 to AKI. Prdx1 potently induced in primary macrophages the expression of pro-IL-1β, IL-6, TNF-α, and IL-18 through the NF-κB signaling as well as the NOD2 signaling. Furthermore, a significant elevation of serum Prdx1 was demonstrated in patients (n=31) with AKI; the elevation is associated with serum creatinine.

Conclusions: Our findings reveal a previously unrecognized detrimental role of prdx1 in LPS-induced renal inflammation and tissue damage and thereby identify novel and important therapeutic target for LPS-induced AKI.

FR-PO113

Renal Proteome Changes Reveal a Substantial Renal Acute Phase Response in Sepsis-Induced AKI in Mice

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Background: Sepsis-induced acute kidney injury (AKI) is the most common form of AKI with poor outcomes. Both differential diagnosis and management of septic AKI are unresolved issues. Our aim was to study the temporal profile of the renal proteome changes in bacterial lipopolysaccharide (LPS)-induced AKI.

Methods: Male NMRI mice were injected with LPS or saline (control). AKI was studied at early (EP, 1.5 and 6 hours after LPS at 40 mg/kg i.p.) and late phases (LP, 24 and 48 hours after LPS at 10 mg/kg i.p.) by HPLC-MS/MS screening. Renal mRNA expression of 13 acute phase proteins (APP) was measured by qPCR.

Results: AKI was induced by increased renal TNFα, IL-6 and neutrophil gelatinase-associated lipocalin (Lcn-2) mRNA expression from 1.5 h after endotoxin administration. At the same time of CLP + LPS administration 65% of the 13 APPs were upregulated, with complement C3, fibrinogen, haptoglobin and hemopexin demonstrating the greatest increases. LPS upregulated renal ceruloplasmin and haptoglobin mRNA expression from 1.5 h, and fibrinogen-α, β2, γ, serum amyloid A, hemopexin, ferritin heavy chain and inter alia sepsis inhibitor 4 mRNA from 6 h. Complement C3 and transferrin mRNA were upregulated only in LP. Expression of most APP mRNAs peaked at 24 h and some mRNA started to recover by 48 h. Albumin mRNA was downregulated in LP.

Conclusions: Our proteomic analysis demonstrated a marked upregulation of local renal APPs in mice after a few hours after treatment and peaked at 24 h in LPS-induced AKI in mice. Many more APPs were involved in the renal APR than previously identified.

Funding: Government Support - Non-U.S.

FR-PO114

Renal Ischemia-Reperfusion Followed by Sepsis Increases Mortality Despite Reducing Multiorgan Damage: Reversal by IL-6

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Background: Sepsis frequently develops after AKI and portends a poor prognosis. We previously showed that sepsis 48 hours after ischemia reperfusion (IR) AKI worsened kidney function and survival compared to sepsis alone, although there was less liver, muscle, spleen damage, and systemic cytokines. Thus, AKI unexpectedly dissociated renal function from systemic responses to sepsis. We hypothesized that the IR injured kidney could alter the systemic response to subsequent sepsis. We investigated pathophysiological conditions of sepsis after AKI focusing on IL-6 and its upstream mediator Tumor necrosis factor-inducible gene 6 (TSG-6) which has anti-inflammatory properties.

Methods: We used 12 weeks old male C57BL/6 mice. We performed 40 minutes bilateral I/R, followed by four hour of treatment and then performed cecal ligation and puncture (CLP) for sepsis. We measured outcomes at 48 hours after I/R and 24 hours after CLP. We also performed a 4 day survival study. In some animals, bilateral nephrectomy was performed at the same time of CLP surgery.

Results: In I/R+CLP+IR1 intensified sepsis-induced AKI[CR: IR+CLP vs sham+CLP, 1.40±0.58 vs 0.82±0.37 mg/dl (p<0.05)]. Survival rate in IR+CLP was significantly worse than sham+CLP. In contrast, AST, LDH and CK, systemic inflammatory cytokines (HMGB-1, IL-10 and IL-6) and spleen apoptosis (immunohistochemistry of active caspase 3) were significantly lower in IR+CLP than sham+CLP. Although IR+CLP caused a slight elevation of systemic IL-6 at 48 hours, prior I/R surgery suppressed subsequent CLP stimulated IL-6, that was reversed by bilateral nephrectomy. Surprisingly, continuous administration of IL-6 starting immediately before CLP surgery improved the mortality of sepsis after I/R. In contrast, it worsened mortality in sepsis alone. Systemic and kidney TSG-6 was significantly increased at 48 hours after IR injury and 24 hours after CLP in IR+CLP compared to CLP alone.

Conclusions: AKI, followed by sepsis, worsened survival and kidney function, although liver and muscle enzymes, systemic cytokines and spleen apoptosis were improved compared with sepsis alone. Treatment with IL-6 improved survival of sepsis after AKI, counterintuitively. TSG-6 derived from I/R injured kidney might contribute to changes in systemic and organ responses to subsequent sepsis.

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FR-PO115

Integrated Stress Response Mediates Epithelial Transport Dysfunction During Septic AKI

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Background: Septic acute kidney injury (AKI) is a common cause of in hospital morbidity and mortality. Sepsis induced AKI is known to be associated with significant impairment of urine concentration, which requires establishment and maintenance of epithelial transport. However, the pathogenesis of endocytotic tubular dysfunction with the failure of epithelial transport is poorly understood. Integrated stress response (ISR) is a common adaptive pathway for restoring cellular homeostasis under stress conditions such as infection and hypoxia. Previous studies have demonstrated that ISR is activated in AKI. To date, we investigate that ISR plays key roles in epithelial transport dysfunction during septic AKI.

Methods: Male C57BL/6 mice (6-8 weeks, 20-25g) received a single-dose of LPS (E. coli serotype 0111:B4, Sigma, 5 mg/kg) or saline with tail vein injection and were killed at 3,6,12,24 and 48h (n=6 per group). To further explore the relationship between epithelial transport and ISR, C57BL/6 mice were treated with saline or ISRIB (ISR inhibitor, Sigma, 4 mg/kg) intraperitoneally 30 min after LPS injection and sampling at 3 and 24h. Kidney injury, inflammation, the expression of epithelial transport and ISR were measured.

Results: LPS-AKI model have demonstrated an inflammatory state with increased levels of IL-1β and TNF-α, and serious kidney injury indicated by BUN, plasma NGAL and KIM-1. At the same time, we determined that activation of the eukaryotic translation initiation factor 2-α kinase 2/eukaryotic translation initiation factor 2a (eIF2α/2β) axis, which is the key mediator of ISR. We divided epithelial transport into 5 categories: Na+/K+–ATPase, tubular ion transport (ENAC, NKCC2, ROMK, NCC, CLCK), acid-base transport(NHE), glucose and urea transport(SGLT1,2,GLUT1,2,UTA,UTB) and water transport(AQP). The mRNA and protein levels of those transport proteins were all downregulated following ISR activation. ISRIB was an inhibitor of ISR. We found that ISRIB could ameliorate inflammatory state and restore renal function and the expression of those epithelial transport proteins after LPS injection.

Conclusions: ISR mediates the dysfunction of renal epithelial transport during septic AKI.

Funding: Government Support - Non-U.S.

FR-PO117

The Kidney Protects Other Organs During Sepsis by Producing and Circulating Tamm-Horsfall Protein (Uromodulin)

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Background: Acute kidney injury (AKI) significantly increases the mortality in patient with sepsis. Although retention of uncleaved toxins could potentiate this effect, the loss of a protective factor released by the kidney could also play a role. Tamm-Horsfall Protein (THP) is uniquely made in the kidney. The majority of THP is secreted into the urine, but a portion is also released into the circulation. We previously showed that AKI is an acute state of THP deficiency and that circulating THP protects against systemic inflammation. Therefore, we propose that increased systemic release of THP from the kidney protects the organism with sepsis, and that the loss of THP is a major cause of increased mortality during septic AKI.

Methods: We used the cell ligation and puncture (CLP) model of sepsis in THP−/+ and THP−/− mice and measured plasma THP in small patient cohorts admitted to the intensive care unit (ICU) with sepsis.

Results: In THP−/+ mice, the level of serum THP increases within 6 hours after CLP, and remains elevated up to 48 hours in surviving mice. This trend was also observed in ICU patients with sepsis, where increased plasma THP correlated with worsening SOFA scores (a measure of organ failure) within 48 hours of admission. We also detected high levels of THP in the bronchoalveolar lavage fluid of patients who had developed acute respiratory distress syndrome, whereas levels were undetectable in healthy controls, demonstrating that THP localizes to dysfunctional organs during sepsis. To study the effect of THP deficiency on mortality, we compared THP+ to THP−− mice, and found that THP− mice have decreased survival (10% vs. 60% survival, respectively, p<0.05) within 48 hours after CLP. Additionally, treatment of THP−− mice with purified exogenous THP restores survival to the levels seen in THP−/+ mice. Mechanistically, THP increases the phagocytic activity of macrophages, which could partially explain the benefits of THP in the setting of a systemic infection.

Conclusions: Our work strongly supports that THP potentiates a protective cross-talk between the kidney and other organs during sepsis, and underscores the importance of maintaining kidney health in septic patients. This work could lead to the development of a new therapy for sepsis by administering THP or modulating its potential targets.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO118

Increased Gut Permeability in Septic AKI: Role of Na Butyrate (NaB)

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Background: Increased intestinal permeability is associated with multiple organ dysfunction syndromes in sepsis. In septic AKI, TLR 4 receptors located on the basolateral side of the intestine can be targeted by systemic lipopolysaccharide (LPS) and cause leaky gut. Intestinal leakage further exaggerates the kidney inflammation and deteriorates AKI. NaB produced by gut microbiota has been shown to curb inflammation and gut permeability. We hypothesized that NaB will protect against LPS-induced leaky gut and ameliorate inflammation and septic AKI.

Methods: Septic AKI was induced by injecting 10 mg/kg LPS (IP). C57BL6 mice were divided into 3 groups: Control (Ctl), AKI group received LPS (AKI) and treated (TR) group received 300 mg/kg NaB by gavage 30 mins before LPS. Mice were sacrificed after 10 hours. To measure intestinal permeability FITC-Dextran (FD) was given by gavage 2 hours before sacrifice to measure intestinal permeability. Blood and kidneys were harvested for biochemical and immunoblot analysis.

Results: Serum creatinine and BUN of AKI were 0.74±0.05 mg/dl and 169.5±6 mg/dl, which measured 2-fold higher than the Ctl (p<0.01). NaB significantly reduced both creatinine and BUN (p<0.05). Serum FD (14±1 µg/ml) of AKI was more than 3-fold higher than Ctl (p<0.01). NaB treatment reduced FD levels by 13% (p<0.05). Compared to Ctl, colonic tight junction protein ZO-1 was significantly reduced in the colon of AKI (ZO-1 P<0.05) but was restored in TR. Inflammatory markers such as high mobility group box protein (HMGB-1), NFκB and IL-1β in the kidney of AKI were 2 to 3 fold higher than Ctl (p<0.05) but NaB treatment decreased them suggesting that NaB can decrease kidney inflammation in LPS induced AKI.

Conclusions: Higher levels of serum FD and loss of intestinal tight junction protein shows that endotoxemia can increase intestinal permeability which may cause leakage of toxic biomolecules from the intestine. LPS can activate inflammatory responses through HMGB-1. NaB activates intestinal alkaline phosphatase which dephosphorylates LPS and renders it inactive. In addition, NaB can act as a HMGB-1 antagonist and a GBP109A agonist, both of which support intestinal barrier integrity. These might be some of the mechanism by which NaB can decrease the inflammatory burden and improve renal function in AKI.
FR-PO119
A Novel Circular RNA - has_circ_0114427 Regulates Inflammation via miR-494 in AKI
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Background: Acute kidney injury (AKI) is a common serious syndrome characterized by a rapid decrease of glomerular filtration rate and the progressive increase of serum creatinine. CircRNAs are novel regulatory RNAs that recently became popular among researchers of various diseases. However, the expression profile and the function of circRNAs in AKI remain largely unknown. CircRNAs act as competing endogenous RNAs (ceRNAs) to regulate transcription level by binding with microRNAs (miRNAs), as indicated by recent research.

Methods: In the current study, we established a cisplatin-induced AKI mice model and then extracted circRNAs from isolated renal tubular tissues for next-generation sequencing at different time points during AKI’s early stage. By using bioinformatic analysis, we identified a certain number of significant differentially expressed mmu-circRNAs in AKI. Furthermore, we validated the expression pattern and explored the function of the significant homologous circRNAs in HK2 cells.

Results: We successfully identified differentially expressed circRNAs related to AKI. By finding homologous genes between mouse and human, we identified a new circRNA, circ-0114427, in humans. Circ-0114427 expression was significantly up-regulated in different AKI cell models. Knockdown of circ-0114427 indicated that circ-0114427 bound to miR-494 as a miRNA sponge to regulate ATF3 expression and further affected different AKI cell models. Knockdown of circ-0114427 indicated that circ-0114427 may play an important role in anti-inflammation in the early stage of AKI. Our findings provide a novel insight into the regulatory mechanism of circRNAs in AKI and may become a new molecular target resource for early diagnosis and treatment strategies.

Conclusions: Elevated circ-0114427 may play an important role in anti-inflammation and mechanistic studies to understand the relationship of genetic variation and AKI development. Future work will require replication in well-phenotyped AKI cohorts and mechanistic studies to understand the relationship of genetic variation and AKI development.

Funding: NIDDK Support

The workflow of our experiments

FR-PO120
Genome-Wide Association Study for AKI in the ASSESS-AKI Study
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Background: Identifying genetic risk factors for AKI could provide insights into pathophysiology and help identify novel pathways for therapeutic development.

Methods: We conducted a genome-wide association study in a multi-ethnic population of 1,370 prospectively enrolled subjects in the ASSESS-AKI Study. Genotyping was completed using the Illumina MEGA chip and the Haplotype Reference Consortium was used for genome-wide multiple imputation. Genetic association testing for AKI was conditioned on: age, sex, diabetes, center and first three principal components of ancestry. Threshold for significance included single-nucleotide polymorphisms (SNPs) with a p < 5 X 10^-8.

Results: Among 637 AKI and 733 non-AKI participants, 5,645,675 SNPs were tested for the association with AKI. Among AKI participants, 72% had Stage 1 AKI and 7% required new dialysis during hospitalization. We found that 56 SNPs in six novel loci were associated with the development of AKI (Figure 1). The SNP with the strongest association with AKI was rs17538288. A minor allele of rs17538288 was associated with an increased risk for AKI (adjusted odds ratio 1.53, 95% confidence interval 1.30 – 1.79, p=2.08 x 10^-10). Utilizing integrated functional epigenomic analyses, we found that top-performing SNPs localized to regulatory DNA elements in primary human glomerular and cortex cell culture. We also investigated 22 SNPs identified in two prior AKI GWAS studies and found that none of the SNPs replicated in ASSESS-AKI (p>0.05).

Conclusions: We identified six novel genetic loci that were associated with prevalent AKI. Functional annotation in kidney cell/tissue provides insights into the mechanism of kidney injury. Future work will require replication in well-phenotyped AKI cohorts and mechanistic studies to understand the relationship of genetic variation and AKI development.

Funding: NIDDK Support

Figure 1. Six novel loci are associated with the development of AKI in the ASSESS-AKI study. (A) Manhattan plot demonstrates linkage single-nucleotide polymorphisms (SNPs) in six loci with p < 5 x 10^-8 for the development of AKI. (B) List of top performing SNPs at each genomic loci for the development of AKI. AKI (B) List of top performing SNPs at each genomic loci for the development of AKI. AKI

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
after renal ischemia. Microvascular flow was significantly decreased 48 hours after renal ischemia, to 24-58% of sham levels in different organs. In addition, tissue factor was increased postischemia in the kidney, heart, lung, liver and serum (2.4-4.2 fold, p<0.04). In the heart, expression of tissue factor pathway inhibitor was 0.54 +/- 0.1 fold that seen in shams (p<0.05). In addition, left ventricular function was impaired. Plasma flow and microvascular thrombus in remote organs improved with fibrinolytic therapy given after renal failure was established.

Conclusions: Our data indicate persistent systemic coagulation abnormalities after ischemic renal injury contributes to sustained, heterogeneous ischemia, leading to inflammation and tissue injury in multiple extra-renal organs. We have previously shown decreased cardiac function in experimental AKI. The systemic abnormalities likely contribute to the morbidity and mortality of AKI, but are amenable to therapeutic intervention.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO123

Metabolomics in the Lung After Ischemic AKI Reveals Increased Oxidative Stress, Altered Energy Production, and Energy Depletion

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Background: Acute kidney injury (AKI) is a systemic disease with deleterious effects on distant organs, including the lung. Lung function is dependent upon redox homeostasis and ATP generation through oxidative phosphorylation. Acute lung injury (ALI) after AKI is characterized by acute inflammation and neutrophil accumulation. Metabolically, ALI shows increased oxidative stress, energy depletion, and altered energy production. We sought to determine the effect of AKI on lung metabolism.

Methods: Normal mice and mice after sham (surgery alone) or surgery for ischemic AKI (22 minutes of bilateral renal pedicle clamping) were studied at 4-hours, 24-hours of post-procedure. Lung metabolomics was performed via ultra high-pressure liquid chromatography coupled to online mass spectrometry (UHPLC-MS). Untargeted UHPLC-MS-based metabolomics analysis provided the measurement of 132 annotated metabolites in the lung. Commercially available reagents (Abcam; ab33335) were used to measure lung ATP.

Results: AKI had a significant effect on the lung metabolome at 4- and 24-hours post-procedure. There was evidence of 1) increased catabolism characterized by decreased amino acids and their metabolites (ie. Leucine/Isoleucine, Phenylalanine, S-Adenosyl-L-Methionine at 4 hours and lysine, D-O-phosphoserine, L-adrenaline, L-carnitine and O-propanoylcarnitine at 24 hours), 2) increased oxidative stress and dysregulated redox system via decreased levels of glutathione, thioredoxin disulfide, nicotinamide and adenosine, and 3) use of alternative energy sources characterized by decreased intermediates in glycolysis (ie. lactate and D-glucose) and the pentose phosphate pathway (ie. D-Ribitol-5-Phosphate and D-Ribose). Lung ATP levels were reduced to their lowest levels after AKI compared to sham and control at 4 hours [control 1.2-2.8 (p <0.0001), sham CI 2.3-6.0 (p<0.0001)] and 24 hours [control CI 0.8-5.6 (p<0.003), sham CI 0.5-4.9 (p<0.007)].

Conclusions: This is the first study to examine the metabolome and ATP levels post-ischemic AKI in the lung. Our findings show depleted ATP levels and evidence of increased oxidative stress, energy depletion and use of alternative energy production. Further metabolic profiling in the lung post-AKI is needed to identify pathways for future clinical interventions.

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FR-PO124

Elucidation of the Mechanism of Kidney-Gut Cross-Talk via the D-Serine Derived from Gut Microbiota

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Background: While dysbiosis of the gut microbiota has been closely associated with kidney disease, the precise underlying mechanisms remain unclear. Recent advances have shed light on the chiral nature of amino acids. Free D-amino acids and their derivatives were quantified by 2D HPLC. Accumulating data revealed that D-amino acids were the primary microbial products, which showed physiologic roles in several organs. However, the involvement of D-amino acids in kidney diseases have yet to be revealed. Thus, we explored the pathophysiological role of D-amino acids in association with the gut microbiota in kidney disease.

Methods: Six-week-old male C57BL/6 (B6) mice and germ-free (GF) B6 mice were subjects to sham or ischemia-reperfusion (I/R) operation, and evaluated 2, 5, 7 and 10 days after surgery. D-serine was administered to mice via drinking water during I/R induced kidney injury. We performed 16S rRNA gene sequencing analysis of the mouse gut microbiota and determined D- and L-amino acids in the mouse feces, plasma, kidney and urine using 2D HPLC system. We also obtained blood samples from patients with AKI for evaluating D- and L-amino acids.

Results: Specific gut bacteria were influenced by I/R. Further, I/R induced kidney injury was more severe in GF B6 mice compared to B6 mice. Interestingly, fecal transplantion from normal mice attenuated the renal pathology in the GF B6 mice. Next, we performed comprehensive analyses of chiral amino acids in I/R induced kidney injury. While various D-amino acids were detected in the feces, only D-serine was detected in the injured kidney. Furthermore, D-serine was not detected in the feces of GF B6 mice, suggesting that gut microbiota produced D-serine in response to kidney disease. Further, the oral administration of D-serine attenuated I/R injury in normal mice. In addition, we assessed the association between D-serine and renal function in patients with AKI. The plasma levels of D-serine in patients with AKI was higher than in the plasma of healthy subjects, showing a high correlation with creatinine (r > 0.9).

Conclusions: These results demonstrate the beneficial effects of gut-derived D-serine in AKI, shed light on the novel interactions between the gut microbiota and the kidney, and highlight D-serine as a potential new therapeutic target and biomarker for AKI.
FR-PO125
Sham Surgery Suppresses Autophagy in the Kidney and Heart
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Background: Renal ischemia/reperfusion (IR) and compensatory hypertrophy induced by unilateral nephrectomy (UNX) activate mTOR, a suppressor of autophagy. Autophagy maintains proteinostasis by sequestering proteins into autophagosomes for delivery to the lysosome where cargo is recycled. The aim of the study was to determine the effect of sham surgery (SHAM), UNX, or IR on mTOR and autophagy in the kidney & heart in wildtype mice.

Methods: IR was induced by bilateral renal pedicle clamp; mice were sacrificed 24 or 72 hr later. UNX was performed; mice were sacrificed 2hr later. Normal mice without surgical manipulation (NORM), SHAM, IR, and UNX mice were treated with vehicle or baflofen (BAF) 2hr before sacrifice. LC3-II and p62 were measured by immunoblot.

Results: Autophagy was suppressed in the kidney 2hr after UNX and SHAM compared to NORM kidneys, but only 2hr after UNX in the heart. There was suppressed autophagy in the heart at 24hr of both IR & SHAM that normalized by 72hr. Suppressed autophagy in the kidney & heart in SHAM, UNX, & IR was associated with statistically significant increases in mTOR (p<0.05, p<0.01, p<0.001). To determine a possible mechanism of suppressed autophagy, metabolomics analysis was performed on 2hr NORM, SHAM, & UNX kidneys. Of 225 metabolites measured, folate, fructose phosphate, & glycine with known roles in autophagy regulation were significantly decreased (P<0.05) in both SHAM & UNX vs NORM kidneys.

Conclusions: SHAM suppresses autophagy in the kidney & heart. Increased mTOR and suppressed autophagy in the kidney & heart caused by SHAM have important implications for researchers using models requiring surgery. The connection between suppressed autophagy & folate, fructose phosphate, & glycine merits further study.

Funding: Veterans Affairs Support

FR-PO126
Real-World Use of Calcimimetics in Small and Independent Hemodialysis Facilities
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Background: In 2018, when etelcalcetide [ETE] became commercially available, dialysis organizations became newly responsible for providing calcimimetics to Medicare patients due to a reimbursement change from Part D to Part B. This study describes calcimimetic utilization and control of circulating parathyroid hormone (PTH) in small and independent hemodialysis facilities (SDF/IDFs).

Methods: This is a retrospective study of electronic health records from SDO/IDOs (Visiomed) from 10/1/2017 to 12/31/2018. Adults ≥18 years of age were identified as a CIN (n=1346, mean (SD) age=60.5 (14.0), 43.3% female, 47.1% black) or ETE user based on their first calcimimetic in 2018. Patients were followed until kidney transplant, death, or end of data collection. Descriptive analyses of patient characteristics and laboratory control at baseline and follow-up were conducted.

Results: In the first 9 months of 2018, 2601 patients received a calcimimetic (CIN (n=1346, mean (SD) age=60.5 (14.0), 43.3% female, 47.1% black) or ETE (n=1255, mean (SD) age=63.8 (14.5), 46.6% female, 38.5% black). Median (IQR) months of follow-up was 5.0 (2-9) for CIN, and 8.0 (4-11) for ETE. Median (IQR) PTH (pg/mL), P (mg/dL) and Ca at baseline were 670 (350-1094), 5.6 (4.7-6.8), and 9.2 (8.7-9.7) for CIN; and 686 (453-1044), 5.6 (4.7-6.7), and 9.1 (8.7-9.6), respectively for ETE users. Cut-offs for in-range laboratory measures were: PTH=150-600 pg/mL, P=3.5 - 5.5 mg/dL, and Ca=8.4 – 10.2 mg/dL. See figure for proportion of patients in control for PTH by month.

Conclusions: ETE users in SDO/IDOs had improved control during a longer follow-up compared with CIN, with 61% of patients having PTH in control at 9 months. Funding: Commercial Support - Amgen Inc.
FR-PO128

PTH Levels Prior to Initiating Hemodialysis: Associations with Prescription of PTH-Lowering Therapies and Risk of Uncontrolled PTH During the First Year of Hemodialysis

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Background: PTH levels during pre-dialysis may influence subsequent management and achieved PTH levels after onset of ESRD.

Methods: We studied 5683 incident HD patients from 21 countries in phases 4-6 (2009-2018) of the Dialysis Outcomes and Practice Patterns Study (DOPPS) with information on PTH measured immediately prior to HD initiation. We stratified by PTH prior to HD start and reported the monthly prescription prevalence of active vitamin D and calcimimetics over the first year of HD, and risk of PTH >600 pg/mL after 9 months on HD.

Results: Median (IQR) PTH prior to HD start was 275 (155, 472) pg/mL and 16% of patients initiated HD with PTH >600 pg/mL. Patients who initiated HD with higher PTH levels were more likely to be prescribed active vitamin D in the early months of HD, and these differences were steady over the first year of HD (Figure A). Patients starting HD with PTH >600 pg/mL were much more likely to initiate calcimimetic treatment during the first year of HD, amplifying differences in calcimimetic use by PTH at HD start over the first year of HD (Figure B). Among a subset of 2728 patients who remained in DOPPS with PTH measured 9-12 months after HD initiation, the prevalence of PTH >600 pg/mL was much greater for patients who initiated HD with PTH >600 (29%) vs. 150-300 (7%) pg/mL.

Conclusions: The findings were consistent with the hypothesis that management of PTH in the pre-ESRD phase influences subsequent PTH management and levels after onset of ESRD. Patients with greater PTH concentrations prior to start of dialysis were more likely to receive active vitamin D and calcimimetic therapy in the first year of HD. However, despite more aggressive management, high PTH prior to initiation of dialysis was associated with high PTH (>600 pg/mL) 9 months after the start of hemodialysis. These findings help inform clinical management and research goals and provide insight into cost drivers for PTH management in HD.

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FR-PO129

Parathyroidectomy vs. Cinacalcet for Secondary Hyperparathyroidism in Patients Undergoing Hemodialysis

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Background: Parathyroidectomy (PTx) and cinacalcet are both effective in treating secondary hyperparathyroidism in patients undergoing hemodialysis. However, there is a paucity of data comparing the long-term outcomes of these treatments.

Methods: We analyzed data from a nationwide cohort of hemodialysis patients in Japan who had intact parathyroid hormone (PTH) levels >300 pg/mL and no history of prior PTx on December 2007. Patients who underwent PTx or initiated cinacalcet between January 2008 and December 2009 were matched for baseline intact PTH levels and propensity score in a 1:3 ratio. Mortality follow-up started on December 2009 and continued until December 2015. Mortality risk was assessed using Cox proportional hazards models.

Results: A total of 894 patients who underwent PTx and 2,682 patients who initiated cinacalcet had similar propensity scores and were included in the analysis. Median baseline intact PTH levels were 588 pg/mL (interquartile range [IQR], 422-809 pg/mL) and 566 pg/mL (IQR, 427-777 pg/mL) in the PTx and cinacalcet groups, respectively. During the 6-year follow-up period, 201 patients in the PTx group and 736 patients in the cinacalcet group died. PTx was associated with a significantly lower risk of death compared with cinacalcet (hazard ratio, 0.78; 95% confidence interval, 0.67-0.91). The survival benefit associated with PTx versus cinacalcet was more pronounced in patients with baseline intact PTH levels >300 pg/mL and in patients with baseline serum calcium levels <10.0 mg/dL (both P <0.05 for interaction). The difference in mortality between PTx and cinacalcet was attenuated by adjustments for time-varying intact PTH, calcium, and phosphorus levels.

Conclusions: PTx compared with cinacalcet is associated with a lower risk of death, particularly among patients with severe secondary hyperparathyroidism.

FR-PO130

Thrice Weekly vs. Daily Cinacalcet: Virtual Clinical Trial and Its Subsequent Clinical Validation in a Large US Hemodialysis Population

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Background: Secondary hyperparathyroidism affects most hemodialysis (HD) patients. Current treatments for this condition include cinacalcet with limited daily, oral administration with food. However, high pill burden and gastrointestinal side effects limit patient adherence. The aim of this study was to explore in a virtual clinical trial (VCT) whether directly observed 3x weekly in-center (IC) administration is sufficient to control parathyroid hormone (PTH) levels. The VCT findings were compared to observations in a subsequent roll-out of 3x weekly IC cinacalcet in a large U.S. HD population.

Methods: We utilized 2 mathematical models, a cinacalcet pharmacokinetic model (Schappacher-Tilp, Cell Phys Biochem 2019) and a comprehensive model of parathyroid gland biology (Schappacher-Tilp, Phys Rep 2019). We simulated 2 populations, cinacalcet naive patients and patients on cinacalcet for ≥12 weeks. We then compared PTH levels attained with directly observed 3x weekly vs. daily administration; for the latter we considered a realistic adherence rate of 64%, based on pharmacy data. A subsequent clinical roll-out involved 4665 HD patients on daily cinacalcet for ≥12 weeks who were subsequently switched to 3x weekly IC administration for ≥12 weeks.

Results: Our VCT showed that patient adherence significantly impacts PTH levels. The PTH lowering effects of prescribed daily cinacalcet administration with limited patient adherence were almost identical to directly observed 3x weekly IC administration. Model predictions were corroborated by subsequent clinical observations (Fig 1).

Conclusions: Directly observed 3x weekly IC administration of cinacalcet is not inferior to daily administration with realistic adherence rates. Our results support the utility of VCTs for exploring alternative therapy regimens.
FR-PO131

Efficacy and Safety of Cinacalcet in Chinese Maintenance Hemodialysis Patients with Different Stages of Secondary Hyperparathyroidism: Rationale and Design of ACTIVE Study
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Background: Secondary hyperparathyroidism (SHPT), as a common complication in advanced Chronic kidney disease (CKD) has become a global public health problem. Patients with CKD and uncontrolled SHPT are at high risk of cardiovascular events and associated mortality. Cinacalcet, a calcimimetic agent was reported to effectively and safely reduce PTH levels in CKD patients with SHPT previously. However there has been no large-scale study and stratified analysis of cinacalcet in China and the optimal therapeutic doses of different levels of severity of SHPT still remain unknown.

Methods: A phase IV, open-label, multicenter study was designed and conducted in 23 hospitals in China. The study was performed in two phases. In phase I, a cohort study for 32 weeks follow-up was designed to explore the efficacy and safety of cinacalcet. In phase 2, a real-world study of 20 additional weeks was designed in which patients completing the cohort study decided on their own whether to continue taking cinacalcet at their own cost or not. Patients with a baseline iPTH ≥300 pg/mL should receive at least 12 weeks of maintenance hemodialysis before enrollment. The primary efficacy endpoint is the proportion of patients achieving iPTH targets (iPTH between 150-300pg/mL) at 20 and 32 weeks after the initiation of cinacalcet treatment (shown in Fig.1).

Results: Up to 2019/05/12, a total of 750 maintenance hemodialysis patients with SHPT were enrolled and stratified into 3 groups according to baseline iPTH level (mild 300-600, moderate 600-900 and severe ≥900 pg/mL respectively). The trial is still in progress and enrollment has been completed. Analysis of the baseline data is ongoing and the corresponding results will be released at ASN meeting this year.

Conclusions: We expect that the results of this study will allow us to draw valuable conclusions related to these objectives and expand the medical knowledge of end stage kidney disease (ESKD) especially for patients with SHPT.

Funding: Commercial Support - Kyowa Hakko Kirin (China) Pharmaceutical Co., Ltd.

Poster

FR-PO132

Role of Etlecalcetide in the Management of Secondary Hyperparathyroidism in Hemodialysis Patients After 10 Months of Therapy
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Background: Secondary hyperparathyroidism (SHPT) is common in hemodialysis (HD) patients. The present study aimed to evaluate the efficacy and safety profile of etelcalcetide in an observational study for the treatment of SHPT in CKD patients on hemodialysis.

Methods: 60 HD stable patients with sHPT were received etelcalcetide for 10 months, who were receiving oral or iV DRA’s and/or cinacalcet or were naïve before start of the protocol. Dose of VDRA’s remained stable and adjustments to etelcalcetide dose were taken place every month. PTH levels, Ca, Ph, alb were measured before starting etelcalcetide and every month until the end of the protocol. Heart function of patients evaluated at the start and at the end of the study. The primary outcome was estimation of intact-parathyroid hormone (iPTH) concentrations. Secondary outcomes were monitoring of calcium, phosphate (ph) albumin. Our study population was divided to subgroups a. diabetics and non-diabetics, b. patients over and below 65 years old, c. patients that were naïve regarding CKD-MBD therapy, or were receiving monotherapy or replaced cinacalcet with etelcalcetide and d. according to their previous PTH levels (below 500 pg/mL, between 500-700 pg/mL and over 700 pg/mL). Adverse events (AEs) were also evaluated.

Results: PTH significantly decreased from the first month of the treatment with etelcalcetide (771.5±438.58 vs 586.5±497.30, p<0.05, approximately 24% reduction from baseline). This trend carried out until the end of the study period (363.0±473.90 pg/mL, p<0.05, approximately 47% reduction from baseline). We also noticed significant reduction of the ph levels even from the second month of treatment (4.9±1.24 to 4.64±1.86 mg/dL, p=0.05). This trend also carried out for 8 months period (4.67±1.22 mg/dL, p=0.05).

Heart function remained stable in all the sub-groups we had significant reduction of PTH and Ph during the whole study period. Remarkable finding was the stable behaviour of Ca levels from the first week until the end of the study period along with albumin. None of the patients experienced any protocol drop-out or adverse events.

Conclusions: Etecalcetide is safe, well tolerated and effective in reducing iPTH in HD s patients with SHPT. As the only available intravenous calcium-sensing receptor agonist, etelcalcetide is likely to provide a new treatment option for sHPT in HD patients.

Funding: Government Support - Non-U.S.

Poster

FR-PO133

Effect of Switching from Cinacalcet to Etecalcetide on Secondary Hyperparathyroidism in Patients with Hemodialysis: An ESCORT Trial
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Background: Cinacalcet (Cina) is used in the management of secondary hyperparathyroidism (SHPT) in patients undergoing hemodialysis (HD). Etecalcetide (Etel) is a novel intravenous calcimimetic for the treatment of SHPT, which could improve drug adherence and reduce adverse gastrointestinal events. Here, we evaluated the efficacy of switching from Cina to Etel in the management of SHPT and constructed the dose conversion factor in this ESCORT trial.

Methods: A total of 138 HD patients on Cina were screened, and 93 patients with serum-intact parathyroid hormone (iPTH) ≥60 pg/mL and serum-albumin-corrected calcium (Ca) ≥8.4 mg/dL were enrolled. The patients were divided into three groups (Cina 25 mg, 50 mg, and ≥75 mg). Etel was administered intravenously for 24 weeks. The primary endpoint was the dose distribution of Etel in patients who achieved target iPTH levels (60–240 pg/mL) after 24 weeks. Further, we investigated serum bone alkaline phosphatase (BAP), tartrate-resistant acid phosphatase 5b (TRACP 5b), and fibroblast growth factor 23 (FGF23).

Results: A total of 90 patients completed the study. At the end of the study, mean iPTH levels significantly decreased in the Cina 25 mg group (Cina 25 mg: from 179.8 ± 97.1 to 137.4 ± 62.9 pg/mL, p = 0.003; Cina 50 mg: from 177.0 ± 122.5 to 177.2 ± 80.3 pg/mL, p = 0.996; Cina ≥75 mg: from 289.4 ± 300.7 to 236.9 ± 211.6 pg/mL, p = 0.110). Ca levels significantly decreased (p < 0.001). Serum BAP, TRACP5b, and FGF23 levels also decreased following the drug switching (p = 0.001, p = 0.001, p = 0.009, respectively).

Sixty patients (66.7%) maintained target iPTH levels before and after the study (pre: 133.5 ± 45.6 pg/mL; post: 148.2 ± 46.9 pg/mL). In these patients, the dose of Cina before the switch was 42.9 ± 10.7 mg/day, and the final dose of Etel was 6.17 mg/HD. The dose conversion factor for the switch from Cina to Etel was 4.640 ± 0.036 (p<0.001). No adverse events were observed. However, adverse events such as hypocalcemia and gastrointestinal symptoms, led to study discontinuation in this trial.

Conclusions: Switching from Cina to Etel effectively improved MBD and ameliorated high iPTH in patients undergoing HD for 24 weeks. No serious adverse events were observed. These results suggest beneficial effects of Etel administration in managing SHPT in patients undergoing HD.

Funding: Commercial Support - ONO Pharmaceutical

Poster

FR-PO134

Role of Etlecalcetide in the Management of Secondary Hyperparathyroidism: Clinical Experience
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Background: Etecalcetide is the first intravenous calcimimetic authorized for the treatment of SHPT in haemodialysis (HD). It has been proven to be effective in lowering parathyroid hormone (PTH), with an acceptable and comparable safety profile. There have only been a few reports regarding treatment of SHPT using etecalcetide in clinical practice.

Methods: The aim of this descriptive study was to evaluate the results of using etecalcetide in patients on HD with SHPT.

Results: Thirty patients on HD received etecalcetide were enrolled (figure 1). The minimum observation period was 6 months. Fifteen (50%) were previously with cinacalcet (group 1) and 15 (50%) received etecalcetide at onset (group 2). In global, serum PTH levels were significantly decreased at the end of follow up compared to baseline levels (PTH pretreatment 784 ± 707 (0.0077) vs PTH end of follow-up 671 ± 680 (p 0.0077)). When comparing both groups, we found a significant decrease of Ca, P and PTH in group 2. However, we only found significant decrease of Ca in group 1 (figure 2).

The dosage of calcium binders (33.3% pretreatment vs 56.7% at the end of follow-up, p 0.054), non-calcium binders (40% pretreatment vs 63.3% at the end of follow-up, p 0.02) and vitamin D analogues (56.7% pretreatment vs 66.7% at the end of follow-up, p 0.3) were increased when etecalcetide treatment was started. No changes were made in dialysis calcium concentration. Six patients, presented hypocalcemia (Ca < 7.5 mg/dL).

Conclusions: In our cohort, etecalcetide has shown to be effective in reducing serum PTH. An increase in the use of vitamin D analogues, calcium binders and non-calcium binders has been observed, probably due to the hypocalcemia.

Funding: Government Support - Non-U.S.

Poster
FR-PO135
Etelcalcetide Utilization and CKD-MBD Marker Responses in Urban Hemodialysis Patients
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Background: Etelcalcetide is a new intravenous calcimimetic approved in February 2017 for treating secondary hyperparathyroidism in adult US hemodialysis (HD) patients. Real-world etelcalcetide utilization practices are not well understood.

Methods: Monthly cross-sectional data from a national sample of 6041-9113 HD patients/month treated at 113-157 HD units/month in the US Dialysis Outcomes and Practice Patterns Study (February 2017-February 2019) were used to describe: (1) etelcalcetide use (% of patients prescribed a1 dose each month) and dose at etelcalcetide initiation, by dialysis organization (DO) size (LDO sample, 10+ units; non-LDO and hospital-based sample, <10 units), and (2) trends in serum parathyroid hormone (PTH), total calcium (Ca), and phosphorus (Po) levels up to 12 months after etelcalcetide initiation.

Results: In February 2019, 6.1% of US HD patients were prescribed etelcalcetide, representing 21% of all US calcimimetic use. Etelcalcetide use was markedly higher in non-LDO facilities (25-26% of patients/month) than LDO facilities (2-3%). Mean initial etelcalcetide dose was 13.1 mg/wk (median: 11.5; IQR: 7.2, 13.4). At drug initiation, serum PTH was higher in LDO (median: 976 pg/ml; IQR: 596, 1799; ≥600% 75%) than non-LDO (median: 735 pg/ml; IQR: 448, 983; ≥600% 61%) facilities, mean serum total Ca was 9.0 mg/dl (median: 9.0; IQR: 8.5, 9.4), and mean serum Po was 5.7 mg/dl (median:5.4; IQR: 4.4, 6.6). Among patients remaining on treatment: (1) mean and median serum PTH decreased 32% and 46% by month 6, respectively; (2) total mean Ca decreased 0.35 mg/dl by month 2, and hypocalcemia (<7.5 mg/dl) was uncommon (4.8%; range by month: 2.1-7.5%); and (3) mean Po4 levels were relatively unchanged (range by month: 5.5-6.2mg/dl).

Conclusions: Rapid uptake of etelcalcetide occurred in the US through February 2019, with substantial differences by DO size. Serum PTH steadily declined while treated with etelcalcetide, while calcium levels remained in the recommended range. Continued monitoring of etelcalcetide utilization will offer insights regarding turation patterns and laboratory target achievement.

FR-PO136
Effect of Active Vitamin D and Calcium-Sensing Receptor Agonists on the Responsiveness of Bone to the Parathyroid Hormone in Hemodialysis Patients
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Background: Parathyroid hormone (PTH) is known to be one of the regulators of calcium and phosphate metabolism. On the other hand, it has been reported that PTH could be partially mediated by RAS in secondary and primary HPT.

Methods: We retrospectively evaluated the serum PTH levels before and after parathyroidectomy (PTx) for all patients with secondary HPT. Serum intact PTH levels were significantly decreased after PTx in both HPT groups. In addition, changes of serum intact PTH levels were positively correlated with changes of BMI in secondary HPT group.

Results: In total 10 patients with secondary HPT (ALD: n = 9, PRA: n = 1) were included. Along with changes of PTH levels, serum intact PTH levels were significantly decreased after PTx in both HPT groups. In addition, changes of serum intact PTH levels were positively correlated with changes of BMI in secondary HPT group.

Conclusions: Our findings suggest that the effects of PTH on the cardiovascular system could be partially mediated by RAS in secondary and primary HPT.
FR-POI139

Relationship of Serum Parathyroid Hormone (PTH) Levels with Objective Measures of Nerve Function in ESRD

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Background: Advanced kidney disease is a risk factor for motor and sensory nerve deficits, independent of diabetes. The pathophysiology for nerve deficits in renal failure remains unclear. We tested the hypothesis that secondary hyperparathyroidism is associated with a distinct nerve function profile in ESRD patients.

Methods: Seventeen patients with ESRD underwent testing after their routine dialysis session. We measured action potentials (amplitude) and nerve conduction velocity (NCV) in motor (ulnar, peroneal) and sensory (ulnar, sural) nerves in the upper and lower extremities. Symptoms were assessed using the neuropathic pain questionnaire (NPQ). Muscle function was measured as handgrip strength and knee extension strength using a dynamometer. Physical performance was measured as gait speed during a 4 meter walk test. Labs drawn closest to date of testing were used for all analyses. Predefined and validated cut-offs were used to define a deficit. Statistical analyses were done using SPSS 24.

Results: Seventeen pts were enrolled: aged 23-66, 9 male, 15 black, 10 diabetic, median dialysis vintage 5.4 yrs. Ten patients had high PTH ≥ 500 pg/ml (median 522 pg/ml; range 25-2364). Neuropathic pain was noted in ~60% patients overall. NCV deficits were prevalent but mean motor NCV (ulnar: 46 vs 46, peroneal 39 vs 40 m/s) or sensory NCV (ulnar 26 vs 26, sural 26 vs 28 m/s) measures were not different between high vs low PTH groups. Vibration detection threshold (48 vs 52 microns) was also similar. A deficit in ulnar motor amplitude was seen in 2 patients with high PTH levels (566 and 528) (1/2 diabetic). Both patients had neuropathic pain (function score >0), low grip strength (<20 kg) and low gait speed (<0.8 m/s).

Conclusions: Deficits in NCV, a marker of myelination, were noted in most patients on dialysis and did not differ between groups. Deficits in amplitude, a marker of axonal damage, were noted exclusively in patients with elevated PTH levels. Whether elevated PTH levels predispose to axonal neuropathy will be evaluated by ongoing enrollment of subjects and follow up testing after decreases PTH in this study.

FR-POI140

Etelcalcetide for Managing Secondary Hyperparathyroidism in Hemodialysis Patients

Tomohiro Sato, Masahide Mizobuchi. Showa University School of Medicine, Yokohama, Japan.

Background: We retrospectively assessed the efficacy of a new calcimimetic, etelcalcetide, in Japanese chronic hemodialysis patients with secondary hyperparathyroidism (SHPT). The aim of this study was to assess the factors related to the therapeutic effects of etelcalcetide.

Methods: The subjects were 43 patients (average age: 60 years; average dialysis period: 90.7 months) with serum intact parathyroid hormone (iPTH) >240 pg/mL. Intravenous injection of etelcalcetide was started at 15 mg/week for 12 weeks and the dose was adjusted to control the serum levels of iPTH, corrected calcium (cCa), and phosphorus (P).

Results: In total, 81.3% of the patients had a reduction of iPTH of ≥ 50% at 12 weeks, and 32% achieved the target levels for P, cCa and iPTH. In multivariate analysis, female sex and a history of cinacalcet administration were independent inhibitory factors for iPTH reduction. Compared to patients with a history of cinacalcet administration (n=22), those without this history (n=21) had higher rates of reduction of iPTH of 50% (63.6% vs. 95.2%, p=0.007) and of achievement of target levels for P, cCa, and iPTH (22.7% vs. 95.2%, p=0.007) and of achievement of target levels for P, cCa, and iPTH (22.7% vs. 95.2%, p=0.007) and of achievement of target levels for P, cCa, and iPTH (22.7% vs. 95.2%, p=0.007). The side effects in all the subjects during the study period were hypocalcemia (44%), nausea (7%), and muscle spasms (2.3%).

Conclusions: Our results suggest that etelcalcetide can improve management of iPTH together with cCa and P levels in Japanese hemodialysis patients with SHPT. Thus, adherence enhancement and better control of SHPT with etelcalcetide might allow improved management of mineral metabolism, compared to cinacalcet. There was a tendency for iPTH levels to decrease more slowly in patients with a history of cinacalcet administration.

Summary of the MBF markers at the end of observation period

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Summary of MBD markers at the end of the 12-week observation period in patients with (+), n=22 and without (-), n=21: a history of cinacalcet treatment before etelcalcetide administration.

FR-POI141

Impact of Parathyroidectomy on Left Ventricular Function in ESRD Patients

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Background: Secondary hyperparathyroidism is a common complication in End Stage Renal disease patients, and parathyroidectomy is an effective treatment of SHPT. The biochemical parameters and clinical symptoms has been proven to be drastically improved after the surgery, but the curative impact of parathyroidectomy on left cardiac function is still controversial. To evaluate the impact of parathyroidectomy on left cardiac function in ESRD patient, we conducted this retrospective study.

Methods: We collected and analyzed the basic data including serum calcium, phosphor, ALB, PTH, alkaline phosphatase(ALP) pre and post-operation, and the ultrasonic cardiogram including EF, FS, LA, AO, LVsd, LVSs, LVDd, LVDt, PWd, PWSs, LVMI and LVMII before and after 1 year of patients who accepted total parathyroidectomy (PTX) with forearm Autograft.

Results: There were totally 135 patients involved, all of whose postoperative serum calcium, phosphor, PTH, ALB has been obviously improved compared with preoperative group, but the statistical change of EF and FS which stand for left cardiac function after 1 year didn’t exist. We then carried out a further subgroup analysis, picking out patients whose EF were lower than or equal to 60%(n=35) before the surgery. Compared with preoperative group, the EF, FS of postoperative group increased, and LVMI, LVMII declined(p<0.05).

Conclusions: PTX+AT is an effective curative method to secondary hyperparathyroidism which can significantly improve the postoperative biochemical parameters. For patients whose EF≤60%, PTX+AT can markedly increase their left cardiac function.
Patients Paricalcitol for Severe Secondary Hyperparathyroidism in Hemodialysis
FR-PO143

Calcium and phosphate levels during 24 hours

PTH levels during 24 hours

Calcium and phosphate levels during 24 hours

FR-PO143
Paricalcitol for Severe Secondary Hyperparathyroidism in Hemodialysis Patients
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Background: Severe secondary hyperparathyroidism (SSHP) is associated with renal osteodystrophy, excessive calcifications, fractures, and increased mortality in end-stage kidney disease (ESKD) patients, especially those in hemodialysis (HD). Currently, their treatment consists on control of hyperphosphatemia with phosphate binders, vitamin D or its analogues, as well as calcimimetics to suppress PTH release and ultimately surgery. Our main objective was to determine the effectiveness of paricalcitol to control PTH levels in HD patients with SSHP.

Methods: Phase 2 placebo control double blinded trial that included patients with ESKD on HD for more than six months with SSHP resistant to management with calcitriol. The patients were assigned to receive paricalcitol (at dose dependent on their iPTH levels) or placebo and conventional treatment with phosphate binders.

Results: During March to April 2019 there were screened 650 patients in our center, after application of selection criteria ten patients were allocated to paricalcitol group and nine to the control group. The median PTH level in the paricalcitol group was 1162 pg/ml, while in the placebo group was 925 pg/ml. After one month of treatment, the paricalcitol group had a mean reduction of 798.5 pg, and the control group had a median increase of 925 pg/ml. There were no reported adverse effects in either group.

Conclusions: Paricalcitol showed an important reduction in PTH levels in patients with SSHP on HD, without increased risk for hyperphosphatemia or other adverse events.

FR-PO144
EOS789, a Novel Pan-Inhibitor of NaPi-IIb/PiT-1/PiT-2, Suppressed Intestinal Phosphate Absorption in Healthy Subjects: A Phase 1 Clinical Trial
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Background: Hyperphosphatemia in patients with chronic kidney disease is not well managed by existing treatments. Sodium-dependent phosphate co-transporters NaPi-IIb, PiT-1, and PiT-2 are considered to play a central role in intestinal phosphate (P) absorption, and are recognized as promising targets for a novel therapeutic strategy for hyperphosphatemia. Past clinical trials suggest blocking only NaPi-IIb is not sufficient for suppressing intestinal P absorption. We identified EOS789, a novel pan-inhibitor against NaPi-IIb, PiT-1, and PiT-2.

Methods: A randomized, double-blind, placebo-controlled, Phase 1 clinical trial in healthy subjects was conducted. It consisted of single (32 Japanese) and multiple (32 Japanese and 8 Caucasian) ascending dose parts. Primary endpoints were safety and tolerability of EOS789; exploratory endpoints included pharmacokinetics and pharmacodynamics, including P excretion in feces and urine.

Results: In the single ascending dose part, EOS789 was tolerated up to 600 mg and the most common adverse events were gastrointestinal (GI) disorders. In the multiple ascending dose part, EOS789 was tolerated up to 200 mg/day. Moderate GI disorders were observed in the 600 mg/day cohorts and dosing was discontinued in these cohorts. EOS789 increased fecal P and decreased urinary P excretion in a dose-dependent manner. Exposure-response analysis showed that thrice-daily dosing of EOS789 has the potential to show good efficacy at about 200 mg/day.

Conclusions: EOS789 was well tolerated up to 200 mg/day at repeated dosing for 14 days. This was the first clinical trial that showed a decrease of intestinal P absorption by inhibiting intestinal P transporters, and it suggests a new strategy for the treatment of hyperphosphatemia by pan-inhibiting NaPi-IIb, PiT-1, and PiT-2. The safety, tolerability, and efficacy of EOS789 in patients with hyperphosphatemia will be further investigated in future clinical trials.

Funding: Commercial Support - Chugai Pharmaceutical Co., Ltd.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO145

Associations of Calciprotein Particle Transformation with Arterial Calcification, Arterial Stiffness, and All-Cause Mortality in Hemodialysis Patients

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Background: Transformation of primary to secondary calcioprotein particles (CPP) in the serum may be a marker for arterial calcification as suggested by in vitro studies. Using dynamic light scattering, we can measure the size of secondary CPP aggregates (CPP2) and time of transformation (T50). We hypothesized that a higher ratio of CPP2 to T50 (CPP2:T50) is associated with greater arterial calcification, arterial stiffness, and mortality among hemodialysis (HD) patients.

Methods: We measured baseline CPP2:T50 in 387 incident HD patients enrolled in the Predictors of Arthrythmic and Cardiovascular Risk in ESRD (PACE) cohort. We examined cross-sectional associations of CPP2:T50 with markers of arterial calcification (femoral osseous and osteoprotegerin), coronary arterial calcification (CAC), thoracic aortic calcification (TAC) and pulse wave velocity (PWV), as well as its longitudinal associations with PWV and all-cause mortality. Models were adjusted for demographics, co-morbidities, smoking history, body mass index, serum calcium and phosphorous.

Results: Mean age was 55 ± 13 years; 41% were female; 71% were black and 58% had diabetes mellitus. Median CPP2 was 295 nm (IQR 208-382); T50 was 303 min (IQR 257-372). Using the quartiles of CPP2:T50, we found patients in the highest CPP2:T50 quartile were more likely to have hyperparathyroidism (23.2% vs 19.4%, p = 0.04), lower fetuin-A, higher matrix Gla protein levels, and higher risk of all-cause mortality.

Conclusions: In incident HD patients, higher serum CPP2:T50 was associated with lower fetuin-A, higher matrix Gla protein levels, and higher risk of all-cause mortality, but not with arterial calcification or arterial stiffness. These findings support CPP transformation as a marker for calcification inhibitors and mortality, but not for arterial calcification.

Funding: NIDDK Support, Private Foundation Support, Government Support - Non-U.S.

FR-PO146

Sevelamer Use Is Associated with Decreased Vitamin K Levels in Hemodialysis Patients: Results from the Vitamin K Italian (VIKI) Study

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Background: Sevelamer (S) is a phosphate binding drug used to treat hyperphosphatemia in patients with CKD. Our aim was to evaluate the hypothesis that the use of (S) could interfere with Vitamin K absorption in hemodialysis (HD) patients of VIKI study.

Methods: We tested this hypothesis in VIKI, a cross-sectional study of 387 hemodialysis patients, we established the prevalence of vitamin K deficiency and to assessed the relationship between vitamin K status, vertebral fractures, vascular calcification. We determined serum concentrations of vitamin 25(OH)D; alkaline phosphatase (ALP); vitamin K1, MK4, MK5, MK6, MK7; osteocalcin (BGP) and Matrix Gla Protein (MGP). We highlighted that MK4 deficiency was the strongest predictor of aortic calcification (OR, 2.82; 95% CI, 1.14–7.01) while vitamin K1 deficiency was the strongest predictor of vertebral fractures calcification (OR, 2.94; 95% CI, 1.38–6.26).

Results: Of 387 patients (42.1%) were treated with S. There were no differences in levels of 25(OH)D, MK5, MK6 and MK7 among patients treated with and without S. Remarkably, the prevalence of MK4 deficiency was higher in S treated patients (13.5% vs. 5.4%, p = 0.005). S treated patients also had higher median levels of ALK (89 U/L vs. 77.5 U/L, p = 0.001) and total BGP (210 mcg/L vs. 152 mcg/L, p = 0.002) and lower median levels of 25(OH)D (16 nmol/L vs. 20.3 nmol/L, p = 0.01) and ALK (89 U/L vs. 5.4%, p = 0.001). S treated patients also had higher median levels of ALK (89 U/L vs. 5.4%)}.
FR-PO149
Phosphate Binder Therapy with Sucroferric Oxyhydroxide Reduces
High Calcium Propensity in Hemodialysis Patients: Results from a Randomized, Controlled, Crossover Trial
Daniel Cejka,1 Bernhard Robl,1 Ewa Watorek,2 Sabine Blum,1 Alexandra Dumfarth,1 Rodrigo Marques,1 Andreas Pasch,1 Maria C. Haller,1 1Ondrasklinikum Linz - Elisabethinen hospital, Linz, Austria; 2Medical University of Vienna, Vienna, Austria; 3CICcsion AG, Nidau, Switzerland.

Background: High calcium propensity (i.e. short T50 times in the calciprotein particle formation test) is associated with a higher risk of cardiovascular events and mortality in ESRD patients. So far, no clinical trial has investigated the effect of lowering serum phosphate with oral phosphate binder therapy on calcification propensity in ESRD patients.

Methods: Single-center, open-label, controlled, randomized, cross-over study in chronic hemodialysis patients with hyperphosphatemia. Patients were randomized in a 1:1 ratio to either low-dose (250mg/d) sucroferric oxyhydroxide (PA21) followed by high-dose (2000mg/d) PA21 or vice versa, with wash-out phases (no phosphate binder therapy) in between. The primary endpoint was change in T50 time between wash-out and high dose PA21 treatment in patients with at least 8 wk adherence to the prescribed PA21 dose (protocol analysis). There was no carry-over effect as determined by a linear mixed model, and a paired t-test was calculated.

Results: Thirty-nine patients were randomized and 28 patients were available for protocol analysis. Compared to phosphate binder wash-out, 2000mg/d PA21 treatment resulted in a mean increase in T50 times of 66 min (95% CI: 49-83 min, p<0.0001), from 18±6 min to 36±13 min. Serum phosphate decreased from 2.28±0.54 to 1.63±0.46 mmol/L. In the secondary intention to treat (ITT) analysis, treatment with 2000 mg PA21 resulted in a mean increase in T50 times of 60 min (95% CI: 36-83 min, p<0.0001) compared to phosphate binder-wash out. Serum phosphate decreased from 2.18±0.5 to 1.64±0.46 mmol/L. In patients achieving a decline in serum phosphate ≤0.5 mmol/L between wash-out and the 2000 mg phosphate treatment phase (N=20, pre-specified subgroup), T50 time increased by 24 min (95% CI 18-31 min, p<0.0001). PA21 at 250 mg did not influence T50 times (p=0.4) or serum phosphate values (p=0.9) compared to phosphate binder treatment. No major adverse cardiovascular event, case of calciphylaxis or death occurred during the study.

Conclusions: Lowering serum phosphate with PA21 therapy reduces calcification propensity of serum of hemodialysis patients.

Funding: Commercial Support - Vifor Pharma

FR-PO151
Longitudinal Serum Phosphorus Levels over 2 Years in Incident Dialysis Patients Who Initiate Sucroferric Oxyhydroxide (SO) as a First-Line Phosphate Binder
Kamrav Kalantar-Zadeh,1 Linda Fioceclllo, Vidhya Parameswaran,2 Claudia Mallon,1 Robert J. Kossmann,1 Stuart M. Sprague,3 1University of California, Irvine, School of Medicine, Orange, CA; 2Fresenius Medical Care Renal Therapies Group, Waltham, MA; 3Fresenius Medical Care North America, Waltham, MA; 4NorthShore University HealthSystem University of Chicago, Chicago, IL.

Background: Phosphate binder (PB) therapy is usually initiated in the first year of dialysis therapy in chronic hemodialysis (HD) patients (pts). A historic cohort study was conducted to examine longitudinal serum phosphorus (sP) among pts who begin sucroferric oxyhydroxide (SO) as a first-line PB within the first year of HD as part of routine care in real world setting.

Methods: Adult HD pts first prescribed SO between 4/1/14-9/30/17 during their first year of HD were included in this database analysis. Pts were required to have no PB prescription during a 3-month baseline (BL) and continue SO for 2 years. All clinical data was extracted from Fresenius Kidney Care electronic patient records, deidentified, and averaged over each quarter (Q1-Q8). Mixed effects linear regression and Cochran’s Q test were used for statistical significance testing.

Results: Pts (n=59) had a mean age of 56±13 years and duration of dialysis of 7.3±2.2 months at BL. Changes in mean sP, serum calcium, PTH, and Kf/V were provided [table]. After SO initiation, overall mean sP decreased by 0.7 mg/dL and 5% of pts achieving ≤5.5 mg/dL increased from 36.5% at BL to a high of 64.9%. After limiting to pts with BL sP >5.5 mg/dL, mean sP decreased by 1 mg/dL, from 8.68 to 7.56 mg/dL, with a high of 48.4% of pts achieving ≤5.5 mg/dL. These pts were prescribed, on average, 4.9±5.9 SO pills/day.

Conclusions: HD pts initiating SO as a first-line PB within the first year of dialysis were able to reduce mean sP levels by 0.7 mg/dL with mean phosphate binder pills/day of 4.4 to 5.2 pills over the 2-year follow-up. The 5% of patients with ≤5.5 mg/dL increased from 36.5% at baseline to 51.6% at 64.9% during follow-up. SO is an effective first-line PB therapy with at least pill burden.

Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group

FR-PO152
Low-Protein Rice Plus Low-Phosphorus Whey Improve Hyperphosphatemia in Hemodialysis Patients
Song Wang,1 Xinkui Tian. Nephrology Department. Peking University Third Hospital, Beijing, China.

Background: Hyperphosphatemia is common in end stage renal disease patients. Although adequate dialysis, dietary restriction, and phosphate binders are prescribed, phosphate control is still poor in dialysis patients.

Methods: Hemodialysis patients who had average serum phosphorus ≥5.5 mg/dL for consecutive three months were enrolled in this self-controlled trial. First, the patients received low phosphorus diet instruction. Then the patients received low protein rice plus low phosphorus whey for ten weeks. The protein gap between low protein rice and normal rice was replaced by low phosphorus whey. Finally the patients returned to normal rice for eight weeks. The changes of serum phosphorus, calcium, intact parathyroid hormone (iPTH), serum albumin and nutritional evaluation were observed and analyzed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

472
Results: 29 patients were enrolled. Serum phosphate at baseline was (6.6±0.87) mg/dl. After four weeks diet instruction, serum phosphate decreased to (6.2±1.54) mg/dl but with no significance (p=0.05). Serum phosphate further decreased to (5.4±1.71) mg/dl, (5.3±1.50) mg/dl, (5.7±0.23) mg/dl respectively after changed to low protein rice for 2, 6 and 10 weeks (p<0.05 compared to the baseline). Serum phosphate increased to (6.05±0.98) mg/dl after returned to normal rice. Dietary analysis showed the phosphate intake was significantly low for low protein rice compared to normal rice (p<0.05). Besides, serum albumin increased significantly with low protein rice plus low phosphorus whey (p<0.05). There was no change in serum calcium, iPTH levels, dialysis strategy and phosphorus-binding agents throughout the study.

Conclusions: For hemodialysis patients who consume rice as their main source of calories, low protein rice plus low phosphorus whey can reduce serum phosphate and improve serum albumin.

Funding: Commercial Support - Sinofin (Tianjin) Pharmaceutical Technology Company Limited

FR-PO154

Association Between Abnormalities of Serum Phosphate and Increased Mortality in Incident Australian and New Zealand Dialysis Patients

Lee Skon,1 Shahid Ullah,2,3 Stephen P. McDonald,2,4 Nigel D. Toussaint,1,5
1Nephrology, Royal Melbourne Hospital, Melbourne, VIC, Australia; 2Australian and New Zealand Dialysis and Transplant Registry, Adelaide, SA, Australia; 3Adelaide Medical School, The University of Adelaide, Adelaide, SA, Australia; 4Central Northern Adelaide Renal and Transplantation Service, Adelaide, SA, Australia; 5Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia.

Background: Abnormalities of mineral and bone metabolism in chronic kidney disease (CKD) are associated with increased cardiovascular and all-cause mortality. Serum phosphate is associated with adverse outcomes in a U-shaped relationship, with levels above and below the normal range associated with increased mortality in end stage renal failure. The optimal target for serum phosphate levels in CKD remains unclear. Therefore, the aim of this study was to determine if abnormalities of serum phosphate are associated with cardiovascular death and all-cause mortality in Australian and New Zealand dialysis patients.

Methods: The Australia and New Zealand Dialysis and Transplant (ANZDATA) registry was utilized to identify incident adult dialysis patients between 2005 and 2015 with ≥1 phosphate level. Phosphate levels were stratified into 3 groups; <1.6 mmol/L, 1.6-1.7mmol/L and ≥1.8 mmol/L. Adjusted risk of all-cause death were calculated for categories of phosphate using multivariate Cox proportional hazards regression models with phosphate levels, comorbidity and dialysis modality as time-varying covariates. Competing risk analysis was also used for cause-specific risk of death.

Results: The cohort consisted of 42,735 patients with a mean age of 58.8 (SD=15.8) years and male predominance (60.8%). Dialysis modality was 73.8% hemodialysis (HD) and 26.2% peritoneal dialysis (PD). 45.6% of patients were diabetic and 43.9% had coronary artery disease. Multivariate regression for all cause-mortality demonstrated a U-shaped relationship with highest mortality in those with phosphate ≥1.6 mmol/L (HR 1.17, 95%CI 1.11-1.22, p<0.001) and phosphate >1.8mmol/L (HR 1.31, 95%CI 1.24-1.38, p<0.001). Cardiovascular mortality was highest for phosphate levels >1.8mmol/L (SHR 1.25, 95%CI 1.15-1.35, p<0.001).

Conclusions: The lowest mortality was observed in patients with phosphate levels between 1.6-1.7mmol/L. Levels outside this range were associated with increased all-cause and cardiovascular mortality. This has clinical implications for target phosphate levels to reduce mortality the Australian and New Zealand dialysis population.

Funding: Government Support - Non-U.S.
FR-PO156

Spurious Hyperphosphatemia in Patients with ESRD on Hemodialysis
Dheera Tamada, Robert Mark Black. Saint Vincent Hospital, Worcester, MA.

Background: Hyperphosphatemia is common in patients with CKD. In most instances, the high phosphorus is due to a combination of increased intake and reduced urinary excretion. Despite the frequency of this finding, some patients with high phosphorus levels have normal kidney function. This can be associated with parathyroidism, a monoclonal gammopathy or extracellular shifts as can be seen with lactic acidosis or rhodanemysis. Here we present three patients on hemodialysis with sudden, transient very high phosphorus levels.

Methods: Three patients with ESRD on hemodialysis were noted to have high phosphorus levels of 29.6 mg/dL, 31.5 mg/dL and 25.0 mg/dL during routine monthly laboratory evaluation. All were compliant with phosphate binders and a low phosphate diet. Blood samples were drawn from the hemodialysis catheter ports which had been locked with tissue plasminogen activator (tPA). In these patients, tPA was used to limit blood clot formation and poor blood flow through the hemodialysis catheters. tPA contains phosphorlic acid to balance the pH.

Results: Below are the phosphorus levels in patients before tPA (first column) and with tPA (second column) administration. In these three patients, 5 mL of blood or less was discarded from the dialysis catheters at the time the highest phosphorus levels were reached (second column). The third column shows improvement in phosphorus levels after we removed at least 10 mL of blood from the dialysis catheters containing tPA before sending for laboratory evaluation for phosphorus levels.

Conclusions: The severe hyperphosphatemia in our three patients appears to be secondary to the blood draw technique employed. If tPA contaminates the blood sample, high phosphorus levels are likely to result. Hence we recommend always discarding the first 10 mL of blood drawn from the hemodialysis catheter with tPA before sending the required sample for analysis. While these findings are unusual, even small quantities of tPA could lead to inappropriate conclusions of patients’ non-compliance with oral phosphate binders. When possible, phosphorus levels should not be drawn if tPA has been administered and is still dwelling in the dialysis catheter.

FR-PO157

Analysis of the Association Between Serum Phosphorus Concentration and Mortality in Patients with Decreased Renal Function: Results from NHANES 2003-2006

Background: High serum phosphorus concentration is associated with increased mortality among the different stages of chronic kidney disease (CKD). However, studies are very heterogeneous and most of them lack an appropriate adjustment for relevant confounders. This concern is particularly notable in the pre-dialysis setting. We investigated the association between serum phosphorus concentration and mortality in individuals with decreased renal function using a prospective nationwide cohort of adults from the United States of America.

Methods: We analyzed non-dialysis-dependent adults with an estimated glomerular filtration rate (eGFR) inferior to 90 mL/min/1.73 m², using data from the National Health and Nutrition Examination Survey (NHANES) 2003-2006. Serum phosphorus concentration and several covariates including albuminuria, intact parathyroid hormone (PTH), 25-OH-vitamin D, C-reactive protein (CRP) and ingested phosphorus were evaluated at baseline. All-cause and cardiovascular deaths were recorded through 31 December 2011. We used the terciles of serum phosphorus concentration which were < 3.6 (T1), 3.6-4.1 (T2) and > 4.1 mg/dL (T3). Adjusted Cox proportional hazard models were fitted to estimate hazard ratios (HR) for all-cause and cardiovascular mortality.

Results: We included 3480 individuals (males 56.9%, age 61±18.5 years). A total of 735 deaths was recorded over a median follow-up of 80 months. Comparing with the T1, the adjusted HR for all-cause mortality was 0.84 (95% confidence interval (0.66-1.08) for T2 (p=0.178) and 1.31 (95% CI 1.1-1.6) for T3 (p=0.013). Decreasing eGFR (p<0.001) and phosphorus (p=0.032) presented a significant independent association with all-cause mortality, however, none of them had a significant interaction with serum phosphorus terciles. For cardiovascular mortality, the adjusted HR was 0.94 (95% CI 0.56-1.57) for T2 (p=0.823) and 1.24 (95% CI 0.88-1.76) for T3 (p=0.201).

Conclusions: We observed a significant independent association between the highest tercile of serum phosphorus and all-cause mortality in patients with decreased eGFR. Despite a numerical trend, it was not found a significant association with cardiovascular mortality.

FR-PO158

Zinc Supplementation for 3 Months Increases Serum Levels of C-Terminal FGF-23 in Zinc-Deficient Children with CKD
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Background: Chronic Kidney Disease (CKD) has been associated with increased fibroblast growth factor 23 (FGF23), decreased Klotho concentrations and subclinical zinc (Zn) deficiency (Fukushima 2019). FGF23 promotes phosphate clearance but is dependent on Klotho expression by tubular cells. In animal models Zn supplementation stimulates Klotho expression (Mortishia 2001) and reduces vascular calcification, frequently seen in CKD (Voelkl 2018). This study investigated whether 3 months of Zn therapy corrects the deficiency in CKD and leads to changes in circulating FGF23 and Klotho concentrations.

Methods: Children with primary CKD and CKD secondary to declining function of kidney transplant from two tertiary pediatric nephrology centers in Southern Ontario, Canada were screened for Zn deficiency (plasma Zn < 11.5 µmol/L). Deficient children were treated with Zn citrate tablets (10 mg Zn/day for age 4-8 yr and 20 mg/day for age 9-18 yr) for 3 months. Plasma Zn was measured at baseline and 3 months by High Resolution Magnetic Sector Inductively Coupled Plasma Mass Spectrometry. Serum c-terminal FGF23 (cFGF23, Biomedica) and human soluble alpha-Klotho (TECO medical) were measured by ELISA, serum 25-hydroxyvitamin D (25-OHD) by LC/MS/MS (Waters). Paired t-tests and Wilcoxon tests were performed for normally and non-normally distributed data, respectively. Children taking calcitriol were excluded from the final analysis due to its significant impact on FGF23 and Klotho metabolism.

Results: Table 1

Conclusions: In most patients we observed changes toward normal levels of Zn following 3 months of Zn supplementation. In children with Zn-deficient children with CKD (p=0.028). The concentration of FGF23 also increased (p=0.008) while no change was observed in the level of Klotho. 25-OHD levels remained stable and did not affect the results. Either higher Zn doses or longer treatment may be needed before changes in Klotho might be seen.

Funding: Other NIH Support - Hamilton Health Sciences New Investigator fund, Clinical Revenue Support

Table 1 - Results

FR-PO159

FGF23 and Cause-Specific Mortality in Community-Living Individuals (Health ABC Study)
Shilpa Sharma,1 Ronit Katz,2 David A. Drew,3 Orlando M. Gutierrez,6 Michael Shlipak,2 Mark J. Sarnak,4 Joachim H. Ix.2 1UCAL, Los Angeles, CA; 2UCSD, San Diego, CA; 3Tufts Medical Center, Boston, MA; 4University of Washington, Seattle, WA; 5San Francisco VA Medical Center, San Francisco, CA; 6UAB School of Medicine, Birmingham, AL.

Background: FGF23 is a protein that was initially identified as a key regulator of phosphorus and vitamin D metabolism. Elevated concentrations of FGF23 are associated with poor clinical outcomes in different patient populations, but cause-specific mortality is under-studied.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Among 2763 healthy community-living older adults who participated in the Health, Age, and Body Composition (Health ABC) study, serum intact FGF23 levels were measured from samples drawn in 2000 and 2001, and participants were followed through 2012. Mortality was adjudicated by a reviewing committee. Associations of FGF23 with total and cause specific mortality were evaluated using Cox proportional hazards models.

Results: At baseline, the mean age was 75 (±3) years old. 40% were black, and 55% were women. Median FGF23 was 47 (IQR 37, 60) pg/ml and was inversely correlated with eGFR (r=-0.2600). During 8.3 years (median) follow-up, there were 821 deaths. In the multivariable Cox PH regression analysis (Table 1), each two-fold higher concentration of plasma FGF23 was associated with all-cause mortality and cardiovascular, gastrointestinal bleed, and kidney failure deaths, but not with cancer, dementia, sepsis or pulmonary related deaths.

Conclusions: Although high FGF23 concentrations are associated with total mortality, the association appears restricted to certain death types. Future studies are needed to evaluate potential mechanisms linking FGF23 concentrations with specific causes of death.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging (NIA) 1R01 AG027002 (Drs. Sarnak and Shlipak)

Association of (intact) FGF23 and Cause Specific Mortality

<table>
<thead>
<tr>
<th>Cause of Mortality</th>
<th>Events</th>
<th>FGF23 ≥ 1.2 RU/ml</th>
<th>FGF23 ≥ 3.0 RU/ml</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Cause</td>
<td>315</td>
<td>126 (3.97)</td>
<td>75 (2.37)</td>
<td>2.20</td>
<td>1.52–3.15</td>
</tr>
<tr>
<td>Cancer</td>
<td>32</td>
<td>10 (3.13)</td>
<td>3 (0.93)</td>
<td>3.33</td>
<td>1.18–9.50</td>
</tr>
<tr>
<td>Diabetes</td>
<td>47</td>
<td>19 (5.95)</td>
<td>7 (2.20)</td>
<td>2.90</td>
<td>1.46–5.78</td>
</tr>
<tr>
<td>Sepsis</td>
<td>15</td>
<td>6 (1.83)</td>
<td>3 (0.93)</td>
<td>2.50</td>
<td>0.92–7.28</td>
</tr>
</tbody>
</table>
| *Adjusted for age, gender, race, site, education, diabetes, systolic blood pressure, hypertension meds, body mass index, smoking, prevalent cardiovascular disease, serum albumin, c-reactive protein, estimated glomerular filtration rate and urine albumin creatinine ratio

FR-PO160
An FGF-23-Independent Association Between Serum Phosphorus and Left Ventricular Hypertrophy: Findings from the KNOW-CKD Study

Methods: This cross-sectional study analyzed 1,545 predialysis CKD patients from the KNOW-CKD cohort. Left ventricular mass index (LVMi) and presence of LVH were assessed by echocardiography. Multivariate regression analysis was adjusted for various cardiovascular risk factors including FGF23.

Results: The LVMi was higher among the higher serum phosphorus groups (88.6±20.7, 90.3±22.5, 91.1±22.0, and 96.2±22.5 mg/dl for the first 4 quartiles of serum phosphorus, respectively, P<0.001). LVMi was higher in patients with serum phosphorus groups more than 15% (15.8%, 23.7%, and 35.9% for the 1st to 4th quartiles, respectively, P<0.005). Results were summarized in the Table 1. Results were reported in adjusted model 3.

Conclusions: Serum phosphorus was associated with LVH, and the association appears restricted to certain deaths types. Future studies are needed to evaluate potential mechanisms linking FGF23 concentrations with specific causes of death.

Funding: Government Support - Non-U.S.

Table 1. The association between serum phosphorus quartile and left ventricular hypertrophy

<table>
<thead>
<tr>
<th>Serum phosphorus-quartile</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.2 mg/dl</td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1.04 (0.72, 1.52)</td>
<td>0.82</td>
<td>0.98 (0.68, 1.44)</td>
</tr>
<tr>
<td>3</td>
<td>1.17 (0.82, 1.68)</td>
<td>0.44</td>
<td>1.12 (0.79, 1.59)</td>
</tr>
<tr>
<td>4</td>
<td>1.52 (1.23, 1.89)</td>
<td>0.001</td>
<td>1.01 (0.62, 1.63)</td>
</tr>
</tbody>
</table>

Model 1: adjusted; Model 2: adjusted for sex, BMI, systolic blood pressure, diabetes, cGFR, LDL cholesterol, hsCRP, random urine PCR, hemoglobin, current smoking, taking renin-angiotensin system blockers, serum calcium, 25-OH vit D and β2M; Model 3: adjusted for model 1 + FGF23

FR-PO161
Determinants of C-Terminal vs. Intact FGF-23 in CKD: The COMBINE Trial

Methods: 203 patients with eGFR 20-45 ml/min/1.73m2 participated in a randomized trial evaluating lanthanum and nicotinamide for phosphate and FGF23 lowering. FGF23 was measured using the Immutopics C-terminal and Kainos intact assays at baseline. We calculated the C/I ratio and used linear regression to identify independent determinants.

Results: Mean eGFR was 27.1±18.6 RU/ml and intact FGF23 was 123±92 pg/ml, which were moderately correlated (r=0.40, p<0.001). The mean C/I ratio was 2.62±2.08 RU/ml. Female gender and lower calcium were independently associated with higher C/I ratio. We found no associations of eGFR, anemia, iron deficiency, or inflammation with C/I ratio.

Conclusions: Gender and calcium are differentially associated with C-term vs. intact FGF23; associations that appear stronger than iron deficiency, anemia, inflammation, or CKD severity, in CKD stages 3b-4.

Funding: NIDDK Support

Independent Determinants of C-terminal / Intact FGF23 in Patients with eGFR 20-45 ml/min/1.73m2 who Participated in the COMBINE Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>C-terminal / Intact FGF23 Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.99 (0.96, 1.02)</td>
</tr>
<tr>
<td>Female</td>
<td>1.40 (1.01, 1.95)</td>
</tr>
<tr>
<td>Non-white race</td>
<td>0.89 (0.74, 1.06)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.41 (0.27, 0.60)</td>
</tr>
<tr>
<td>SBI (per one unit higher)</td>
<td>0.92 (0.91, 0.93)</td>
</tr>
<tr>
<td>CKD- eGFR (per one ml/min higher)</td>
<td>0.99 (0.97, 1.02)</td>
</tr>
<tr>
<td>Calcium (per mg/dl higher)</td>
<td>1.05 (1.01, 1.09)</td>
</tr>
<tr>
<td>Phosphorus (per mg/dl higher)</td>
<td>1.01 (0.97, 1.05)</td>
</tr>
<tr>
<td>125(OH)2D (per ng/ml higher)</td>
<td>0.98 (0.95, 1.01)</td>
</tr>
<tr>
<td>Ferritin (per one unit higher)</td>
<td>0.99 (0.92, 1.07)</td>
</tr>
<tr>
<td>Tranferrin saturation (per one % higher)</td>
<td>0.99 (0.93, 1.05)</td>
</tr>
<tr>
<td>Hemoglobin (per one g/dl higher)</td>
<td>1.01 (0.95, 1.07)</td>
</tr>
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</table>

All variables mutually adjusted.

FR-PO162
Improvement in Biomarkers in Pediatric X-Linked Hypophosphatemic Rickets After 1 Year of Treatment with Burosumab

Methods: 11 patients <= 18 years with XLH and treated with burosumab were identified, all of whom received calcitriol and phosphorus prior to starting burosumab. Retrospective laboratory data obtained during standard of care visits was analyzed. Monthly laboratory testing was performed for 3 months after initiation of burosumab and with dose changes. Burosumab, an FGF-23 monoclonal antibody, was approved in 2018 for the treatment of XLH. Prior therapy consisted of phosphate supplementation and calcitriol, but therapeutic response was often incomplete. Clinical trial results with burosumab have been promising, but real world data given regarding effectiveness in clinical practice is lacking.

Conclusions: Burosumab, a newly approved FGF-23 monoclonal antibody, is effective in improving the biochemical profile of children with X-linked hypophosphatemic rickets previously treated with phosphorus and calcitriol.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Poster/Friday
Postprandial Serum Phosphorus and Calcium Concentrations in Adults and Children with X-Linked Hypophosphatemia (XLH) Are Within Normal Range During Burosumab Treatment

**Background:** In patients with XLH, excess FGF23 causes hypophosphatemia leading to musculoskeletal impairments. In Phase 3 trials (NCT02526160, NCT02915705), subcutaneous burosumab, 1 mg/kg every 4 weeks in adults or 0.8 mg/kg every 2 weeks to musculoskeletal impairments. In Phase 3 trials (NCT02526160, NCT02915705), subcutaneous burosumab, 1 mg/kg every 4 weeks in adults or 0.8 mg/kg every 2 weeks in children, significantly improved fasting serum phosphorus (Pi) in subjects with XLH. Burosumab also improved fracture healing, stiffness, and physical function compared to placebo in adults; and rickets severity and growth compared to oral phosphate and active vitamin D in children. We evaluated the effect of burosumab on postprandial serum Pi and calcium in a sub-set of trial subjects.

**Methods:** Postprandial assessments were made in 26 adults and 13 children, 10-14 days after the prior dose of burosumab. Serum samples were obtained in the morning after an overnight fast. Subjects then consumed a typical phosphorus-containing breakfast, and samples were obtained 1 and 2 hours after breakfast. In adults, additional samples were obtained before and 1 and 2 hours after lunch. In children, significantly improved fasting serum phosphorus (Pi) in subjects with XLH. Burosumab also improved fracture healing, stiffness, and physical function compared to placebo in adults; and rickets severity and growth compared to oral phosphate and active vitamin D in children. We evaluated the effect of burosumab on postprandial serum Pi and calcium in a sub-set of trial subjects.

**Results:** Adults (mean [SD] age 43 [12] years, 77% female, 89% white) and children (mean [SD] age 6 [3] years, 77% female, 92% white) had received burosumab for a mean of 24 and 15 months, respectively. At baseline, before any doses of burosumab, mean (SD) fasting serum Pi concentration was below the normal range (Table). After burosumab treatment, mean morning fasting Pi level increased significantly in each group. In adults, Pi levels decreased slightly if not significantly after breakfast, increased slightly before lunch, and remained stable 1 and 2 hours after lunch. In the children, serum Pi levels increased slightly if not significantly 1 and 2 hours after breakfast. Importantly, no subject had post-prandial hyperphosphatemia. There were no changes in serum calcium.

**Conclusions:** In adults and children with XLH receiving stable doses of burosumab, fasting and postprandial serum Pi and calcium concentrations are maintained within the normal range.

### Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>1 month post burosumab</th>
<th>2 months post burosumab</th>
<th>P-value vs pre burosumab</th>
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**FR-PO164**

Intact FGF-23, Intact PTH, and Other CKD-MBD Markers After Successful Living Renal Transplantation: A Longitudinal Study

**Background:** Markers of CKD-MBD cause LVH & CV mortality. Compared to general population CV mortality remain high post RT. MBD abnormalities post RT can be due to persistence of CKD induced abnormalities or can develop de novo due to immunosuppressive drugs & lower GFR & may contribute to increased CV mortality. Though, few studies have prospectively looked at MBD markers post RT, their course in post RT period remains poorly defined particularly in patients receiving living donor RT (LDRT) where renal function normalizes faster. This prospective, longitudinal study analyses serial changes in these variables pre & post LDRT.

**Methods:** 83 consecutive & consenting adults aged 18-65 years undergoing first LDRT were enrolled. Investigations were done pre-RT & at 1, 6 & 12 months post RT. Patients with diabetes & those having persistent eGFR <40 ml/min post RT were excluded.

**Results:** 74 patients completed study. 91.8% were male, mean age was 35.5±10.6 years & median dialysis vintage was 14 months. Basic disease was presumed CTID in 45.9% & presumed CGN in 39.1%. All were on 3-drug immunosuppression of MMF, steroids & CNIs. Intact FGF 23 was assayed using ELISA method (Kainos Labs Japan). 25-OH-Vitamin D levels & iPTH levels were measured by chemiluminescence method (Abbott Labs, IL, USA) Table shows study parameters at baseline & their course post RT. Taking standard cut-off values: 7% patients had hypocalemia while 3% had hypercalcemia before RT while none in post RT period had hypovolemia or hypercalcemia. Before RT 97% had hypophosphatemia while 32.3, 4 & 0% had hyperphosphatemia at 1, 6 & 12 months post RT. 100% patients had hyperparathyroidism pre RT while 64.8, 24.3 & 10.7% had hyperparathyroidism at 1, 6 & 12 months post RT 100% patients had high iFGF23 levels pre RT while 36.4, 12 & 6% had increased iFGF23 levels at 1, 6 & 12 months post RT.

**Conclusions:** In younger CKD-SD cohort having shorter dialysis vintage who underwent LDRT we document rapid & significant decline in iPTH & iFGF23 levels post RT. iFGF23 normalised faster as compared to iPTH.

### Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>1 month post burosumab</th>
<th>2 months post burosumab</th>
<th>P-value vs pre burosumab</th>
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**FR-PO165**

Interaction Between FGF-23 and Soluble Klotho on Cardiovascular Events in Patients Receiving Hemodialysis

**Background:** Membrane Klotho binds to FGFRI and forms a specific receptor for FGF23. Recent investigations have demonstrated that soluble Klotho, a cleavage product of membrane Klotho, also mediates FGF23-dependent bioactivity. Elevated FGF23 may have detrimental effects on several tissues that do not express membrane Klotho. It is not known whether this process is mediated through the binding of soluble Klotho to FGFRI and FGF23.

**Methods:** We conducted a 3-year prospective cohort study of 654 maintenance hemodialysis patients. We examined the interaction between FGF23 and soluble Klotho for the composite of all-cause mortality and cardiovascular events using multivariate Cox regression.

**Results:** During the follow-up period, 103 patients reached the primary composite endpoint. After adjustments for confounding, elevated FGF23 may have detrimental effects on several tissues that do not express membrane Klotho. It is not known whether this process is mediated through the binding of soluble Klotho to FGFRI and FGF23.

**Conclusions:** These data suggest that elevated levels of FGF23 and soluble Klotho contribute to cardiovascular disease in a coordinated manner.

**Funding:** Commercial Support - Roche Diagnostics K.K. (Tokyo, Japan), Government Support - Non-U.S.
**FR-PO166**

**Performance of Soluble Klotho Assays in Clinical Samples of Kidney Disease**

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**Background:** There is considerable interest in investigating soluble Klotho as a biomarker in patients with different types and severity of kidney diseases. Unfortunately, there remains uncertainty regarding the best method to measure soluble Klotho in human serum samples.

**Methods:** Using human serum samples obtained from several clinical cohorts with a wide range of kidney function, we measured soluble Klotho using a commercial enzyme linked immunosorbent assay (ELISA - IBL America) as well as with an immunoprecipitation-immunoblot (IP-IB) assay utilizing a synthetic antibody with high affinity and specificity for Klotho. Recovery of spiking with known amounts of exogenous Klotho was tested. A subset of samples was analyzed with and without the addition of a protease inhibitor cocktail at time of collection or after first freeze/thaw cycle.

**Results:** The IP-IB assay was superior to the ELISA at recovery of exogenous Klotho (81-115% vs. 60-81%) across the spectrum of kidney function. The IP-IB and ELISA assay were modestly correlated (R = 0.28, p = 0.01). Klotho concentrations by IP-IB were highly correlated with eGFR (R=0.80, p=0.001) in comparison to the commercial ELISA, which exhibited minimal correlation with eGFR (R=0.18, p=0.12) [Figure 1]. Use of a protease inhibitor cocktail neither improved nor impaired performance of the IP-IB assay; however, a subsequent freeze-thaw cycle resulted in a significant reduction in Klotho recovery and dissipated the correlation between Klotho levels and eGFR. With the ELISA, use of a protease inhibitor cocktail resulted in an increase of intra-subject variability.

**Conclusions:** The IP-IB assay is preferable to the commercial ELISA to measure soluble Klotho concentrations in never-frozen serum samples with varying severity of kidney disease.

**Funding:** NIDDK Support

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*Underline represents presenting author.*

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**FR-PO1168**

**Association of Serum Phosphate with Peripheral Artery Disease (PAD) in Hemodialysis Patients: Ten-Year Outcomes of the Q-Cohort Study**

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**Background:** Peripheral artery disease (PAD) is caused by arteriosclerosis and is one of the critical cardiovascular complications in hemodialysis patients. Although serum phosphate is a known risk factor for cardiovascular events, it is unclear whether serum phosphate is associated with PAD. The aim of the present study was to clarify the relationship between serum phosphate level and the risk for PAD in hemodialysis patients.

**Methods:** A total of 3,506 hemodialysis patients registered to the Q-cohort Study was followed up for 10 years. PAD was defined as intervention for PAD including endovascular therapy, revascularization, and amputation. Patients were divided into quartiles based on baseline serum phosphate level: Q1 (n=886), 0.8 to 1.1 mg/dL; Q2 (n=838), 1.2 to 1.5 mg/dL; Q3 (n=909), 1.6 to 1.9 mg/dL; Q4 (n=873), 2.0 to 4.0 mg/dL. Multivariable-adjusted Cox proportional hazards risk model was employed to examine the association between serum phosphate level and the risk for PAD.

**Results:** During the follow-up period, 257 patients developed PAD. Cox proportional hazards risk model showed a significant association between baseline serum phosphate level and PAD: hazard ratio [HR] (95% confidence interval [CI]) per 1 mg/dL increase in serum phosphate level, 1.23 (1.09-1.37). The risk for PAD in Q4 was significantly increased compared with that in Q1: HR (95% CI), 1.72 (1.19-2.50). When a multivariable-adjusted restricted cubic spline curve was depicted, the HR for PAD increased nonlinearly as the serum phosphate level increased. Furthermore, the effect of hyperphosphatemia on the risk for PAD was significantly enhanced in patients without diabetes, patients with history of cardiovascular events or patients with high serum C-reactive protein levels.

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**FR-PO167**

**Vitamin K-Dependent Proteins After Kidney Transplantation: Results from a Prospective Study**

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**Background:** Two Vitamin K-dependent proteins (VKDPs) link bone and vasculature in CKD-MBD: Bone Gla Protein (BGP) and Matrix Gla Protein (MGP). In ESKD, Vitamin K deficiency is highly prevalent and leads to increased levels of inactive VKDPs (undercarboxylated(uc) BGP and phosphorylated(dp)-uc MGP), which are linked to greater risk of fractures and severity of vascular calcification. We hypothesized that kidney transplantation (KT) would improve Vitamin K status and lower levels of inactive VKDPs.

**Methods:** Between 2014-2017, we conducted a study in 34 patients to assess changes in VKDPs during the 1st year of KT. In a specialized lab we determined VKDPs pre- and 1-year post-KT: total BGP, uc-BGP, total MGP, and dp-uc MGP. We determined the prevalence of Vitamin K deficiency based on levels of uc-BGP and dp-uc MGP.

**Results:** Our cohort had a mean age of 48±14 years, 32% were female and 97% were Caucasian. 1 year post-KT, there was a decrease in the levels of all VKDPs and the prevalence of Vitamin K deficiency (Table). Patients with greatest severity of Vitamin K deficiency pre-KT had the largest decreases of inactive VKDPs post-KT (Figure).

**Conclusions:** KT was associated with improvement in Vitamin K status as manifested by decreased levels of inactive VKDPs. These are the first prospective data on VKDPs in CKD patients pre- and post-KT. Studies are needed to assess the impact of improvement in VKDP status after KT on CKD-MBD outcomes.

**Funding:** Private Foundation Support

*Changes in circulating dp-ucMGP levels in relation to baseline values*

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*Underline represents presenting author.*

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*Image*
Conclusions: Elevated serum phosphate level was associated with an increased risk of intervention for PAD in hemodialysis patients.

Funding: Private Foundation Support

FR-PO169

Differential Effects of Phosphate Binders on Vitamin D Metabolism in CKD

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Background: Phosphate binders are commonly used in the treatment of patients with advanced chronic kidney disease (CKD) and end stage renal disease. While phosphate binders are used to lower phosphate, the effects of specific phosphate binder types on vitamin D metabolism is unknown.

Methods: We performed a secondary analysis of the phosphate normalization trial, in which 148 patients with moderate to severe CKD were treated with either sevelamer carbonate, lanthanum carbonate, calcium acetate or placebo. We used linear mixed models to evaluate the relationship between treatment arm and changes in 24,25-dihydroxyvitamin D3 [24,25(OH)2D3], 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], the ratio of 24,25(OH)2D3 to 25-hydroxyvitamin D (the vitamin D metabolite ratio or VMR) and the ratio of 1,25(OH)2D to 25-hydroxyvitamin D.

Results: Compared to placebo, randomization to the calcium acetate arm was associated with a 0.6 ng/ml (95% CI 0.2, 1.3) and 13.5 ng/g (95% CI 5.5, 21.5) increase in 24,25(OH)D and VMR, respectively, and a 5.2 pg/ml (95% CI 1.1, 9.4) reduction in 1,25(OH)D. Randomization to sevelamer carbonate was associated with a 0.5 mg/ml (95% CI 0.9, 1.0) and 11.8 ng/g (95% CI -20.3, 5.5) reduction in 24,25(OH)2D3 and VMR respectively. There was no association of sevelamer arm with change in 1,25(OH)2D3, D and VMR.

Conclusions: Administration of different phosphate binder classes to patients with moderate-severe CKD results in unique changes in vitamin D metabolism. These findings may have important clinical implications in the management of hyperphosphatemia and vitamin D deficiency.

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Adjusted differences in vitamin D metabolite concentrations, by treatment group

FR-PO171

Effect of Hypomagnesemia on Vascular Calcification in Peritoneal Dialysis Patients

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Background: Vascular calcification is a non-traditional risk factor for cardiovascular disease in patients with chronic kidney disease (CKD) and main cause of this is disturbance in the mineral and bone metabolism. Magnesium (Mg) was known as a calcification inhibitor and there was a high prevalence of hypomagnesemia in peritoneal dialysis (PD) patients. However, a longitudinal study of the effects of hypomagnesemia on vascular calcification in PD patients was rare.

Methods: 167 patients with PD were included from Seoul National University Hospital. We investigated the relationship between lower serum magnesium and vascular calcification progression. Patients were categorized as hypomagnesemia (n=20), normal magnesium (n=85), and hypomagnesemia (n=62). Vascular calcification was assessed by abdominal aortic calcification (AAC) score with lateral lumbarosus X-ray. The study end point was vascular calcification progression, defined as the change in AAC score per year >0.

During the median follow-up period of 3.1 years [interquartile range 2.0-43 years; maximum 7.6 years], 38 (42.7%) patients developed vascular calcification progression. In a multivariable logistic regression model, the hypomagnesemia group was associated with higher risk of vascular calcification progression (1, serum Mg ≤1.7 mg/dl, OR 27.3 [1.67 – 691.2], P=0.045), as compared with the normal range magnesium group. All-cause mortality was not associated with hypomagnesemia in a multivariable hazard model (C1, serum Mg ≤1.7 mg/dl, HR 0.7 [0.07 – 6.89], P=0.755).

Conclusions: Hypomagnesemia is associated with vascular calcification progression in peritoneal dialysis patients.

FR-PO172

Effect of Spironolactone on the Progression of Coronary Calcification in Hemodialysis Patients

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Background: Aldosterone, through its action on the mineralocorticoid receptor, has been recognized as a factor involved in osteoinductive pathways of vascular calcification (VC). Clinical and experimental studies have shown that the use of spironolactone is related to the prevention of VC progression. The aim of this study was to evaluate the effect of spironolactone on the progression of coronary calcification (CC) in hemodialysis patients.

Methods: Patients with coronary calcium score (CCS) > 30 AU; evaluated by multiple-detector computed tomography (MDCT), were randomized into two groups: treatment group (GT) group, n=22) corresponding to patients receiving spironolactone and control group (GC) group, n=23), those who did not undergo drug intervention and did not receive placebo. The main outcome was a percentage change in CCS (relative progression rate). At the end of the follow-up period, which was one year. The patients were evaluated monthly, through consultations and collection of laboratory tests. At the end of the study, a new MDCT was performed in order to evaluate the progression of CC. Patients with a relative progression rate≥ 15% were considered progressed.

Results: Data from 35 patients who completed the follow-up period were analyzed, being 18 in the GT group and 17 in the CG group. The relative progression of CCS was similar in both groups, being 21.5% and 27% in the GT and GC groups, respectively. The majority of the patients progressed to the CC, 61.1% in the GT group and 70.6% in the CG group. At the end of the follow-up period, there was an increase in intact parathyroid hormone (p=0.035) and a decrease in sclerostin (p=0.002) in the GT group. Among the groups, also at the end of the study, total alkaline phosphatase was lower in the GT group when compared to the CG group (p=0.002).

Treatment with spironolactone determined an increase in high-density lipoprotein and cholesterol was not associated with hypomagnesemia in a multivariable hazard model (C1, serum Mg ≤1.7 mg/dl, HR 0.7 [0.07 – 6.89], P=0.755).

Conclusions: Hypomagnesemia is associated with vascular calcification progression in peritoneal dialysis patients.
Conclusions: The use of spironolactone did not attenuate the progression of the CC in patients undergoing hemodialysis. The use of spironolactone was safe in the study population.

FR-PO173
Coronary Calcification in Peritoneal Dialysis Patients: The Contribution of Traditional and Uremia-Related Risk Factors
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Background: Coronary calcification (CC) is commonly observed in dialysis patients and is associated with cardiovascular and all-cause mortality. Its pathogenesis is complex and involves a series of markers that interact in the vascular microenvironment. There are very few studies that assess the presence of CC in peritoneal dialysis (PD). The aim of this study was to evaluate the frequency and the factors associated with CC in PD patients.

Methods: A total of 81 patients were enrolled. Coronary calcification was assessed using a multislice coronary tomography. Patients with a coronary calcium score (CCS) of 30 or above were considered as having CC. Demographic data were collected and the serum levels of biochemical and bone-derived biomarkers, including sclerostin and fetuin-A, were measured.

Results: Thirty-eight patients (47%) presented with CC. Calcified patients were older adults (p < 0.001), presenting with more comorbidities, such as diabetes mellitus (p = 0.043), dyslipidemia (p = 0.040), and smoking (p = 0.003). Calcified patients presented higher serum levels of sclerostin (p = 0.005). There was a tendency for calcified patients to have lower levels of fetuin-A (p = 0.05). In a multivariate logistic regression analysis, age, serum sclerostin level, and smoking were independently associated with CC. For each increase of 100 units in the serum level of sclerostin, there was a 13% increase in the likelihood of CC. CCS was positively correlated with age, time on PD, and serum sclerostin levels.

Conclusions: Coronary calcification is highly prevalent in PD patients and is associated with older age, diabetes and smoking. Serum levels of sclerostin were independently associated with CC.

FR-PO174
Effect of Warfarin on Progression of Vascular Calcification
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Background: Advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD), as well as diabetes are potent risk factors for medial arterial calcification, a lesion associated with poor cardiovascular outcomes. Warfarin use may be an additional risk factor, possibly by reducing levels of matrix gla protein, a vitamin K-dependent inhibitor of vascular calcification. To quantify the effect of warfarin on medial arterial calcification and determine if this is augmented in CKD and ESRD or diabetes, we retrospectively measured the progression rate of breast arterial calcification (BAC), a marker of systemic medial arterial calcification in women with or without warfarin use.

Methods: Subjects with and without warfarin use were identified from an electronic medical record search of all digital mammograms at Emory Healthcare. Records were manually reviewed to identify mammograms performed during warfarin use. Subjects without baseline calcification were excluded. Control patients were selected to match the eGFR range in warfarin patients. Lengths of calcified arteries were measured on digital mammograms separated by ≥ 1 year. Progression rates are reported as mm/breast/y and are expressed as medians and interquartile ranges. Statistical significance was determined by the Mann-Whitney U and Wilcoxon tests.

Results: Of the 77 sets of mammograms, eGFR was >60 in 36 and <60 in 28, and ESRD was present in 11. Diabetes was present in 44%. In subjects with eGFR >60, warfarin use was associated with faster progression of BAC compared to controls: 10.0 (3.8-17); n=36 vs 2.6 (0.8-7.0); n=58, P=0.002. A similar effect was seen in ESRD but resulted in much higher rates: 46.9 (31-183); n=11 vs 15.2 (7-52); n=32, P=0.025. Warfarin’s effect was not augmented in patients with CKD (eGFR 17-58) or in diabetics vs. non-diabetics. Mammograms before or after warfarin use were available in 11 and 13 patients. BAC rate increased after starting warfarin (13.8 [7.6-39] vs. 2.1 [0.3-3.9]; P=0.01) and slowed, but not significantly, after stopping warfarin (1.9 [7.4-6.8] vs. 8.8 [3.1-10]; P=0.11).

Conclusions: Warfarin accelerates progression of medial arterial calcification. This effect is magnified in ESRD, resulting in marked increases in calcification in this population. These data suggest that warfarin should be used with caution in ESRD, particularly in patients with extensive vascular calcification.

FR-PO175
Associations Between Undercarboxylated Osteocalcin and Peripheral Vascular Calcification in CKD5
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Background: Increasing evidence proposes a link between bone and vasculature in CKD. Osteocalcin (OCN) is the most abundant non-collagenous peptide found in the mineralized bone matrix. In vitamin K deficiency, such as advanced CKD and dialysis, OCN is predominantly in the undercarboxylated form (ucOCN). We hypothesized that ucOCN levels are associated with peripheral VC in patients with advanced CKD.

Methods: We studied 34 patients with CKD5-5D. Radial artery (RA) and Tibial artery (TA) VC were quantified by high-resolution peripheral computed tomography (HRpQCT), a validated tool to assess VC. Using specialized assays, we measured total OCN (LIASON® Osteocalcin Assay 310950 Diasorin Inc., Stillwater MN, USA) and ucOCN (Glu-OC EIA Kit MK118 Takara Bio Inc., Otsu, Shiga, Japan). Spearman correlation analysis determined relationships between uc- and total circulating OCN and VCs.

Results: Our cohort had a mean±SD age of 48±14 years, 32% were female and 97% were Caucasian. Higher levels of ucOCN were associated with: (1) the presence of VC at the radius (p=0.04, p<0.03) but not at the tibia (p=0.5, p>0.06); and (2) greater severity of VCs at the TA (p=0.4, p=0.04) but not at the RA (p=0.3, p=0.07). Total OCN was not associated with either the presence of RA or TA VCs (p=0.1 and p=0.2 respectively) or the severity of RA and TA VCs (p=0.1 and p=0.3 respectively).

Conclusions: ucOCN is associated with the presence and severity of peripheral VC in patients with advanced CKD. This association has not been previously described in the literature. Larger studies are needed to confirm and determine mechanisms underlying this association and whether vitamin K supplementation improves peripheral VC severity.

Funding: Private Foundation Support

FR-PO176
Prevalence and Risk Factors of Vascular Calcification Among Chinese Patients with Early CKD
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Background: Extensive evidence suggests that vascular calcification (VC) independently predicts the risk of all-cause and CVD mortality. Here, we retrospectively studied the prevalence and risk factors of VC among Chinese patients with chronic kidney disease (CKD).

Methods: 138 patients diagnosed with CKD in Sun Yat-sen Memorial Hospital were included for analysis. Abdominal aortic calcification (AAC), Coronary artery calcification (CAC) were assessed by plain lateral lumbar radiograph and multi-detector computed tomography (MDCT) respectively. The AAC score will be classified into three levels(0-5, 5-16 and 16) and the CAC score will be classified into four levels(0-100, 100-400, 400-1000 and ≥1000). Risk factors were analyzed using logistic regression.

Results: Among the 138 patients, 63 (45.7%) were diagnosed with early CKD(stage 1-3) who had an eGFR of 30 mL/min/1.73 m or greater. Of the 63 patients, 30 (47.6%) were found abdominal aortic calcification who had AAC score greater than 0; Specifically, level 1 accounted for 30.2%; level 2 for 17.5% and level 3 for 1.6%. The high prevalence rate of AAC among patients with CKD stage 1-3 is similar to stage 4-5(49.3%) but the latter is more severe on calcification degree. At the same time, we found that 41.1% patients of early CKD have coronary artery calcification while 52.8% patients of advanced CKD(stage 4-5). Both the prevalence rate and severity of CAC among patients with stage 4-5 are higher than stage 1-3. The multivariate logistic regression identified that older age [OR (95%CI) 1.313 (1.060, 1.606), P=0.001], DM [OR (95%CI) 6.523(1.490, 28.544), P=0.013] and increased SUA [OR (95%CI) 1.006(1.001, 1.011), P=0.028] were the risk factors of VC among Chinese patients with early CKD. However, except for age and DM, it was SBP [OR (95%CI) 1.037(1.005,1.070), P=0.022] but not the SUA(OR=5.033) increased the risk of VC among patients with advanced CKD.

Conclusions: There is limited knowledge about the impact of VC on Chinese patients with CKD, causing poor prognosis and inadequate management. We were surprised to find such a high prevalence of VC in patients with early CKD. Now, we are conducting a multicenter, large sample prospective study (ChiCTR1900020925) for establishing a predictive model for VC in patients with chronic kidney disease(stage 1-3) and hope to help us prevent it more effectively.

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FR-PO177
Quantitative Systems Pharmacology Model of Metabolic Bone Disorder and Vascular Calcification in CKD
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Background: Changes in Calcium (Ca) and Phosphorus (P) metabolism in patients with Chronic Kidney Disease (CKD) and associated Mineral Bone Disorder (MBD) and Vascular Calcification (VC) pose significant morbidity and mortality risk in this patient population. We propose a Quantitative Systems Pharmacology (QSP) model of CKD-related MBD / VC to enable precision dosing of pharmacologic agents used in treatment of these conditions.

Methods: Based on the published data, we developed a QSP model of Ca / P metabolism. The model represents the movement of Ca and P between serum, gut, bone, kidney, and the soft tissue. The model also includes the FGF23 pathway and the effects of calcimimetic, vitamin D, and P binders. We validated the model against recently published clinical data describing the effect of CKD on the markers of MBD progression. We also investigated the ability of the model to predict different treatment effects in a virtual CKD patient.

Results: The impact of kidney function decline on Ca, P,PTH, Calcitriol, FGF23, and the Ca fluxes between serum, bone, and soft tissue predicted by the model is shown in the six plots below. The model correctly captures the decrease in serum Ca and the increase in P andPTH. In addition, the model correctly identifies the changes in Calcitriol and FGF23. Predicted changes in bone-to-serum and serum-to-soft tissue Ca fluxes are consistent with the pathophysiology of CKD-MBD-VC. The effects of combined P binder, Calcitriol, and a calcimimetic administration are consistent with the expected mechanism of action.

Conclusions: We propose a QSP model of Ca / P homeostasis and their effect on bone and vascular health. Validation against published clinical data proves the feasibility of the model. The model will be used to benchmark personalized treatment options to minimize the impact of MBD/VC in CKD patients.

Funding: Veterans Affairs Support

FR-PO178
CPP (Calciprotein Particle) Is a More Sensitive Marker That Predicts Vascular Calcification in Patients with CKD
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Background: Vascular calcification in atherosclerotic diseases is an important issue related to the prognosis in patients with chronic kidney disease (CKD). Since vascular calcification occurs in an early stage of CKD, it should be evaluated to improve the prognosis by early intervention. Phosphorus, parathyroid hormone and FGF-23 are identified as markers of CKD-mineral bone disease, but are within normal range in an early stage of CKD. CPP stands for calciprotein particles, which are nanoparticles composed of calcium-phosphate (CaP) crystals and mineral binding proteins such as Fetuin-A. Serum CPP levels could be a useful marker of vascular calcification in an early CKD patients. In this study, we determined whether CPP is a more sensitive marker of vascular calcification of patients with CKD than existing markers.

Methods: In a single-center longitudinal study of 58 patients with CKD stage G1-5, we evaluated clinical parameters (s-Cr, eGFR, CPP, FGF-23, intact-PTH, 1.25 ViD3) and arterial calcification score (ACS) of lower extremities by MDCT at the start and one year later to determine the risk factors related to the development of vascular calcification in CKD.

Results: Average age and average s-Cr were 69.0±12.9 years and 1.78a±1.26mg/dl, respectively. CPP significantly correlated with serum phosphorus but not with s-Cr or eGFR. The rate of change in s-Cr, eGFR, FGF-23, intact-PTH, and 1.25 ViD3 did not show significant correlation with the rate of change in ACS of the lower extremities, but the rate of change in CPP showed significantly negative correlation with the rate of change in ACS (r = -0.292, P = 0.028), and the rate of change in CPP was also an independent risk factor (p = 0.0144) in the progression of vascular calcification in multivariate analysis.

Conclusions: CPP effects protectively for vascular calcification by capturing calcium and phosphorus. CPP is a more sensitive marker of arterial calcification than other CKD-MBD markers such as FGF-23.

FR-PO179
Clarification of the Mechanism of Acute GFR Change by SGLT2 Inhibition with In Vivo Imaging Technique

Background: SGLT2 inhibition (SGLT2i) exerted the effects to lower the risk of kidney failure in patients with type 2 diabetic kidney disease (DKD). Improvement of glomerular hyperfiltration via tubuloglomerular feedback (TGF) has been considered to be involved in this mechanism. We have successfully developed the novel method to measure single nphron GFR (SNGFR) in mice using multiphoton laser microscopy (MPM). We demonstrated that adenosine/adenosine 1 receptor (A1AR) pathway plays a pivotal role in the TGF mechanism in type 1 diabetic model, Akita mice (Circulation 2019). The purpose of this study is to clarify the acute effects of SGLT2i on glomerular hemodynamic in type 2 diabetic rat.

Methods: Zucker lean (ZL) rats and Zucker diabetic fatty (ZDF) rats were used. Both rats were divided to the following groups; luseogliflozin (10mg/kg, gavage) group, luseogliflozin + adenosine A1 receptor (A1AR) antagonist (8-cyclopentyl-1,3-dipropylxanthine, 1mg/kg) group, and insulin group. SNGFR was measured after four weeks of treatment. For the acute phase study, catheter was inserted into the ureter to collect urine. Serial urine-collections of urine were performed every 30 minutes after administration of luseogliflozin. Urinary excretions of glucose, sodium, and adenosine were measured. At the same time points, SNGFR was measured to evaluate the correlation between urinary excretions of these parameters and GFR change.

Results: SNGFR in the untreated ZDF group was significantly higher than in the ZL group. Luseogliflozin treatment increased urinary sodium and glucose excretion and reduced serum glucose level in the ZDF group. SNGFR significantly declined after 30 minutes and became stabilized until 90 minutes after administration, with inverse relationship to urinary sodium. The A1AR-antagonist group showed similar urinary excretion pattern, but initial decline of SNGFR was not observed.

Conclusions: Adenosine/A1AR pathways play an important role in the regulation of GFR and is involved in the acute decline of GFR by SGLT2i treatment.

FR-PO180
Empagliflozin Attenuates PGE2-Mediated Inhibition of Arginine Vasopressin-Stimulated Water Reabsorption in Type II Diabetic (db/db) Mouse Collecting Duct
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Background: Sodium-glucose cotransporter 2 inhibitors such as empagliflozin (EMPA) are promising therapeutics in diabetic kidney disease (DKD) since they lower blood glucose, induce diuresis, and reduce glomerular hyperfiltration and proteinuria. Prostaglandin E (PGE), the main renal product of cyclooxygenase 2 (COX2), inhibits vasopressin (AVP) mediated water reabsorption in the collecting duct via its EP1 and EP3 receptors. We examined whether PGE2 inhibition of AVP-mediated water transport is affected by EMPA.

Methods: Four groups of male mice were studied: control (db/m), db/m+EMPA (10 mg/kg/day in chow for 6 weeks), diabetic (db/db), and db/db+EMPA. Collecting ducts were microdissected for quantitative PCR and water transport studies. Isolated perfused inner medullary collecting ducts were stimulated with 10-3 M AVP followed by 10-4 M PGE2.

Results: Collecting ducts from db/db mice expressed elevated mRNA for COX2, EP1 receptors, and vasopressin V2 receptors (n=4-6) compared to db/m mice, but levels were unaffected by EMPA. Urine PGE2 by ELISA was increased in db/db mice (n=5), but not altered by EMPA. AVP-stimulated water reabsorption was comparable in db/m and db/db mice (62%), and this PGE2, attenuation was significantly reduced in response to EMPA.

Conclusions: EMPA significantly reduced diuresis by 50%, and this reduction was unaffected by EMPA. However, a greater attenuation of AVP-mediated water transport in response to PGE2 was observed in db/db mice (62%), and this PGE2 attenuation was significantly reduced in response to EMPA, to 28% (n=3-4).

Conclusions: PGE2 levels and EP1 receptor expression are increased in type II diabetic mice, leading to attenuation of collecting duct AVP-stimulated water reabsorption. This attenuation is reduced in response to EMPA treatment, which may prevent excessive water losses.

Funding: Government Support - Non-U.S.
FR-PO181

SGLT2 Inhibition Attenuates ROS Production by Regulating Cytochromes P450 and Their Metabolites in Diabetic Kidney

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Background: Diabetic kidney disease (DKD) is currently the major common cause of end-stage renal disease worldwide. DKD is a main contributor to the increased risk of cardiovascular death in diabetes consequently increasing the global burden of diabetes-associated morbidity and mortality. Sodium–glucose cotransporter 2 (SGLT2) inhibitors, a new class of oral antihyperglycemic agents, revealed promising cardiact and renal protection in diabetic patients. However, the complete spectrum of pathways that can be affected by SGLT2 inhibition is not yet fully elucidated. Arachidonic acid (AA) is metabolized by several cytochromes 450 (CYP) isoforms to produce 20-hydroxyeicosatetraenoic acid (20-HETE) and epoxyeicosatrienoic acids (EETs). CYPs of the 4A and 4F subfamilies form EETs. Previous data from our lab show that alteration in CYPs metabolites contribute to renal damage in a diabetic milieu by altering ROS production. Moreover, CYPs have been shown to be significant sources of oxidative stress in kidneys and other organs. In this study we aim to investigate the mechanistic pathway by which SGLT2 inhibition exerts its pro-protective effect.

Methods: Dapagliflozin (SGLT2 inhibitor), HET0016 (20-HETE inhibitor), and AUDA (seIH inhibitor increasing EETs availability) were administered to Type-2 diabetic mice. Functional, histological and biochemical studies were performed.

Results: In our study, we show that diabetes-induced extracellular matrix accumulation, increases glomerular hyperfused, induces glomerulosclerosis and albuminuria. These observations were accompanied by increased ROS production associated with alteration in CYPs 4A and 2C11 expression concomitant with alteration in 20-HETE and EETs formation. Diabetes-induced glomerular injury was blocked by HET0016, an inhibitor of CYP 4A or by the use of AUDA, an EET activator. Of interest, SGLT2 treatment restored glomerular integrity and renal function by decreasing 20-HETE production and increasing EETs formation. Concomitantly, SGLT2 inhibition regulated the observed increase in the expression and accumulation of TGF-β, known to play a major role in glomerulosclerosis.

Conclusions: These findings suggest a new mechanistic pathway by which SGLT2 inhibitors exert their protective effect in DKD.

FR-PO182

SGLT2 Inhibition Promotes Restoration of Podocyte Number and Regression of Diabetic Nephropathy in BTBR ob/ob Mice

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Background: The SGLT2 inhibitor empagliflozin (EMPA) lowers blood glucose in diabetic patients via enhanced urinary excretion of glucose and ameliorates complications of type II diabetes, including cardiovascular disease and nephropathy (DN) through additional mechanisms, not fully defined.

Methods: Cohorts of 18 week old BTBR ob/ob and BTBR WT littermates (n=12) were fed chow formulated with 300 mg/kg EMPA with and without concurrent losartan (LOS) treatment, normal chow or were given leptin (LEP) for 6 weeks.

Results: Treatment with LEP, EMPA and EMPA+LOS but not LOS alone all resulted in significant reductions of blood glucose and HbA1c. BTBR ob/ob mice have elevated alanine aminotransferase (ALT) (737 mg/μg); treatment with EMPA, EMPA and EMPA+LOS all reduced ALT (88, 224, 162 μg/μg respectively, p<0.01). Morphologic analysis of silver stained tissue sections demonstrated significant reductions in mesangial matrix accumulation as percentage of glomerulus (G) tuft area in all treatment groups except LOS (ob/ob 20.8%, LEP 13.3%, EMPA 14%, EMPA+LOS 12.5%, p<0.01; LOS 18.4%, ns). Podocyte density increased with EMPA treatment vs. untreated ob/ob (ob/ob 89.2, LEP 119.1, EMPA 143.5, EMPA+LOS 171.1 cells/ μm², p<0.001). EMPA treatment decreased Mac2+ macrophages within glomeruli (ob/ob 1.85, EMPA 0.95 Mac2+ cells/G, p<0.01), but EMPA+LOS had numbers of glomerular macrophages similar to the untreated ob/ob mice (1.64 Mac2+ cells/G, ns). In contrast, qPCR for 3 inflammatory cytokines, MCP-1, IL-6 and TNFα were unchanged with SGLT2 inhibition. These may all be contributing factors in the improvement seen in human diabetic patients treated with SGLT2 inhibitors.

Funding: Commercial Support - Boehringer Ingelheim

FR-PO183

Identification of a Novel Smad Target in SGLT2-Mediated CTGF/CCN2 Expression

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Background: Drugs inhibiting Sodium Glucose Transporter 2 (SGLT2) activity are providing unexpected and significant benefits by the reduction of a number of conditions including cardiovascular death and mortality in diabetic patients. The precise mechanisms underlying the benefits are not fully understood. Proximal tubule cell SGLT2 is believed to be the major site of action for these drugs. We have investigated putative signaling pathways in these cells regulating SGLT2 induced effects, and have now identified a target already known to be involved in cardiovascular disease and fibrosis.

Methods: PTECs (primary proximal tubule epithelial cells) were cultured on collagen IV. They were treated with D glucose 7m M (control), 25m M (high) or 7m M + 18m M L glucose (osmotic control). †/† TGβ1 at 0.75mg/ml. The cells were also administered Dapagliflozin and MEK Inhibitor U0126 (0.1, 1, 10m M). Western blotting was used to detect the level of Connective Tissue Growth Factor (CTGF/CCN2), phosphorylated extracellular signal regulated kinase 2 (ERK 2), Smad3, and Smad3 linker serine 204 (LR) protein.

Results: Our high glucose (HG) †TGβ1 treated PTECs significantly upregulated CTGF/CCN2 protein (P<0.05). This rise was significantly attenuated by Dapagliflozin (P<0.001). Hence, we investigated a potential converging of the glucose and TGβ1 signaling. TGβ1 phosphorylated ERK 2 (42kDa) from 5 - 60 min after treatment with HG (P<0.01), while HG treatment exclusively phosphorylated ERK 2 from 15 - 45 min (P<0.05). Smad3 (52kDa) was phosphorylated by TGβ1 from 5 - 60 min, +/− high glucose (P<0.01). HG+TGβ1 treatment at 30 min caused a significant rise of LR (25kDa) phosphorylation (P<0.05), which was significantly reduced in the presence of U0126 (P<0.05).

Conclusions: SGLT2 mediates high glucose induced CTGF/CCN2 in the presence of TGβ1. We have identified a novel alternative mechanism by the convergence of TGβ1 and HG treatment; phosphorylation of a serine on the Smad3 LR. Hayashida (2013) showed that glucose mediated ERK activation of LR potentiates Smad regulated transcription in mesangial cells. As MK inhibition was able to reverse LR phosphorylation in our PTECs, our data indicates an important role for ERK in facilitating the observed glucose mediated pro-fibrotic effect.

FR-PO184

Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) Deficiency Attenuates Hypermicysis, Hypertension, and Nephropathy via Downregulation of Sodium-Glucose Co-Transporter 2 Expression in db/db Mice

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Background: Sodium-glucose co-transporter 2 (Sglt2) expression is up-regulated in renal proximal tubules (RPTs) in the diabetic kidney. The underlying molecular mechanisms, however, remain undefined. We have identified putative nuclear factor erythroid 2-related factor 2 (Nrf2)-responsive elements (REs) in mouse and human Sglt2 gene promoters. We investigated the impact of global Nrf2 knockout (KO) in db/db mice and transgenic (Tg) mice specifically overexpressing Nrf2 in renal proximal tubules (RPTs) on Sglt2 expression and studied the underlying mechanisms of Nrf2-regulation of Sglt2 transcription in vitro.

Methods: Male and female db/m, dbnNf2 KO, db/db and dbnNf2 KO mice were studied up to age 16 weeks. Body weight (BW), blood glucose (BG), systolic blood pressure (SBP) and urinary albumin/creatinine ratio (ACR) were measured at week 16. Nr2d and Sglt2 expression in isolated RPTs were assessed by RT-qPCR and western blotting. Tg mice specifically overexpressing Nr2f in their RPTs by employing kidney-specific androgen-regulated promoter were studied. In vitro, the effect of oligoprid (Olz), an Nr2f activator) and overexpression of Nr2f RNA on Sglt2 expression and Sglt2 promoter activity in human RPTC (H-RPTC) were assessed.

Results: BW, BG, SBP, kidney weight/tibia length ratio, ACR, Nr2f and Sglt2 expression in RPTs were significantly increased in db/db mice as compared to db/m mice. Genetic deletion of Nr2f significantly attenuated these changes except BW in db/ Nf2 KO mice. Nr2f and Sglt2 expression were also significantly increased in RPTs of Nr2-Tg mice compared to non-Tg mice. In vitro, Olz or overexpression of Nr2f RNA significantly increased Sglt2 expression and Sglt2 promoter activity via Nr2f-REs in the Sglt2 promoter in HK-2.

Conclusions: Nr2f deficiency attenuates hypermicysis, hypertension, kidney injury and RPT Sglt2 expression in db/db mice. Overexpression of Nr2f increases RPT Sglt2 expression in Nr2-Tg mice. NR2f stimulates Sglt2 transcription via NR2f-REs in HK-2. These results identify a novel mechanism by which Nr2f mediates hypermicysis-stimulation of Sglt2 expression in diabetic kidneys.

Funding: Government Support - Non-U.S.
Loss of Heterogeneous Nuclear Ribonucleoprotein F in Renal Tubules Attenuates Hyperfiltration and Kidney Injury in Diabetic Mice via Downregulation of SGLT2 Expression

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Background: We previously showed that tubular deficiency of heterogeneous nuclear ribonucleoprotein F (hnrNPF) results in up-regulation of renangiotensinogen (Agt) and down-regulation of sodium-glucose co-transporter-2 (SGLT2) in mice. Non-diabetic tubule-specific hnrNPF knockout (FKO) mice developed hypertension and renal fibrosis but had similar blood glucose (BG) levels or glomerular filtration rate (GFR) as control mice. Here, we investigated the effects of FKO in diabetic Akita mice, a murine model of type 1 diabetes.

Methods: FKO mice were generated via cross-breeding of Pax8-Cre mice with floxed hnrNPF mice on a C57BL/6 background. Akita-FKO mice were created by cross-breeding of female FKO mice with male heterozygous Akita mice. Both male and female Akita-FKO mice and Akita control littersmates were studied (n=8/group). Body weight (BW), BG, and systolic blood pressure (SBP) were monitored up to age 24 weeks. GFR was measured by inulin-FITC clearance in awake mice; kidneys were processed for histology (PAS, Masson’s trichrome, electron microscopy).

Results: Akita-FKO mice had better glycemic control, lower kidney weight/BW ratio, and lower GFR/BW ratio than Akita control mice: SSBP was significantly higher in male but not in female Akita-FKO mice as compared to Akita. Urinary albumin/creatinine ratio did not differ in the two groups. Renal histology in Akita-FKO mice showed an attenuated glomerulosclerosis and tubulointerstitial fibrosis with improved G5M thickness and foot process effacement cf. Akita. Real-time qPCR on kidney cortex confirmed down-regulated expression of SGLT2 and fibrosis marker genes (fibromectin 1, α-smooth muscle actin, collagen 1) and up-regulated Agt expression in Akita-FKO mice cf. Akita.

Conclusions: Kidney hypertrophy and glomerular hyperfiltration were attenuated in Akita-FKO mice, likely due to SGLT2 down-regulation activating tubuloglomerular feedback. The renoprotective effect of SGLT2 down-regulation overcomes the renal injurious effect of Agt when these opposing factors coexist. The Akita-FKO mouse is a unique tool for studying the molecular mechanisms of SGLT2 regulation in diabetes.

Funding: Government Support - Non-U.S.

FR-PO186

Empargliflozin Attenuates Diabetic Tubulopathy by Improving Mitochondrial Fragmentation and Autophagy

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Background: We examined the effects of empagliflozin, a selective inhibitor of sodium glucose cotransporter-2 (SGLT-2) on mitochondrial quality control and autophagy in renal tubular cells in a diabetic environment in vivo and in vitro.

Methods: Human renal proximal epithelial cells (hRPCs) were incubated in high-glucose conditions. Diabetes was induced with streptozotocin in male C57BL/6J mice. Results: Improvements in mitochondrial biogenesis and balanced fusion/fission protein expression were noted in hRPCs after treatment with empagliflozin in high-glucose media. Empagliflozin also increased autophagic activities in renal tubular cells under high glucose environment which was accompanied with mTOR inhibition. Moreover, reduced mitochondrial ROS production and decreased apoptotic and fibrotic protein expression were observed in hRPCs after treatment with empagliflozin, even in hyperglycemic circumstance. Importantly, empagliflozin restored AMPK phosphorylation and normalized the levels of AMP:ATP ratios in human renal tubular cells subject to a high-glucose environment which suggested the way of empagliflozin to involve in mitochondrial quality control. Empagliflozin effectively suppressed SGLT2 expression and ameliorated renal morphologic changes in the kidneys of STZ-induced diabetic mice. Electron microscopic analysis showed that mitochondrial fragmentation was decreased, and 8-OHdG content was low in the renal tubular cells of the empagliflozin treatment groups compared with those of the diabetic control group.

Conclusions: We suggest one mechanism related to the renoprotective actions of empagliflozin, which reverses mitochondrial dynamics and autophagy.

Funding: Government Support - Non-U.S.

FR-PO187

Effect of Canagliflozin on Glomerular Hyperfiltration Evaluated by Transcutaneous GFR Monitor in Spontaneously Diabetic Torii Fatty Rats

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Background: Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce glomerular hyperfiltration, thereby preventing the progression of diabetic kidney disease. However, since consecutive measurements of total nephron GFR in a same experimental model is not fully established, it is difficult to assess the precise effects of SGLT2 inhibitors on tubuloglomerular feedback (TGF). Transcutaneous GFR monitor (MediBeacon®) allows consecutive measurements by detecting fluorescence of FITC-sinistrin in the same animal, including multiple measurements with no sampling. Therefore, we assessed the effects of canagliflozin (CANA) on glomerular hemodynamic effects using transcutaneous GFR monitor in Spontaneously Diabetic Torii fatty rats (SDT-fatty rat), an obese type 2 diabetic model.

Methods: Eight week-SDT-fatty rats were given 100 mg/kg of CANA. Sprague Dawley (SD) rats were used as control. Fluorescence monitoring device was placed onto back of rats, and FITC-sinistrin was injected intravenously. After 2 hours, device was removed and half-life of sinistrin was measured, and then GFR was calculated. GFR could be measured one day before, 2 hours after, and 1 week after the treatment with CANA in the same rat. Adenosine production in response to increased sodium chloride reabsorption by CANA is evaluated by measuring urinary adenosine levels. SDT-fatty rats are treated with selective A1 adenosine receptor (A1aR) antagonist before administration of CANA.

Results: Serum glucose levels significantly increased in SDT-fatty rats (235.1 mg/dL vs 133.8 mg/dL). Baseline GFR in SDT-fatty rats was significantly higher than that in SD rats (23.7 ml/min/kg, 15.3 ml/min/kg, respectively). Treatment with CANA dramatically reduced diabetes-induced increased GFR at 2 hours after administration (17.3 ml/min/kg) compared to baseline (p<0.01 vs baseline GFR). GFR at 1 week after administration with CANA in a same rat returned to baseline level without glucosuria (22.7 ml/min/kg, p=0.49 vs baseline GFR). Urinary adenosine levels at 2 hours after administration with CANA and the effects of co-administration with A1aR antagonist on CANA-induced reduction of GFR will be evaluated.

Conclusions: SGLT2 inhibition plays a pivotal role in the regulation of GFR via TGF in SDT-fatty rats, which may contribute to renal protective effects reported in clinical trials.

Funding: Government Support - Non-U.S.
Reno-Protective Effect of GLP-1 Receptor Agonists: Silencing the J Am Soc Nephrol 30: 2019
Diabetic Kidney Disease: Basic - II

Conclusions: The results suggest a novel mechanism linking DPP4 to impair mitochondrial quality control during tubular injury in the pathogenesis of DKD and suggest SDF-1α/CXCR4/STAT3 pathway may become a potential therapeutic point to ameliorate DKD.

Funding: Government Support - Non-U.S.

FR-PO191

GSK3-β Inhibition Attenuates Progression of CKD in Lepr−/− Mice with Type 2 Diabetes (T2D) Beyond Standard-of-Care Therapy (SOC) with Metformin/Ramipril/Empagliflozin

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Background: Dual RAS/SGLT2 inhibition significantly reduces cardiovascular, renal morbidity in patients with T2D but further retarding progression of CKD remains a global unmet medical need. GSK3β inhibitor BIO (6-bromo-indirubin-3'-oxime) was shown to promote podocyte differentiation in vitro, to limit Adriamycin-induced podocyte loss in vivo, hence we hypothesized that BIO’s specific mechanism-of-action would have therapeutic effects beyond SOC therapy on diabetic kidney disease (DKD).

Methods: Male IKS-Lepr−/− mice with obesity-related T2D their respective non-diabetic IKS-Lepr−/− controls underwent uninephrectomy (1K) at 6 weeks of age to mimic CKD G2, accelerated progression of DKD. From week 12-16, all 1K mice were put to SOC therapy (1500mg/kg metformin, 6mg/kg ramipril, 480mg/kg empagliflozin) and randomized to either additional BIO (2K). Primary endpoint: Lepr−/− mice without proteinuria at week 12 were excluded from the study. N=10-11 per group. GFR, albuminuria, Blood glucose were monitored at regular intervals. Glomerular tuft area, density of WT-1+ podocytes and glomerulosclerosis were quantified in cortical and juxtamedullary glomeruli. Density of tertiary podocyte foot processes was analyzed as a marker of terminal podocyte differentiation by STEM microscopy

Results: Primary endpoint: Lepr−/− mice, GFR increased after uninephrectomy with a progressive decrease later (A). SOC+BIO significantly attenuated GFR loss during treatment interval compared to SOC therapy alone (B). Secondary endpoints: In Lepr−/− mice, albuminuria was significantly attenuated by SOC therapy (C). SOC+BIO therapy significantly increased podocyte densitimy juxtamedullary glomeruli (D). BIO showed significantly better preservation of tertiary podocyte foot processes (E).

Conclusions: GSK3-β inhibitor BIO has renoprotective effects beyond SOC therapy in a clinically meaningful model of progressive DKD. Optimizing animal models of DKD to better mimic the study population, co-medication, study endpoints used in clinical trials may improve the notoriously poor predictive value of animal models of DKD.

Funding: Other U.S. Government Support, Private Foundation Support

FR-PO189

Reno-Protective Effect of GLP-1 Receptor Agonists: Silencing the J Am Soc Nephrol 30: 2019
Diabetic Kidney Disease: Basic - II

Conclusions: The results suggest a novel mechanism linking DPP4 to impair mitochondrial quality control during tubular injury in the pathogenesis of DKD and suggest SDF-1α/CXCR4/STAT3 pathway may become a potential therapeutic point to ameliorate DKD.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Diabetic Kidney Disease: Basic - II
Poster/Friday

morphogenesis 2 protein, binds the Wnt effector Disheveled, nuclear actin and mediates Wnt-induced cytoskeletal changes. We now aimed to study possible contributions of DAAM2 to DN.

Methods: We assessed DAAM2 by immunostaining in non-cancerous regions of human nephropathy (NX), DN and normal transplant donor kidney tissues. NX patients were matched with those with coronary atherosclerosis. ACEi- or glipizide-treated DN mice (db/db/eNOS-/- model) were compared with vehicle-treated DN mice. Primary cultured podocytes were exposed to high glucose or mannitol, and DAAM2 was knocked down by siRNA to study effects on podocyte injury.

Results: Diabetic podocytes exhibited increased ALK1 expression (1.36 ± 0.07 vs. 0.90 ± 0.04). Glucose-induced ALK1 expression was further increased in both nephropathy and DN compared with normal donors. DAAM2 gradually decreased with increasing severity of DN, from class II to class III or IV (2.19 ± 0.15 vs 1.58 ± 0.14 vs 1.40 ± 0.10). Glucose and ACEi reduced DAAM2 expression in mice DN, accompanied with decreased proteinuria and maintained GFR and more preserved WTI+ podocytes. DAAM2 mRNA was increased in cultured podocytes treated with high glucose vs mannitol (0.36 ± 0.01 vs 0.17 ± 0.03). ROCK1, the downstream kinase of Wnt/Rho/ROCK signaling pathway, regulates podocyte process elongation. High glucose induced more ROCK1 expression than mannitol (0.14±0.04 vs 0.9 ±0.13), which was reversed by DAAM2 knockdown (0.04±0.07).

Conclusions: DAAM2 is up-regulated in podocytes in both nephropathy and DN, which we postulate could be contributed to both by glomerular hypertrophy, prevalent in both DN and NXs, and high glucose. We hypothesize that DAAM2 may regulate podocyte function through the Rho/ROCK signaling pathway.

Funding: NIDDK Support

FR-PO193
Podocyte and Endothelial-Specific Elimination of BAMBI Identifies Differential TGF-β Pathways Contributing to Diabetic Glomerulopathy
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Background: Transforming growth factor-β (TGF-β) is considered a central mediator of diabetic nephropathy (DN). The effect of TGF-β, mediated by type I TGF-β receptor, ALK5, and subsequent Smad2/3 activation is shown to result in podocyte apoptosis and increased ALK1-Smad1/5-mediated angiogenesis in DN, significant EC proliferation was observed only in the glomeruli of diabetic EC-Bambi-/- mice. Therefore, to evaluate the glomerular cell-specific effects of TGF-β, we examined the effects of the podocyte- or EC-specific loss of BAMBI.

Methods: Diabetic mice with podocyte- or EC-specific loss of BAMBI (Pod- or EC-Bambi-/-) were compared with vehicle-treated DN mice. Primary cultured podocytes were exposed to high glucose vs mannitol (0.36 ± 0.01 vs 1.58 ± 0.14). Glucose and ACEi reduced DAAM2 expression in mice DN, accompanied with decreased proteinuria and maintained GFR and more preserved WTI+ podocytes. DAAM2 mRNA was increased in cultured podocytes treated with high glucose vs mannitol (0.36 ± 0.01 vs 0.17 ± 0.03). ROCK1, the downstream kinase of Wnt/Rho/ROCK signaling pathway, regulates podocyte process elongation. High glucose induced more ROCK1 expression than mannitol (0.14±0.04 vs 0.9 ±0.13), which was reversed by DAAM2 knockdown (0.04±0.07).

Conclusions: DAAM2 is up-regulated in podocytes in both nephropathy and DN, which we postulate could be contributed to both by glomerular hypertrophy, prevalent in both DN and NXs, and high glucose. We hypothesize that DAAM2 may regulate podocyte function through the Rho/ROCK signaling pathway.

Funding: NIDDK Support

FR-PO194
A Novel Role for NPY-NPY2R Signalling in Albuminuric Kidney Disease
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Background: Albuminuria is an independent risk factor for the progression to end-stage kidney failure and premature mortality. It is well-established that podocyte damage is a major cause of albuminuria, yet the pathways involved are incompletely understood. In this study, we investigated the role of the neuropeptide NPY- and its receptor NPY2R in podocytes to identify molecules regulated in podocyte damage and novel pathways regulating albuminuria in diabetes. This revealed that Neuropoetin Y (Npy) was highly downregulated in insulin-resistant podocytes. While NPY is implicated in many conditions including obesity, diabetes and insulin resistance, a role for NPY in albuminuric kidney disease has not been established.

Methods: Gene expression was analysed in vitro in conditionally-immortalised podocytes using RNA sequencing and focused qPCR arrays, and in vivo in the Pima type-2 diabetic nephropathy cohort and the “nephropes” database. The effect of reduced Npy expression on albuminuria was analysed in streptozotocin (STZ)-induced diabetic mice and in diabetic and AdriaMycin nephropathy models, using wild-type and NPY-deficient (Npy-/-) mice. Conditionally-immortalized human and mouse podocytes were studied in vitro to determine the effects of NPY signalling. The effects of pharmacological NPY2R inhibition were investigated in vitro and in vivo, using BIIE0246.

Results: Transcriptional analysis demonstrated that Npy was significantly down-regulated in insulin-resistant vs insulin-sensitive mouse podocytes. Human diabetic nephropathy (DN) patients also had reduced glomerular NPY expression in both early- and late-stage DN. However, NPY-/− mice had reduced levels of albuminuria and podocyte injury in both diabetic and non-diabetic kidney disease models. Furthermore, both human and mouse podocytes responded to NPY stimulation, via activation of P3K and ERK MAPK signalling cascades, as well as the calcium-dependent activation of NFAT; responses which were mediated through NPY2 receptor (NPY2R) activity. The normalised gene inhibition of NPY2R in vivo significantly reduced albuminuria in adriamycin-treated mice.

Conclusions: Our findings reveal a novel role for the NPY system in the glomerulus and suggest that manipulating NPY/NPY2R signalling in albuminuric kidney disease may be therapeutically beneficial.

Funding: NIDDK Support

FR-PO195
The Evolving Importance of mTORC2/Rictor in Autophagy Dysregulation and Diabetes-Associated Kidney Disease
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Background: Accumulating evidence suggests that autophagy plays an important role in many critical aspects of normal and disease states of the kidney including diabetic kidney disease (DKD). Podocyte integrity has been described to rely on basal autophagy. However, the exact role of autophagy in podocyte dysfunction and the mechanisms underlying diabetic-induced podocyte loss must be elucidated. Several signaling pathways such as mTORC1, NADPH oxidase, and the Liver-X-Receptor (LXr) pathways have been shown to orchestrate podocyte integrity in DKD. Yet, the role of mTORC2 in autophagy and its crosstalk with these key mechanistic pathways remains to be identified.

For this, we investigated the role of the Nox1/Lxr/mTORC2 axis on autophagy and their possible link to podocyte integrity in vitro and in animal models of type 1 and type 2 diabetes.

Methods: A conditionally immortalized human podocyte cell line was used for the in vitro studies. In vivo studies were conducted in mice by streptozotocin injections and type 2 diabetes was initiated by high-fat diet followed by low-dose STZ injections. Pharmacological means were utilized to alter the expression of Nox4 (GTK), LXr (T0) and the mTORC2 (Rl) signaling pathways and functional, pathological, and biochemical studies were performed.

Results: High glucose (HG)-induced podocyte injury is reflected by alterations in the slit diaphragm proteins and podocyte depletion accompanied by autophagy dysregulation. This was paralleled by activation of the mTORC2 pathway. HG also increased the levels of Nox4 and NADPH oxidase activity. Inhibition of mTORC2, activation of LXr, or inhibition of Nox4 decreased HG-induced ROS generation, restored autophagy homeostasis, regulated podacin levels, and reduced podocyte loss. In isolated glomeruli from the diabetic mice, there was a similar activation of the mTORC2 signaling pathway with an increase in Pod-α, Pod-β, and NADPH oxidase activity. Activation of mTORC2, activation of LXr or inhibition of Nox4 restored podacin levels, reduced podocyte depletion, attenuated glomerular injury and albuminuria and regulated autophagy levels. Moreover importantly, Chloroquine treatment, an autophagy inhibitor, mimicked the effect of HG by increasing podocyte injury.

Conclusions: Our data provide evidence for a novel function of mTORC2 in regulating autophagy and its role in DKD.

Funding: NIDDK Support

FR-PO196
Mesenchymal Stem Cells Attenuate Diabetic Kidney Disease by Inhibiting the mTOR Signaling Pathway
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Background: Diabetic kidney disease is one of the most serious complications of diabetes worldwide. The earliest clinical manifestation of DKD is increased albuminuria, which eventually progresses to overt proteinuria. Glomerular injury is characterized by hyperpertrophy, mesangial matrix expansion, basement membrane thickening, and podocyte loss. Emerging body of evidence has revealed that mesenchymal stem cells treatment reduces the levels of albuminuria through differentiation or by acting in a paracrine manner. However, the mechanistic pathway has not yet been identified. We and others have previously shown that in the glomeruli of diabetic animals, the mTORC1/p70 S6Kinase and Rictor/mTORC2 pathways are activated, promoting podocyte injury. In addition, we demonstrated that mTORC1 and mTORC2 inhibition attenuates HG-induced NADPH oxidase upregulation and decreases NADPH oxidase and Nox4 expression. The present study aims to assess the reno-protective role of MSCs and to investigate the mechanistic pathway by which MSCs exert this protective role.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Sprague-Dawley rats were divided into the following groups: a control group, a streptozotocin-induced type 1 diabetic group each treated with medium, MSCs-derived medium, or 1x10^6 MSCs. After eight weeks of treatment from diabetes onset, functional, histological, biochemical, and molecular parameters of the kidneys were assessed.

Results: MSCs treatment restored normal urinary albumin excretion levels. Protection against DKD imparted by MSCs was denoted by decreased glomerulosclerosis. Moreover, MSCs treatment restored podocyte foot process effacement and glomerular basement membrane thickening and reversed podocyte depletion. More importantly, and for the first time, we show that partial inhibition restored the mTORC1/mTORC2 complex integrity. This was paralleled by a decrease in NADPH oxidase activity and NOX4 protein expression. All of these observations were mirrored when diabetic rats were treated with MSCs-derived medium.

Conclusions: Collectively this work reveals the physiologically important role of podocyte IGF1R signaling and that only a fraction of receptor activity is required to maintain function. We also show that partial inactivation of podocyte IGF1R is beneficial in some disease settings.

Funding: Private Foundation Support

FR-PO197
Honokiol Improves Diabetic Kidney Disease by Activating SIRT3 to Regulate Podocyte Mitochondrial Function

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Background: Diabetic kidney disease(DKD) is the main cause of end-stage renal disease. Current studies have shown that podocyte mitochondrial dysfunction is closely related to the progression of DKD.

Materials and Methods: Eight-week-old db/db and db/m mice were injected with honokiol(5 mg/kg)intraperitoneally for 5 consecutive days. STZ was used to induce diabetes mellitus in wild type( WT) and SIRT3 knockout (SIRT3 KO) mice and HKL was injected intraperitoneally for 5 days. ACR of mice in each group were detected. The morphological changes of mitochondria were observed under electron microscopes. The activity of podocytes mitochondrion complex I and II were detected by extracting mitochondrial DNA. The expression of mitochondrial metabolism related genes and mitochondrial DNA copy was detected by RT-PCR. In vitro, western blot was used to detect the expression of SIRT3 in podocytes after high glucose stimulation for 48h with or without HKL(5mM/L). Mitochondria lysates and DNA kits were used to detect the morphology and function of mitochondria. Flow cytometry (V-FITC/PI) was used to detect the apoptosis of podocytes.

Results: The expression of mitochondrial complex I and II in podocytes of db/db mice was lower than that of db/m mice, accompanied by the decrease of mitochondrial DNA Copy. The expressions of SIRT3, PGC1α and TFAM in db/db mice were significantly lower compared with db/m mice. The number of podocytes in db/db mice was decreased by immunohistochemistry. It was found that HKL restore the expression of SIRT3 in podocytes of db/db mice and STZ-induced diabetic mice. Aslo, the mice treated with HKL had lower ACR and improved mitochondrial morphology, but no significant improvement was observed in SIRT3 KO mice. The expression of mitochondrial complex I, II, mitochondrial DNA Copy in podocytes of db/db mice and WT mice were upregulated by HKL. In vitro, it was also found that HKL could upregulate the expression of SIRT3 in podocytes. Compared with high glucose alone, HKL treatment increased podocytes potential decreased in podocytes co-stimulated by high glucose and HKL, and ROS production decreased. Also, flow cytometry (V-FITC/PI) showed that podocyte apoptosis was reduced with HKL incubation.

Conclusions: Honokiol can improve the morphology and function of podocyte mitochondria by upregulating the expression of SIRT3, thus reduce the apoptosis of podocytes.

Funding: Government Support - Non-U.S.

FR-PO198
The Insulin/Insulin-Like Growth Factor Axis Is Critical for Podocyte Function but Partial Inhibition of IGF1 Signalling Is Physiologically Beneficial

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Background: Abnormalities in insulin signalling through the insulin receptor (IR) have previously been found to be critical for podocyte function and this study aims to define the physiological importance of the related insulin-like growth factor 1 receptor (IGF1R) and combined IR/IGF1R in podocytes.

Materials and Methods: A mouse model was used to generate mice with podocyte-specific IGF1R and simultaneous IR/IGF1R gene inactivation. In vitro models of receptor knockdown were engineered by applying extrinsic lentiviral Cre recombinase to podocytes derived from IR, IGF1R and IR/IGF1R floxed mice. IGF1R and IGF1R/IGF1R knockdown (podIFG1RKO) mice were crossed with mice expressing CRE recombinase under the control of a podocin promoter. Despite 80% knockdown of the IGF1R in this model, podiIFG1RKO mice exhibited no changes in renal histology or urinary albumin:creatinine (uACR) at 9 months when compared with littermate controls. However, when these mice were concomitantly fed with ACR 50% lower than IGF1R sufficient controls. To increase the efficiency of knockout and understand if there was compensation within the IR/IGF1R axis we also generated two additional models using a new podocyte specific Cre driver that is not subject to episomal deletion (podIFG1RKO and podIR/ IGF1R DKO mice). podIGF1RKO mice were albuminuric at 24 weeks while podIR/ IGF1R DKO mice developed a severe kidney phenotype with global sclerosis, renal failure and death between 4 and 24 weeks. >95% loss of IGF1R in cultured podocytes augmented AKT and ERK activation in response to insulin but resulted in ~50% cell death within the IR/IGF1R axis we also generated two additional models using a new podocyte specific Cre driver that is not subject to episomal deletion (podIFG1RKO and podIR/ IGF1R DKO mice). podIGF1RKO mice were albuminuric at 24 weeks while podIR/ IGF1R DKO mice developed a severe kidney phenotype with global sclerosis, renal failure and death between 4 and 24 weeks. >95% loss of IGF1R in cultured podocytes augmented AKT and ERK activation in response to insulin but resulted in ~50% cell death.

Conclusions: Collectively this work reveals the physiologically important role of podocyte IGF1R signaling and that only a fraction of receptor activity is required to maintain function. We also show that partial inactivation of podocyte IGF1R is beneficial in some disease settings.

Funding: Government Support - Non-U.S.

FR-PO200
Podocyte Nos5 Expression Increases Microparticle Formation and Oxidative Stress in Mice

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Background: Oxidative stress from isolated MPs were assessed by immunoblotting and DHE/HPLC, respectively. For mouse studies, Nos5+/- mice and nontransgenic littermates were either implanted with angiotensin II-containing miniosmotic pumps (400mg/kg/day) or either implanted with angiotensin II-containing miniosmotic pumps (400mg/kg/day) or sham operated. Systolic blood pressures were determined by tail cuff plethysmography. Urinary MP formation was quantified once per week for 5 weeks using 24 hour urine collections. A significant increase in urinary MP formation was noted two weeks following angiotensin II administration increased albumin permeability were recovered significantly by rKL.

Conclusions: The results support that podocyte-specific functional and morphological podocyte injury were recovered by exogenous klotho, and this may implicate klotho as a potential therapeutic target for treatment of podocyte injury of DN.

Funding: Government Support - Non-U.S.
Coupling of Transient Receptor Potential Canonical Channel (TRPC6) and Phosphodiesterase 1 (PDE1) Activity in Diabetic Nephropathy

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Background: Diabetic Nephropathy (DN) is a major complication of diabetes and the incomplete understanding of its molecular mechanisms is highlighted by the limited treatments options. Our investigation focused on the link between TRPC6 and the calcium activated PDE1. Three isoforms of PDE1 are differentially expressed in vascular smooth muscle cells, renal tubular epithelial cells, podocytes, and mesangial cells. While TRPC6 renal expression is associated with DN and inhibition of PDE1 causes vasodilation, their interaction in the context of DN has not been studied. We hypothesized that the diabetic milieu stimulates TRPC6-mediated calcium flux which in turn activates PDE1 and propagates kidney injury.

Methods: To investigate the role of PDE1 and TRPC6 mediated calcium flux and apoptosis, cultured human mesangial cells or isolated rat glomeruli were treated with TRPC6 agonist HYP990 with or without a pan-PDE1 inhibitor. Apoptosis was measured using high throughput imaging platform using caspase 3/7 as a marker. The role of PDE1 in hypertension and DN was evaluated in telemeterized spontaneously hypertensive rats (SHR) and in hypertensive type 2 diabetic (db/db) mice over expressing the renin gene.

Results: TRPC6 mediated calcium flux induced apoptosis in human mesangial cells and isolated rat glomeruli, which was attenuated by both TRPC6 and PDE1 inhibitor thereby suggesting a functional coupling between TRPC6 (as a source of calcium) and PDE1 (as an effector of calcium). Renal cell protection with PDE1 inhibition was tested in PDE1 mouse model of DN, featuring a combination of diabetes, nephron loss and arterial hypertension. In this model a novel PDE1 inhibitor caused a significant reduction of albuminuria up to 69% after 6 weeks of treatment compared to vehicle. This was accompanied by a significant reduction in serum creatinine and several urine biomarkers of inflammation and injury. Histopathological analysis revealed substantial improvement in glomerular sclerosis, interstitial fibrosis and reduction in mesangial matrix compared to vehicle. Gene expression analysis of the kidney revealed changes the gene clusters associated with innate immunity and fibrosis.

Conclusions: The results demonstrate that TRPC6 mediated calcium flux is linked to the activation of PDE1 and its inhibition leads to renoprotective effects in DN.

Funding: Commercial Support - Eli Lilly and Company

FR-PO203

The COX-2 Thromboxane Axis Plays a Critical Role in Podocyte Injury Induced by High Glucose

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Background: Podocyte injury is a vital factor in the onset and progression of diabetic nephropathy (DN), thus is a promising therapeutic target to prevent DN. The cyclooxygenase 2 (COX-2) thromboxane axis has been proved to play a critical role in podocyte injury whereas the underlying mechanism is still unknown. The aim of this study is to get a further insight of COX-2 thromboxane axis in podocyte injury.

Methods: In vitro study was performed with a high glucose medium of 30mmol/L to set up a podocyte injury model as previous described. Both the inhibitor and activator of the axis, small interfering RNA, ELISA, western blot and confocal were used to investigate the underlying mechanism of COX-2 thromboxane axis mediating podocyte injury.

Results: High glucose induced podocyte injury accompanied with increasing expression of COX 2 and excessive TXA2, indicating that the COX-2 thromboxane axis was activated. Small interfering RNA was used to silence the thromboxane/prostaglandin receptors (TP-t) or block the TP-t with inhibitor SQ29548 alleviated the injury. Furthermore, the stimulation of high glucose led to the over-activation of Rho/ROCK1 pathway, resulting in an increased phosphorylation of Dp1, a critical protein regulating mitochondrial fission. As expected, pretreatment of Y26432 could block the ROCK1 release protective effect when the cells were exposed to high glucose. What’s more, we further investigated the underlying mechanism mediating the renal protective effects of puerarin in DN.

Conclusions: High glucose may activate the COX-2 thromboxane axis, leading to an activating activity of TP-t to induce the downstream effect of ROCK1 activation, resulting in excessive mitochondrial fission, and finally podocyte injury (Fig 1).

Funding: Government Support - Non-U.S.

FR-PO202

Hyperoside Inhibits Podocyte Epithelial-Mesenchymal Transition in Diabetic Kidney Disease via Regulating Insulin Resistance-Related Signaling Pathways, Compared with Rosiglitazone

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Background: Hyperoside (HYP), a bioactive component of Aborosma manihot, has been widely applied to clinical therapy in the diabetic kidney disease (DKD) patients. However, it remains elusive whether HYP can alleviate podocyte damage in DKD. The aim of this study was to investigate the effect of HYP on podocyte injury in DKD, featuring a combination of diabetes, nephron loss and arterial hypertension. In this model a novel PDE1 inhibitor caused a significant reduction of albuminuria up to 69% after 6 weeks of treatment compared to vehicle. This was accompanied by a significant reduction in serum creatinine and several urine biomarkers of inflammation and injury. Histopathological analysis revealed substantial improvement in glomerular sclerosis, interstitial fibrosis and reduction in mesangial matrix compared to vehicle. Gene expression analysis of the kidney revealed changes the gene clusters associated with innate immunity and fibrosis.

Conclusions: The results demonstrate that TRPC6 mediated calcium flux is linked to the activation of PDE1 and its inhibition leads to renoprotective effects in DN.

Funding: Commercial Support - Eli Lilly and Company

FR-PO204

Puerarin Attenuates Diabetic Nephropathy by Promoting Autophagy in Podocytes

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Background: Puerarin, an active compound of radix puerariae, is a major compound used in Chinese herbal medicines to treat patients with diabetic nephropathy (DN). In the previous studies, we showed that puerarin exerts renoprotective effects in a mouse model of streptozocin (STZ) induced diabetic nephropathy (DN). However, the underlying mechanisms are still unknown. The aim of this study was to determine the molecular mechanisms mediated by puerarin in DN using both vivo and in vitro models. Immunoprecipitation combined with western blot analysis was used to determine acetylation of LKB1. shRNAs were used to knockdown HMOX1 and Sirt1 in cultured podocytes.

Results: We found that puerarin ameliorated STZ-induced kidney injury as shown by kidney histology. We also found that puerarin restored podocyte differential markers such as P-cadherin and ZO-1 in diabetic glomeruli. We also found that expression of HMOX-1 and Sirt1 in diabetic glomeruli was suppressed in diabetic glomeruli but restored by puerarin treatment as shown by both real-time PCR, western blot analysis, and immunostaining. In conditions immortalized mouse podocytes, puerarin inhibited HG-induced apoptosis and restored the protein and mRNA levels of ZO-1, P-cadherin, HMOX-1, and Sirt1. Interestingly, we showed that puerarin decreased LKB1 acetylation, thereby promoting AMPK-dependent autophagy. Knockdown of HMOX-1 and Sirt1 expression or treatment with the autophagy inhibitor 3-MA abolished the protective effects of puerarin in HG-treated podocytes.

Conclusions: Taken together, these results suggest that puerarin protects podocytes from diabetes-induced injury through a novel mechanism involving HMOX1, Sirt1 and AMPK-dependent autophagy, a novel mechanism explaining its renal protective effects in DN.

Funding: Government Support - Non-U.S.
FR-PO205
Effect of Exosomes from High Glucose-Treated Mesangial Cells on Healthy Podocytes
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Background: Urinary space compartments can mediate cell communication. This paracrine communication may have a relevant role in the diabetic nephropathy (DN). This study investigated whether podocytes communicate with each other as secretory cells. Podocytes can secrete exosomes, which are small membrane-bound vesicles. However, the role of exosomes secreted by podocytes on the healthiness of podocytes remains unknown.

Methods: In the present study, mesangial cells were cultured in high glucose (HG) medium for 24 hr. Exosomes (Exos) secreted to the culture medium (HG-Exos) were collected by ultracentrifuge and analyzed by western blot and transmission electron microscopy.

Results: HG-Exos were secreted by mesangial cells in an increased amount of size and concentration ratio compared to the control. These Exos contained nephrin, synaptopodin, podocin, and α-actinin. HG-Exos induced changes in podocyte morphology and function, including increased endocytosis and decreased cell adhesion.

Conclusions: These findings suggest that exosomes secreted by podocytes may mediate cell communication between podocytes and other cells in the kidney. Further studies are needed to investigate the mechanisms underlying these effects.

Funding: Government Support - Non-U.S.

FR-PO206
Diabetic Nephropathy Is Associated with Reduced Fraction of Glomerular Basement Membrane Surface Area Opening into the Subpodocyte Space
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Background: Diabetic nephropathy (DN) is the leading cause of end-stage kidney disease worldwide. However, the underlying mechanisms have not been fully elucidated. In diabetic kidneys, changes in the urinary space compartments are increased in DN. This study assessed the relationship between the fraction of glomerular basement membrane surface area opening into the subpodocyte space (SPS) and the progression of DN.

Methods: In this study, kidney biopsies from 9 T2D patients and 5 normal controls were analyzed. The fraction of SPS was calculated using transmission electron microscopy. The relationship between the fraction of SPS and DN progression was assessed using statistical analysis.

Results: In the diabetic group, the fraction of SPS was reduced compared to the control group. The reduction in SPS was associated with the progression of DN.

Conclusions: These findings suggest that changes in the urinary space compartments contribute to the progression of DN.

Funding: NIDDK Support, Private Foundation Support

FR-PO207
The Mineralocorticoid Receptor Antagonist Finerenone Limits Podocyte Injury in High-Salt Loaded db/db Mice
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Background: Diabetic kidney disease (DKD) is a leading cause of end-stage kidney disease worldwide; however, the underlying mechanisms have not been fully elucidated. In diabetic kidneys, changes in the urinary space compartments are increased in DN. This study investigated the effect of finerenone, a mineralocorticoid receptor (MR) antagonist, on podocyte injury in high-salt loaded db/db mice.

Methods: In this study, mice were randomized to a control group or a finerenone group. The effect of finerenone on podocyte injury was assessed using transmission electron microscopy.

Results: In the finerenone group, podocyte injury was reduced compared to the control group. The reduction in podocyte injury was associated with the reduced production of podocyte markers.

Conclusions: These findings suggest that finerenone may limit podocyte injury in diabetic kidneys.

Funding: Commercial Support - Bayer Yakuhan

FR-PO208
Diabetic Condition Induces Hypertrophy and Mitotic Catastrophe in Parietal Epithelial Cells Through Cell Cycle Re-Entry
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Background: Parietal epithelial cells (PECs) are located in the proximal tubules of the kidney and play a crucial role in fluid and electrolyte homeostasis. However, little is known about the effects of diabetic conditions on PECs.

Methods: In this study, PECs were cultured in high glucose (HG) and analyzed using fluorescence microscopy and flow cytometry.

Results: HG induced hypertrophy and apoptosis in PECs. However, HG also induced mitotic catastrophe in PECs. The mechanism of mitotic catastrophe was elucidated using cell cycle re-entry.

Conclusions: These findings suggest that diabetic conditions can induce hypertrophy and mitotic catastrophe in PECs, which may contribute to kidney injury.

Funding: Commercial Support
Intraglomerular Cross-Talk Between Mesangial Cells and Podocytes Inhibits Normal Endoplasmic Reticulum-Associated Degradation Processes and Induces Podocyte Injury in Diabetics

Daisuke Fujimoto, Takashige Kuwabara, Yusuke Hata, Shuro Umemoto, Tomoko Kanki, Yoshihiko Nishiguchi, Teruhiko Mizumoto, Manabu Hayata, Yuichiro Izumi, Yutaka Kakizoe, Massashi Mukoyama. Department of Nephrology, Kumamoto University, Kumamoto, Japan; 2Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; 3Kumamoto University Graduate School of Medicine, Kumamoto, Japan; 4Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; 5Kumamoto University, Kumamoto, Japan.

Background: Mesangial lesion and podocyte injury are essential for the progression of diabetic kidney disease (DKD). Although cross-communication between mesangial cells (MC) and podocytes is recently suggested by single cell RNA-seq analyses, its molecular mechanisms remain elusive. Our previous experiment on cDNA microarray of diabetic mice glomeruli suggested that ER stress might be involved in DKD progression. The aim of this study is to clarify the effects of MC-podocyte crosstalk on ER stress response of podocytes in diabetic conditions.

Methods: First, we conducted quantitative PCR array focused on ER stress-associated genes. Using cultured mouse podocytes (MPC5) and mouse macrophages (Mφ) stimulated with MC-cultured medium (MC-sup) under high-glucose condition (HG), we evaluated podocyte and specific responses. Further evaluations of ER stress responses of MPC5 were made by Western blotting, real-time PCR and TUNEL staining. The effects of an ER-associated degradation (ERAD) inhibitor Eyerestatin 1 (EerI) in MPC5 and db/db mice were also examined.

Results: In vitro, stimulation with HG MC-sup suppressed ERAD-related factors (XB1, Derlin), and enhanced apoptotic responses in both protein and mRNA levels specifically in MPC5, but not in Mφ. TUNEL staining of MPC5 also showed increased apoptotic cells by HG MC-sup. Those results were augmented by HG MC-sup compared to MC-sup under low-glucose condition. Of note, treatment with EerI recapitulated similar responses, namely suppressed IRE1α, spliced XB1 and Derlin-2 in MPC5. In vivo, such alterations were also observed in isolated diabetic glomeruli. Administration of EerI significantly exacerbated albuminuria in db/db mice. Expression of genes related to inflammation and fibrosis increased, and immunohistochemistry showed lowered expression of Derlin-2 and nephrin in the glomeruli.

Conclusions: It is recently reported that ERAD pathway may play important roles in the maintenance of podocytes to avoid ER stress in several glomerular diseases including DKD. In this study, we first reveal that intraglomerular crosstalk between MC and podocytes inhibits normal ERAD processes, potentially causing podocyte injury in diabetic conditions.

Calcitriol Plays a Protective Role in Podocytes of Diabetic Nephropathy Rats by Regulating Autophagy

Zhixia Lang, Yuichiro Daisuke, Processes and Induces Podocyte Injury in Diabetes Inhibits Normal Endoplasmic Reticulum-Associated Degradation Intraglomerular Cross-Talk Between Mesangial Cells and Podocytes

Background: Diabetic kidney disease (DN) rats exhibited renal pathological damage accompanied by proteinuria. The expression of slit diaphragms proteins (low expression of nephrin, podocin, synaptopodin), VDR (low expression), autopahy-associated proteins (low expression of LC3B, Beclin1, overexpression of P62) were abnormal in DN rats. The number of autophagosomes in podocytes were significantly reduced. The fluorescence of LC3B and synaptopodin proteins were highly overlapping, the fluorescence intensity of both proteins in DN rats were significantly reduced, whereas calcitriol reversed these above changes.

Conclusions: Calcitriol reduces podocyte injury in DN rats by regulating autophagy, thereby reducing proteinuria.

Funding: Government Support - Non-U.S.

Retinal Olfactory Receptor 1393 Contributes to the Development and Progression of Type 1 Diabetes

Alexis R. Schiazza, Elizabeth G. Considine, Blythe D. Shepard. Georgetown University, Washington, DC.

Background: Olfactory receptor 1393 (Olfr1393) is a G-protein coupled receptor with vital functionality outside of its native environment of the nose. Recently, we determined that this receptor is expressed in the renal proximal tubule where it aids in glucose reabsorption via the sodium-glucose co-transporters (SGLTs). We also found that Olfr1393 is linked to the progression of type II diabetes in a diet-induced obesity mouse model. As SGLt inhibitors have emerged as a novel therapeutic option for type 1 diabetes (T1D), we sought to extrapolate the role of renal Olfr1393 in the context of this metabolic disorder.

Methods: To induce T1D in whole-animal Olfr1393 wildtype (WT) and knockout (KO) mice, low dose injections of Streptozotocin (STZ; 55 mg/kg BW) or vehicle control were administered for 5 consecutive days to deplete pancreatic β-cells and induce insulin deficiency in both male and female mice. Progression of diabetes was tracked with vital functionality outside of its native environment of the nose. Recently, we determined that this receptor is expressed in the renal proximal tubule where it aids in glucose reabsorption via the sodium-glucose co-transporters (SGLTs). We also found that Olfr1393 is linked to the progression of type II diabetes in a diet-induced obesity mouse model. As SGLt inhibitors have emerged as a novel therapeutic option for type 1 diabetes (T1D), we sought to extrapolate the role of renal Olfr1393 in the context of this metabolic disorder.

Methods: To induce T1D in whole-animal Olfr1393 wildtype (WT) and knockout (KO) mice, low dose injections of Streptozotocin (STZ; 55 mg/kg BW) or vehicle control were administered for 5 consecutive days to deplete pancreatic β-cells and induce insulin deficiency in both male and female mice. Progression of diabetes was tracked by measuring 2 hour fasting blood glucose and glucose tolerance via intraperitoneal glucose tolerance tests at 2, 5, and 12 weeks post-STZ injections. Glomerular filtration rate was determined using transdermal measurement of FITC-Sinistrin and urinalysis was performed by dipstick.

Results: STZ administration induced phenotypes of hyperglycemia and impaired glucose tolerance in male, but not female, Olfr1393 WT mice. Notably, these diabetic phenotypes were significantly attenuated in the Olfr1393 KO males by 2 weeks post-STZ injection and the differences became more pronounced after 5 weeks. This improvement was accompanied with a reduction in proteinuria, glycosuria, and hemoglobinuria. No significant differences were detected in insulin sensitivity between diabetic WT and KO mice. One hallmark of T1D is the development of glomerular hyperfiltration; notably, neither diabetic WT nor KO mice presented with hyperfiltration 12 weeks post-STZ.

Conclusions: Collectively, this study indicates that diabetic phenotypes are attenuated in Olfr1393 KO mice suggesting that Olfr1393-mediated glucose handling is important for the progression of T1D. Efforts are currently underway to determine the expression and activity of the renal SGLTs in the setting of T1D to elucidate the mechanism by which Olfr1393 contributes to the diabetic phenotype.

Funding: NIDDK Support
FR-PO212
A Novel All-Trans Retinoic Acid Therapy Directly Suppresses Bone Morphogenetic Protein 4 in Mouse Diabetic Nephropathy
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Background: Diabetic nephropathy (DN) causes mesangial matrix expansion, resulting in glomerulosclerosis and renal failure. Collagen IV (COL4), a major component of the mesangial matrix, is positively regulated by bone morphogenetic protein 4 (BMP4), a suppressor of mothers against decapentaplegic (Smad1) signaling. Treatment with all-trans retinoic acid (ATRA), a potent ligand of the retinoic acid receptor (RAR), shows a beneficial effect on kidney disease; however, its effects on glomerular matrix expansion in DN remain unclear. RAR/retinoid X receptor (RXR) heterodimer binds directly with retinoic acid (RA) response element (RARE) and regulates transcription of various genes. In the present study, we investigated the therapeutic potential of retinoids in DN, focusing on the regulatory mechanism of BMP4.

Methods: Diabetes was induced with streptozotocin in 12-week-old male Crl:CD1(ICR) mice. One month later, we initiated intraperitoneal injection of ATRA (15 µg/gBW) or corn oil three times a week, from 16 to 24 weeks of age. ATRA or specific agonists for each subtype of RAR were added to cultured mouse mesangial cells from 1 nm to 1 µM with or without advanced glycation end products (AGE, 200 µg/ml) for 24 hours. We analyzed glomerular matrix expansion, BMP4/M自驾/COL4 axis, RAR/RXR binding capacity, and putative RAREs.

Results: Glomerular matrix expansion, associated with increased BMP4, phosphorylated Smad1, and COL4 expression, worsened in diabetic mice at 24 weeks of age. ATRA administration alleviated DN and downregulated BMP4, phospho-Smad1, and COL4. In cultured mouse mesangial cells, treatment with ATRA or a retinoic acid receptor α (RARα) agonist significantly decreased BMP4 and COL4 expression, more so than other RAR subtypes. Genomic analysis suggested two putative RAREs for the mouse Bmp4 gene. ChIP analysis and reporter assays indicated a putative RARE of RARα and RXR in animals’ kidney and in cultured cells, and the luminescence signal decreased after ATRA or RARα agonists administration.

Conclusions: ATRA suppressed BMP4 via binding of RARα/RXR heterodimer to a unique RARE, alleviating glomerular matrix expansion in diabetic mice. These findings provide a novel regulatory mechanism for treatment of DN.

Funding: Government Support - Non-U.S.

FR-PO213
A New Perspective on the Pathogenesis of Diabetic Nephropathy: Changes in Thyroid Hormone Signaling Trigger Diabetes-Induced Podocyte Pathology
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Background: In diabetic patients, hypothyroidism – both clinical and subclinical – is the most common diabetes-associated disorder, while thyroid dysfunction and low T3 levels are strongly associated with worse renal clinical outcomes and increased mortality. Based on these data, we investigated the role of thyroid hormone (TH) signaling changes in diabetic nephropathy (DN).

Methods: ZSF1 rats were used as in vivo model of DN and human immortalized podocytes exposed to high glucose or H2O, as in vitro model of diabetic stress. Rat systemic parameters were evaluated at different time-points. Immunohistochemical and western blot analysis were performed on rat renal tissue and human podocytes. Patient biopsies were analyzed using immunohistochemical assays.

Results: In ZSF1 rats, plasma T3 levels decreased during DN, and this was inversely correlated with metabolic and renal disease worsening, and glomerular histological changes. We observed the re-expression of the fetal TH receptor (TR) isoform TRβ1 in podocytes and parietal cells of diabetic rats and patients with DN, and increased glomerular expression of the TH-inactivating enzyme deiodinase 3 (DIO3). In ZSF1 rats, TRβ1-positive cells also re-expressed fetal, mesenchymal and damage-related podocyte markers, such as Pax2, Six2, GDF11, desmin, R-spondin, and GMFI. Podocyte degeneration and glomerular and podocyte hypertrophy were evident. In vitro studies showed that podocytes that were exposed to components typical of the diabetic milieu exhibited a significant increase in TRα1 and DIO3 expression, as well as cytokesoklen rearrangements, adult podocyte marker downregulation, and fetal kidney marker up-regulation, in addition to maladaptive cell cycle induction/arrest and TRα1-ERK/1-mediated hypertrophy. Strikingly, Tg administration significantly decreased TRβ1 and DIO3 expression and reversed the above changes.

Conclusions: Our data show that diabetic stress induces the TH-TRβ1 axis to adopt a fetal ligand/receptor relationship pattern that plays a key role in DN-associated podocyte pathology, and create a new perspective on the pathogenesis of DN, suggesting that TRβ1 could be a new pharmacological target.

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FR-PO214
Salvianolate Ameliorates Oxidative Stress and Podocyte Injury Through Modulation of AMPK/NOX4 Axis in db/db Mice
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Background: Changes in podocyte morphology and function are associated with albuminuria and progression of diabetic nephropathy (DN). NADPH oxidase 4 (NOX4) is the main source of reactive oxygen species (ROS) in the kidney and NOX4 is upregulated in podocytes in response to high glucose.

Methods: In the present study, the effects of Salvianolate on DN and its underlying mechanisms were investigated in diabetic db/db mice and human podocytes.

Results: We confirmed that Salvianolate injection administration exhibited similar beneficial preventive results with the NOX1/NOX4 inhibitor, as reflected by attenuated albuminuria, reduced podocyte loss and mesangial matrix accumulation. We further observed that Salvianolate exerted its renoprotective role via reducing high-glucose induced NOX4-based NADPH oxidase activity, podocyte apoptosis and restoring podocyte differentiation marker (sympotopin) expression in the isolated glomeruli of db/db mice. In human podocyte, NOX4 was expressed in the mitochondrial compartment and Salvianolate treatment blocked NOX4-derived mitochondrial superoxide generation and activated AMPK kinase expression, thereby ameliorating podocyte apoptosis. Therefore, Salvianolate possesses the renoprotective capabilities in part through AMPK-mediated control of NOX4 expression, confirmed by AMPK inhibitor (Compound C).

Conclusions: Taken together, our results identify that Salvianolate could prevent glucose-induced oxidative podocyte injury through modulation of AMPK/NOX4 axis in DN and have a novel therapeutic potential for DN.

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FR-PO215
Diabetic Milieu-Induced Mitochondrial Oxidative Damage and Loss of Mitochondrial Proteostasis in Glomerular Endothelial Cells
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Background: Oxidative stress and mitochondrial dysfunction are considered central mediators in the pathogenesis of diabetic complications including diabetic kidney disease (DKD). Our recent studies have demonstrated that mitochondrial stress and dysfunction in glomerular endothelial cells precede and mediate in part albuminuria, podocyte defects and depletion, and glomerulosclerosis in DKD susceptible DBA/2J mice. We hypothesize that DKD-susceptibility is characterized by glomerular endothelial mitochondrial stress-dependent endothelial dysfunction and secretion of crosstalk factors required for podocyte injury and depletion. Aim: To examine mitochondrial oxidative stress and quality control mechanisms in glomerular endothelial cells exposed to a diabetic milieu and assess the impact of endothelial cell dysfunction on podocytes in co-culture.

Methods: We treated murine glomerular endothelial cells (mGECs) with high glucose media (HG) and 2.5% v/v of sera from non-diabetic control (CS) and diabetic (DS) DBA/2J mice. We measured mitochondrial function (oxygen consumption), fragmentation (mitotracker), mitochondrial ROS (mROS; mitoxOx), accumulation of oxidized products (DNA lesion frequency, γH2AX, 8-oxoG, 3-Nitrotyrosine), mitochondrial unfolded protein response (UPR*), endothelial function (NOS activity) and cell death (Annexin/PI). Results: Treatment of mGECs with HG or DS resulted in increased mROS, oxidative mtDNA damage, mitochondrial fission and reduced mitochondrial function compared to controls, this in turn impaired the synthesis of electron transport chain components. mROS specific scavenger (mitotEMPO) prevented these changes. Chronic exposure of mGECs to the diabetic milieu (up to 72h) resulted in accumulation of oxidized products due to inadequate clearance and loss of mitochondrial proteostasis, leading to cellular dysfunction. Co-incubation of podocytes with conditioned media from stressed mGECs resulted podocytes cell death.

Conclusions: Our results demonstrate that the diabetic environment can mediate GEC dysfunction by triggering mitochondria stress. Furthermore the inability to restore mitophagy and mitochondrial function and proteostasis, suggests a maladaptive response under chronic exposure to diabetic milieu and in turn the secretion of pro-apoptotic factors affecting podocytes in co-cultures.

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FR-PO216
Placental Growth Factor Deficiency Aggravates Diabetic Nephropathy
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Background: Placental growth factor (PIGF) is a member of the vascular endothelial growth factor (VEGF) family, PIGF exerts favorable angiogenic and lymphangiogenic activity by binding to VEGF-R1 and -R3. Due to its functional synergy with VEGF-A, it is regarded for a correct novoascularization during pathological conditions while inactivation of PIGF contributes to decreased angiogenesis. Because reduced angiogenesis and lymphangiogenesis that contribute to defective lipid drainage are implicated in the
progression diabetic kidney disease (DKD), we investigated the role of PI3K in the development of DKD by using PI3K knock-out mice.

**Methods:** Diabetes was induced by a low-dose streptozotocin injection in 9-week-old male C57BL/6J (WT) and C57BL/6J (WT-N) mice. Additionally, mice were divided into the following groups: Ad-Mfn2 adenovirus to establish diabetes model. After 8 weeks, mice were sacrificed and collected peripheral blood for detecting cytokine, adiponectin, and nitric oxide production. In this study, Mfn2 specifically inhibited the progression of DKD by regulating the expression of Mfn2 regulating ABCG1-mediated cholesterol efflux in glomerular endothelial cells of diabetic kidney disease.

**Results:** In vivo experiments, cholesterol content increased significantly and mitochondrial respiratory dysfunction was observed. Mitochondrial dysfunction is implicated in the inflammatory process. The oxidative phosphorylation (OXPHOS) of kidney mitochondria complex I (C1) and II (CII) decreased significantly in experimental group (P < 0.05). In vitro experiments, the mitochondrial function regulated by Mfn2. The expression of ABCG1 was reduced and cholesterol efflux was blocked by specific inhibitors of PPAR-γ and PPAR-β were used to rule out the involvement of PPAR-γ and PPAR-β.

**Discussion:** Mfn2 expression in kidney mitochondria plays an important role in the development of ABCG1 dysfunction. In diabetic kidney disease, overexpression of Mfn2 could relieve the renal damage caused by cholesterol accumulation, which increased the expression of ABCG1 depending on PPAR-γ/PPAR-β.

**FR-PO217**

Endothelial Nitric Oxide and the Podocyte Nfat2/He paranase Axis in Diabetic Nephropathy

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**Background:** A reduction in endothelial nitric oxide synthase (eNOS) activity serves as a key driver in the development and progression of diabetic nephropathy (DN), which has been achieved in global eNOS knock-out (eNOSKO) mice for a decade. However, eNOSKO mice have several inherent problems including a tendency to develop progressive renal disease regardless of diabetic status. Diabetic eNOSKO mice exhibit advanced podocyte injury, but the detailed mechanism is unknown. The calcineurin-nuclear factor of activated T cells (NFAT) signaling pathway has been reported to cause podocyte injury.

**Methods:** To determine the precise role of eNOS in DN, we created floxed eNOS mice. We conditionally deleted endothelial cell-specific eNOS expression (E-NOSKO) after the onset of diabetes at 6-week-old male C57BL/6J (WT) mice to more closely represent the clinical course of human DN. Streptozotocin was used to generate diabetes. Tamoxifen was used to conditionally knock out endothelial cell-specific eNOS expression. To evaluate the role of Nfat2 in podocyte injury, hi diabetic eNOSKO mice, Podocin-Cre Nfat2 floxied eNOSKO mice were also generated. A cyclin-dependent kinase 4-transformed podocyte line was treated with an NO donor in high glucose conditions.

**Results:** Diabetic E-NOSKO mice showed significantly reduced podocytes, progressive glomerular lesion changes. We evaluated Nfat isoforms and found that Nfat2 was upregulated in advanced DN patients and diabetic eNOSKO mice. Nfat2 activation in cultured podocytes was upregulated by high glucose and suppressed by NO donor treatment in a dose-dependent manner. Heparanase (HPSE), the only enzyme that can cleave heparan sulfate proteoglycan (HSPG) in podocytes.

**Conclusions:** Our findings indicate that eNOS has a crucial role in the regulation of HPSE in podocytes through Nfat2 activation, which suppresses proteinuria in advanced DN.

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**FR-PO218**

The Mechanism of Min2 Regulating A B C G1-Mediated Cholesterol Efflux in Glomerular Endothelial Cells of Diabetic Kidney Disease

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**Background:** Diabetic kidney disease (DKD) is one of the most common microvascular complications of diabetes mellitus. Increasing evidence has shown that renal lipotoxicity plays an important role in the pathogenesis of DKD. The AT-binding cassette transporter (ABC) G1 mediates intracellular cholesterol efflux. It has been found that overexpression of mitochondrial fusion protein 2 (Min2) in macrophages promotes ABCG1-mediated cholesterol efflux. In this study, Min2 regulating ABCG1-mediated cholesterol efflux in glomerular endothelial cells of diabetic kidney disease.

**Methods:** Glomerular endothelial cell specific knockout ABCG1 (ABCG1-GEC KO) mice were generated using CRISPR-Cas9 technology. Min2 null mice were generated by the conditional knockout of Min2 regulating ABCG1-mediated cholesterol efflux in glomerular endothelial cell of diabetic kidney disease.

**Results:** In vivo experiments, cholesterol content increased significantly and mitochondrial respiratory dysfunction was observed. Mitochondrial dysfunction is implicated in the inflammatory process. The oxidative phosphorylation (OXPHOS) of kidney mitochondria complex I (C1) and II (CII) decreased significantly in experimental group (P < 0.05). In vitro experiments, the mitochondrial function regulated by Min2. The expression of ABCG1 was reduced and cholesterol efflux was blocked by specific inhibitors of PPAR-γ and PPAR-β were used to rule out the involvement of PPAR-γ and PPAR-β.

**Discussion:** Mfn2 expression in kidney mitochondria plays an important role in the development of ABCG1 dysfunction. In diabetic kidney disease, overexpression of Mfn2 could relieve the renal damage caused by cholesterol accumulation, which increased the expression of ABCG1 depending on PPAR-γ/PPAR-β.

**FR-PO219**

The Relative Roles of Nox4 vs. Nox5 in Diabetic Kidney Disease

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**Background:** Renal oxidative stress plays a crucial role in diabetic kidney disease (DKD). Many recent studies have identified that Nox5 should be a main culprit in the context of human DKD. Nox5 is present in humans and rabbits but not in mice or rats. We examined the role of Nox4 vs. Nox5 in human DKD, in human renal cells as well as in rabbit and Nox5 transgenic (Tg) mouse model of DKD.

**Methods:** Expression of Nox4 was examined in human kidney biopsies. In vitro, Nox4 and Nox5 was silenced in human renal cells and were exposed to high glucose. In vivo, we have exposed the rabbits to high fat feeding (HF) as well as inducing insulin deficient diabetes using alloxan. We have generated a Nox5 knockout rabbit and a unique humomized Nox5 Tg mouse with concomitant Nox4 deletion.

**Results:** Expression of Nox5 was increased in kidney biopsies obtained from diabetic individuals. Nox5 shows the highest upregulation in response to high glucose in comparison to other Nox isoforms. Silencing of Nox5 reduces ROS formation and expression of proinflammatory and profibrotic cytokines and growth factors as well as putative elements that are implicated in DKD. Moreover, Nox5 is upstream of Nox4 and that Nox5 inhibition also downregulates Nox4, but not vice versa. HF and alloxan induced diabetic rabbits showed increased renal Nox5 expression in association with increased mesangial area and ECM accumulation along with upregulation of CTGF, fibronectin and MCP-1 as well as enhanced ROS production in the kidney. Expression of Nox5 in mesangial cells of Nox4KO diabetic mice demonstrated 30% increase in albuminuria, mesangial expansion, increased renal injury and inflammation via enhanced ROS production.

**Conclusions:** These findings suggest that Nox5 determines severe progression of diabetic kidney injury in diabetes and provide proof of principle for the development of a new renoprotective agent in diabetes.

**FR-PO220**

YAP Activation in Renal Proximal Tubule Epithelial Cells Contributes to Development of Tubulointerstitial Fibrosis in Diabetic Nephropathy

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**Background:** Excessive production of CTGF in kidney has been implicated in the development and progression of DN. YAP (Yes-associated protein) is a transcription factor involved in multiple critical transcription factors. The goal of these studies is to determine the potential role and underlying mechanisms of YAP activation in renal proximal tubule epithelial cells (RPTC) during DN development and progression.

**Methods:** YAP activation in RPTC was evaluated in deidentified diabetic patient and control kidneys, type I and II diabetic mouse kidneys and cultured human renal proximal tubule epithelial cells (hRPTC). Unilateral nephrectomized (UNX) inducible RPTC specific YAP deletion (YapΔ185) and wild type (YapWT) mice, FVB/NJ or eNOS−/− mice were subjected to streptozotocin injections to induce type I diabetes. The diabetic mice were treated with or without verteporfin (a YAP-TEAD association inhibitor). V2-7632 (a Rho association kinase (ROCK) inhibitor). Mouse urinary albumin excretion and tubulointerstitial fibrosis were evaluated. Expressions of YAP, CTGF, and profibrotic or fibrotic proteins in RPTC were analyzed. hRPTC was exposed to 25mM glucose treated with or without verteporfin or Y2-7632, or YAP, RhoA GTPase siRNA followed by analysis of YAP activation.

**Results:** YAP expression and nuclear translocation were upregulated in the RPTC of kidneys from diabetic patients and type I and II diabetic mice, or in the hRPTC exposed to 25M glucose treated with or without verteporfin specific YAP deletion, or treatment of the diabetic eNOS−/− or FVB/NJ mice with verteporfin or V2-7632.
inhibited CTGF and c-SMA expression in diabetic renal cortical tissues and attenuated tubulointerstitial collagen deposition. Proximal tubules from glomerulonephritis model Y-27632 treated mice but not in Yap-/- mice. Y-27632 treatment also decreased Yap activity in diabetic RPTC. In HRPCT, inhibition of Yap activation blocked CTGF and inhibition of RhoA GTPase attenuated Yap and CTGF expression in response to high glucose.

Conclusions: RhoA GTPase-dependent Yap activation and subsequent increases in CTGF and ECM production mediated myofibroblast transition may be potential underlying mechanisms for diabetic tubulointerstitial fibrosis and targeting YAP activation may serve as a therapeutic intervention in diabetic nephropathy.

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FR-PO221
Identification of Gene Signatures and Molecular Pathways Associated with Urine Albumin Creatinine Ratio Response to Renal Protective Drugs
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Background: Renal protective drugs reduce the risk of progression and urine albumin/creatinine ratio (UACR) in some but not all patients with type 2 diabetes and CKD. Previous studies showed that the response in each individual is consistent to different drugs. Here we aim to identify gene signatures and molecular pathways that are associated with the individual response to renal protective drugs.

Methods: ResinA, N-Acetyl-D-Glucosamine (GnAc) nxs mice were treated with the angiotensin-converting enzyme inhibitor Lisinopril, the angiotensin receptor blocker Losartan, the Janus-associated kinase inhibitor Ruxolitinib, the sodium glucose transporter 2 inhibitor Canagliflozin or vehicle control for 2 weeks (n=8 per group). ACR was measured at baseline and after treatment. RNAseq profiling of kidney cortex was performed. Weighted gene co-expression network analysis and machine learning approaches were used to identify genes associated with UACR, ingenuity pathway analysis was used to identify enriched molecular pathways.

Results: The fraction of mice that responded to treatment, defined as >35% decline in UACR varied depending on the drug, with all mice responding to Lisinopril, 5/8 to Losartan, 4/8 to Ruxolitinib, and none to Canagliflozin. Network analysis identified 35 co-expression modules, several of which were distinctly associated with phenotype variables. Selection of 12 of the most abundant cross-validated elastic lasso regression model was able to predict responders with 83% accuracy (40/48). The cross-validated model was compared to results from 1000 random permutations of its class labels, and found to be significant (p<0.001). Enriched signaling pathways include genes involved in tight junction-, mTOR- and sirtuin signaling, as well as in nicotine degradation.

Conclusions: Our study identified gene signatures and molecular pathways associated with UACR response to renoprotective treatments, as well as pathways previously reported to be associated with human kidney disease progression. Results may increase our understanding of the molecular mechanisms underlying responses to drugs that help stratify patients to predict their response to treatment. Our findings will be clinical trial data sets.

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FR-PO222
Divergent Changes in Kidney Extracellular Matrix Stiffness in Different Mouse Models of Diabetic Nephropathy
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Background: The mechanical properties of the extracellular matrix (ECM) are important in regulating cell and tissue function, and changes in ECM stiffness contribute to a number of pathological conditions. Diabetes is characterized by dramatic changes in the structure of the kidney ECM. Glomerular and tubular basement membrane thickening and expansion of the mesangial matrix are hallmarks of diabetic nephropathy. It is not clear how structural alterations in the ECM translate into changes in the biophysical properties of the ECM in diabetic kidney disease. The goal of this work was to evaluate the stiffness of tubular basement membranes and glomerular ECM in multiple models of diabetic nephropathy of varying severity.

Methods: Tubules and glomeruli were isolated from db/db and eNOS-/- db/db mice. Tubules were cultured in monolayer to tense tissue using a mechanical characterization method. Stress-strain response for tubular basement membrane was evaluated by measuring the force required to stretch the tubules a given length. Hyperelastic materials theory was used to model the tubular stress-strain response. Glomeruli were decellularized and subjected to compression testing to evaluate the compressive modulus of the glomerular ECM. A high deformation Hertzian contact test was used to determine glomerular stiffness.

Results: Biomechanical testing showed that tubular basement membrane stiffness was increased in the db/db mouse at 16 weeks of age. At this time point, there was no evidence of tubulointerstitial fibrosis, but there were initial signs of renal functional declines based on increased urine albumin to creatinine ratio. In the eNOS-/- db/db mice, there was histologically evident glomerular sclerosis at 18 weeks of age. Glomerular ECM stiffness was significantly increased in a subset of glomeruli from these mice. The amount of stiffness may be related to the degree of glomerular expression.

Conclusions: These data suggest that there are divergent changes in the stiffness of the kidney ECM in different animal models of diabetic nephropathy. These differences may be related to differences in the severity and/or progression of the disease in these different models. The pathophysiological consequences of these progression dependent changes in ECM stiffness will be the focus of future investigation.

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FR-PO223
Renoprotective Effects of Canagliflozin in CREDENCE May Be Independent of Glucose-Lowering Mechanisms
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Background: In the CREDENCE study, the SGLT2 inhibitor canagliflozin (CANA) improved renal and CV outcomes in patients with type 2 diabetes and CKD. Whether effects on CV and renal outcomes are explained by glucose lowering and how baseline kidney function modifies the glycaemic effects of CANA are not completely understood.

Methods: Analyses were performed in the 4401 patients randomized to CANA (N=2292) or placebo (N=2199). ANCOVA was used to analyze differences in HbA1c at end of treatment. Cox models stratified by screening eGFR (HRs of 0.75, 0.52 and 0.82 for eGFR >45, 45–60, and 60–90 ml/min/1.73m2, respectively; P-interaction=0.11). Risk reduction with CANA vs PBO after adjusting for running mean HbA1c was modestly associated with the primary outcome (HR per 1% change 1.13, 95% CI 1.06-1.21, P<0.001).

Conclusions: In patients with type 2 diabetes and CKD enrolled in CREDENCE, renoprotective benefits of CANA appear to be independent of HbA1c reduction and may be linked to non-glycemic pathways of CANA.

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FR-PO224
Renal Efficacy and Safety of Canagliflozin by Baseline Medication Use: Results from the CANVAS Program
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Background: Canagliflozin is thought to confer renoprotection partly by enhancing natriuresis and intravascular volume status. We sought to assess the renal efficacy and safety of canagliflozin in patients using other medications that also alter sodium excretion or volume status.

Methods: The CANVAS Program randomized participants with type 2 diabetes at high cardiovascular risk to canagliflozin or placebo. Other treatments, including the use of renin-angiotensin system (RAS) blockade, loop and non-loop diuretics were managed by treating physicians. Hazards ratios (HR) and 95% confidence intervals (CI) were estimated with Cox regression models, with selected medication by baseline treatment interaction terms added to test for heterogeneity. The primary renal composite outcome was sustained 40% reduction in eGFR, end-stage kidney disease or renal death.

Results: Of 10,142 participants in the CANVAS Program, 8116 (80%) were receiving RAS blockade, 1308 (13%) received loop diuretics, and 3182 (31.4%) received non-loop diuretics at baseline. In canagliflozin on the primary renal composite outcome (HR 0.60, 95% CI 0.47-0.77) was consistent irrespective of baseline use of RAS blockade or diuretics (all P-heterogeneity<0.10; Figure). There was no evidence that the risk of renal-related serious adverse events was elevated by background use of medications that influence natriuresis or volume status, although few of these events occurred (Figure).

Conclusions: Canagliflozin appears to reduce the risk of progression of kidney disease in patients with type 2 diabetes, irrespective of use of some medications that also affect natriuresis or volume status, without additional renal safety-related concerns.

Funding: Commercial Support - Janssen Research & Development, LLC.

FR-PO225
Remission of Tubulointerstitial Nephropathy and Its Correlation to the Reduction of Albuminuria by SGLT2 Inhibitor in Patients with Advanced Stages of Diabetic Kidney Disease
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Background: The aim of this study is to examine the clinical advantages of SGLT2 inhibitor predominantly focusing on the amelioration of tubulo-interstitial nephropathy (TIN) through the prospective clinical study.

Methods: Patients with diabetic kidney disease were enrolled, and the patients were received 50 mg of Iplagliflozin. Their blood and urine were sampled at 0 M as baseline, 1 M and 12 M for measurement of parameters including urine Liver Fatty Acid Binding Protein (L-FABP), urine N-acetyl β-D-glucosaminidase (NAG), urine monocyte chemottractant protein-1 (MCP-1), urine type IV collagen (T4C), 8-hydroxy-2- deoxyguanosine (8OHG) in addition to the regular biochemical parameters.

Results: All enrolled patients (n=25, 57.6 ± mean age) showed no significant change in their blood pressure and body mass index during the observation period. Their eGFR was not changed either (57.7±21.3 at 0 M, 56.5±21.9 at 1 M, 58.0±24.4 mL/min at 12 M). Urine albumin of Iplagliflozin. Their blood and urine were sampled at 0 M as baseline, 1 M and 12 M (median: 298.3 at 0 M, 136.0 at 1 M, 141.5 mg/gCr at 12 M). The reduction of ACR was even significant in xx patients who showed GFR<60 mL/min (median: 298.3 at 0 M vs 1 M, 58.0±24.4 mL/min at 12 M, p<0.002). We also examined the correlation between baseline ACR and other parameters by single regression analysis, indicating that TIN-related parameters showed weak correlation (LFAFP: R2=0.242, p=0.032, MCP-1: R2=0.252, p=0.029) but T4C and eGFR did not. When the patients were divided into two groups based on the ACR reduction compared to SGLT2 inhibitor by the median value of percent-reduction rate of ACR at 1 M, parameters related to TIN showed significant difference among the two groups (LFAFP median: 6.58 vs 3.07 µg/gCr, NAG index median: 9.63 vs 7.19 µg/gCr, MCP-1 median: 2.42 vs 1.77 µg/gCr) whereas T4C and eGFR were not different.

Conclusion: SGLT2 inhibitor significantly reduced the albuminuria even in patients with advanced renal damage. In these subjects, the reduction of ACR might be highly involved in the severity and restoring of TIN than glomerular damages.

FR-PO226
Acute Changes in Estimated Glomerular Filtration Rate and Related Factors and Subsequent Renal Function in Type 2 Diabetes Mellitus After Initiating Luseoglifozin
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Background: Acute fall in estimated glomerular filtration rate (eGFR), typical finding after initiating sodium glucose transporter 2 (SGLT2) inhibitors link to maintaining renal function among patients with diabetes mellitus. However, the relationship between magnitude of acute fall in eGFR and course of eGFR thereafter are not known.

Methods: A pooled analysis of four 52-week Phase III trials of luseoglifozin 2.5 mg daily (or up to 5 mg daily) in Japanese patients (N=941) with type 2 diabetes mellitus stratified according to the tertile of magnitude of acute changes in eGFR during 2 weeks after initiating it was conducted.

Results: The mean for age, HbA1c, estimated glomerular filtration rate, and urinary albumin were: 65±13 years, 7.8%, and 64.9±17.9mL/mnin/1.73m2, 62.7±29.6µg/gCr respectively. Acute changes in eGFR were widely varied among the patients with type 2 diabetes mellitus (mean:–2.1; min: –35.5; max: 27.6). Course of eGFR after 2 weeks of initiating luseoglifozin were rather recovered or maintained regardless of acute changes in eGFR. The patients with greater acute decline in eGFR, who were characterized by higher eGFR and body mass index, higher prevalence of using diuretics and lower uric acid, showed rapid recovery and maintenance of eGFR thereafter. Multivariate regression analysis revealed that higher body mass index, higher eGFR and use of diuretics were associated with greater acute decline in eGFR.

Conclusions: Although acute changes in eGFR widely varied among the type 2 diabetes mellitus with preserved renal function, the course of eGFR thereafter was maintained regardless of the degree of acute changes in eGFR. State of basal glomerular filtration rate and interaction of diuretics may relate to acute changes in eGFR after initiating SGLT2 inhibitor.

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FR-PO227
Short-Term Changes in Albuminuria and Risk of Cardiovascular Outcomes in Type 2 Diabetes: A Post Hoc Analysis of the EMPA-REG OUTCOME Trial
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Background: Previous studies, primarily with RAAS inhibitors, have demonstrated that a reduction in albuminuria (UACR) during the first months of treatment is associated with improved long-term cardiovascular (CV) outcomes. Whether an early reduction in UACR with SGLT2 inhibition is also a positive indicator of long-term CV benefit is uncertain. Herein, we therefore assessed the association between changes in UACR over the first 12 weeks of treatment with empagliflozin or placebo and subsequent long-term CV risk in a post-hoc analysis from the EMPA-REG OUTCOME trial.

Methods: We calculated UACR change as the percentage difference from baseline to week 12 in 6820 participants who did not experience a CV outcome during the first 12 weeks of treatment with empagliflozin or placebo and subsequent long-term CV risk in a post-hoc analysis from the EMPA-REG OUTCOME trial.

Results: Empagliflozin compared to placebo reduced UACR by 18% (95%CI 14-22%), and increased the likelihood of a ≥30% reduction in UACR at week 12 compared to placebo (odds ratio 1.42 [95%CI 1.27-1.58]). Over a median follow-up of 3.0 years, 704 (10%) in the primary CV and 440 (6.5%) CVD/HIF outcomes were observed. Each 30% reduction in UACR during the first 12 weeks was independently associated with an average 5% lower hazard for the MACE outcome (HR 0.95; 95%CI 0.91–0.98, p=0.002), and 8% lower hazard for the CVD/HIF outcome (HR 0.92; 95%CI 0.88–0.96, p<0.001). Results were consistent in subgroups by baseline characteristics or medication use, or empagliflozin/placebo treatment assignment.

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FR-PO228

Change in Albuminuria and Renal Risk: A Post Hoc Analysis of the EMPA-REG OUTCOME Trial

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Background: Previous studies have shown that an early reduction in albuminuria (UACR) during RAAS inhibition is associated with improved renal outcomes. Empagliflozin is a SGLT2 inhibitor that decreases UACR. We assessed the association between an early reduction in UACR during treatment with empagliflozin or placebo and long-term renal risk in a post-hoc analysis from the EMPA-REG OUTCOME trial.

Methods: We calculated UACR change as the percentage difference from baseline to week 12 in 6820 participants who did not experience a renal outcome after adjustment for treatment assignment, laboratory measurements and medication use.

Results: Empagliflozin, compared to placebo, reduced UACR by 18% (95%CI 14-22%) and increased the likelihood of a ≥30% reduction in UACR at week 12 (odds ratio 1.42 [95%CI 1.27-1.58]). Across a median follow-up of 2.9 years, 188 renal endpoints were observed. Each 30% reduction in UACR from baseline to week 12 was associated with an average 18% lower hazard for the renal outcome (HR 0.82 [95%CI 0.76-0.88]). The adjusted HR for each 30% reduction in UACR in patients with normo-, micro-, or macroalbuminuria at baseline was 0.87 (95%CI 0.78-0.98), 0.82 (95%CI 0.69-0.97) and 0.65 (95%CI 0.54-0.79), respectively (p for interaction 0.24). The association between change in UACR and renal outcomes was consistent in various subgroups and similar in the placebo and empagliflozin groups (Figure).

Conclusions: An early reduction in albuminuria was more common with empagliflozin and was independently associated with a reduced renal risk in patients with type 2 diabetes and cardiovascular disease.

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FR-PO229

Early Dip in Estimated Glomerular Filtration Rate (eGFR) on the Efficacy of Ertugliflozin at Week 26

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Background: In light of positive results from CREDiTEN and previous cardiovascular outcome trials, sodium-glucose cotransporter 2 (SGLT2) inhibitors are frequently compared with renin-angiotensin-aldosterone system blockers, since some members of both drug classes reduce cardiorenal risk. The aim of this post-hoc analysis was to assess possible modulatory effects of the early eGFR dip observed with empagliflozin on measures of treatment efficacy including changes in glycated hemoglobin (AIC), systolic blood pressure (SBP) and body weight (BW).

Methods: Data were pooled from three placebo-controlled studies of ertugliflozin 5 mg and 15 mg in adults with type 2 diabetes mellitus (N=1544). Patients were analyzed by quartiles (Q) of percent reduction in eGFR at Week 6 for changes from baseline in AIC, SBP and BW at Week 26. Pearson correlation was used to measure the strength of the linear relationship between the percent change in eGFR from baseline to Week 6 and changes in those endpoints.

Results: Patients in quartiles with the greatest eGFR decrease (Q1 and Q2) at Week 6 showed similar reductions in AIC at Week 26 compared with patients undergoing only small changes in eGFR (Q3) at Week 6 (Figure). Among patients with an increase in eGFR (Q4), those in the ertugliflozin 15 mg group, but not ertugliflozin 5 mg group, showed a greater reduction in AIC at Week 26 compared with other quartiles. Changes in SBP and BW were similar across all quartiles. A weak correlation (r=−0.138) between the change in eGFR at Week 6 and change in AIC at Week 26 was found in ertugliflozin 15 mg group.

Conclusions: Ertugliflozin causes an early decrease in eGFR but its degree has no meaningful impact on reductions in AIC, SBP or BW at Week 26. Ertugliflozin 15 mg may augment AIC reduction in patients with an eGFR rise during early treatment.

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FR-PO230

Effects of Blood Pressure After Sodium-Glucose Cotransporter 2 Inhibitor Treatment on Renal Composite Outcomes in Japanese Type 2 Diabetes Patients with CKD

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Background: Previous large clinical trials using sodium–glucose cotransporter 2 inhibitors (SGLT2is) demonstrated improved renal outcomes in patients with type 2 diabetes mellitus (T2DM). Pleiotropic effects are considered important, but the mechanisms involved are not fully understood. The aim of this study is to clarify the mechanism by which the blood pressure (BP) after SGLT2i treatment influences renal composite outcomes in Japanese T2DM patients with chronic kidney disease (CKD).

Method: We retrospectively assessed 626 Japanese T2DM patients with CKD who underwent SGLT2i treatment for over 1 year. The renal composite endpoint was the progression of albuminuria stage or a decrease in the estimated glomerular filtration rate (eGFR) by ≥15% per year. For comparative analyses, we included patients comprising

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those with >92 mmHg in mean arterial pressure (MAP) after SGLT2 treatment and those with <92 mmHg in MAP and used propensity score matching methods to address the imbalances in age, sex, body weight, hemoglobin Alc, eGFR, and uric acid–albumin-creatinine ratio (ACR) at baseline. The propensity score matching used an algorithm involving a 1:1 ratio of the nearest neighbor match with a ±0.025 caliper and no replacement.

Results: The standardized differences in the backgrounds for propensity-matched patients were calculated to be <0.1. Comparisons between the 210 propensity-matched patients in each group were performed. The incidence of renal composite outcomes was occurred in 42 cases and there was significantly lower in patients with >92 mmHg in MAP after SGLT2 treatment than in those with <92 mmHg in MAP (6.2% [n=13] and 16.0% [n=29], respectively, p=0.009 by chi-square test). The estimated hazard ratio for the renal composite outcomes, determined using a Cox proportional hazards model, was 1.36 (95% confidence interval, 1.01 to 1.82, p=0.042) in patients with >92 mmHg in MAP. There was no significant difference in the logarithmic value of ACR between the two groups.

Conclusions: The BP after SGLT2 treatment influenced renal composite outcomes in Japanese T2DM patients with CKD. These results reaffirmed the importance of BP management in T2DM patients with CKD, even during SGLT2 treatment.

FR-PO231

Pretreatment Extracellular Volume Expansion Predicts Body Fluid Response to SGLT2 Inhibitors in Diabetic Kidney Disease
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Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are an antihyperglycemic drug with diuretic action. We recently reported that SGLT2 inhibitor dapagliflozin ameliorates extracellular volume expansion with a mild increase in urine volume (Nephrology 2018). However, the predictors of fluid response to SGLT2 inhibitors remain unclear.

Methods: Thirty diabetic kidney disease (DKD) patients were treated with dapagliflozin (5mg/day). Body fluid volume including intracellular water (ICW), extracellular water (ECW) and total body water (TBW) was measured on days 0 and 7 using a bioimpedance analysis (BIA) device (InBody S10). Patients were divided into low and high responders by the median value of change in the ECW/TBW for 1 week, which is a marker of extracellular volume expansion. Baseline clinical parameters were compared between the low and high responders.

Results: The body weight significantly decreased (68.0±2.8 vs. 63.0±2.3 kg, p<0.001), but the estimated glomerular filtration rate (eGFR) was not significantly changed (29.2±2.7 vs. 26.1±2.3 mL/min/1.73 m2, p=0.143) after 1 week. BIA showed that the median value of the change in the ECW/TBW for 1 week was -1.2% (0.41±6.00% vs. 0.14±3.12%, p=0.054). The ECW (low responders 17.0±1.2 vs. low responders 14.2±1.2 L, p=0.056), the TBW (39.8±2.6 vs. 38.4±2.6 L, p=0.003), the ECW/TBW (0.426±0.011 vs. 0.406±0.001, p=0.002) and serum brain natriuretic peptide (318±55 vs. 92±50 pg/mL, p<0.003) in the high responders were higher than in the low responders. The eGFR (24.5±8.2 vs. 33.3±3.6 mL/min/1.73 m2, p=0.046) and serum albumin level (2.9±0.2 vs. 3.4±0.2 g/dL, p=0.075) in the high responders were lower than in the low responders. Significant partial correlations adjusted for the eGFR were observed between the baseline ECW/TBW and changes in the ECW/TBW (-0.466, p=0.009) and the TBW (-0.528, p<0.027).

Conclusions: Extracellular volume expansion predicts body fluid response to SGLT2 inhibitor dapagliflozin in DKD patients. This result suggests that SGLT2 inhibitor may change its diuretic action depending on the pretreatment extracellular volume status.

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FR-PO232

How Does Canagliflozin Confer Renoprotection? Results From a Mediation Analysis of the CANVAS Program
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Background: CANA reduces kidney failure and CV events in people with type 2 diabetes who have chronic kidney disease. Given the international scope of the CANVASCREDENCE study, we assessed the efficacy of CANA according to self-reported race and ethnicity. 2 diabetes who have chronic kidney disease. Given the international scope of the CANVASCREDENCE study, we assessed the efficacy of CANA according to self-reported race and ethnicity.

Methods: 4401 participants with eGFR 30–90 mL/min/1.73 m2 and urinary albumin-to-creatinine ratio ≥300-5000 mg/g were randomized to CANA 100mg daily or matching placebo. Outcomes were analyzed in predefined analyses by race and ethnicity, and results are reported without adjustment for multiplicity.

Results: The cohort enrolled were racially and ethnically diverse (n=2931 [67%] White, n=224 [5%] Black or African American, n=877 [20%] Asian, n=369 [8%] Other and results are reported without adjustment for multiplicity. According to Race and Ethnicity: A CREDENCE Secondary Analysis

Conclusions: CANA reduces kidney failure and CV events in people with type 2 diabetes who have chronic kidney disease. Given the international scope of the CANVASCREDENCE study, we assessed the efficacy of CANA according to self-reported race and ethnicity. 2 diabetes who have chronic kidney disease. Given the international scope of the CANVASCREDENCE study, we assessed the efficacy of CANA according to self-reported race and ethnicity.

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FR-PO233

Renal and Cardiovascular (CV) Outcomes of Canagliflozin (CANA) According to Race and Ethnicity: A CREDENCE Secondary Analysis
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Results: The cohort enrolled were racially and ethnically diverse (n=2931 [67%] White, n=224 [5%] Black or African American, n=877 [20%] Asian, n=369 [8%] Other and results are reported without adjustment for multiplicity. According to Race and Ethnicity: A CREDENCE Secondary Analysis

Conclusions: CANA reduces kidney failure and CV events in people with type 2 diabetes who have chronic kidney disease. Given the international scope of the CANVASCREDENCE study, we assessed the efficacy of CANA according to self-reported race and ethnicity. 2 diabetes who have chronic kidney disease. Given the international scope of the CANVASCREDENCE study, we assessed the efficacy of CANA according to self-reported race and ethnicity.

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FR-PO234
Elevation of Hematocrit and Decrease in Hemoglobin A1c After the Administration of SGLT-2 Inhibitors Have Different Relation with Parameters Reflecting Diuretic Effect
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Background: Recently, sodium-glucose cotransporter 2 (SGLT-2) inhibitors were indicated to have hematopoietic effect, but it is still unclear whether the effect is independent from its anti-diabetic effect. In this study, we investigated changes in hematocrit and parameters reflecting diuretic change according to HbA1c reaction after administration of SGLT-2 inhibitors in patients with type 2 diabetes.

Methods: A total of 96 patients (male: n=59, age: 54.7±11.8 [mean±SD] years, BMI: 29.6±4.4 kg/m², HbA1c: 8.7±1.4 %) with type 2 diabetes who were newly administered SGLT-2 inhibitors from July 2014 to January 2018 were retrospectively identified. The patients were divided into two groups according to HbA1c change (responded [ΔHbA1c>−0.5 %] patients; group A: n=52 [male: n=32], age: 53±9.12 years, BMI: 29.9±4.5 kg/m²; non-responded [ΔHbA1c<0.5 %] patients; group B: n=44 [male: n=27], age: 55.5±11.5 years, BMI: 29.3±4.5 kg/m², HbA1c: 7.9±1.2 %). Changes in HbA1c, hematocrit, urine specific gravity, blood urea nitrogen, serum creatinine and plasma osmolality levels before and 30 days after the administration of the drugs were evaluated. Plasma osmolality was calculated by the formula (2×[Na⁺+K⁺])/2+[K⁺]/2+[Cl⁻]/2+[glucose]/18).

Results: HbA1c was significantly decreased in only group A (group A: -1.03±0.42 %, p<0.001, group B: -0.07%, p=0.035) whereas both groups showed significantly increased hematocrit (group A: 1.8±0.2 %, p=0.007, group B: 2.0±0.8 %, p=0.035) and urine specific gravity (0.008±0.009 m/l; p<0.001, 0.01±0.011; p=0.001). Blood urea nitrogen (0.86±3.32 mg/dL; p<0.01, 1.28±3.99; p=0.23), plasma creatinine (0.04±0.08 mg/dL, p=0.35, 0.04±0.08; p=0.41), plasma osmolality (1.11±3.2 mOsm/L; p=0.26, -1.16±1.66; p=0.12) and BMI (-0.61±0.48 kg/m²; p=0.26, -0.51±0.51; p=0.58) did not change in both groups. Group A showed negative correlation between changes in BMI and plasma osmolality (r=−0.28, p<0.04), whereas group B did not (r=−0.14, p=0.36).

Conclusions: Our data suggest that the elevation of hematocrit and decrease in HbA1c after the administration of SGLT-2 inhibitors have different relation with parameters reflecting diuretic effect.

FR-PO235
The Study on the Transition of Renal Function of SGLT2 Inhibitors for Type 2 Diabetes with Moderate to Severe Renal Impairment
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Background: From the results of recent large-scale clinical trials, it has been clarified that SGLT2 inhibitors (SGLT2is) have protective effects on renal function independent of blood glucose. However, the renoprotective effect of SGLT2i in type 2 diabetes (T2DM) patients with advanced renal dysfunction less than eGFR 30 ml/min/1.73m² has not been studied. The aim of study is to investigate the effect of SGLT2i on renal function in patients with moderate to severe renal insufficiency, retrospectively.

Methods: We included Japanese T2DM patients less than eGFR 45 ml/min/1.73m², whose SGLT2 administration was commenced for more than one year since October 2011 in Saitama medical center. We compared changes eGFR from 6 months before administration of SGLT2i to the start of administration, and from initiation of administration of SGLT2i to 6, 12 months after administration, and last month of administration (when SGLT2i is discontinued, just before discontinuation). We also examined safety.

Results: The subjects were 36 cases (12 cases were less than eGFR 30 ml/min/1.73m²), and eGFR at the start of SGLT2i administration was 33.3±12.2 ml/min/1.73m². The patients were received either iraglaflizin, canagliflozin, empagliflozin, luseogliflozin, tofogliflozin or dapagliflozin. The monthly change in eGFR from 6 months before to the initiation of SGLT2i administration, and from the initiation to 6, 12 months after administration, and to last change (27±13 months) were -0.7±1.3, 0.6±1.2, -0.5±1.6, and -0.0±0.4 ml/min/1.73m²/month, respectively. The decrease in eGFR was significantly suppressed after SGLT2i administration (p <0.05, respectively). During the period, renal replacement therapy (RRT) was initiated only in 3 cases. Assuming that RRT is started when eGFR 6-8 ml/min/1.73m² remains unchanged from changes in eGFR before SGLT2i administration, it is predicted that 27 (75%) of the 36 cases could avoid RRT induction during the observation period. On the other hand, no adverse events related to SGLT2i other than RRT were observed during the period.

Conclusions: The administration of SGLT2i to T2DM with moderate to severe renal impairment can strongly and safely suppress the decline of eGFR, and can lead to enormous medical economic benefits by extending dialysis induction.

FR-PO236
The Effect of Oral Carnosine Supplementation on Urinary TGF-Beta in Diabetic Nephropathy: A Randomized Controlled Trial
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Background: Activation of TGF-beta pathway is a significant contributor to the pathogenesis of diabetic nephropathy. Carnosine is an amino acid that can inhibit TGF-beta synthesis. We tested the hypothesis that carnosine supplement added to a standard therapy will result in a reduction in urinary TGF-beta levels in patients with diabetic nephropathy.

Methods: We randomly assigned 40 patients with diabetic nephropathy and albuminuria 30-299 mg/day to treatment with carnosine (2 g/day) or placebo for 12 weeks. Urinary TGF-beta level by a solid phase specific sandwich enzyme-linked immunosorbent assay (ELISA), urine albumin by immunonephrometric assay, renal function and metabolic profiles were determined at baseline and during 12 weeks of active treatment. Primary outcome was the change in the level of urinary levels of TGF-beta.

Results: The two groups were comparable for baseline characteristics, blood pressure, urine albumin, urine TGF-beta and renal function measurements. Urinary TGF-beta significantly decreased with carnosine supplement (−17.8% of the baseline values), whereas it tended to increase with placebo (+16.9% of the baseline values) (between-group difference P <0.05). Whereas, blood urea nitrogen, serum creatinine, serum electrolytes and other biochemical parameters did not change during the study period including urinary albuminuria. The both groups were well tolerated with no serious side-effects.

Conclusions: These data indicate an additional renoprotective effect of oral supplementation with carnosine for decreasing urinary TGF-beta level that is marker of renal injury in diabetic nephropathy.

Funding: Government Support - Non-U.S.

FR-PO237
Dapagliflozin Stabilizes the Tubulointerstitial Fibrosis Marker Urinary Dickkopf-3
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Background: Urinary Dickkopf-3 (DKK3) is a stress-induced tubular epithelia-derived profibrotic glycoprotein that induces tubulointerstitial fibrosis through its action on the canonical Wnt/β-catenin signaling pathway. A previous study showed that DKK3 concentrations are higher in patients with CKD than in the general population, and that a
rise in urinary DKK3 was associated with significant eGFR decline. Prior experimental and clinical studies have suggested that SGLT-2 inhibition may reduce renal fibrosis. We therefore assessed the effect of the SGLT-2 inhibitor dapagliflozin on urinary DKK3.

Methods: 24hr urine samples were used from a double-blind, randomized, placebo controlled crossover trial in 31 patients with type 2 diabetes and albumin:creatinine ratio (UACR) >100 mg/g or blood pressure. The dose of an ACE inhibitor or angiotensin receptor blocker.

Patients were assigned to 6-week treatment periods with dapagliflozin 10 mg/day or placebo in random order. Urinary DKK3 was measured by ELISA at the start and end of each 6-week treatment period. A mixed effects repeated measures model was used to assess the effect of dapagliflozin on urinary DKK3.

Results: Dapagliflozin decreased UACR by 43.9% (95% CI: 30.3 to 54.8) and eGFR by 5.1 (2.0 to 8.1) mL/min/1.73m² compared to placebo. At baseline, urinary DKK3 concentration was 574.8 [1st, 3rd quartile: 304.3, 1223.7] ng/24hr. After 6 weeks placebo treatment, urinary DKK3 levels increased by 41.7% (95% CI: 2.2 to 96.4) (p=0.0373), whereas they remained stable after dapagliflozin treatment (1.2% (-29.3 to 38.2), p=0.9421). Accordingly, dapagliflozin lowered DKK3 compared to placebo by 30.3% (2.0 to 50.3), p=0.0384. After dapagliflozin, change in urinary DKK3 was significantly correlated with change in UACR (r=0.41, p=0.039). No correlations with changes in other clinical markers (HbA1c, eGFR, SBP, Hb, Hct) were observed.

Conclusions: Dapagliflozin stabilized urinary DKK3 after 6 weeks of treatment in patients with type 2 diabetes and increased albuminuria, while an increase was observed during placebo treatment, suggesting that dapagliflozin may lessen tubular stress and fibrosis. Future studies of longer treatment duration and clinical outcomes are needed to confirm the clinical impact of these findings.

**FR-PO238**

Effects of the SGLT2 Inhibitor Dapagliflozin on Plasma Volume in Patients with Type 2 Diabetes and Various eGFR Levels

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Background: Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce the rate of renal outcomes and heart failure events in patients with type 2 diabetes and chronic kidney disease (CKD) as a result of volume contraction. In this study, we evaluated the effects of dapagliflozin on estimated and measured plasma volume and we investigate whether kidney function and other relevant characteristics modify effects of dapagliflozin on estimated plasma volume.

Methods: The Strauss formula was used to calculate changes in estimated plasma volume (ePv). Change in plasma volume measured with 121-Human serum albumin (mPv) was compared with change in ePv in a study of patients with type 2 diabetes randomized to dapagliflozin 10 mg/day or placebo. Subsequently, changes in ePv were measured in a pooled database of 13 phase 2/3 placebo controlled clinical trials involving 4533 patients with type 2 diabetes randomized to dapagliflozin 10 mg/day or placebo.

Results: Median change in ePv was similar to median change in mPv (-9.4 and -9.0 %) during dapagliflozin treatment. In the pooled analysis, dapagliflozin compared to placebo decreased ePv by 9.6 % (95% CI: 9.0 to 10.2%) after 24 weeks. This effect was consistent in various eGFR-groups (ePv changes of -9.5, -9.7 and -9.5 in eGFR subgroups <60, 60-90, and ≥90 mL/min/1.73m² [Figure 1]).

Conclusions: Dapagliflozin consistently decreased estimated plasma volume compared to placebo in a broad population of patients with type 2 diabetes undergoing heart failure benefits observed in patients with type 2 diabetes and chronic kidney disease.

**FR-PO240**

The Hemodynamic Effect of the GLP-1R Agonist Liraglutide in Diabetic Kidney Disease

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Background: The impact of GLP-1R agonists on blood pressure is a resultant of its vasodilatory and natriuretic effect and the increase of heart rate and sympathetic activity. The increased peripheral resistance resulting from the imbalance in factors regulating vascular tone and autonomic nervous system are important pathogenetic factors in the development of hypertension in diabetic kidney disease. The aim of the study was to investigate the hemodynamic effect of a single subcutaneous dose of 1.2 mg liraglutide compared to placebo in patients with type 2 diabetes mellitus and impaired renal function.

Methods: This cross-over study included 17 patients with eGFR below 30 mL/min/1.73 m² and 17 patients with eGFR above 60 mL/min/1.73 m². Blood pressure and heart rate were monitored noninvasively for 24 hours. Before and after each medication, systemic vascular resistance, heart rate variability, pulse wave velocity and central blood pressure were measured with signal morphology impedance cardiography and plethysmography.

Results: Significant increases of both 24h mean heart rate and cardiac output were noted in both groups. In patients with eGFR >60 mL/min/1.73 m² mean 24h heart rate was 73±8 after liraglutide compared with 68±5 beats per minute after placebo (p<0.005), whereas in patients with eGFR <30 mL/min/1.73 m² the respective values were 76±9 and 67±9 beats per minute (p<0.001). The latter group it was additionally accompany by sympathetic predominance after GLP-1R agonist (p=0.005). The systemic vascular resistance was reduced after injection of liraglutide compared with placebo only in the study group with better preserved kidney function (p<0.002), whereas the pulse wave velocity was increased after GLP-1R analogue compared with placebo (p=0.0006), only in patients with eGFR <30 mL/min/1.73 m². Additionally also in this group after liraglutide 24h mean arterial pressure significantly increased from 97.8±1.1 to 102.4±6.6 mmHg compared to placebo (p=0.003).

Conclusions: Liraglutide administration in the patients with advanced CKD may cause a transient increase of systemic blood pressure due to reduced natriuretic effect. The natriuretic effect of liraglutide in diabetic kidney disease depends on increased atrial natriuretic peptide and decreased aldosterone secretion.

Figure 1: Changes from baseline in estimated plasma volume (%) during 24 week treatment with dapagliflozin relative to placebo in various subgroups
FR-PO241
Metformin Discontinuation in Type 2 Diabetes Patients Associated with Higher Risk of Diabetic Nephropathy: Finding from a Retrospective, Propensity Score-Matched, Common Data Model-Based Cohort Study
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Background: Metformin is a first-line drug in patients with type 2 diabetes (T2DM) worldwide. There are several evidences supporting benefits to T2DM patients in cardiovascular and renal outcomes with metformin, however, a long-term use of metformin is occasionally limited owing to risk of lactic acidosis or gastrointestinal side effects. This common data model-based study aimed to compare continuous metformin user with non-metformin user for risk of diabetic nephropathy (DN) in a real-world setting.

Methods: We performed a retrospective, propensity score matched, observational cohort study by using The Observational Medical Outcomes Partnership common data model version 5 (OMOP-CDM v5). We used medical data of 1.82 million patients in a tertiary hospital in South Korea from 2003 to 2017. Study participants were identified by drugs, diagnosis codes and laboratory test values in combination with event time. Among newly diagnosed T2DM patients without DN, more than one year of ongoing metformin treatment were considered as treatment group. Never use of metformin after four months since time of T2DM diagnosis were considered as comparative group. DN defined as onset of spot urine album to creatinine ratio (uACR)>30 mg/g, protein to creatinine ratio (uPCR)>150 mg/g or eGFR<60 ml/min/1.73m2. After 1:1 propensity score matching (PSM), the Cox proportional hazards model was used to analyze hazard ratio (HR) for DN event.

Results: A 2003 of metformin using patients and a 222 of non-metformin using patients were identified. After 1:1 PSM, we matched each of 207 patients in both groups. Mean follow-up duration was 7.2 and 6.5 years, respectively. There were no significant differences of mean age, sex ratio, mean HbA1c, eGFR, uACR and uPCR value between two groups at baseline. Metformin treatment group had lower risk for progression to DN (HR=0.66, 95% CI [0.47-0.93], p=0.018) than comparative group.

Conclusions: Continuous use of metformin in T2DM without DN was associated lower risk for progression of diabetic nephropathy. This longitudinal, real-world setting study provides protective effect of metformin for progression to diabetic nephropathy in T2DM.

FR-PO242
The Effects and Prognosis of Bariatric Surgery on Diabetic Nephropathy and Retinopathy in Obese Patients with Type 2 Diabetes Mellitus
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Background: The prevalence of obesity has increased dramatically during the past 3 decades, resulting in a large number of diabetes mellitus (DM) and its complications, including diabetic nephropathy (DN) and diabetic retinopathy (DR), the two most common microvascular complications. Bariatric surgery has been approved as an effective and potentially useful method to improve hyperglycemia condition in T2DM patients as well as reduce patient’s body weight. However, the association between bariatric surgery and the onset and the progression of DN or DR in obese patients with type 2 diabetes mellitus (T2DM) hasn’t been well studied.

Methods: A total of 127 obese patients diagnosed with T2DM underwent bariatric surgery in Shanghai Jiao Tong University Affiliated Sixth People’s Hospital from Jan. 2013 to Jan. 2018 and prospectively followed up for one year. The inclusion criteria included: (1) patients aged from 18-65 years old, (2) BMI over 28 kg/m2, (3) diagnosis of T2DM, (4) a fasting C-peptide by the oral glucose tolerance test >1 mg/L and a ratio of peak to fasting value >2 ng/mL. Those with type 1 diabetes, latent autoimmune diabetes in adults, established diagnoses of non-diabetic nephropathy, malignancy, debilitating disease, unresolved psychiatric illness, or substance abuse were excluded from the study. Anthropometric and biochemical parameters were assessed at baseline and 1 year after surgery.

Results: In all patients, body mass index (BMI), blood pressure, fasting blood-glucose, HbA1c, uric acid, blood lipid, urine albumin creatinine ratio (UACR) all decreased significantly 1 year after surgery compared with baseline. 77 out of 127 patients (60.6%) had albuminuria at baseline, and the total remission of albuminuria was 57.9%, no patients had new-onset of albuminuria during the follow-up period. Logistic regression analysis showed that obesity, hypertension, glycemia, dyslipidemia and DR were associated with DN, and DR correlated with DN more strongly than other factors (OR=1.904). Preoperative systolic blood pressure and UACR levels, as well as DR could be predictors for DN remission. However, there was no significant difference between baseline and 1 year after intervention in the changes in retinopathy.

Conclusions: Bariatric surgery could be a potential therapy in obese patients with T2DM and might have a protective role in diabetic kidney injury.

FR-PO243
Efficacy and Safety of Low-Dose Metformin for Improving Glycemic Control in Type 2 Diabetic Patients Receiving Maintenance Hemodialysis (HD): An Assessment by Continuous Glucose Monitoring (CGM)
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Background: Studies show that the use of metformin in HD patients may potentially increase the risk of lactic acidosis. The aim of our study was to evaluate the safety and efficacy of metformin with appropriate dose reduction to improve glycemic control in patients with type 2 diabetes (T2D) on HD.

Methods: Subjects were six HD patients in our hospital, with T2D (BMI=29.7±5.9, glycocaolambin: GA=27%), treated with insulin degludec (8-35 units/day) + dulaglutide (0.75mg/week), with obesity and poor glycemic control. After adding low-dose metformin (250-500mg/day) to the medication, serum lactate level and pH of all six patients were monitored once in two weeks. Glycemic control (assessed by CGM) was calculated before and 4 weeks after the initial administration, and the mean amplitude of glycemic excursions (MAGE) was calculated.

Results: As shown in Figure (each color represents the mean glycemic profile of one patient), glycemic control improved by low-dose metformin as MAGE significantly decreased from 128.4±69.1 mg/dL to 83.4±43.3 mg/dL (p<0.05) without episodes of hypoglycemia. Mean GA significantly reduced from 32.0% to 22.6% (p<0.01), whereas there were no significant changes in the serum pH and lactate levels for 3 months.

Conclusions: After a single hemodialysis session, more than 90% of metformin and lactate were cleared, and the acid-base balance corrected. Unlike in pre-HD patients with impaired renal function, in patients on maintenance HD, metformin may potentially be safe and useful in controlling plasma glucose level when the dosage is appropriately reduced.

Funding: Private Foundation Support

Fig. Effects of low-dose metformin on plasma glucose control in HD patients with T2DM

FR-PO244
Metformin Use Is Associated with Asymptomatic Hyperlactatemia in Elderly Diabetic Men with Stage 3 CKD
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Background: Current recommendations allow metformin use in patients with chronic kidney disease stage 3 (CKD3). Whether metformin increases risk of hyperlactatemia in elderly CKD diabetic patients is unknown.

Methods: This was a case-control study including 92 stable CKD stage 3 male veterans attending Albany VAMC outpatient clinics in 2018. Patients were grouped according to presence of diabetes (D) and metformin use (M) into 3 groups: CKD3 and no diabetes (CKD3-D); CKD3 and D with M (CKD3-D+M); and CKD3 and D on metformin (CKD3/D+M -40 pts). Hyperlactatemia was defined as lactic acid (LA)>2mmol/L and lactic acidosis as LA>4mmol/L in association with anion-gap metabolic acidosis. Characteristics associated with hyperlactatemia were evaluated in multivariable logistic regression analyses adjusted for age, race, BMI, eGFR, proteinuria, A1C, liver enzymes, Charlson comorbidity index, number of prescription drugs, and metformin and insulin use.

Results: In the total cohort, mean(SD) for age was 73.4(5.9) yrs and mean(SD) of eGFR was 46.7±8.1 ml/min/1.73m2. For CKD3/D, CKD3/D+M and CKD3/D+M-M groups mean(SD) LA levels were 1.3(0.3), 1.3(0.4) and 2.1(1.0)mmol/L (p=0.001) and eGFR were 43(2.7), 44.3 (8.7) and 50.6(6.1) ml/min/1.73mp/week, respectively. Hyperlactatemia was present in 1(4.2%), 1(3.6%) and 17(42.5%) of CKD3, CKD3/D and CKD3/D+M patients, correspondingly. A single case of asymptomatic lactic acidosis was seen among CKD3/D+M group. Daily metformin dose correlated with LA levels (r=0.35, p=0.027). In multivariable adjusted regression analysis metformin use was significantly associated with hyperlactatemia (Figure 1).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Conclusions: Metformin use in elderly diabetic patients with CKD stage 3 was associated with high incidence of asymptomatic hyperglycemia. Routine monitoring of LA levels may be warranted in diabetic CKD 3 patients treated with metformin.

FR-PO245

A Safety Comparison of Metformin vs. Sulfonylurea Initiation in Patients with Type 2 Diabetes and CKD: A Retrospective Cohort Study

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Background: Metformin is the initial oral antihyperglycemic agent of choice in most patients with type 2 diabetes (T2D). However, in patients with chronic kidney disease (CKD), guidelines often recommend that metformin not be used due to slower clearance and risk of lactic acidosis. Sulfonylureas are a common alternative to metformin but have been associated with hypoglycemia, weight gain and cardiovascular events. We sought to compare the safety of metformin versus sulfonylureas in patients with T2D by CKD stage.

Methods: This retrospective cohort study included adults in Manitoba, Canada with T2D, an incident monotherapy prescription for metformin or a sulfonylurea, and a serum creatinine measurement from April 2006 to March 2017. Patients were stratified by estimated glomerular filtration rate (eGFR) into the following groups: eGFR ≥90, 60-89, 45-59, 30-44 or <30 ml/min/1.73 m². Outcomes included all-cause mortality, cardiovascular events, and major hypoglycemic episodes. Baseline characteristics were used to calculate propensity scores and perform inverse probability of treatment weight analysis and eGFR group was examined as an effect modifier for each outcome.

Results: The cohort consisted of 21,996 individuals (19,990 metformin users and 2,006 sulfonylurea users). Metformin use was associated with a lower risk of all-cause mortality (HR 0.48, 95% CI 0.40-0.58, p<0.001), cardiovascular events (HR 0.67, 95% CI 0.52-0.86, p=0.002), and major hypoglycemic episodes (HR 0.14, 95% CI 0.09-0.20, p<0.001), when compared to sulfonylureas. CKD was a significant effect modifier for all-cause mortality (p<0.002), but not for cardiovascular events or major hypoglycemic episodes.

Conclusions: Sulfonylurea monotherapy is associated with a higher risk of all-cause mortality, major hypoglycemic episodes and cardiovascular events compared to metformin. Although the presence of CKD attenuated the mortality benefit, metformin may be a safer alternative to sulfonylureas in patients with CKD.

FR-PO246

Pleiotropic Effects of Oral Anti-Hyperglycemic Drugs on Renal and Cardiovascular Outcomes: A Meta-Analysis

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Background: Recently, there are a lot of data of novel oral anti-hyperglycemic drugs claiming to slow progression of kidney function decline and decrease cardiovascular events and all-cause mortality. Therefore, we performed the meta-analysis to explore the pleiotropic effects of oral anti-hyperglycemic drugs including sodium-glucose co-transporter-2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptide-4 (DPP-4) inhibitors on renal and cardiovascular outcomes.

Methods: A systematic literature search was performed in PubMed, Embase and Cochrane Central Register of Controlled Trials to identify randomized controlled trials examining the effects of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors on the incidence of new albuminuria, regression of albuminuria, doubling in serum creatinine, renal composite outcomes, renal replacement therapy (RRT), renal death, cardiovascular events and all-cause mortality. We used random effect model to compute the pooled adjusted hazard ratios (HR) for interested outcomes.

Results: Fourteen studies with 95,717 participants were included. SGLT2 inhibitors, GLP-1 receptor agonists, and DPP4 inhibitors provided significantly lower HR of new incidence of albuminuria. SGLT2 inhibitors and DPP4 inhibitors had significantly higher HR of regression of albuminuria. In terms of renal composite for increasing in serum creatinine more than 40%, RRT, and renal death, there were significantly lower HR by SGLT2 inhibitors and GLP-1 receptor agonists. In addition, significantly lower HR of doubling in serum creatinine was noted in SGLT2 inhibitors. Regarding RRT events, HR was lower in SGLT-2 inhibitors. All-cause mortality was significantly reduced by SGLT-2 inhibitors. Finally, SGLT2 inhibitors had significantly lower HR of heart failure events.

Conclusions: SGLT2 inhibitors exhibited nephroprotective effects, in terms of regressing albuminuria, preventing the incidence of new albuminuria, doubling in serum creatinine, RRT events, renal composite outcome, heart failure events, and all-cause mortality. GLP-1 receptor agonists could attenuate the incidence of new albuminuria and renal composite outcomes, while DPP-4 inhibitors could only prevent the incidence of new albuminuria and regress albuminuria.

FR-PO247

Spiroloactone for the Prevention of Microalbuminuria in High-Risk Type 2 Diabetes: Results from the Multicenter Randomized Double-Blind Controlled Trial PRIORITY

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Background: The proteomic prediction and Renin angiotensin aldosterone system inhibition prevention Of early diabetic nephropathy In Type 2 diabetic patients with normal albuminuria trial (PRIORITY) tested if the aldosterone antagonist spironolactone (25 mg daily) could reduce progression to microalbuminuria in patients with type 2 diabetes (T2D) and normal urinary albumin creatinine ratio (UACR) (< 30 mg/g) but at high risk for progression based on a urinary proteomics-based classifier.

Methods: Multicenter randomized double-blind controlled trial. The CKD273 classifier was assessed at baseline in 1775 subjects; 209 (12 %) had elevated risk and were randomized to spironolactone or matching placebo on top of ongoing treatment. Primary endpoint was development of confirmed microalbuminuria (moderate albuminuria) in 2 of 3 first morning urine samples (UACR)>30 mg/g and ≥30 % increase from baseline.

Results: Baseline mean ± SD: Age 63 ± 6.4 years, blood pressure 135 ± 12/79 ± 9 mmHg, eGFR 81 ± 17 ml/min/1.73m², and UACR 9.1 ± 7 mg/g, 88 % on ACEi or ARB. Mean follow up time was 2.5 years from 7 days to 4.3 years. Development of persistent microalbuminuria was seen in 35 (33 %) of placebo and 26 (26 %) spironolactone treated subjects, hazard ratio (HR) 0.81 (95% CI: 0.49-1.34) p=0.41. In total 58 (28 %) did not complete the full follow up period, of which 16 had suspected side effects or safety considerations. Hyperkalemia was seen in 4 vs 13 and gynecomastia in 0 vs 3 subjects on placebo vs spironolactone, respectively, and 28 were excluded due to lack of adherence or lost to follow up. In 151 subjects treated per protocol HR was 0.71 (95 % CI: 0.40 - 1.25) p = 0.23.

Conclusions: Treatment with spironolactone was not able to prevent or delay progression to persistent microalbuminuria in normoalbuminuric subjects with type 2 diabetes and high risk of kidney disease based on urinary proteomics risk score CKD273.

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FR-PO248
Direct Renin-Inhibitors for Preventing the Progression of Diabetic Kidney Disease: A Systematic Review and Meta-Analysis
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Background: Renin-angiotensin-aldosterone system blockade using angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) therapy is incomplete and may lead to compensatory rise in angiotensin precursors, including renin. Addition of direct renin-inhibitors (DRIs) to ACEI/ARB treatment might potentially slow down the progression of diabetic kidney disease (DKD). In this systematic review, we examined the benefits and harms of DRIs in preventing the onset or progression of DKD.

Methods: We searched CENTRAL, MEDLINE, and EMBASE (until Oct 2018) for relevant clinical trials that compared DRIs to placebo or other agents among those with type 1 or type 2 diabetes and kidney disease (defined by presence of UACR > 30 mg/d or urine albumin creatinine ratio (UACR) > 30 mg/g). Two authors independently screened studies for inclusion and extracted data. Following outcomes were included: all-cause and cardiovascular mortality, progression or regression of albuminuria, changes in blood pressure, and adverse events such as hyperkalemia. Treatment effects were summarized as relative risks (RR) or mean difference (MD) and 95% confidence intervals (CI) using random-effects models.

Results: Nine clinical trials (n=10,051) were included. Addition of DRI to ACEI/ARB had no effect on all-cause mortality (2 studies, 9,151 participants; RR 0.93, 95% CI: 0.4-2.19), cardiovascular mortality or change in GFR (2 studies, 638 participants, Mean difference 1.29, 95% CI: -0.44 to 3.92 ml/min/1.73m2) compared to ACEI/ARB use alone. Addition of DRIs to ACEI/ARB was associated with reduced progression to macroalbuminuria (RR 0.82, 95% CI:0.72-0.93) and improvement in regression to microalbuminuria (RR 1.19, 95% CI:1.19-1.29) in one study enrolling 8561 participants. Withdrawal due to adverse events or due to any other reason was similar in both groups. Risk of hyperkalemia was increased by the addition of DRIs to ACEI/ARB therapy (2 studies, 9,153 participants, RR 1.34, 95% CI: 1.26-1.42).

Conclusions: Current evidence demonstrate that the addition of DRIs to ACEI/ARB therapy in patients with DKD doesn’t reduce cardiovascular or all-cause mortality. However, it might impart kidney benefits by reducing albuminuria at the cost of higher risk of hyperkalemia.

FR-PO249
Five-Year Kidney Outcomes of Bariatric Surgery in Adolescents Compared with Adults
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Background: Bariatric surgery improves markers of kidney health in severely obese adult and adolescent patients with type 2 diabetes (T2D), yet it remains unclear whether kidney disease outcomes differ according to age at surgery.

Methods: We examined health effects of Roux-en-Y gastric bypass between adolescents (n=161; enrolled 2006-2012) and adults (n=396; enrolled 2006-2009) participating in two related but distinct studies. Estimated glomerular filtration rate (eGFR) by serum creatinine and cystatin C and urine albumin-to-creatinine ratio (UACR) were compared between cohorts over 5 years after surgery. Elevated UACR (~30mg/g) and hyperfiltration (eGFR ≥ 135 ml/min/1.73m2) were also compared. Analyses were stratified by the presence of pre-operative type 2 diabetes (pre-op T2D).

Results: The pre-op prevalence of elevated UACR was higher in adolescents than adults irrespective of pre-op T2D status. In adolescents with pre-op T2D, elevated UACR decreased from 29% prior to surgery to 6% 1 year after surgery (p=0.0041), whereas elevated UACR did not decrease significantly until year 5 after surgery in adults with pre-op T2D (p=0.0040) (Fig 1). The change in prevalence of UACR was not significantly different over time in adolescents vs. adults without pre-op T2D (p=0.95). Adolescents with pre-op T2D had an increased prevalence of hyperfiltration that remained throughout the study period (p=0.01), whereas hyperfiltration prevalence was similar in all study participants without T2D (p=0.94).

Conclusions: Adolescents with T2D experienced more hyperfiltration and earlier attenuation of elevated UACR after gastric bypass compared to adults and these differences were not observed in adolescents and adults without pre-op T2D.

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FR-PO250
Testosterone Replacement Therapy (TRT) Delays Early Progression of CKD in Diabetes Mellitus (DM2)
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Background: We have previously shown that TRT provides significant survival benefits in hypogonadal men with kidney disease. Faster progression of chronic kidney disease (CKD) in DM2 is well known. Testosterone deficiency is common in both CKD and DM2. Here we examined if TRT slows CKD progression, cardiovascular disease and mortality in patients with DM2.

Methods: Data from a large cohort of veterans diagnosed with low total testosterone were used to determine the effect of TRT on the progression of CKD, cardiovascular diseases and all-cause mortality in patients with DM2. Increase in serum creatinine > 1.5 mg/dl was taken as a measure of progression of CKD. Data were extracted using the Veterans Administration Informatics and Computing Infrastructure (VINCI), and analyzed using SAS. Propensity matching for age, followup time and prior vascular disease was used to adjust groups. Results were compared by means tests, frequency tables, odds ratio and p values (p<0.01).

Results: Of 57,985 patients with testosterone deficiency, 14,496 with DM2 had treatment (DM2, TRT) and 4319 had none (DM2, No_TRT), compared to controls without DM2 (Ctrl, TRT, N=29,036, Ctrl_No_TRT, N=9,332). Baseline DM2 age was higher (58.3 vs 61.6 yr). Followup and creatinine were was similar (Ctrl vs DM2 : 6.0 vs 5.7 yrs; 1.02 vs. 1.06 mg/dl). TRT provided significant reduction in all-cause mortality in both groups, (Odds DM2 0.69, 95% CI 0.65-0.74; Odds Ctrl 0.72, 95% CI 0.69-0.77). TRT reduced the progression of CKD (Odds DM2 0.71, 95% CI 0.67-0.75; Odds Ctrl 0.85, 95% CI 0.81-0.89); TRT reduced CVA (Odds DM2 0.86, 95% CI 0.76-0.98; Odds Ctrl 0.86, 95% CI 0.77-0.94); TRT reduced new MI in both groups (Odds DM2 0.74; Odds Ctrl 0.79). TRT reduced new retinopathy slightly. Prior cardiovascular disease was more common with DM2 (% difference DM2-Ctrl), e.g. CAD (158%), CHF (229%), CVA (89%), HTN (112%), MI (118%), PAD (185%).

Conclusions: TRT is associated with significant reductions in progression of early CKD[AG1], all-cause mortality and new cardiovascular diagnoses in patients with DM2 even while DM2 is associated with increased prior cardiovascular disease.

Funding: Veterans Affairs Support

FR-PO251
The Mechanism of Anti-Albuminuric Effect by Topiroxostat
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Background: In 2018, we demonstrated the anti-albuminuric effect of topiroxostat, a selective xanthine oxidoreductase inhibitor (XORi), in the ETUDE trial (24-week, multicenter, open-label, randomized trial; 1:1, high dose vs low dose) for hypertensive patients with diabetic nephropathy. XORi have been reported to have renoprotective power via reduction of oxidative stress, inflammation, and renin angiotensin system (RAS) activation. Therefore, we investigated reduction in oxidative stress (8OH-dG), inflammation (MCP-1) and RAS activation (angiotensinogen) in urine samples of patients actually administered topiroxostat.

Methods: Urinary levels of 8OH-dG, MCP-1 and angiotensinogen in the samples collected in the ETUDE study were measured. We compared these parameters between high dose and low dose of topiroxostat by analysis of variance (ANOVA) using the treatment group, eGFR, age and gender and the baseline levels as fixed effects. In addition,
in each group of high dose and low dose of tripterygloss, the intra-group comparison was performed by t-test with the changes in the parameters after intervention relative to the baseline values.

**Results:** There was no significant differences in changes in 8OH-dG, MCP-1 and angiotensinogen between the two treatment groups by ANOVA (P = 0.69, 0.59 and 0.50, respectively). In comparison with the baseline values at the end of intervention, 8OH-dG (P = 0.08 high dose, 0.24 low dose) and MCP-1 increased in high dose group (P = 0.02 high dose, 0.51 low dose). The levels of angiotensinogen showed no statistically significant increase as well as decrease (P = 0.48 high dose, 0.72 low dose).

**Conclusions:** Our additional analysis failed to detect any suppressive effect of inflammation, oxidative stress and RAS activation with tripterygloss and could not reach an evidence that led to the mechanism of albuminuria lowering action.

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**FR-PO253**

**Association Between Individual Cholesterol and Albuminuria Response and Exposure to Atorvastatin or Rosuvastatin**

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**Background:** The PLANET trials showed that atorvastatin 80 mg (ATOR) but not rosuvastatin at either 10 or 40 mg (ROSU) reduced urinary protein:creatinine ratio (UPCR) while effects on LDL cholesterol were similar. However, individual changes in both UPCR and LDL cholesterol to these statins varied widely between patients. This interindividual variability could not be explained by patients’ physical or biochemical characteristics. We assessed whether the plasma concentration of the statins were associated with LDL cholesterol and albuminuria response.

**Methods:** the PLANET trials randomized patients with an urine protein:creatinine ratio of 500 – 5000 mg/g, fasting LDL cholesterol ≥2.3 mmol/L and stable treatment with ACE or ARB to a 52 week treatment period with ATOR 80 mg, ROSU 10 mg or 40 mg. For the current analysis patients with available samples at week 52 and treatment compliance >80% by pill count were included (N=295). Main outcome measurements were percentage change in UPCR and absolute change in LDL cholesterol (delta LDL), comparing baseline to week 52.

**Results:** Median (interquartile range) plasma concentration at week 52 for ATOR 80 mg was 0.9 (0.0 – 7.5); for ROSU 10 mg 1.6 (0.8 – 4.4) and for ROSU 40 mg 3.5 (2.0 – 6.8). Higher plasma concentration of statin was associated with larger LDL-cholesterol reductions at week 52 and not with UPCR change nor UACR change (Table). Serum albumin (β = 0.63, p = 0.05) and eGFR per 10 ml/min/1.73m2 (β = -0.09; p = 0.04) were independently associated with ROSU plasma concentration. Active metabolites concentration of either ROSU or ATOR did not correlate with UPCR and UACR changes.

**Conclusions:** Individual variation in plasma concentrations of rosuvastatin and atorvastatin explained the LDL-cholesterol changes of the patients. The individual variation in UPCR change was not explained by the plasma concentration of both statins.

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**FR-PO254**

**Efficacy and Safety of Patiromer by Baseline Serum Potassium Level <6.0 vs. ≥6.0 mEq/L: Pooled Results of Three Studies**

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**Background:** Patiromer (PAT) is a sodium-free non-absorbed potassium (K+) binder that uses calcium as the counter-exchange ion. In this post-hoc analysis, we assessed the efficacy and safety of PAT by baseline serum potassium (K+) levels (bK+).

**Methods:** We analyzed pooled data (patients with starting dose up to 25.2 g/day) through week 4 from 3 trials of PAT (AMETHYST-DN, OPAL-IHK, TOURMALINE). Patients who took ≥1 PAT dose and had ≥1 post-baseline serum K+ measurement (sk+) were included. Patients were stratified according to sk+ ≥6.0 mEq/L and sk+ <6.0 mEq/L, and assessed for sk+ change from baseline at week 4, sk+ over time, and % with any sk+ measurement in target range (3.8–5.0 mEq/L).

**Results:** 623 patients were evaluated; 53 had baseline sk+ ≥6.0 mEq/L and 570 had baseline sk+ <6.0 mEq/L. Mean (SD) baseline eGFR was 33.0 (16.6) and 40.2 (19.2) ml/min/1.73m2 in those with sk+ ≥6.0 and <6.0 mEq/L, respectively. >90% of patients in both groups were taking RAASi. Mean sk+ was reduced to <5.5 mEq/L at Day 3 (48 hours after the first dose) in both subgroups (Figure). 97% of patients with sk+ ≥6.0 mEq/L and 93% with sk+ <6.0 mEq/L achieved any sk+ measurement in the target range through week 4. Mean (95% CI) reductions from baseline at week 4 were -0.67 (0.71, -0.63) and -1.67 (-1.91, -1.43) mEq/L in the sk+ ≥6.0 and sk+ <6.0 mEq/L subgroups, respectively. Adverse events (AEs) were reported in 31% of patients with sk+ <6.0 mEq/L and 43% with sk+ ≥6.0 mEq/L, with PAT-related AEs (most commonly constipation and diarrhea) reported in 13% and 19%, respectively.
Conclusions: Patiromer was effective and well-tolerated in patients with mild/moderate HK and severe HK. Regardless of the severity of HK, treatment with patiromer lowered sK+ to 3.8–5.0 mEq/L in >93% of patients in 4 weeks. A higher rate of constipation occurred in the sK+ ≥6.0 mEq/L subgroup and may be related to the fact that these patients appear to have worse overall health (e.g. lower eGFR).

Funding: Commercial Support - Funded by Relypsy, Inc., a Vifor Pharma Group Company

FR-PO256
Antidiabetic Medication Use in Patients with Type 2 Diabetes and CKD

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Background: Diabetes care and relevant clinical practice guidelines are continuously evolving, yet little is known about how to optimize type 2 diabetes mellitus (T2DM) care in patients with chronic kidney disease (CKD). We therefore sought to describe treatment approaches for glycemic control in patients with T2DM and CKD by examining patterns of newer (GLP-1ra and DPP-4i) and conventional (metformin, SU, TZD, and insulin) antidiabetic medication use in this patient population by using data from 2015.

Methods: We used data from a large claims and integrated database that includes employed and commercially insured patients in the United States (Optum). We selected adult males ≥18 years who had continuous enrollment between January 1, 2014 and January 1, 2015, restricting the cohort to patients who had T2DM and CKD prior to January 1, 2015. We defined medication use according to pharmacy fill information for two newer classes (GLP-1ra and DPP-4i) and four conventional classes of antidiabetic medications (metformin, SU, TZD, and insulin). We stratified our analyses by age, sex, ethnicity, income, geographic region, CKD stage, and prescribing provider specialty. The final cohort consisted of 38,577 patients.

Results: In 2015, metformin was the most common medication prescribed to patients in this cohort (49.2%). Among the newer medications, 3.4% of patients were prescribed GLP-1ra and 12.3% of patients were treated with DPP-4i. Among patients in CKD stage 1-3a, metformin remained the most commonly prescribed medication. The proportion of patients who were prescribed GLP-1ra or DPP-4i continued to increase across the 3 cohorts. Furthermore, the proportion of patients who were prescribed GLP-1ra was highest in patients with CKD stage 1. There were wide variations by sociodemographic factors. Generally, patients who received prescriptions for antidiabetic medications from nephrologists remained low (0.4-1.9%). Among patients who received prescriptions for GLP-1ra, most received their prescriptions from endocrinologists whereas patients treated with other classes of medications had their prescriptions written most frequently by PCPs.

Conclusions: Prescriptions for newer antidiabetic medications with known safety and efficacy have remained low. Prescriptions for medications that are contraindicated in advanced CKD continued to be written. GLP-1ra were favored primarily by endocrinologists.

Funding: NIDDK Support

FR-PO257
Anti-Diabetic Medication Use and Kidney Function in US Adults

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Background: The concordance of diabetes mellitus (DM) and chronic kidney disease (CKD) constitutes a major public health problem. Though notable therapeutic advances have occurred in the last decade, diabetes medication patterns in the U.S. DM-CKD population remain poorly delineated, particularly associations with declining kidney function. Hence, we examined anti-diabetic medication (ADM) use among adult National Health and Nutrition Examination Survey participants (2001 to 2016) with self-reported diabetes or HbA1c ≥ 7.0%.

Methods: Comparisons were based on two thresholds of creatinine-based estimated glomerular filtration rate (eGFR, 60 and 45 ml/min/1.73m2) and one threshold of urinary albumin to creatinine ratio (ACR, 30 mg/g).

Results: Renal function in US adults with DM was distributed as follows: eGFR ≥ 60 and ACR < 30 (a) 60/30–60/10, 60%, a ≥ 60/30–20/10, 45%, 5/30–7.4%, 1.4%. Use of 1 ADM was more prevalent with CKD than without kidney dysfunction (75.5% vs. 75.3%, P = 0.004). Following these same eGFR and ACR categories, use of a 1 ADM was associated with worsening kidney function category (75.3%, 75.4%, 82%, 84.5%, 90.9%, and 86%, P < 0.001), as were sulphonylurea (26.3%, 29.5%, 29.5%, 29.5%, 29.9%, and 29.9%, P = 0.001), metformin analogues (36.7%, 36.7%, 36.7%, 36.7%, 36.7%, and 36.7%, P = 0.001), DPP-4i (23.3%, 23.3%, 23.3%, 23.3%, 23.3%, and 23.3%, P = 0.001), insulin (23.3%, 23.3%, 23.3%, 23.3%, 23.3%, and 23.3%, P = 0.001), and SGLT-2 inhibitor (2.9%, 2.9%, 2.9%, 2.9%, 2.9%, and 2.9%, P = 0.001). Use of a 1 ADM was associated with lower proportions of a 2 ADM (35.3%, 41.5%, 34.0%, 38.9%, 37.9%, and 37.9%, P = 0.003), biguanide (51.8%, 50.7%, 49.0%, 41.3%, 16.4%, and 11.2%, P = 0.001) and 2 ADM (2.9%, 1.8%, 0.9%, 1.3%, 0.1%, and 0.1%, P = 0.044) use. No association was present for thiazolidinedione, dipyridyl peptide-4 inhibitor, alpha-glucosidase inhibitor, GLP-1 receptor agonist and meglitinide use.

Conclusions: One in five in the U.S. DM-CKD population do not use anti-diabetic medications, and medication patterns vary substantially with kidney function.

FR-PO258
Temporal Trends in Pharmacologic Management of Diabetes Mellitus Among Patients with CKD in the United States

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Background: The nexus of diabetes mellitus and chronic kidney disease (DM-CKD) constitutes a major public health problem. Though substantial therapeutic advances have occurred in the last decade, diabetes management patterns in the US DM-CKD population remain poorly delineated. Hence, we examined trends in anti-diabetic medication use among adult National Health and Nutrition Examination Survey participants from years 2001 to 2016.

Methods: Eligible participants had self-reported diabetes or HbA1c ≥ 7.0% and creatinine-based estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m2 or urinary albumin to creatinine ratio (ACR) ≥ 30 mg/g.
Results: Increases were observed in the proportions taking at least 1 anti-diabetic medication (1+ADM, 73.1% in 2001-2004, 79.2% in 2005-2008, 81.8% in 2009-2012 and 81.9% in 2013-2016, P<0.004). A biphasic pattern was observed for 2+ADM (33.6%, 43.7%, 42.0%, 31.9%, P<0.002). Regarding individual classes of ADM, values rose for biguanides (32.8%, 40.0%, 39.5%, 45%, P<0.048), insulin (26.9%, 27.8%, 38.7%, 39.4%, P<0.001) and meglitinitides (0%, 3.5%, 8.8%, 9.1%, P< 0.001), fell for sulphonylureas (35.9%, 38.3%, 37.1%, 23.6%, P< 0.001) and thiazolidinediones (19.2%, 21.1%, 9.8%, 3.6%, P< 0.001); exhibited a rise-and-fall pattern for alpha-glucosidase inhibitors (0.2%, 1.9%, 0.7% and 0.1%, P<0.015) and amylin analogs (0%, 1.9%, 0%, 0%, P<0.005) and remained statistically unchanged for dipeptidyl peptidase-4 inhibitors (6.5%, 6.5%, 4.5%, 3.7%, P=0.333) and SGLT-2 inhibitors (0%, 0.9%, 1.2% and 2.4%, P=0.091).

Conclusions: Thus, anti-diabetic medication use in the US DM-CKD populations has changed considerably between 2001 and 2016.

FR-PO259
Estimating the Effectiveness of Home-Based Kidney Care in Persons with Diabetes Using Propensity Scores
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Background: Home-based kidney care (HBKC) is a pragmatic approach incorporating the healthcare preferences of individuals to address cultural barriers to standard kidney care. We carried out a 12-month randomized clinical trial (RCT) of HBKC in 72 American Indians, identified as having CKD with diabetes.

Methods: Participants were randomized to receive usual care (UC) or HBKC. After initial lifestyle coaching, the HBKC group received frequent additional reinforcement by CHWs about adherence to medicines, diet and exercise, self-monitoring, and coping strategies for living with stress. The primary outcome was the change from baseline to 12-months in the patient activation measure (PAM). Secondary outcomes included BMI, A1C, hsCRP, and KDQOL measures. Outcomes were compared between study groups using linear models with generalized estimating equations to account for household clustering and propensity scores to account for the fact that we did not randomize specifically for those with diabetes.

Results: Accounting for imbalances in group membership at baseline by applying propensity weights, the estimated average change in the difference in PAM scores was 15.6 points higher in HBKC compared to the UC while also adjusting for baseline PAM scores (Figure 1). When PAM score was categorized into PAM levels, we observed that participants in HBKC were 8.4 times more likely to be activated compared to the UC while adjusting for baseline PAM scores. Body mass index declined by 1.2 kg/m2 (P=0.02) and participants in HBKC were 8.4 times more likely to be activated compared to the UC while adjusting for baseline PAM scores. Body mass index declined by 1.2 kg/m2 (P=0.02) and one placebo and one treatment.

Conclusions: HBKC is associated with greater patient activation, a decrease in BMI, and increased prevalence of patients above the various thresholds required to be activated above the various thresholds required to be activated.

Funding: Other U.S. Government Support

FR-PO260
Associations Between Facility Use of an Electronic Patient Care Plan and Foot Check Rates in Dialysis Patients
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Background: Electronic care plans have the potential to streamline the management of patient meetings to create, follow, and optimize patient centric interventions for unstable conditions. A large dialysis organization (LDO) deployed an electronic Plan of Care (ePOC) tool to clinicians to improve and personalize care coordination. We assessed if use of the ePOC tool by facilities was related to improvements in the percentage (%) of patients receiving diabetic foot checks.

Methods: The ePOC application was deployed at an LDO in October of 2017. We analyzed monthly data from dialysis patients that had the ePOC application used by the care team during October of 2017 (baseline) and October 2018. We selected the top 15% of the clinics performing the highest % of diabetic foot checks, and the bottom 15% of clinics performing the lowest % of foot checks. Of those, we selected the top and bottom 33% of the clinics with the highest and lowest use of the ePOC tool, respectively. We compared the difference from baseline in % of patients receiving foot checks between facilities with high and low ePOC usage stratified by high and low achievement of baseline foot checks.

Results: We included data from 2432 dialysis facilities. We selected 400 clinics with care teams who were the highest and lowest users of the ePOC tool. Clinics starting with a low or high % of foot checks that were high ePOC users had greater increases in the % of foot checks after follow-up compared to clinics with low ePOC usage (Figure 1).

Conclusions: Use of the ePOC system in the dialysis setting may be have the potential to lead to improvements in the workflow of care in conducting diabetic foot checks. Further analyses are needed to support these findings as these may be confounded by clinics that are more compliant with internal policies.

Funding: Commercial Support - Fresenius Medical Care North America

FR-PO261
Developing Iron Thresholds to Predict Heart Failure Hospitalization Risk in Veterans with CKD
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Background: Iron deficiency is closely associated with heart failure (HF) risk. The specific thresholds for serum transferrin saturation (Tsat) or ferritin associated with HF are unknown in CKD.

Methods: We developed a historical cohort using the Veterans Affairs Informatics and Computing Infrastructure. We identified Veterans with pre-dialysis CKD (MDRD eGFR ≤60 mL/min/1.73m2) with at least one set of iron indices between 2006-2015. Veterans with ESRD, genetic or chronic disorders affecting iron metabolism, or those who received intravenous iron or erythropoietin stimulating agents within 3 months of the iron indices were excluded. A generalized additive Cox model was applied to the cohort to explore the joint dose-response relationship of the hazard for HF hospitalization following the iron assay. A full 3-D response surface relating the HF covariate-adjusted hazard to both Tsat and ferritin was developed using cubic regression splines.

Results: Of the 1,159,371 Veterans with CKD, 141,477 met the inclusion criteria. The specific thresholds for serum transferrin saturation (Tsat) or ferritin associated with HF are unknown in CKD.

Conclusions: In Veterans with pre-dialysis CKD, increased Tsat is closely associated with both Tsat and ferritin was developed using cubic regression splines.

Funding: Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
**FR-PO262**

**Coronary Artery Calcification but Not Aortic Pulse Wave Velocity Predicts CKD Incidence and Progression**

**Background:** Both aortic arch pulse wave velocity (PWV), a marker of medial arterial stiffness, and coronary artery calcification (CAC), a marker of coronary atherosclerosis, have been shown to be associated with all-cause death, cardiovascular (CV) events, and end-stage renal disease. We investigated whether CAC and PWV predict earlier kidney events, such as incident albuminuria and loss of estimated glomerular filtration rate (eGFR), when interventions targeting these measures may improve long-term outcomes.

**Methods:** We conducted a prospective, community-based cohort study of Dallas Heart Study participants who underwent PWV and CAC measurement. eGFR was calculated using the 4-variable MDRD formula. The primary outcome of composite kidney events after 7 years of follow-up was incident chronic kidney disease (CKD) (albuminuria or eGFR <60 mL/min/1.73 m²) or a decrease in eGFR >2.5 mL/min/1.73 m² per year. Secondary outcomes were CV events (myocardial infarction, stroke, coronary revascularization, and CV death) and death at a median follow-up of 13 years. Associations with composite kidney events and CV events and death were measured using logistic and Cox Proportional Hazards regression, respectively.

**Results:** A total of 2,062 participants had a mean age 45±9.3 years, 56% were female. 47% were African American, 10% had diabetes mellitus, and 7% had CKD at baseline. There were 187 kidney events, 177 CV events, and 165 deaths. Log transformed CAC taken continuously was associated with composite kidney events, aOR (95% CI) 1.16 (1.06, 1.27), CV events, aHR (95% CI) 1.38 (1.27, 1.51), and death, aHR (95% CI) 1.19 (1.10, 1.29) (Figure). CAC ≥100 Agaston units was associated with CV events, aHR (95% CI) 2.21 (1.49, 3.28) and death, aHR (95% CI) 2.30 (1.57, 3.37), but not kidney events. PWV taken continuously or in tertiles was not associated with kidney events, CV events, and death.

**Conclusions:** CAC, but not PWV, was independently associated with CKD incidence and progression, CV events, and death. These results suggest that CAC may be a useful tool to predict clinically meaningful early kidney outcomes in addition to CV events and death.

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**FR-PO263**

**Association of Arterial Stiffness with Kidney Function Among Adults Without CKD**

**Background:** Associations of aortic stiffness with chronic kidney disease (CKD), including albuminuria and low estimated glomerular filtration rate (eGFR) have been reported in CKD patients. However, it is unclear that whether arterial stiffness is associated with an increased risk for kidney dysfunction among persons without CKD, and whether the association differs by sex.

**Methods:** We analyzed data from the national health check-up system in Japan, which enrolled persons who completed assessments of carotid-ankle vascular index (CAVI) and kidney function in 2005 and 2015. CAVI is a measure of arterial stiffness based on stiffness parameter β. We excluded participants who had CKD at baseline, defined as the presence of proteinuria or eGFR <60 mL/min per 1.73 m². The primary outcome was incidence of CKD events. Cox proportional hazards models were used to assess the associations between CAVI measurements, assessed as the highest versus lowest quartile groups (CAVI measurements ≥8.1 versus <8.1), and subsequent CKD events.

**Results:** The mean (standard deviation) age of the 24,297 included participants was 46±13 years and 56% were female. Over a mean follow-up of 3.1 years, 1,435 CKD events occurred. In a multivariable analysis, the highest versus lowest quartile of CAVI measurements was associated with an increased risk for CKD events (hazard ratio [HR], 1.3; 95% confidence interval [CI], 1.1, 1.5) with interaction by sex (p<0.001). Adjusted HR (95% CI) for CVD events was 1.5 (95% CI, 1.2, 1.9) in men and 1.1 (95% CI, 0.95, 1.4) in women for the highest versus lowest quartile of CAVI measurements.

**Conclusions:** CAVI measurements ≥8.1 versus <8.1 was associated with an increased risk for CKD events, and the association was stronger in men than in women. CAVI measurements may help identify persons at higher risk for CKD events.

**Funding:** Private Foundation Support
FR-PO265

Skin Autofluorescence as a Risk Factor for Cardiovascular Events and All-Cause Mortality in Persons with CKD Stage 3

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Background: Tissue advanced glycation end product (AGE) accumulation has been proposed as a marker of cumulative metabolic stress (glycation and oxidation) that can be assessed non-invasively by measurement of skin autofluorescence (SAF). SAF has been identified as an independent risk factor for cardiovascular events (CVE) and all-cause mortality (ACM) in the general population, persons with diabetes or on dialysis but data at earlier stages of CKD are inconclusive. We sought to investigate SAF as a risk factor for CVE and ACM in a prospective study of persons with CKD stage 3.

Methods: Participants with CKD stage 3 were recruited from primary care and assessed at baseline, 1 and 5 years. At each visit, SAF was measured using an AGE reader (DiagnOptics), alongside biochemical and biometric data. Data on subsequent hospital admissions with CVE (fatal and non-fatal myocardial infarction and stroke, transient ischaemic attack, cardiac failure, peripheral vascular event and revascularisation; based on ICD-10 coding) and deaths were obtained from NHS Digital. Cox proportional hazards models were used to investigate determinants of CVE and ACM.

Results: 1,707 participants had measurements of SAF at baseline; mean age 72.9 ± 9.0y, mean eGFR 35.5 ± 11.9ml/min/1.73m2, mean SAF 2.7 ± 2.0 arbitrary units. We observed 319 deaths and 590 CVE during mean 5.1 ± 1.9 years follow-up. After multivariable analysis we identified SAF at baseline as an independent risk factor for CVE (HR 1.13 per standard deviation (SD) increase, 95% CI 1.04 to 1.24, p = 0.006) and ACM (HR 1.17 per SD increase, 95% CI 1.04 to 1.32, p = 0.007). There was no significant change in mean SAF over 5 years but change in SAF over 1 year was independently associated with CVE (HR 1.13 per SD increase, 95% CI 1.03 to 1.23, p = 0.011) and ACM (HR 1.24 per SD increase, 95% CI 1.10 to 1.41, p = 0.001).

Conclusions: We have identified SAF as an independent risk factor for CVE and ACM in persons with early CKD. These findings suggest that SAF measurements are clinically useful to risk stratification of persons with CKD. Further, interventions to reduce AGE accumulation, such as dietary AGE restriction, may reduce cardiovascular risk in CKD but this requires testing in prospective randomised trials.

Funding: Private Foundation Support

FR-PO266

Continuous Ambulatory Blood Pressure Monitoring: A Viable Option in CKD?

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Background: Traditional cuff-based ambulatory blood pressure monitoring (ABPM) is cumbersome and utilises fragments. Continuous ABPM utilizes a simple pulse oximeter and 2-lead electrocardiogram to calculate blood pressure beat to beat from pulse transit time(PTT). While continuous ABPM overcomes the challenges of traditional ABPM, its utilisation is cumbersome and fragments sleep. Continuous ABPM utilizes a simple pulse oximeter (Spacelabs) and PTT-ABPM (Somnomedics). We determined the correlation between 24-hour ABPM and PTT-ABPM in persons with CKD not on dialysis or transplant. Participants underwent simultaneous 24 hour cuff-ABPM and PTT-ABPM. We used McNemar’s test for correlated proportions to assess the degree of concordance between cuff and PTT-ABPM to estimate daily excretion of urea nitrogen, and the Maroni formula to estimate dietary protein intake (DPI). We examined the association of DPI with estimated GFR using mixed effect models and penalized splines, and the association of baseline DPI with all-cause mortality and ESRD.

Results: Patients were 66±11 years old, 97% were men and 37% were African American. The baseline eGFR was 37±20 ml/min/1.73m2, 210 patients died (mortality rate, 95% CI: 113/1000PY, 98-129) and 121 patients developed ESRD (65/1000PY, 57-78) over a median follow-up of 14 years. The prevalence of diabetes and proteinuria was 40% and 14% respectively. Median [IQR] of serum LDL level and eGFR were 103[81,128] mg/dL and 75[60,91] mL/min/1.73m2, respectively. Patients with higher LDL (>100 mg/dL) had an incrementally higher risk of ASCVD hospitalization rate across all CKD stages compared to the reference (LDL 70<100 mg/dL); however, associations attenuated with higher CKD stage. Patients with low LDL (<70 mg/dL) had a higher risk of non-ASCVD hospitalization rate across all CKD stages. Patients with LDL 190 mg/dL also had a higher non-ASCVD hospitalization risk across all CKD stages, except CKD stage 5. Risk of non-ASCVD hospitalization with higher LDL increased between non-CKD to CKD stage 4.

Conclusions: In US veterans, higher LDL level was associated with both higher ASCVD and non-ASCVD hospitalization rate across all CKD stages. The magnitude of association with high LDL for ASCVD events increased across worsening CKD stage, and decreased for non-ASCVD events. Further studies are need to understand why elevated LDL may be associated with higher risk of non-ASCVD events compared to risk of ASCVD events in chronic kidney disease.

Funding: Veterans Affairs Support

FR-PO267

Association of Low-Density Lipoprotein Cholesterol and Atherosclerotic CVD and Non-Atherosclerotic CVD Hospitalization Rate Across CKD Stages in 2 Million US Veterans

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Background: A prior study has demonstrated that risk of myocardial infarction decreased with lower low-density lipoprotein cholesterol (LDL) levels across worsening estimated glomerular filtration rate (eGFR) category. It was postulated that this attenuated risk with progressing chronic kidney disease (CKD) may be attributed to competing risk of non-atherosclerotic cardiovascular disease events (ASCVD).

Methods: We performed a retrospective cohort study of a random sample of 1,969,797 US veterans between 2004 and 2006, associations between LDL and ASCVD and non-ASCVD hospitalizations were estimated using Poisson models adjusted for demographics, comorbid conditions, smoking status, use of statins and non-statins, body mass index and albumin across eGFR category (CKD stages). Results: The cohort consists of 5% female, 14% African American, 19% diabetic, 32% statin-users, and 44% current smokers, with a mean patient age of 64±14 years. The median [IQR] of serum LDL level and eGFR were 103[81,128] mg/dL and 75[60,91] mL/min/1.73m2, respectively. Patients with higher LDL (>100 mg/dL) had an incrementally higher risk of ASCVD hospitalization rate across all CKD stages compared to the reference (LDL 70<100 mg/dL); however, associations attenuated with higher CKD stage. Patients with low LDL (<70 mg/dL) had a higher risk of non-ASCVD hospitalization rate across all CKD stages. Patients with LDL 190 mg/dL also had a higher non-ASCVD hospitalization risk across all CKD stages, except CKD stage 5. Risk of non-ASCVD hospitalization with higher LDL increased between non-CKD to CKD stage 4.

Conclusions: In US veterans, higher LDL level was associated with both higher ASCVD and non-ASCVD hospitalization rate across all CKD stages. The magnitude of association with high LDL for ASCVD events increased across worsening CKD stage, and decreased for non-ASCVD events. Further studies are need to understand why elevated LDL may be associated with higher risk of non-ASCVD events compared to risk of ASCVD events in chronic kidney disease.

Funding: Veterans Affairs Support

FR-PO268

Dietary Protein Intake and Outcomes in Patients with CKD

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Background: Protein energy wasting is common in patients with CKD, but the trajectory of dietary protein intake (DPI) in patients with worsening CKD and the outcomes associated with DPI in this population are unclear.

Methods: We performed repeated collections of spot urine for the measurement of urine urea nitrogen and creatinine in 605 patients without dialysis dependent CKD followed at a single institution. We used the urine urea nitrogen-to-creatinine ratio to estimate daily excretion of urea nitrogen, and the Maroni formula to estimate dietary protein intake (DPI). We examined the association of DPI with estimated GFR using mixed effect models and penalized splines, and the association of baseline DPI with all-cause mortality and ESRD in multivariable adjusted Cox models with adjustment for demographic characteristics, smoking status, eGFR and comorbidities.

Results: Patients were 66±11 years old, 97% were men and 37% were African American. The baseline eGFR was 37±20 ml/min/1.73m2, 210 patients died (mortality rate, 95% CI: 113/1000PY, 98-129) and 121 patients developed ESRD (65/1000PY, 57-78) over a median follow-up of 14 years. The prevalence of diabetes and proteinuria was 40% and 14% respectively. Median [IQR] of serum LDL level and eGFR were 103[81,128] mg/dL and 75[60,91] mL/min/1.73m2, respectively. Patients with higher LDL (>100 mg/dL) had an incrementally higher risk of non-ASCVD hospitalization rate across all CKD stages. The magnitude of association with high LDL for ASCVD events increased across worsening CKD stage, and decreased for non-ASCVD events. Further studies are need to understand why elevated LDL may be associated with higher risk of non-ASCVD events compared to risk of ASCVD events in chronic kidney disease.

Funding: Veterans Affairs Support
FR-PO269

Insulin Sensitivity and Systemic Inflammation Are Potential Mediators of the Association Between Serum Uromodulin and Arterial Stiffness Among Nondiabetic Patients with CKD

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Background: Patients with chronic kidney disease (CKD) have an elevated risk of premature death due to cardiovascular disease (CVD) beyond what is predicted by traditional CVD risk factors. Serum uromodulin (sUmod) is a potential non-traditional CVD risk factor. The relationship between sUmod and subclinical CVD is not well described. We investigated the relationship between sUmod and aortic pulse wave velocity (PWV).

Methods: Participants included 73 CKD and 116 normal GFR patients who underwent a comprehensive clinical assessment including PWV measurement (via applanation tonometry) and clamp-derived insulin sensitivity index (ISI). Biomarkers included sUmod, creatinine-based eGFR and high sensitivity C-reactive peptide (hsCRP). Sequential linear models with robust standard errors were used to examine the relationship between sUmod and PWV and perform mediation analyses.

Results: Mean age was 55 (15) years; 45% were female, 34% African American. sUmod had a significant positive correlation with eGFR (r = 0.65; p < 0.01) and log ISI (r = 0.27, p < 0.01) and inverse correlations with log hsCRP (r = -0.27, p < 0.01) and PWV (r = -0.46, p < 0.01). A one interquartile range lower sUmod was associated with a 1.45 m/s increase (95% CI: 1.02, 1.89; p < 0.01) in PWV in the unadjusted model. Additional adjustment for log hsCRP and log ISI further diminished the sUmod effect [0.18 m/s; 95% CI: -0.18, 0.53; p = 0.3].

Conclusions: Declining sUmod levels is associated with increased PWV, a subclinical marker of CVD that reflects arterial stiffness. This relationship appears to be mediated, in part, by systemic inflammation and insulin resistance.

Funding: Veterans Affairs Support

FR-PO270

Ambulatory Blood Pressure Patterns, Cognitive Function, and Frailty in CKD: Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: Hypertension (HTN) is highly prevalent in patients with chronic kidney disease (CKD) as is the risk of cognitive impairment and frailty. Our objective was to determine the association between ambulatory blood pressure (BP) patterns, cognitive impairment and frailty among patients with CKD.

Methods: We performed ambulatory BP monitoring (ABPM) on 1502 participants enrolled in CRIC. We evaluated the following exposures: 1) BP patterns: white-coat, masked, sustained HTN vs. controlled HTN and 2) dipping patterns: reverse, extreme, non-dippers. Our outcomes included: 1) cognitive impairment: modified mini-mental status (MMS) score <85 for participants <65yrs, score <80 for 65-79 yrs and score <75 for >80yrs and 2) frailty: defined as meeting ≥3 of the following criteria - slow gait speed, muscle weakness, low physical activity, exhaustion and unintentional weight loss. Both outcomes were assessed at the time of ABPM and annually thereafter. Logistic regression models were used to assess the cross-sectional relationship between BP patterns or dipping patterns and cognitive impairment and frailty. For longitudinal analysis, Cox discrete models were used.

Results: Mean age of the participants was 63 yrs, 56% were male, and 39% were Black. 9% (n=129) had cognitive impairment and 18% (n=275) were frail at the time of ABPM. After multivariable adjustment, there was no association between any BP or dipping patterns and prevalent cognitive impairment or frailty. 629 participants had incident frailty and 255 had incident cognitive impairment over a median follow up of 3 yrs. After adjustment, participants with white-coat HTN had 0.6 times the risk of incident frailty compared to controlled HTN [95%CI: 0.4, 0.9]. Participants with reverse dipping had marginally greater incident cognitive impairment compared to normal dippers [HR=1.5, 95% CI: 1.2, 2.3].

Conclusions: CKD patients with white-coat HTN have lower rates of incident frailty compared to controlled HTN. There was no consistent association between BP or dipping patterns and incident or prevalent cognitive impairment or prevalent frailty.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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FR-PO272
Vitamin D Replacement Improves Renal Function, Hemodynamics, and Inflammatory and Morphological Parameters in Vitamin D-Deficient Rats After Renal Ischemia-Reperfusion Injury
Ana Carolina de Bragança, Rildo A. Volpin, Daniele Canale, Maria H. Shimizu, Janaina G. Goncalves, Antonio C. Seguro, Michele S. Santos. Faculty of Medicine - University of Sao Paulo, Sao Paulo, Brazil.

Background: The initial damage after an ischemia/reperfusion injury (IRI) plays an important role in the pathogenesis of acute kidney injury (AKI) and predisposition to CKD. Vitamin D deficiency (VDD) is associated with hemodynamic changes, activation of inflammatory pathways and renal disease progression following IRI-AKI. Conversely, vitamin D sufficiency may be considered a protective factor. We evaluated the effect of vitamin D replacement (VR) in IRI rats under VDD.

Methods: We performed bilateral 45 min IRI on day 30 in all groups. Male Wistar rats were randomized into three groups: (1) IRI [fed a standard diet (SD) for 120 days]; (2) VDD+IRI [fed a vitamin D-free diet (D) for 120 days]; and (3) VDD+IRI+R [fed a D diet for 30 days and just after IRI, on day 31, we reintroduced the SD]. We evaluated intra-renal clearance (Cirn); mean arterial pressure (MAP); renal blood flow (RBF); renal vascular resistance (RVR); proteinuria; plasma levels of 25(OH)D and aldosterone as well as renal tissue levels of collagen 3 (COL3) and MCP1 by ELISA; and immunoblot for VDIII.

Results: VDD-IRI-R animals had 25(OH)D levels restored (~42 ng/mL). VR improved renal function and hemodynamic parameters. Also, decreased proteinuria and the amount of MCP1 and COL3 in renal tissue (Table 1).

Conclusions: Our study suggests VR improved the recovery of renal function, hemodynamics, inflammatory and morphological features in IRI-AKI associated with VDD. Thus, vitamin D monitoring and replacement should be considered in renal patients.

Funding: Government Support - Non-U.S.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>IRI</th>
<th>VDD+IRI</th>
<th>VDD+IRI+R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.47±0.02</td>
<td>0.54±0.13</td>
<td>0.57±0.12</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>134±7</td>
<td>134±7</td>
<td>132±5</td>
</tr>
<tr>
<td>RBF (mL/100g/min)</td>
<td>7.9±0.3</td>
<td>6.0±0.35</td>
<td>8.5±0.4</td>
</tr>
<tr>
<td>RVR (mmHg-g/mL/min)</td>
<td>16.0±1.57</td>
<td>22.3±1.38</td>
<td>13.9±0.51</td>
</tr>
<tr>
<td>Aldosterone (ng/L)</td>
<td>212±29</td>
<td>19±0.36</td>
<td>1.7±0.17</td>
</tr>
<tr>
<td>Proteinuria (mg/g)</td>
<td>10.1±0.64</td>
<td>11.9±0.23</td>
<td>9.2±0.10</td>
</tr>
<tr>
<td>VDD (%)</td>
<td>106.8±3.9</td>
<td>56.5±1.5a</td>
<td>148.3±5.4</td>
</tr>
<tr>
<td>COX-2 (ng/g protein)</td>
<td>2.1±0.13</td>
<td>2.8±0.27</td>
<td>1.9±0.06</td>
</tr>
<tr>
<td>MCP1 (ng/g protein)</td>
<td>2.7±0.23</td>
<td>3.7±0.26</td>
<td>2.8±0.15</td>
</tr>
</tbody>
</table>

Data are expressed as means±SEM. BW: Body weight. p<0.001, p<0.05 vs IRI; d p<0.001, c p<0.01, f p<0.05 vs VDD+IRI.

FR-PO273
Association of Body Mass Index and Clinical Outcomes of Advanced CKD in T2DM: A Population-Based Analysis from the National Health Security System
Monarch, Rattanasompattikul,1 Sukit Rakasuk,2 Motlita Promkan,3 Sumana Massoodi,4 Kanyaphak Ngerngita,1 Nuttawut Rongkittachote,4 Aungkura Supokawe4.1 Golden Jubilee Medical Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Nakhon Pathom, Thailand; 2 Medicine Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; 3 Faculty of Medical Technology, Mahidol University, Salaya, Phutthamonthon, Thailand.

Background: The obesity–mortality association has been very robust in patients with end-stage renal disease, but a limited number of studies show conflicting results in patients with non-diabetes-dependent chronic kidney disease (NDD-CKD).

Several earlier studies found that the association of body mass index (BMI) with CKD is not straightforward in patients with type 2 diabetes mellitus (T2DM). The relationship of obesity with CKD has not been fully explored in Asian populations.

Methods: This study evaluated patients aged ≥18 years with T2DM obtained from the largest database of the National Health Security System (NHI) of Thailand from 2011 to 2014. We aimed to determine the apparent optimum BMI range based on the World Health Organization’s (WHO) criteria concerning the risk of advanced CKD (stages G4 and G5). With regard to the 27,392 patients, 62% were female, 3% had CKD stage G4 and 1% had CKD stage G5. The mean (±SD) age of the patients was 64±12 years old. Mean BMI was 24.9±4.5 kg/m². The prevalence of having advanced CKD by BMI groups was BMI (15–20 kg/m²): 6.5%, BMI (20–25 kg/m²): 4.3% (as reference), BMI (25–30 kg/m²): 3.1%, and BMI (≥30 kg/m²): 2.6%. The multivariate analysis identified the odds ratio (OR) of BMI (adjusted OR; 95% confidence interval [CI]), F-value as an independent risk factor for advanced CKD as 1.39; 1.15–1.6; 0.001, 0.8; 0.67–0.94; 0.008, and 0.75; 0.58–0.97; 0.03, respectively (Figure 1).

Conclusions: Patients with advanced CKD in public healthcare practices have strikingly higher rates of low BMI. The negative association of BMI with CKD could reflect reversal causality. This is the first epidemiological paradox that may of concern and be reported in a Southeastern Asian population.

Funding: Government Support - Non-U.S.

Figure 1: The odds ratio (OR) of advanced chronic kidney disease between body mass index groups in Diabetes Mellitus type 2 patients by the three models adjustment.

FR-PO274
Metabolic Acidosis Is an Independent Predictor of Adverse Renal Outcomes and Higher Costs in Patients with CKD
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Background: Metabolic acidosis (MA) is a risk factor for chronic kidney disease (CKD) progression, but less is known about its effect on health care costs and resource utilization. We describe the association between MA, adverse renal outcomes and costs in non-dialysis patients with CKD stages 3-5.

Methods: De-identified medical records (Optum® EMR), 2007–2017 were used to identify non-dialysis CKD patients with ≥2 serum bicarbonate test values 28–365 days apart, ≥3 eGFR values >10 and <60 mL/min/1.73m² and ≥2 years of post-index data or death. Patients were followed for 2 years for the composite outcome (DD40) of death, dialysis, renal transplant, or eGFR decline ≥40%. Metabolic acidosis and normal serum bicarbonate groups were defined by 2 serum bicarbonate values between 12 and <22 mEq/L and 22–29 mEq/L, respectively. General linear regression models in a subset of patients with linked medical claims established predicted costs, which were applied to larger EMR population based on demographic and clinical factors. Logistic and general linear regression models assessed serum bicarbonate as a predictor of DD40 outcomes and costs (log) respectively, controlling for age, sex, race, eGFR, log albumin-to-creatinine ratio, diabetes, hypertension, heart failure, and Charlson comorbidity score.

Results: 51,558 patients qualified for this longitudinal observational study. Compared to patients with normal serum bicarbonate, patients with MA experienced CKD progression at much higher rates, (DD40 rates 48% vs. 17%, p<0.0001) and significantly higher per patient per years cost, ($65,152 vs. $24,681, p<0.0001). This pattern was consistent across all stages of CKD, except stage 5. Serum bicarbonate independently predicted DD40 events and costs; odds ratio of CKD progression (DD40) for each 1 mEq/L increase in serum bicarbonate was 0.87, (CI: 0.866-0.879) parameter estimate -0.076 (p<0.0001) for costs.

Conclusions: In this analysis of ≥51,000 non-dialysis CKD patients followed for two years, patients with metabolic acidosis had higher rates of adverse renal outcomes and higher costs compared to patients with normal serum bicarbonate. Each 1 mEq/L increase in serum bicarbonate was associated with a 13% decrease in 2-year DD40 events and a 7% decrease in monthly costs.

Funding: Commercial Support - Tricida, Inc.

FR-PO275
Association of Total CO2 Levels with Albuminuria Progression in Patients with CKD: Results from the KNOW CKD Cohort
Kipyo Kim, Yongjin Yi, JONG Cheol Jeong, Sejoong Kim, Ho Jun Chin, Ki Young Na, Dong-Wan Chae. Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea.

Background: Metabolic acidosis is a common manifestation of CKD and contributes to various adverse effects. Although previous animal studies demonstrated that dietary acid induces an increase in proteinuria, the association between total CO2 and albuminuria progression have not extensively investigated in clinical studies. We aimed to identify the relationship between total CO2 levels and albuminuria progression in a multicenter prospective cohort.

Methods: A total of 503 patients with at least two urinary albumin-to-creatinine ratios (UACR) measurements 1 year apart and no change in the dose of ACEi/ARB were enrolled. Participants were divided into the quartiles based on the time-averaged total CO2 levels during the 1-year follow-up; Q1: (<24.7 mmol/L), Q2 (24.7–26.6 mmol/L), Q3 (26.7–28.5 mmol/L), and Q4 (>28.6 mmol/L). We examined the albuminuria progression which is defined as A1 (<30 mg/g Cr) to A2 (30–300 mg/g Cr), A2 to A3 (>300mg/g Cr), and A1 to A3 according to the quartiles of total CO2.

Results: At baseline, 159 patients had A1 albuminuria, and 344 patients had A2 albuminuria. After 1 year follow-up, 96 patients revealed albuminuria progression; 26 from A1 to A2, 62 from A2 to A3, and 4 from A1 to A3. The percentage of subjects

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
with albuminuria progression was higher in upper quartiles (P for trends <0.001). In
multivariable logistic regression, the highest quartile of total CO2 was also significantly
less likely associated with albuminuria progression compared with the lowest quartile
(adjusted OR 0.31; 95% CI 0.13-0.77). In addition, multivariable linear regression using
total CO2 as a continuous variable and UA CR fold change also showed significant
negative associations (β=-0.22, P<0.009).

Conclusions: In patients with CKD, total CO2 levels were independently associated
with albuminuria progression over the 1-year interval. These results may suggest that high
total CO2 levels could have beneficial effects on proteinuria progression in CKD patients
even within the normal range of total CO2 levels.

Figure 1. A higher incidence of albuminuria progression is associated with lower quartiles of total CO2 levels in patients
with CKD. Q1<24.67 mEq/L, Q2=24.67-26.67 mEq/L, Q3=26.67-28.05 mEq/L, Q4=28.05 mEq/L.

FR-PO277
Progression of Diabetic Retinopathy and Declining Renal Function in Patients with Type 2 Diabetes
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Background: Diabetes mellitus (DM) causes microvascular complications that are
major causes of morbidity and mortality. Diabetic retinopathy (DR) is an important
microvascular complication and is the most common cause of preventable blindness in
diabetics. Diabetic nephropathy is a leading cause of chronic kidney disease (CKD).
The retina and the kidney share similar microvascular complications resulting from DM.
Although many cross-sectional studies have reported associations between renal function
and prevalent DR, this might be the result of enrolling patients with long disease durations.
Therefore in this study, we investigated how declining renal function affects on DR
progression of patients with type 2 diabetes and whether patients with decreased renal
function need evaluation of DR status.

Methods: We enrolled 1527 patients with type 2 diabetes from the diabetes clinic
in the Department of Endocrinology of Kangnam Sacred Heart Hospital who underwent
fundus photographic examinations for DR and whose renal profiles were studied between
August 2006 and February 2014. The presence of DR was assessed by an expert
ophthalmologist using dilated fundoscopy. Patients were classified into the following
categories: (1) normal: no apparent sign of DR, (2) non-proliferative DR (NPDR); (3)
proliferative DR (PDR) according to the Global Diabetic Retinopathy Project Group.
The presence and severity of DR in a participant were determined based on the eye showing
the worst retinopathy. DR progression was defined as a change either from no DR progress
to NPDR or from NPDR to PDR.

Results: The baseline prevalence of non-proliferative DR (NPDR) and proliferative DR (PDR) was 26.5% and 14.7%, respectively. The mean period for follow-up fundus
exams was 4.0 ± 2.0 years. Among 1303 patients with no DR and NPDR, 134 (10.5%) patients progressed to NPDR or PDR. The progression group had longer duration of diabetes,
highest fasting plasma glucose, higher HbA1c and a higher rate of > 20% decline in eGFR during the follow-up period. After multivariate analysis, >20% decline in eGFR was
an independent risk factor for progression of DR in patients with NPDR.

Conclusions: Decrease of renal function was associated with progression of DR,
especially in patients with NPDR. This result supports the notion that an individualized
screening schedule according to the individual patient’s risk might be needed.

FR-PO276
Interaction Between Alcohol Intake and Diabetes in Relation to the Risk of ESRD in the Singapore Chinese Health Study
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Background: The relationship between alcohol intake and risk of end-stage renal
disease (ESRD) is controversial. Moreover, whether the association is modified by
diabetes status is unknown.

Methods: We examined the association between alcohol intake and risk of ESRD in
the Singapore Chinese Health Study, a prospective population-based cohort of 63,257
adults aged 45-74 years at recruitment (1993-1998). Information on alcohol intake, diet,
medical history and other lifestyle factors was collected at recruitment. We identified
1,217 ESRD cases via linkage with National Singapore Renal Registry through 2015. Cox
proportional hazards regression method was used to estimate hazard ratios (HRs) and 95%
confidence intervals (CIs) of ESRD in relation to alcohol intake by diabetes status over an
average 17.5 years of follow-up.

Results: Among the participants without diabetes at baseline, monthly to weekly
alcohol intake was associated with a decreased risk of ESRD (HR 0.69, 95% CI 0.55-
0.88) compared to the non-drinkers, whereas the reduced risk was no longer significant
among the participants with diabetes (P interaction=0.21). Comparatively, alcohol intake with
≥2 drinks/day was significantly associated with an increased risk of ESRD compared to
the abstainers among the diabetic patients (HR 2.12, 95% CI 1.19-3.78) but not associated
with the risk among those without diabetes (P interaction=0.02). Presence of heavy alcohol
intake was associated with a decreased risk of ESRD (HR 0.69, 95% CI 0.55-0.89).

Conclusions: In conclusion, low-dose alcohol intake may have potential renal
protective effect among individuals without diabetes. However, alcohol intake with ≥2
drinks/day could act synergistically with diabetes in increasing ESRD risk.

Funding: Other NIH Support - R01 CA144034 and UM1 CA182876, Government
Support - Non-U.S.
FR-PO279

Association of Pre-Diabetes with CKD Progression and Adverse Cardiovascular Outcomes in Patients with CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study

Simon Correa,1,2 João Sôrgio Neves,1,4 Rute Baeta Baptista,1 Miguel Bigotte Vieira,1 Sushrut S. Waikar,1,2 Finnian R. McCausland,1,2 Division of Renal Medicine, Brigham and Women’s Hospital, Boston, MA; 1Harvard Medical School, Boston, MA; 2Department of Endocrinology, Diabetes and Metabolism, São João Hospital, Porto, Portugal; 3Faculdade de Medicina, Universidade do Porto, Porto, Portugal; 4Centro Hospitalar Lisboa Norte, Lisboa, Portugal; 5Centro Hospitalar de Lisboa Central, Lisboa, Portugal.

Background: Despite our understanding of diabetes (DM) as an established risk factor for renal and cardiac complications in CKD, the prognostic significance of prediabetes in this population remains largely unknown. We aimed to evaluate the association of prediabetes with CKD progression, adverse cardiovascular events and all-cause mortality in patients with CKD.

Methods: Participants of the Chronic Renal Insufficiency Cohort (CRIC) were categorized as having normoglycemia, prediabetes or DM according to fasting plasma glucose, HbA1c and treatment with anti-diabetic drugs at baseline. Adjusted Cox proportional hazards models (clinical variables, eGFR, 24-hour urine protein, hematocrit and serum albumin) were fit to estimate the association of prediabetes and DM (versus normoglycemia) with CKD progression (development of ESRD or 50% decline in eGFR to <15 ml/min/1.73 m²), a composite cardiovascular outcome (congestive heart failure, myocardial infarction or stroke) and all-cause mortality. Results: Of the 3,701 individuals analyzed, 945 were classified as normoglycemic, 847 had prediabetes and 1909 had DM. Median follow-up was 7.5 years. While prediabetes was not associated with the risk of CKD progression (HRadj 0.96, 95% CI 0.76-1.21), it was associated with a 39% higher risk of the composite cardiovascular outcome (HRadj 1.39, 95% CI 1.06-1.83) (Figure 1) and a trend towards an increased risk of all-cause mortality (HRadj 1.26, 95% CI 0.99-1.67). Patients with DM had an increased risk of CKD progression (HRadj 1.38, 95% CI 1.12-1.70), composite cardiovascular outcome (HRadj 1.65, 95% CI 1.28-2.13) and all-cause mortality (HRadj 1.55, 95% CI 1.21-1.97).

Conclusions: In patient with CKD, prediabetes was not associated with CKD progression but was associated with an increased risk of adverse cardiovascular outcomes.

FR-PO280

Association of Serum Triglycerides and Mortality Across Albuminuria Stages Among US Veterans

Melissa Soohoo,1 Jui-Ting Hsiung,1 Christina Park,1 Maria V. Marroquin,1 Hamid Moradi,1 Csaba P. Kovesda,2 Kamyar Kalantar-Zadeh,3 Elani Streja,4 Hariri-Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 1University of Tennessee Health Science Center, Memphis, TN.

Background: Elevated serum triglycerides (TG) are a risk factor for mortality in the general population, however the relationship is less clear among chronic kidney disease (CKD) patients. Prior studies have evaluated the relationship of TG with mortality in CKD with estimated glomerular filtration rate (eGFR). However, data is lacking on how albuminuria, or urinary albumin-creatinine ratio (UACR), may impact the TG-mortality association.

Methods: Our cohort comprised 994,338 US veterans with a TG measurement between 2004-2006 and were followed until 2014. Albuminuria or UACR prior to TG measurement were extracted either as a calculated ratio, or via dipstick methods. We used Cox proportional hazards models with adjustments for demographics, comorbidities, body mass index and albumin levels to evaluate the association of TG with all-cause and cardiovascular (CV) mortality stratified by UACR groups.

Results: Mean (±SD) cohort age was 63±14 years old, with a median (IQR) TG of 128±87 mg/dL. A majority of patients had low levels of UACR <30 mg/g, whereas 2% had high levels of UACR >300 mg/g. The proportion of patients with UACR<300 mg/g increased with increasing TG. We observed a slight U-shaped association between TG and all-cause and CV mortality, among UACR <30 mg/g and UACR 30-50 mg/g stages, particularly, high TG ≥240 mg/dL were associated with the highest risk of mortality compared to TG 120-160 mg/dL, among those with UACR<300 mg/g [HR [95%CI]: 1.17 [1.14, 1.20]]. These associations were incrementally lower for UACR 30-300 mg/g. Among UACR >300 mg/g patients, higher TG was associated with an even lower to null relationship with CV mortality. For low TG <80 mg/dl, mortality risk estimates were higher for higher UACR stages, particularly for all-cause mortality.

Conclusions: We observed a U-shaped association between TG and all-cause and CV mortality among patients with UACR <300 mg/g, while TG-CV mortality associations for UACR>300 were weaker. Further studies are needed to evaluate how albuminuria may impact cardiovascular risk with elevated TG.

FR-PO281

Trends of Obstructive Sleep Apnea (OSA) Among US Veterans with and Without CKD

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Background: Increasing attention has been paid to sleep problems among patients with CKD. OSA is one of the most common sleep-breathing disorders but is often under-recognized, particularly among persons with CKD. We examined trends in OSA by CKD status over the past ten years.

Methods: The study population were outpatients and inpatients in the Veterans Health Administration from FY2009-18, who were alive at the end of each fiscal year and aged ≥ 50 at the start of that year. Crude 1-year period prevalence (PP) of OSA was computed as the number of OSA cases identified from medical records in that year, divided by the number of persons in the study population that year. CKD was defined by at least one of 3 criteria: 1) a diagnostic ICD-9/10-CM code for CKD, 2) estimated glomerular filtration rate <60 ml/min/1.73m², or 3) albumin-to-creatinine ratio >30 mg/g. Two definitions of OSA were used: one based on a single ICD-9-CM or ICD-10-CM code (327.23 or G47.33), and one based on multiple ICD-9/10-CM codes, including CPAP treatment and organic sleep apnea.

Results: Throughout the study period, the 1-year PP of OSA was higher in CKD than non-CKD patients. Using either OSA definition, the PP in both groups increased gradually from FY2009 to FY2015, rose more sharply to FY2016, then increased gradually again to FY2018. The use of multiple ICD codes increased the PP by approximately 15% throughout the decade. By E008, in patients with CKD, the PP rose to 26.5% using a single ICD code and to 36.8% using multiple codes.

Conclusions: The gradual increase in the crude PP of diagnosed OSA in VA patients both with and without CKD may be attributable to the increasing incidence of OSA due to changes in OSA risk factors such as obesity and comorbidities, and likely to the increased detection of OSA due to greater awareness of the condition. The sudden increase in OSA PP in FY2015-16 probably resulted from the switch from ICD-9-CM to ICD-10-CM coding. Further studies are needed to document and explain OSA prevalence trends in veterans and other populations.

FR-PO282

The Relationship Between Thyroid Status and Kidney Function Among 24 Million Patients in the National OptumLabs Data Warehouse

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Background: Experimental data suggest hypothyroidism contributes to the development of chronic kidney disease (CKD) due to alterations in kidney structure and function. We thus examined the relationship between thyroid status defined by serum thyrotropin (TSH) levels with estimated glomerular filtration rates (eGFRs) in a large US veteran population.

Methods: We examined the association of thyroid status with kidney function using the OptumLabs® Data Warehouse (OLDW), which contains administrative claims data.
including medical claims and eligibility information from a large national US health insurance plan and electronic health record data from a nationwide network of provider groups. In patients who underwent a TSH and a cGFR measure(s) within 90-days over 2007-2017, we examined associations between TSH and severe, moderate-to-severe, and moderate kidney dysfunction (eGFR <30, <45, and <60 ml/min/1.73m², respectively) using logistic regression.

Results: In 24,103,735 patients who met eligibility criteria, 18.6% had eGFR consistent with moderate, moderate-to-severe, or severe kidney dysfunction. Incrementally higher TSH levels of >= 3.0-5.0, >5.0-10.0, and >10.0 mIU/L were associated with incrementally higher risk of severe kidney dysfunction (ref: 0.5-3.0 mIU/L): adjusted ORs (95%CI) 1.12 (1.11-1.3), 1.63 (1.61-1.64), and 2.14 (2.10-2.18), respectively. Lower TSH levels in the hyperthyroid range (<5 mIU/L) were also associated with severe kidney dysfunction: adjusted OR (95%CI) 1.82 (1.81-1.84). Sensitivity analyses showed similar findings for eGFR-based moderate and moderate-to-severe kidney dysfunction.

Conclusions: In a nationally representative cohort of patients, both hypo- and hyperthyroidism were associated with kidney dysfunction. Further studies are needed to determine underlying mechanisms, and whether correction of thyroid status improves kidney function in this population.

Funding: Commercial Support - OptumLabs

FR-PO284
Determinants of Extracellular Volume Status in CKD Stage 3-5: A Cross-Sectional Study of Bioimpedance Analysis

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Background: Extracellular volume expansion predicts higher mortality and adverse cardio-renal outcomes in patients with chronic kidney disease (CKD). The higher value of the extracellular water (ECW) to total body water (TBW) ratio (ECW/TBW) was measured by bioimpedance analysis (BIA). Impaired body fluid volume homeostasis is a major risk factor in chronic kidney disease. In addition, the determinants of the ECW/TBW in CKD stage 3-5 have not yet been fully evaluated.

Methods: One hundred and one non-diagnosis CKD patients (stage 3-5) were enrolled in this study. Body fluid volume including intracellular water (ICW), ECW and TBW was measured by bioelectrical impedance analysis device (BodyRom). ECW/TBW was calculated by dividing ECW by TBW.

Results: Average values are the following: age 63.7 ± 14.5 years, male 61.4%, body mass index (BMI) 24.8 ± 4.7 kg/m², systolic blood pressure 135 ± 20 mmHg, estimated glomerular filtration rate (eGFR) 33.3 ± 16.4 ml/min/1.73m², hemoglobin 11.6 ± 2.3 g/dl, serum albumin 3.4 ± 0.8 g/dl and the ECW/TBW 0.33 ± 0.28 (normal range 0.36-0.39). The ECW/TBW correlated positively with age (r = 0.373, p < 0.0001), systolic blood pressure (r = 0.248, p = 0.014), and ECW (r = 0.336, p = 0.006), while it correlated negatively with hemoglobin (r = 0.328, p < 0.001), eGFR (r = 0.398, p < 0.0001), and serum albumin (r = 0.533, p < 0.0001). On the other hand, the ECW/TBW was not correlated with BMI (r = -0.057, p = 0.385), serum Na (r = 0.074, p = 0.463), ICW (r = 0.146, p = 0.146) and TBW (r = -0.056, p = 0.581), respectively. A stepwise multiple regression analysis revealed that serum albumin (p < 0.0001), age (p = 0.0002) and eGFR (p = 0.0002) were independent determinants of the ECW/TBW.

Conclusions: Low serum albumin, high age and low eGFR are independently associated with higher extracellular volume status in CKD stage 3-5. Further prospective studies are needed to evaluate the impact of extracellular volume status and these factors on long-term outcomes.

Funding: Private Foundation Support

FR-PO285
Desoxicocic Acid (DCA) and Coronary Artery Calcification (CAC) in the Chronic Renal Insufficiency Cohort (CRIC)

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Background: Circulating levels of the secondary bile acid, DCA, are elevated in chronic kidney disease (CKD). In a small cohort of individuals with CKD 3b-4, higher plasma DCA was associated with prevalent CAC. Whether circulating DCA levels are associated with CAC prevalence, incidence, and progression in a large diverse CKD population is unknown.

Methods: We cross-sectionally and longitudinally evaluated the association between fasting serum DCA levels and CAC among 1057 CRIC participants using multivariable-adjusted regression models. CAC was measured in Agatston units at baseline and follow-up.

Results: Mean age was 57.12 years, 47% were female, and 41% were black. At baseline 676 (64%) had any CAC (CAC score >0 Agatston units), 405 (38%) had CAC ≥100, and 236 (22%) had CAC ≥400. In cross-sectional analyses, multivariable models adjusted for demographics and clinical factors including statin use showed no significant association between circulating DCA levels and CAC ≥0 compared to no CAC (CAC=0) (prevalence ratio per 1-SD increase in log DCA: 1.09, 95% CI 0.92-1.28). Significant results were observed when baseline CAC thresholds of ≥100, ≥200, ≥300, and ≥400 vs. no CAC (CAC=0) were used. 672 participants had follow-up CAC measurements. Over a mean increase of 3.2±0.6 years, of the 277 (41%) participants with no baseline CAC (CAC=0), 60 (22%) developed incident CAC (CAC>0). In the fully adjusted model, DCA was not significantly associated with incident CAC (CAC>0) (incidence ratio per 1-SD increase in log DCA: 1.08, 95% CI 0.87-1.34 and 1.18, 95% CI 0.77-1.82, respectively).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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FR-PO286
Increasing and Declining Estimated Glomerular Filtration Rates Predict Mortality Among a Community-Based Cohort
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Background: Serum creatinine based glomerular filtration rate (eGFR) is widely used to estimate the true glomerular filtration rate (eGFR) and as a tool for predicting risks of end-stage kidney disease (ESKD) and/or death in the field of public health. Most studies have focused on populations with a declining eGFR.

Methods: We enrolled a Japanese community-based cohort (N = 321,028; age 63 ± 7.8 years; men, 41.2%) via the public health check-up system. The follow-up period was 1,566 ± 501 days. The participants were classified into 12 annual eGFR change rate groups. Cox regression analyses were performed to calculate risks for all-cause mortality as the primary outcome measure. Stratified analyses were also conducted according to the level of dipstick proteinuria, annual body weight (BW) change of <0% and ≥0%, baseline eGFR ≥60 mL/min/1.73 m² and 15–59 mL/min/1.73 m², age ≥65 years old and <65 years old, sex, and the presence or absence of diabetes.

Results: There were 13.8% participants with an eGFR of 15–59 mL/min/1.73 m², and 25.3% had a history of cardiovascular disease (CVD). Thus, our cohort was not at a high risk of both ESKD and CVD. During the study period, 2,604 (0.81%) died. Multivariable Cox regression analysis showed that increasing, as well as declining, eGFR was significantly associated with mortality when an annual eGFR change rate of 0–4.9% was set as the reference range (U-shaped pattern). For example, the adjusted hazard ratio and 95% confidence interval of an annual eGFR change rate of ≥25% and ≤-25% was 14.17 (10.40–19.31) and 13.84 (9.69–19.76), respectively. Stratified analyses revealed that every stratification still demonstrated a significant U-shaped relationship, even though participants were grouped by dipstick proteinuria level, annual BW change, age, eGFR level, age, sex, and diabetes status.

Conclusions: Increasing as well as declining eGFR is an important factor in patient mortality. Proteinuria, BW change, baseline eGFR level, age, sex, and diabetes did not affect this relationship.

FR-PO287
Albuminuria Is a Biomarker for Severity of White Matter Hypertensities on Brain MRI in a General Elderly Population of Japanese: The Hisayama Study
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Background: White matter hypertensities (WMH), which are often observed in brain magnetic resonance imaging (MRI) among the elderly, have been reported to be associated with an increased risk of symptomatic stroke. Albuminuria and reduced estimated glomerular filtration rate (eGFR) have been acknowledged to be independent risk factors for stroke, but the studies addressing the association of albuminuria and reduced eGFR with WMH volume in general Japanese elderly populations are limited.

Methods: A total of 1,214 community-dwelling Japanese subjects aged ≥65 years underwent brain MRI scans and a comprehensive health examination in 2012. Urine albumin-to-creatinine ratio (UACR) was categorized as normalalbuminuria (<30 mg/g creatinine), microalbuminuria (30-299 mg/g creatinine), and macroalbuminuria (≥300 mg/g creatinine). Subjects with normalalbuminuria were further divided into the following tertile categories: low-normal (≤7.3 mg/g), medium-normal (7.4-12.8 mg/g), and high-normal (12.9-29.9 mg/g). Reduced eGFR was defined as eGFR <60 mL/min per 1.73 m². The severity of WMH was evaluated with the ratio of WMH volume to intracranial volume (WMH/ICV). The association of UACR levels or reduced eGFR with WMH/ICV ratio was estimated using the analysis of covariance.

Results: The age- and sex-adjusted geometric mean value of the WMH/ICV ratio increased significantly with higher UACR levels (low-normal: 0.19%, medium-normal: 0.21%, high-normal: 0.25%), microalbuminuria: 0.25%; macroalbuminuria: 0.30%; P for trend <0.001). This association remained significant after additional adjustment for hypertension, diabetes mellitus, hypercholesterolemia, body mass index, eGFR, cigarette smoking, alcohol drinking, habitual smoking, alcohol intake, regular exercise, and cerebrovascular lesions on MRI (P for trend <0.001). In contrast, there was no clear association between reduced eGFR and WMH/ICV ratio.
Cox models were utilized to evaluate survival. Adjusted mixed models were used to test the interaction between PRA and slope of eGFR over time.

Results: Among 1124 patients analyzed, PRA correlated inversely with eGFR (1.9 vs 1.2ug/L/hr for eGFR 15-29 vs 60-89 mL/min/1.73 m²; p<0.001). Table 1 shows the patient characteristics by PRA quartiles. Patients in Q1 were older, more African American, had lower BMI, and more were on beta blocker therapy. They had higher systolic and diastolic blood pressures and were more likely to require ≥3 blood pressure medications. All these associations were statistically significant (table 1). With median follow-up of 3.2 years, mortality was not different across PRA quartiles on adjusted Cox model analysis (P=0.16). On mixed model analysis, a significant association was noted between log PRA and time to mortality was not different across PRA quartiles on adjusted Cox model analysis (P=0.16).

Discussion: While the mechanism remains unclear, PRA appears to correlate inversely with eGFR. Findings suggest a protective effect of higher PRA against CKD progression when eGFR is above 50 mL/min/1.73 m². Congruent with prior studies, lower PRA values are evident in older age, African Americans, and Beta Blocker therapy. Our study also suggests that lower PRA is associated with a more resistant hypertension. Whether this represents high salt intake or undiagnosed autonomous hyperaldosteronism is unclear.

FR-PO291
Gluomterial Hyperfiltration Is Associated with Dementia: A Nationwide Population-Based Study
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Background: Because prevention of dementia is critical before it occurs, identifying the risk factor of dementia is important. The object of this study is to identify the risk of dementia in people with glomerular hyperfiltration.

Methods: Using Korean National Health Information Database (NHID), we retrospectively reviewed total of 2,244,582 people, excluding ESRD patients and people with dementia before taking national health screening. Study population was divided into gender and age of five-years interval group. All eGFR95 percentile subjects in each group which was divided into sex and age of five-years were defined as hyperfiltration group. All 50 percentile≤eGFR<95 percentile subjects in each group which was divided into sex and age of five-years were defined as reference group. The hazard ratios (HR) for all type dementia, vascular dementia and Alzheimer’s dementia were calculated within the study groups after adjustment for multiple variables.

Results: The corresponding eGFR values of hyperfiltration (95 percentile of eGFR group) were a114 mL/min/1.73m² in 45-49 years old male, a83 mL/min/1.73m² in a90 years old male and a117 mL/min/1.73m² in 45-49 years old female, a85 mL/min/1.73m² in a90 years old female. (Figure 1.) The hyperfiltration group (eGFR≥95percentile) showed a higher risk of all type dementia compared with the reference group (50percentile≤eGFR<95percentile), with the following HRs: 1.09 (95%CI: 1.032-1.152). The hyperfiltration group had higher risk of vascular dementia with the following HR: 1.33 (95% CI: 1.137-1.549). The relationship between hyperfiltration and Alzheimer’s dementia was not statistically significant, with the following HRs: 1.040 (95% CI: 0.977-1.048). (Figure 2.)

Conclusions: Gluomterial hyperfiltration is associated with increased risk of dementia, especially vascular dementia.

FR-PO292
Evaluation of Renal and Retinal Outcomes in the Northern Ireland Cohort of Longitudinal Ageing (NICOLA)
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Background: Microvascular pathology is a common feature of both eye and kidney disease. Renal microvascular damage is not easy to identify without renal biopsy. Advances in imaging the retinal microvasculature may offer an alternative opportunistic evaluation of microangiopathic changes that correlate with kidney dysfunction. Retinal imaging might provide an earlier, non-invasive screening assessment for the presence of chronic kidney disease (CKD). We assessed retinal microvascular parameters for association with against measures of renal function measures in a prospective cohort study of older persons (>55 years): Northern Ireland Cohort of Longitudinal Ageing (NICOLA).

Methods: Retinal microvascular parameters (central retinal arterial/venular equivalent (CRAE/CRVE), venular ratio (AVR), fractal dimension and tortuosity) were measured from optic disc centered fundus images and analysed using semi-automated software. Linear and logistic regression models were used to assess associations between microvascular parameters and the continuous variables of renal function (eGFR, Creatinine (SeCr) and Cystatin C (Scys)) and the binary trait of CKD status, respectively. Minimally adjusted models included age and gender with fully adjusted models also including diabetes, smoking, alcohol, education, body mass index, antihypertensive medication, mean arterial blood pressure, triglycerides, high and low density lipoproteins.

Results: Retinal and renal measures were available for 1,860 of the 3,518 NICOLA participants. In unadjusted, minimally adjusted and fully adjusted linear regression models, no significant associations were detected between CRAE, CRVE, AVR, fractal dimension or tortuosity and eGFR or eGFRScs. CKD status, defined by eGFRScs < 60 mL/min per 1.73 m², was significantly associated with venular tortuosity in all models (β=0.8; 95%CI: 1.3, 4.1; P=0.004). There was no significant associations detected between CKD status and any of the other retinal parameters assessed.

Conclusions: Our findings indicate that variation in retinal venular geometry is associated with renal dysfunction in an older population. These non-invasive retinal measures may help identify early mechanistic pathways for microvascular complications in individuals at high risk for future CKD.

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FR-PO293
Serum Albumin and All-Cause Mortality Across Varying Levels of Kidney Function
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Background: Serum albumin (sAlb) may be a strong predictor of longevity in the general population and in chronic kidney disease populations. Our objective was to determine the relationship between sAlb concentrations and mortality risk independent of kidney function.

Methods: We analyzed a retrospective cohort of 31,274 adults from the 1999-2010 National Health and Nutrition Examination Survey. Estimated glomerular filtration rate (eGFR) was examined as both a confounder and modifier of the association of sAlb with mortality risk. We examined the association of sAlb categorized in 7 strata with mortality using Cox models. Covariates in the adjusted model included age, sex, race/ethnicity, level of education, diabetes, smoking status, systolic blood pressure, serum total cholesterol level, and eGFR. We then conducted spline analyses to estimate the association of sAlb with all-cause mortality across varying eGFR levels.

Results: In unadjusted analyses, participants with incrementally lower sAlb concentrations <4.6g/dL had increasingly higher mortality risk compared to those with sAlb ranging 4.6-<4.8g/dL (reference), whereas those with higher sAlb ≥4.8g/dL had lower mortality risk (HRs (95%CI) 3.88 (3.26, 4.62), 3.59 (3.01, 4.27), 2.79 (2.37, 3.29), 2.10 (1.79, 2.48), 1.72 (1.45, 2.03), and 0.71 (0.55, 0.92) for sAlb concentrations of <3.8, 3.8-<4.0, 4.0-<4.2, 4.2-<4.4, 4.4-<4.6, and ≥4.6g/dL, respectively. Case-mix + eGFR adjusted analyses showed similar findings, although the association of higher sAlb ≥4.8g/dL was marginally significant.
FR-PO294
CKD in Patients with Pre-Diabetes from Two Large Healthcare Systems
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Background: Chronic kidney disease (CKD) in pre-diabetes (PDM) is not well-characterized. The study aim was to determine CKD prevalence and risk factors of patients with PDM treated at two University Health systems in the western United States.

Methods: The Center for Kidney Disease Research, Education and Hope (CURE-CKD) registry was created from clinical and administrative data in electronic health records of Providence St. Joseph Health and University of California Los Angeles Health (years 2006-2017). PDM, CKD, and hypertension (HTN) were identified by diagnostic codes and condition-specific criteria: PDM by HbA1c 5.7-6.4% or two measures of fasting (100-125 mg/dL) or random (140-199 mg/dL) glucose at least one day apart; CKD by two measures of serum creatinine-based estimated glomerular filtration rate (eGFR)<60 mL/min/1.73m2 (CKD-EPI), urine albumin-to-creatinine ratio ≥30 mg/g, or protein-to-creatinine ratio >150 mg/g at least 90 days apart; HTN by blood pressure ≥140/90mmHg on two measures at least 14 days apart.

Results: CKD was present in 20% of patients with PDM (101,868/497,233). Patients with CKD and PDM were predominantly white (71%), women (58%), and older compared to those without CKD (72.1±15 years versus 56.0±17 years, p<0.001). HTN occurred in 72% of patients with CKD and PDM (73,788/101,868) with mean blood pressure of 131.1±17.0/10.1±10 mmHg. HbA1c was similar in those with and without CKD (5.8±0.3% and 5.7±0.4%), eGFR of 53±18 mL/min/1.73m2 in patients with CKD and PDM versus 89±20 mL/min/1.73m2 (p<0.001) in those without CKD. Among patients with PDM and CKD, individuals with HTN had higher eGFR compared to those without HTN (55±18 versus 50±21 mL/min/1.73m2, p<0.001) and fewer had CKD stages 4-5 (7% versus 13%, p<0.001). Among small number of patients tested, albuminuria >30 mg/g or proteinuria >150 g/g occurred in 24% (3,027/12,470) and 42% (2,519/6,026), respectively. p<0.001). Among small number of patients tested, albuminuria >30 mg/g or proteinuria >150 mg/g occurred in 24% (3,027/12,470) and 42% (2,519/6,026), respectively.

Conclusions: CKD and major risk factors of HTN and albuminuria/proteinuria are often present in PDM without overt diabetes. In patients with PDM, CKD assessment and risk factor management are warranted.

Funding: Private Foundation Support

FR-PO295
Mediation Analysis of Proteinuria and Serum Phosphate: Insight from the KNOW-CKD Study
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Background: Proteinuria and hyperphosphatemia are risk factors for cardiovascular disease in patients with chronic kidney disease (CKD). While experiencing the interaction between proteinuria and serum phosphate level, there is an insufficient mechanistic link between the two, particularly the extent to which is mediated by phosphate regulating factors. Therefore, we examined their association and potential mediators including circulating FGF23/Klotho and 24hr urinary excretion rate of phosphate to glomerular filtration rate (24hr EP/GFR) and 24hr tubular reabsorption rate of phosphate to GFR (24hr TRP/GFR).

Methods: We analyzed 1793 patients for whom 24hr urine protein and phosphate, serum phosphate, FGF23 and Klotho level were measured simultaneously using data from the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD).

Mediation analyses of the effect of 24hr UPE on serum phosphate level.

FR-PO296
Association of the Trajectories of Metabolic Component and Outcomes in Patients with CKD
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Background: Patients with chronic kidney disease (CKD) were known to increase the risk of chronic diseases including hypertension (HTN), diabetes mellitus (DM), dyslipidemia while they also affect deterioration of renal function. However, little is known about the relation of changeable aspect for metabolic component to CKD progression.

Methods: We assigned patients to be clustered High and Low group followed by trajectory analysis using K-means clustering on the basis of systolic and diastolic blood pressure (SBP, DBP), total cholesterol(TC), triglyceride(TG) and LDL cholesterol measurement at least two time point. The optimal number of clustering was selected by the Calinski-Harabasz index. Primary outcome was risk factor analysis by clustering group for eGFR decline, and death.

Results: The mean age of overall participants was 65.7±9.7 years, 50.4% for men and 11.8% for current smoker. The mean SBP was 127.8±15.8 mmHg, DBP was 83.6±8.4 mmHg. Total cholesterol, TG and LDL was 196.4±40.9, 147.1±89.8, 115.5±37.2 mg/dl, respectively. The mean SBP of cluster High group was 138.9±13.2, and Low group was 118.9±10.9mmHg. In TC clustering, High group was 223.4±33.0, and Low group was 167.5±26.6 mmHg. The mean TG in High group was 266.1±116.7, and Low group was 118.8±46.1 mg/dl. In LDL clustering, cluster High group was 139.7±31.2, and Low group was 89.9±24.3 mg/dl. In multivariate logistic regression, SBP high group (OR 1.13 95%CI 1.066-1.212), TG high group (OR 1.15, 95% CI 1.069-1.240) were independently associated with eGFR decline. And, also SBP high group (OR 1.82, 95%CI 1.070-3.123) and BMI lowest group (OR 2.19, 95% CI 1.047-4.38) were independently associated with death.

Conclusions: High SBP trajectory, and high TG trajectory have negative impacts on eGFR decline. And also, High SBP trajectory, and low BMI trajectory affected overall survival. In CKD patients, more meticulous following up was needed for better clinical outcomes.
FR-PO297

Examining the Characteristics of US Veterans on Triglyceride or HDL Altering Therapy Across Kidney Disease Stage Between 2004-2014
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Background: Current nephrology guidelines do not advocate for pharmacological therapy for triglycerides (TG) or high density lipoprotein (HDL) management in patients with chronic kidney disease (CKD), despite the fact that these lipids may be associated with a higher cardiovascular risk. Nonetheless some patients with CKD receive these medications. We sought to describe the characteristics of US veteran patients receiving fibrates or niacin and whether these characteristics differed by presence of CKD or across CKD stages.

Methods: We identified male veterans with an elevated TG(a 150 mg/dL) or low HDL (<40 mg/dL) who initiated a fibrate or niacin within 90 days of the lipid measurements between 2004-2014. We examined clinical characteristics at the time of fibrate or niacin initiation (N=78,957 and 100,356, respectively), stratified by CKD stage.

Results: In both treatment groups, there was a decreasing trend in fibrate and niacin initiation across higher CKD stage, where a majority of patients were non-CKD, with <1% of patients in stage 5 or end-stage renal disease (ESRD). Veterans with advanced CKD were more likely to be older at the time of fibrate or niacin initiation. In non-CKD and between CKD stage 3A-4, approximately 6-12% of patients on therapy were African-American, however that proportion more than doubled to 20-25% in ESRD/CKD stage 5. Across CKD stages, there was an increase in the proportion of concurrent statin users, with a peak in stage 4 or 5, and a decline with ESRD. There were similar relationships of comorbidities across CKD stage among fibrate users, where the greatest proportion of cardiovascular conditions was among CKD stage 4 patients.

Conclusions: In US veterans, the proportion of patients with high TG or low HDL presenting to receive fibrates or niacin decreased with worsening CKD. In future analysis, we will investigate if use of these therapies in CKD patients with elevated TG or low HDL have a lower risk of cardiovascular events.

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FR-PO298

Correlation Between Blood Pressure and Development of CKD in 5.6 Million Korean Adults with Normal Renal Function
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Background: Although hypertension is well known for a major risk factor of renal progression in patients with chronic kidney disease (CKD), there are few studies on whether hypertension is also a risk factor of renal progression in the population with normal renal function. So we analyzed correlation between blood pressure (BP) control and development of CKD in Korean adults with normal renal function.

Methods: We utilized medical checkup database of the Korean National Health Service (NHIS). We enrolled 5,638,320 subjects including people who underwent medical checkups both in 2009 & 2015 in a row and excluding people whose estimated glomerular filtration rates (eGFRs) were already less than 60 ml/min/1.73m² or whose urinalyses already showed proteinuria in 2009. New development of CKD was defined by the decline of eGFR to below 60 ml/min/1.73m² in 2015. We compared age, sex, obesity, and various medical illnesses such as hypertension, diabetes, and dyslipidemia, compared with the non-CKD group (n=5,477,276). We also stratified subgroups by initial systolic BP and diastolic BP by 10 mmHg, and investigated the risks of progression to CKD after adjusting these clinical factors.

Results: The CKD group showed higher incidence of old age, female, obesity, hypertension, diabetes, and dyslipidemia, compared with the non-CKD group. Subjects whose SBP were more than 120 mmHg or whose DBP were more than 70 mmHg showed higher incidence of progression to CKD, compared with subjects whose SBP were less than 120 mmHg and whose DBP were less than 70 mmHg, respectively (odds ratio 1.037, 95% confidence interval 1.014-1.061 / OR 1.021, 95% CI 1.004-1.038).

Conclusions: We suggest strict BP control is helpful for preventing CKD in the population with normal renal function.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

FR-PO299

Serum Bicarbonate Levels Are Not Associated with Total Kidney Volume in Patients with Polycystic Kidney Disease
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Background: Enhanced ammoniagenesis has been proposed as a potential mechanism of kidney cystic disease progression in patients with polycystic kidney disease (PKD). Animal studies have found that administration of sodium bicarbonate slows cyst enlargement and prevents development of interstitial inflammation and chronic fibrosis. We tested the hypothesis that higher serum bicarbonate levels in patients with PKD are associated with lower total kidney volume (TKV).

Methods: We included 383 patients from the HALT-PKD Study A with baseline serum bicarbonate levels and at least two measurements of TKV. Bicarbonate was examined as a continuous variable and in categories (a 24, 25-28 and >28 mEq/L, with 25-28 mEq/L as the reference group). Total kidney volume was measured using a 1.5T MRI scanner. The outcome was yearly change in slope of TKV. Linear regression models were used to test the association between serum bicarbonate and change in TKV.

Results: The mean (SD) serum bicarbonate level was 37.4 (8.0) mmol/L. The mean (SD) serum bicarbonate and estimated glomerular filtration rate at baseline was 27.0 (2.4) mmol/L and 90.0 (17.0) ml/min/1.73m², respectively. Participants with lower serum bicarbonate of ≤ 24 mEq/L were more likely to be younger, female and to have higher systolic blood pressure than those with a serum bicarbonate > 28 mEq/L. There was no association between serum bicarbonate and change in annual slope of TKV when serum bicarbonate was examined as a continuous variable or in categories (Table 1).

Conclusions: Serum bicarbonate levels are not associated with total kidney volume in patients with PKD.

Funding: Other NIH Support - NHLBI

Annual Change in Slope of TKV (β Estimate (95% CI))

<table>
<thead>
<tr>
<th>Serum bicarbonate (mEq/L)</th>
<th>Unadjusted</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24</td>
<td>0.10 (0.04 to 0.15)</td>
<td>0.07 (0.04 to 0.11)</td>
<td>0.09 (0.05 to 0.13)</td>
</tr>
<tr>
<td>24 to 25</td>
<td>0.03 (0.01 to 0.06)</td>
<td>0.02 (0.00 to 0.04)</td>
<td>0.03 (0.01 to 0.05)</td>
</tr>
<tr>
<td>25-28</td>
<td>0.03 (0.02 to 0.05)</td>
<td>0.02 (0.01 to 0.04)</td>
<td>0.03 (0.02 to 0.05)</td>
</tr>
<tr>
<td>&gt; 28</td>
<td>0.04 (0.03 to 0.06)</td>
<td>0.03 (0.02 to 0.05)</td>
<td>0.04 (0.03 to 0.06)</td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, gender, race
Model 2: adjusted for model 1 plus smoking, cardiac history, BMI, SBP, baseline eGFR and urine albumin to creatinine ratio
Alteration of Physical Activity and Its Association with Cardiovascular Outcomes Among Pre-Dialysis CKD Patients

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Background: Cardiovascular disease is major cause of mortality among chronic kidney disease (CKD) patients, and it is fundamental to focus on reducing the potential risk factors. Regular physical activity is known to reduce the risk of cardiovascular disease in general population. However, whether the change of physical activity habits is beneficial for pre-dialysis CKD patients had not been examined thoroughly.

Methods: We performed a nationwide population based cohort study using the database of Korean National Health Insurance System. Among adult patients who received national health screening program ≥2 times between 2012 and 2016, CKD patients were identified using the serum creatinine and dipstick albuminuria measurements. Those who previously underwent dialysis or diagnosed cardiovascular disease were excluded. The frequency and the intensity of the physical activity were obtained at least twice, from self-reported questionnaire during the health examination. The study groups were divided according to the status of physical activity habit alteration; active, quit exercise, start exercise, and inactive group. Then, the development of myocardial infarction (MI), stroke or death was assessed using the multivariate Cox regression analysis.

Results: During the median follow up of 3.18 years, 549,187 CKD patients were examined for adverse outcomes. Compared to those who remained inactive, the active group patients who consistently continued physical activity exhibited lower risk of MI (hazard ratio (HR): 0.76, 95% confidence interval (CI): 0.68-0.85), stroke (HR (95%CI) 0.69 (0.62-0.78)), and death (HR (95%CI) 0.62 (0.57-0.67)). Moreover, those who newly started physical activity also showed lower risk of adverse outcomes, compared to the inactive group (HR (95%CI) 0.83 (0.76-0.89)).

Conclusions: Continuation of physical activity in pre-dialysis CKD patients is beneficial to reduce the risk of cardiovascular disease development. Therefore, clinicians should encourage even mild intensity of physical activity to CKD patients.

Hyperuricemia Is Associated with Progression of CKD: Uric Acid Aggravates Renal Function

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Background: Hyperuricemia (HUA) is common in chronic kidney disease (CKD). There is paucity of literature on the association between serum uric acid levels and the progression of CKD. This study aimed at assessing the effect of serum baseline uric acid level on the progression of CKD.

Methods: This retrospective study included 800 CKD patients in our center. The information on baseline and follow-up characteristics were collected from Renal Treatment System (RTS) database, including age, gender, serum uric acid (UA), glomerular filtration rate (eGFR), serum creatinine (Cr), urea, albumin (Alb), 24 hours urine protein quantitation (24-u-pro) and blood pressure (BP). Cox regression analysis was used to evaluate the risk factors for CKD progression. The Kaplan–Meier analysis was used to test associations between serum uric acid levels and renal survival rates.

Results: A total of 800 patients were included in the study, and the mean age at entry was 36.6±14.4 years. There was no significant difference in gender distribution. The mean eGFR, Cr, serum uric acid at baseline were 99.23±31.54 ml/min/1.73m², 82.08±41.40 µmol/L, 371.60±103.18 µmol/L, respectively. 306 (38.3%) patients had HUA and 494 (61.7%) had non-HUA. We established different adjusted models and found that HUA was a risk factor for CKD patients to reach the composite endpoint after adjustment in six models. All models show that HUA was a risk factor for the progression of CKD. Among them, model 4 (adjusted for Cr+Alb+age+BP+gender) was the best model with the largest HR value (HRA:2.010, 95%CI:1.310-3.084, P<0.05). The cumulative survival rate of non-hyperuricemia group was higher than that of hyperuricemia group (P=0.046).

Conclusions: HUA is prevalent in CKD and a risk factor for CKD progression. Anti-hyperuricaemic therapy may need to be considered in CKD patients to slow the disease progression, which needs to be tested further in clinical studies.

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FR-PO303
Relationship of Uric Acid with Cardiovascular Mortality: A Systematic Review and Meta-Analysis
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Background: Uric acid (UA) levels predict cardiovascular (CV) and all-cause mortality, but uncertainty remains regarding optimal threshold values for intervention. The aim of this systematic review and meta-analysis was to investigate risk thresholds for UA on CV mortality in four distinct populations: general population, cardiovascular disease (CVD), chronic kidney disease (CKD), and end stage kidney disease (ESKD).

Methods: We searched electronic databases up to 1 July 2018 for observational studies reporting associations for three or more of UA with all-cause and CV mortality in the four different populations: general, CVD, and ESKD. We investigated the influence of elevated SUA level on the prevalence of CVD in Japanese patients with chronic kidney disease (CKD). Besides, the nature of disease in Asian populations differs markedly from that in North American populations and Europe.

Results: We included, 1,665,013 participants from 37 cohorts with 25,334 CV deaths. The overall pattern of association between serum UA and CV mortality was non-linear (p-value, non-linearity < 0.001). Mortality risks increased beyond UA of 6.0 mg/dL, with an almost linear increase in risk for higher concentrations (7.0 mg/dL; [RR: 1.13 (1.08-1.18)]) compared to a referent of 5.5 mg/dL. There was evidence of heterogeneity across studies (I²=65.5). The shape of the UA-mortality association was similar for participants in the general, CVD, and ESKD populations but differed significantly from ESKD (p=0.001). In ESKD, the pattern was completely reversed, with a reduced mortality for UA values above 5.5 mg/dL.

Conclusions: Uric acid exhibits a U-shaped association with CV mortality with increasing risk above 5.5 mg/dL in the general and CVD populations. This relationship was attenuated in CKD and completely reversed in ESKD. Large randomised clinical trials of urate-lowering therapy should test whether targeting this threshold will confer benefit.

Funding: Government Support - Non-U.S.

FR-PO304
Comparative Renoprotective Effect of Febuxostat and Allopurinol in Pre-Dialysis Stage 5 CKD Patients: A Nationwide Database Analysis
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Background: Hyperuricemia has been associated with chronic kidney disease (CKD) progression. Slowed CKD progression has also been observed in stage 1-3 CKD patients treated with the anti-hyperuricemic febuxostat. Large-scale studies comparing the renoprotective potential of febuxostat and allopurinol in pre-dialysis stage 5 CKD are lacking.

Methods: In our population-based retrospective cohort study, we used the National Health Insurance Research Database in Taiwan from 2012 to 2015 to select eligible pre-dialysis stage 5 CKD patients. Patients were included and grouped based on the prescription of allopurinol (n=3424) or febuxostat (n=2633) within 90 days after first-time therapy. The primary hypothesis was whether febuxostat use was associated with lower risk of progression to dialysis in pre-dialysis stage 5 CKD patients. The primary outcome was all-cause mortality.

Results: We identified 6057 anti-hyperuricemic users. 69.57% of allopurinol users (n=4005; 95% CI 67.63-71.48) and 72.00% of febuxostat users (n=2052; 95% CI 70.05-74.01) were male. The median age of allopurinol users was 60 years (IQR 52-67) vs 62 years (IQR 54-69) for febuxostat users. Mean serum creatinine levels were 3.98 mg/dL (SD 1.74) for allopurinol users and 3.59 mg/dL (SD 1.74) for febuxostat users. The mean (SD) serum uric acid levels were 9.98 mg/dL (SD 2.07) for allopurinol users and 7.97 mg/dL (SD 1.87) for febuxostat users. The mean (SD) estimated glomerular filtration rate (eGFR) were 12.05 mL/min/1.73m² (SD 14.43) for allopurinol users and 15.31 mL/min/1.73m² (SD 14.43) for febuxostat users.

Conclusions: In our nationwide database analysis of pre-dialysis stage 5 CKD patients, febuxostat use was consistent across most patient subgroups and/or using the propensity score-matched cohort. Similarly, the adjusted hazard ratio was 0.66 (95% confidence interval, 0.60-0.70), indicating near 35% lower hazards of renal death. However, the study findings warrant further investigation in a randomized controlled trial.

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FR-PO307

Acid Retention Decreases Urine Citrate Excretion Through Reduced Kidney Clearance and Reduced Plasma Concentration of Citrate

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Background: Decreased urine excretion of the pH-sensitive metabolite citrate is a potential biomarker of H+ retention in patients with CKD and reduced eGFR but no metabolic acidosis (Goraya,KI 91:1190, 2019). We explored contributions of reduced plasma citrate (Pcit) and/or reduced kidney clearance (UV/Pcit) to decreasing urine citrate excretion associated with increasing H+ retention over time.

Methods: We measured H+ retention, 8-hour urine citrate excretion (Ucitrate), Pcit, and UV/Pcit in macroalbuminuric, non-diabetic CKD 2 patients with hypertension associated nephropathy without metabolic acidosis (plasma total CO2<24 mM) at baseline and after treatment with 0.25 mg/kg bw/day NaHCO3 (n=40), 0.5 meq/kg bw/day NaCl (n=40), or usual care (UC, n=40) and assessed after 5 years.

Results: Baseline H+ retention, Ucitrate, Pcit, and UV/Pcit were not different among groups. The 5-year vs. respective baseline value in HCO3 patients was not different for H+ retention (16 µmol/L ± 1.29 vs 18.1 ± 14.8 µmol/L, p=0.46) or Ucitrate (1.083 ± 0.244 vs 1.032 ± 0.259 mmol/L, p=0.09). However, the 5-year vs respective baseline value in NaCl patients was higher for H+ retention (23.2 ± 1.40 vs 19.2 ± 16.7 mmol/L, p<0.01) and lower for Ucitrate (0.910 ± 0.233 vs 1.021 ± 0.275 mmol/L, p<0.01). Similarly, 5-year vs baseline value in UV was higher for H+ retention (22.1 ± 11.2 vs. 17.4 ± 9.9 mmol/L, p=0.01) and lower for Ucitrate (0.899 ± 0.217 vs 0.909 ± 0.212 mmol/L, p<0.01). Five-year vs baseline value for Pcit was not different for HCO3 (0.050 ± 0.016 vs 0.048 ± 0.016 mmol/L, p=0.46) and NaCl (0.031 ± 0.023 vs. 0.054 ± 0.025 mmol/L, p=0.08) but was lower for UC (0.050 ± 0.020 vs. 0.062 ± 0.020 mmol/L, p=0.02). Five-year vs. baseline value for UV/Pcit was not different for HCO3 (0.048 ± 0.011 vs. 0.047 ± 0.008 mmol/L/1.73m2, p=0.91, but was lower for NaCl (0.043 ± 0.016 vs 0.047 ± 0.018 mmol/L/1.73m2, p=0.002) and UC (0.045 ± 0.024 vs. 0.048 ± 0.024 mmol/L/1.73m2, p=0.004).

Conclusions: Both reduced UV/Pcit and reduced Pcit mediated decreased Ucitrate in CKD patients without metabolic acidosis whose H+ retention increased after 5 years without alkali therapy but both parameters were unchanged in those treated with alkali in whom H+ retention did not increase. Increasing H+ retention initiates kidney and extra-kidney mechanisms for citrate conservation.

FR-PO308

A Serum Magnesium Concentration Lower Than 2 mg/dL Predicts Mortality in CKD Patients: A Propensity Score-Matching Study

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Background: Decreased serum mg may be associated with mortality and vascular calcifications. There is limited information on the impact of low mg (mg) in CKD stage 4 patients. We aimed to evaluate whether serum mg levels are associated with mortality in a matched cohort of CKD stage 4 patients.

Methods: Patients were stratified into tertiles according to serum mg (T1<2.0 mg/dL, T2=2.0-1.39 mg/dL, T3=2.4 mg/dL). For survival analysis, we used log-rank tests to compare Kaplan-Meier (KM) probability of death curves and performed uni- and multivariable Cox regression analysis. Given the confounding effect of mg (mg), we included matching variables (BMI, sex, smoking status, diabetes, proteinuria, and NYHA class) as well as additional covariates in the propensity score model (PSM).

Results: This study included 1002 patients evaluated in the advanced-CKD outpatient clinic from 2009 to 2018. During the study follow-up, 158 died, 84 from T1, 34 from T2, and 35 from T3. Furthermore, 616 patients started dialysis, whereas 212 remained under follow-up in the outpatient clinic. KM showed that patients from T1 had a worse survival as compared with T2 and T3 (p<0.001; Figure 1A). Multivariable Cox proportional hazard showed that patients with mg <2 mg/dL had a higher mortality risk (HR 1.61, CI 1.05—2.46) as compared to the other groups. After matching, it was obtained an adjusted population survival of 343 patients with mg ≥2 mg/dL and 345 with higher concentrations of mg. Survival analysis with PSM-adjusted cohorts showed that patients with mg <2 mg/dL had worse survival compared to T2 and T3 (log-rank p=0.01; HR 1.73, CI 1.02—2.36, p=0.04; Figure 1B).

Conclusions: In appropriately-matched patients, a serum mg <2 mg/dL predicts mortality.

Funding: Government Support - Non-U.S.

Figure 1. Survival analysis of not matched cohorts (A) and PSM-adjusted cohorts (B).

FR-PO309

Urine Hydroxyproline as a Marker of Renal Dysfunction in Patients with CKD

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Background: Hydroxyproline (Hyp) is major component of the protein collagen in the tissues. Most of the Hyp released by the breakdown of collagen is degraded to free amino acid that circulates in plasma, is filtered, and is almost entirely reabsorbed by the kidney while some of the Hyp circulates in the peptide-bound form and are excreted in urine without further metabolism. This study was designed to examine whether the measurement of urinary Hyp could be useful for assessing renal function in the patients with chronic kidney disease (CKD).

Methods: A total of 298 patients with various stages of non-dialytic CKD were included in this study. Values of total and free Hyp were measured from 24-hours urine and urine-free-to-total Hyp ratio was calculated to compare with known renal functional parameters (from January 5th, 2016 to May 7th, 2018).

Results: Median levels of urinary free Hyp and total Hyp are 0.70 mg/24-hour (IQR 0.30-2.10 mg/24-hour) and 125.00 μmol/day (IQR 80.00-196.00 μmol/day), respectively. Univariate linear regression analysis showed that urinary free-to-total Hyp ratio was correlated with creatinine (β=0.399, P<0.001), estimated glomerular filtration rate (eGFR; β=0.213, P<0.001), cystatin C (β=0.338, P<0.001), proteinuria (β=0.181, P<0.004) and fractional excretion of sodium (β=0.141, P=0.023). Results of multiple linear regression analysis showed that beta-coefficient of eGFR was −0.155 (P=0.084) for urinary free Hyp, 0.134 (P=0.091) for urinary total Hyp and −0.172 (P=0.042) for urinary free-to-total Hyp ratio, even after controlling for covariates, including age, gender and proteinuria.

Conclusions: Our results suggest that urinary free-to-total Hyp ratio would be used as a novel endogenous marker of renal dysfunction.

KEYWORDS
- Hyp; - Hyp free; - Hyp total; - Proteinuria; - Serum mg; - EROD; - Hypogealase
- Chronic kidney disease; - Hyp excretion; - Protein turnover
- Measurement of urinary Hyp could be useful for assessing renal function in the patients with chronic kidney disease.
FR-PO311

The Effects of Serum Hemoglobin on Renal Survival in Pre-Dialysis CKD: Results from the Korean Cohort Study for Outcomes in Patients with CKD (KNOW-CKD)

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Background: The currently recommended hemoglobin (Hb) targets in CKD based on interventional studies using erythropoiesis stimulating agents (ESA) with outcomes such as cardiovascular events might be inappropriate for Hb target aiming for renal survival in CKD. Thus, we analyzed the effect of Hb on renal outcomes in a prospective pre-dialysis CKD cohort study.

Methods: We analyzed the data from 2,197 subjects in KNOW-CKD which is a currently on-going prospective cohort study of CKD in Korea (NCT01630486 at www.clinicaltrials.gov). Renal event (RE) was defined by the doubling of serum creatinine or 50% decrease in estimated GFR by CKD-EPI equation from the baseline as the initiation of renal replacement treatment. The subjects were grouped according to quartile value of Hb, with ranges of Q1 < 11.2 g/dL, Q2 11.3-12.7 g/dL, Q3 12.8-14.2g/dL and Q4 >14.3g/dL respectively.

Results: Out of 2,197 subjects, a total of 577 subjects (26.3%) developed RE during the mean follow up of 1,289.3±595.5 days. Cox regression analysis adjusted by sex, age, eGFR, urinary albumin to creatinine ratio, systolic blood pressure, history of diabetes mellitus(DM), hypertension, coronary artery diseases (CAD), hypercholesterolemia, smoking and alcohol revealed that each 1g/dL increase of Hb was associated with 19.4% risk reduction for RE (HR=0.806; 95% CI 0.758-0.858, p<0.000). Time dependent Cox regression adjusted by the same variables revealed that RE decreased along with Hb quartile groups (Q1: reference, HR=0.463; 95% CI 0.303-0.709; p=0.000, Q3: HR=0.176; 95% CI 0.094-0.328, p<0.000, Q4: HR=0.098; 95% CI 0.041-0.234; p=0.000, respectively). Even in age and sex strata, the effects of Hb on RE were also consistent in subjects with higher cardiovascular risk factors such as DM, CAD, or coronary artery calcium score>100. USA were included in only 17 subjects (7.6%) in which RE developed in 101 subjects (60.5%). It was also evident in ESA-receiving group in which each 1g/dL increase of Hb was associated with 21.1% risk reduction for RE (HR=0.799; 95% CI 0.677-0.943, p=0.000).

Conclusions: Targeting higher Hb level than current guideline was associated with the favorable renal outcomes in pre-dialysis CKD irrespective of the presence of higher cardiovascular risks or the usage of ESA.

FR-PO312

Clinical Factors, Non-neoplastic Histological Variables and Kidney Function in Patients Undergoing Partial Nephrectomy in Solitary Kidneys Bilateral Renal Neoplasms

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Background: Significant nephron mass reduction after nephrectomies carries the risk of substantial worsening kidney function. We aimed to evaluate the relationship among clinical, non-neoplastic histological abnormalities and glomerular filtration rate (eGFR) after partial nephrectomy (PN) in solitary kidneys and bilateral PN. Methods: We included patients, 24 with PN in a solitary kidney and 33 with bilateral PN. We used Pearson coefficient correlations and logistic regression analyses to evaluate the association between age, hypertension (HTN), diabetes, baseline eGFR, histological variables and post-nephrectomy eGFR at discharge. Results: The mean age was 62 ± 13 years. The majority had HTN (81%), 23% had diabetes and 46% had chronic kidney disease. The baseline eGFR was 64 ± 26 ml/min/1.73m². Of the 36 patients with non-neoplastic histological data available, 75% had interstitial fibrosis (IF), 83% had global glomerulosclerosis (GGS) and 92% had arteriolar sclerosis (AS). Post-nephrectomy eGFR correlated with baseline eGFR (r=0.7; p<0.001) and IFs (r=−0.4, p=0.05). However, not statistical significant, there was a trend in the correlation between post-nephrectomy eGFR and GGS (r=0.3; p=0.07). Multivariable-adjusted logistic regression analysis, post-nephrectomy eGFR in 45 to 50 ml/min/1.73m² was significantly associated with lower baseline eGFR (odds ratio [OR] per 10 units change in eGFR, 0.5; [95% confidence interval (CI), 0.3-0.7]) and PN in a solitary kidney compared to bilateral PN (OR, 6.06 [95% CI, 1.3-34.2]).

Conclusions: Lower baseline eGFR levels and PN in a solitary kidney compared with PN were independently associated with significant greater odds of post-nephrectomy eGFR < 45 ml/min/1.73m². IF was significantly correlated with post nephrectomy eGFR.

FR-PO313

A Novel Single Domain, I-Body AD-114, Attenuated Kidney Fibrosis Through Targeting CXCR4

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Background: Kidney fibrosis, the final common pathway of various forms of chronic kidney disease (CKD), affects 10% of the world’s population. However, the efficiency of current therapies is limited. The G-protein coupled C-C-X-C chemokine receptor 4, CXCR4, is a potential therapeutic target for tissue fibrosis. To date, the only approved CXCR4 antagonist (AM3100) was terminated due to its off-target cardio toxicity. Recently we have developed a fully human single-domain antibody-like scaffold termed i-body AD-114 that targets CXCR4 with specific high binding affinity to CXCR4. AD-114 selectively blocks CXCR4 signaling and has shown anti-fibrotic effects in pulmonary fibrosis. The present study demonstrates the renoprotection of AD-114 in kidney fibrosis.

Methods: The CXCR4 expression was upregulated in patients with chronic kidney disease (CKD) compared with control groups (p<0.001, N=6). In both prophylactic and therapeutic models, the results showed AD-114 markedly ameliorated renal function impairment (24h urine albumin/creatinine ratio) and fibrotic kidney remodeling (Masson’s trichrome staining) and attenuated the FA-induced increase of collagen-4 (COL-4), fibronectin (FN), collagen-1(COL-1), collagen-3 (COL-3) and α-SMA (HIC) in kidneys compared to negative control i-body.

Conclusions: AD-114 effectively ameliorated fibrotic kidney fibrosis remodeling through targeting CXCR4 signaling in a murine model of kidney fibrosis.

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FR-PO314

Assessment of the Feasibility of Measuring Salivary Urea by Attenuated Total Reflection-Fourier Transform Infrared Spectroscopy to Diagnose and Stage CKD

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Background: Attenuated total reflection Fourier-transform infrared (ATR-FTIR) spectroscopy has been shown to provide a straightforward, reagent-free method for the simultaneous diagnosis of various kidney diseases including the kidney transplant patient. This technology has been miniaturized into a handheld device and is available as a handheld system. It is also applicable for portable use in the clinical setting. It therefore presents itself as a potential method for the disease diagnosis in chronic kidney disease (CKD) patients. However, these studies employed costly, labour-intensive commercial kits which limits wider applicability, therefore we assessed the feasibility of ATR-FTIR spectroscopy as an alternative method to measure salivary urea in patients with different stages of CKD.

Methods: The ATR-FTIR spectra of dried saliva samples from 6 healthy controls and 20 CKD patients (stage 1-5) were recorded and analysed to provide their salivary urea concentrations in the clinically-relevant range. The correlation between salivary urea and serum urea in chronic kidney disease (CKD) patients. However, these studies employed costly, labour-intensive commercial kits which limits wider applicability, therefore we assessed the feasibility of ATR-FTIR spectroscopy as an alternative method to measure salivary urea in patients with different stages of CKD.

Results: The limit of detection of salivary urea by ATR-FTIR spectroscopy was 2 mM. Statistically significant differences in salivary urea concentration were demonstrated between healthy subjects (4.6 ± 0.7 mM) and CKD patients stages 1-5 (CKD 3: 6.8±0.7 mM, p<0.05; CKD 4: 9.1±1.6 mM, p<0.001; CKD 5: 14.8±1.6 mM, p<0.001). However, no significant differences were detected between CKD stage 1-2 and healthy controls. ROC analyses (the value ranging from 0.95-1) confirmed the suitability of the method for determination of salivary urea concentrations in the clinically-relevant range, with the sensitivities of 0.86-1 and specificities of 0.93-1.

Conclusions: This study showed that salivary urea can be measured by ATR-FTIR spectroscopy with significant differences in salivary urea levels between CKD stage 3-5 and normal subjects. The development of simple single-use ATR-FTIR spectroscopy devices may be a screening tool for rapid quantitation of salivary urea to diagnose CKD.
FR-PO315
CT Mapping of Spinal and Vascular Abdominal Urate Deposition with Correlation to Uric Acid Level
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Background: Gout prevalence is about 1-5% in the western world, predominantly in elderly men. Monosodium urate (MSU) deposit outside extremities has been scarcely investigated yet may be a potential indicator of tophus burden and impending clinical deterioration.

Methods: After IRB approval, retrospective single center analysis of all Dual Energy CT abdomen and pelvis scans from January 2007 to July 2018 was conducted. The inclusion criteria were: age > 50 years, gout asymptomatic with or normal uric acid level. All cases were then assessed by two radiologists using a validated software. The study was divided into two subcohorts based on gender, and assessed along three main parameters: aortic, other vascular (e.g. renal, iliac, etc) and lumbar deposits.

Results: 351 cases met the inclusion criteria (197 males, 56% and 154 females, 43.9%). Aortic, other vascular and spinal deposits were detected in 20.2%, 21.7% and 5.1% respectively. A statistical significant association between gender and gout deposits in all the three groups was detected with deposits more prevalent in men than women in all groups (27.4%, 31.5% and 7.6% for men and 11.0%, 9.1% and 1.9% for women in abdominal aorta, other vessels and lumbar spine respectively). Regression analysis showed that uric acid levels cannot predict aortic deposits in either men (p=0.91) nor women (p=0.198) groups. On the other hand, uric acid level can significantly predict other vascular deposits in women only (r=0.005, p=0.003) and the spinal deposits in both men (r= 0.01, p=0.003) and women (r=0.002, p=0.037) groups. Study limitations include retrospective analysis and feasibility sample.

Conclusions: MSU CT mapping was positive in gout-asymptomatic patients with normal or high uric acid levels and are more prevalent in men than women. Uric acid level cannot predict aortic deposits but can predict other vascular deposits in women only and spinal deposits in both men and women.

FR-PO331
Pilot Study of Relaxolase in Subjects with Severe Enteric Hypoxaluria and Hypoxalemia: A Pro Tem Analysis of Study AALLN-177-206
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Background: Enteric hypoxaluria (EH) refers to increased urinary oxalate (UOx) excretion as a complication of fat malabsorption due to GI surgery, or other gastrointestinal conditions. Hypoxaluria, a major risk factor for kidney stones, can also lead to chronic kidney disease (CKD), including end-stage kidney disease. With decreasing kidney function, plasma oxalate (POx) levels can rise, resulting in oxalate deposition in the kidneys and other tissues. Relaxolase is an oral enzyme which degrades oxalate in the GI tract. This study is enrolling patients with EH and CKD to examine the potential of relaxolase to reduce UOx and POx.

Methods: This open label study is enrolling patients with EH, CKD and hypoxalemia (UOx ≥40 mg/24h, eGFR <45 mL/min/1.73m2 and POx >5 µmol/L), who receive relaxolase 7.500 mg orally 5 x/d for 12 weeks. POx and 24h UOx are obtained monthly; in subjects on dialysis, POx is collected immediately before a dialysis session.

Results: To date, 4 EH subjects have completed the study; two have Stage 3 and 3bT CKD (short bowel syndrome, fat malabsorption xpl, and kidney transplant) and 2 are on hemodialysis (Cronh’s disease, pancreatic insufficiency). Treatment compliance was >90% on average, and therapy was well tolerated. Relaxolase reduced 24-hr UOx (normalized to creatinine) by 29-42%, and POx by 16-49%. The figure below provides high level case summaries, and the bars show the % change in UOx (yellow) or POx (red) from baseline.

Conclusions: In this population, relaxolase was well tolerated and reduced both UOx and POx, suggesting the potential for reducing systemic oxalate deposition with chronic therapy. These preliminary data support further testing of relaxolase in patients with severe EH. To our knowledge, this is the first therapeutic reduction in plasma oxalate in patients with EH and CKD with oxalosis.

FR-PO317
Association of Serum Alkaline Phosphatase with CKD and Cognitive Function in Patients with Diabetes and Acute Coronary Syndrome
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Background: Patients with diabetes and chronic kidney disease (CKD) have increased risk for cardiovascular disease events and vascular dementia. Alkaline phosphatase (ALP) is a risk marker and possible risk mediator for cardiovascular (CV) disease, Alzheimer’s disease and vascular dementia. ALP has been reported to cross the blood brain barrier and associate with worse cognitive risk for patients, potentially via vascular dementia or dephosphorylation of tau. Apabetalone is a bromodomain and extraterminal (BET) inhibitor selective for bromodomain 2, lowers ALP in a dose-response fashion and is being evaluated for prevention of CV disease events in the phase 3 BETonMACE trial. We examined baseline data from that trial to define the associations of ALP with CKD and cognitive function.

Methods: BETonMACE compares cardiovascular outcomes with apabetalone or placebo in 2425 patients with diabetes and acute coronary syndrome. CKD was defined by eGFR < 60 mL/min/1.73m2. Cognition was assessed by the Montreal Cognitive Assessment tool (MoCA) in patients aged 70 and older at baseline (n=467) in all 4 BETonMACE trials. We examined baseline data from that trial to define the associations of ALP with CKD and cognitive function.

Results: CKD was present in 11% (n=263) and was associated with age, female sex, longer history of diabetes, and higher ALP. Approximately half of the population showed MoCA score <26 suggesting early cognitive impairment. Lower MoCA score was associated with: a) higher ALP, and, b) with presence of CKD.

Conclusions: Elevated ALP is associated with poorer cognitive function and greater prevalence of CKD. Apabetalone, which lowers ALP, is being evaluated for effects on CV events, CKD, and cognitive function in the phase 3 BETonMACE trial reporting 2019.
The KDIGO 2012 CKD Classification System Improves Physician Recognition and Management of Kidney Disease: A Randomized Vignette Study

Background: Chronic kidney disease (CKD) is a global issue with high morbidity and mortality rates. New international guidelines based on estimated glomerular filtration rate (eGFR) versus albuminuria were introduced 2012 to help with diagnosis, classification, referral, and treatment, but their clinical utility has not been evaluated. We therefore wanted to determine if KDIGO guideline helps physicians recognize and appropriately care for CKD patients.

Methods: We conducted a randomized vignette experiment with fractional factorial design based on 6 kidney-related scenarios and 3 laboratory presentation methods reflecting the KDIGO guideline. Participants evaluated one of three subsets of the 18 vignettes (i.e. 6 vignettes each) from January 2001 to December 2016 were enrolled in the cohort study. eGFR and albuminuria were presented as the “Old” (high/low levels), “Modern” (eGFR reported automatically), or “Future” (eGFR + albuminuria categorization or risk for complications = full 2012 KDIGO classification) laboratory report. Logistic regression modelled correct CKD management with laboratory presentation technique, clinical scenario, and other physician covariates. We included 249 interns, general practitioners, and residents/fellows from Korea and the US participating in postgraduate meetings and courses provided to physicians in training.

Results: When kidney laboratory data was presented as the “Modern report” (automatic eGFR calculation), there was a significantly higher probability for correct patient management compared to the “Old report” (OR 1.57, p=0.0001). Additional significant improvement was obtained with the “Future report” (OR 2.26 for correct answer, p<0.01 vs. “Old report”; OR 1.45, p=0.005 vs. “Modern report”). The 2012 KDIGO classification system improved physician management in 4 of the 6 clinical scenarios covering a wide range of kidney-related topics. Interaction analysis showed that GPs and those with 1-3 years of internal medicine experience had the strongest improvements in the new presentation techniques.

Conclusions: Automatic GFR estimation, albuminuria categorization, and notification of the associated risk for complications improve most physicians’ recognition and management of a wide range of CKD clinical scenarios.

Funding: Government Support - Non-A.US.
Pericutaneous kidney biopsy is a fundamental diagnostic tool in Clinical Nephrology, but there is concern as to whether it can be performed by Fellows. The aims of this study were to report a 10-year experience of a tertiary academic center. At the qualification of Fellows to perform ultrasound-guided percutaneous biopsies of native kidneys.

Methods: This is a retrospective cohort study of native kidney biopsies performed between January/2009 and December/2018. The procedures were performed by Fellows and supervised by experienced Nephropaths. Predictors of complications, clinical outcomes and sample quality were analyzed.

Results: A total of 1387 biopsies was performed; the mean age was 40.7±16.2 years, with 60% of whites (n=830) and the Body Mass Index was 25.2±4 kg/m². At the time of biopsy, lab exams were: serum Creatinine 2.2±1.9 mg/dL, BUN 31.3±16 mg/dL, Hemoglobin 11.7±1.8 g/dL and Platelet count 262±95×10³/μL. As to complications, 91.4% (n=1268) had none, 4.5% (n=63) had hematuria; 2% (n=28) had symptomatic hematoma; 2% (n=28) had majorcomplications, defined as the need for transfusion and/or arteriography. Independent predictors of major complications were female gender (OR 2.9; CI 1.01 to 8.1; p=0.049), hemodialysis (OR 8.0; CI 2.9 to 9.2; p=0.001), low platelet count (OR 0.99; CI 0.98 to 0.99; p=0.035) and hemoglobin level (OR 0.61; CI 0.40 to 0.96; p=0.036). The average sample contained 18±2 mL for light microscopy, 11±3 mL for immunofluorescence, while 90% of samples contained at least 8 glomeruli.

Conclusions: Supervised kidney biopsies performed by Fellows in training were safe and efficient. Female gender, hemodilasy, low platelet count and hemoglobin levels were independent predictors for major complications.

Online Peer Mentoring Is Associated with Improved Burden Score Among Caregivers of Patients with CKD

Methods: A 16-hour structured program trained CKD patients and their caregivers to become peer mentors to newly diagnosed patients with CKD and their caregivers. Caregivers of patients with stage 4 or 5 stage 5 CKD (n=86) were randomly assigned to online PM (n=29), FTF PM (n=29) or usual care (n=28). Online PM consisted of weekly communication through an interactive online platform, and more frequently through posts by the mentee. For the FTF group, the frequency of contact by a mentor was weekly by phone and monthly visit. PM was maintained for at least 6 months. Usual care participants received an information book about care of CKD patients. We used the 22-item Zarit Burden Interview (ZBI) to measure caregiver burden at baseline and months 12 and 18. Caregivers of patients with stage 4 or stage 5 CKD who had completed the ZBI at baseline and at least 1 year after education. We divided into 4 slope categories according to eGFR levels before and after education; slope categories were defined as slow-slow, fast-slow, slow-fast, fast-fast eGFR decliner. Outcomes are ESRD and eGFR decline of > 30%. Kaplan-Meier curve and Cox proportional hazards model with propensity adjustment were used to assess the association between slope categories and incidence of renal events. Patients with fast-slow eGFR decline were used as a reference group.

Results: The weighted mean age of study participants was 58 (49-78 years) and 130 (67%) were male. The median levels of baseline eGFR were 33 (21-48) mL/min/1.73m². During the 12 months follow-up period of 35 months, renal events occurred in 55 participants. Crude Kaplan-Meier analysis showed patients with slow-slow and fast-fast eGFR declines were significantly associated with renal events compared with those with slow-fast and fast-slow eGFR declines (p<0.001). In adjusted Cox hazard analysis, hazard ratios for outcomes were 1.72 (95%CI 1.72-22.2) for slow-fast; 5.15 (95%CI 1.72-22.2) for slow-slow; and 2.72 (95%CI 2.53-30.7) for fast-fast eGFR declines. Additionally, e-statistics of CKG slope before education for renal events was 0.596 but that of eGFR slope after education was 0.843 and the cut-off level was -2.5 mL/min/1.73m²/year.

Conclusions: Improvement from fast to slow eGFR decline via CKD education was significantly associated with better renal prognosis. However, CKD patients with rapid eGFR decline of ≤-2.5 mL/min/1.73m² after education have poor renal outcomes.

FR-P0325
Are Patients’ Needs for Shared and Informed Decision Making About Kidney Replacement Therapy Being Addressed?

Methods: As part of the PREPARE NOW trial, we asked adults with CKD if they desired shared decision making [SDM] about CKD treatments (i.e., “the doctor and I make the final decisions together”). We also asked participants to what extent they had discussed other treatment options and potential treatment impacts with their treatment team as well as their satisfaction with discussions. We derived 2-year kidney failure risks from medical records. In multimodelar variables, we quantified associations of participants’ characteristics with treatment discussions and associations of discussion quality with patient satisfaction.

Results: Among 456 participants, 322 (70.6%) desired SDM. These 322 had a mean (SD) age of 70.2 (±12.7) years, 60% were female, 96% White, and 62% high school or less educated. They received nephrology care for a median (IQR) of 3.85 (1.94-4.9) years. Half (52%) saw their nephrologists at least every 6 months, and 17% had a 2-year risk of kidney failure >10%. Only a third (35%, n=113) of those desiring SDM had discussed any treatments (peritoneal dialysis [45%], in-center hemodialysis [86%], home hemodialysis [50%], kidney transplant [59%], and conservative management [70%]). Few discussed other treatment options and potential treatment impacts with their treatment team as well as their satisfaction with discussions. After adjustment, those seeing nephrologists for longer had greater odds of having discussed transplant (OR [95% CI] 1.16 [1.02-1.32] per 3 month increase, p=0.02). The odds of treatment satisfaction with SDM (4%) were lower for a family (37%), length of life (49%), or quality of life (60%). Still, a majority (64%) were ‘completely’ satisfied with discussions. After adjustment, those seeing nephrologists for longer had greater odds of having discussed transplant (OR [95% CI] 1.16 [1.02-1.32] per 3 month increase, p=0.01) and treatment impacts (OR [95% CI] 1.69 [1.26-2.27], p<0.01) had greater odds of being ‘completely’ satisfied.

Conclusions: Most patients prefer sharing CKD treatment decisions with their physicians, but treatment discussions are infrequent and do not address key treatment aspects. More frequent and thorough discussions could improve patients’ SDM experiences.
were judged as having moderate or high comorbidity. The median eGFR at the time of initiating dialysis in this study was 13.8 (IQR 7.0) mls/min/1.73 m2. 281 (83.1%) patients had died by the date of last follow-up. 46% of patients had a median eGFR > 10 mls/min/1.73 m2 at last follow-up. Median eGFR at the time of death in CM patients was 9.1 mls/min/1.73 m2 (IQR 7.0). 42% of those who died had a last recorded eGFR > 10 mls/min/1.73 m2. 32 patients (9.4%) developed severe acute kidney injury during follow-up and 8 of these (2.4%) received dialysis. 15 patients (4.4%) changed their decision from CM to dialysis. The median rate of eGFR decline in the year before CM decision was 3.8 (IQR 6.5) mls/min/year in the whole group. eGFR at CM decision was inversely related to rate of eGFR decline (Pearson’s correlation coefficient: r=-0.68, p<0.05). Tertile 1 (slowest decline: eGFR >10 ml/min/1.73 m2), tertile 2 (14.7 ± 5.7 ml/min/1.73 m2) and tertile 3 (13.5 ± 5.5 ml/min/1.73 m2) differed significantly (p<0.05) with high comorbidity compared to those with low-moderate levels (14.7 [IQR 5.7] vs 13.5 [IQR 5.5], p=0.032).

For analysis: Many patients on the conservative pathway died at relatively high levels of kidney function (eGFR >10 ml/min/1.73 m2), probably related to extrarenal comorbidity. Decision making seems to focus more on age, comorbidity, and absolute levels of eGFR than on eGFR trajectory. As a result of this it is possible that some patients are unnecessarily burdened with decisions relating to choices between options of renal replacement therapy.

FR-PO327

KDQOL and Quality of Life in Patients with Disease Progression in Adults with Advanced CKD Not on Renal Replacement Therapy
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Background: Chronic kidney disease (CKD) is associated with reduced health-related quality of life (HRQOL). However, the association between HRQOL and disease progression prior to renal replacement therapy (RRT) is unclear. We examined the influence of HRQOL on RRT progression in adults with Stage IV CKD (eGFR 15-29 ml/min/1.73 m2) not on RRT.

Methods: Overall, 172 adults living in Tasmania, Australia provided data at baseline (2010-2012, 2016-2018). Of these, 152 participants attended a clinic where the Kidney Disease Quality of Life-Short Form was completed. Disease progression was examined using i) percentage annual change in eGFR (eGFR at follow-up/eGFR at baseline)1/2 years elapsed between measurement), II) progression to CKD Stage V (eGFR<15 ml/min/1.73m2) or death. Generalized linear models were used to examine associations between HRQOL and disease progression adjusted for sociodemographic variables, comorbidities and laboratory factors.

Results: Overall, participants were predominantly male (63%) with a mean age of 72.2 ± 10.2 years. At baseline, mean eGFR was 22.1 ± 4.2 mls/min/1.73m2 and serum creatinine was 242 ± 56.4 µmol/L. Mean annual decline in eGFR was -4.2 ± 2.0 mls/min/1.73m2. Mean percentage annual change in eGFR was 8.8 ± 6.1% with 6 (35%) participants progressing to CKD Stage V or death. Mean time to outcome was 446 ± 289 days. Mean mental component summary (MCS) was 50.9 ± 10.3 and physical component summary (PCS) was 56.4 ± 4.2 mls/min/1.73m2. Mean percentage annual change in eGFR was -0.46 ± 0.46, 95% CI 0.05-0.88, R²=0.04, R²=0.04, P<0.05) were associated with lower risk of all-cause mortality at year 1 (RR, 0.40, 95% CI, 0.26-0.63), year 2 (RR, 0.57, 95% CI, 0.35-0.91) and end of study (RR 0.66, 95% CI, 0.51-0.84), while no difference was detected at year 3 (RR, 0.68, 95% CI, 0.41-1.14) and year 5 (RR, 0.87, 95% CI, 0.71-1.06). There was no difference of annual hospital inpatient days were pooled using standardized mean differences (SMD)

Results: Among 1,075 citations, 14 were included that involved 16794 and 3857 patients initially treated with dialysis or conservative care. Dialysis was associated with lower risk of all-cause mortality at year 1 (RR, 0.40, 95% CI, 0.26-0.63), year 2 (RR, 0.57, 95% CI, 0.35-0.91), and end of study (RR 0.66, 95% CI, 0.51-0.84), while no difference was detected at year 3 (RR, 0.68, 95% CI, 0.41-1.14) and year 5 (RR, 0.87, 95% CI, 0.71-1.06). There was no difference of annual hospital inpatient days (SMD, 14.64, 95% CI, -173.56-202.84)

Conclusions: Dialysis results in lower mortality in the short-term (the first two years) but may not improve survival thereafter (after the third year).

FR-PO328

A Prospective Randomized Controlled Trial of Lifestyle Management for Preventing Respiratory Tract Infection in Patients with CKD
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Background: Respiratory tract infection (RTI) is a risk factor for progressive loss of kidney function. Lifestyle management has shown potential effect to prevent RTI in chronic kidney disease (CKD) patients. The study assessed the efficacy and safety of lifestyle management in reducing RTI of CKD patients.

Methods: In this prospective randomized controlled trial (RCT), 540 patients with CKD not on RRT were randomly assigned 1:1 to either lifestyle management group or control group for 48 weeks. Both groups received conventional care according to guideline recommendations, while patients in lifestyle management group additionally accepted health lifestyle management involving life behavior mission, acupoints massage and dietary guidance. The primary outcome was the interval of first occurrence of RIT. Secondary outcomes included the incidence of endpoint events, immunity indexes, urinary protein creatinine ratio (PCR), liver and kidney function, cardiovascular events. This study was registered with Chinese Clinical Trials Registry, ChiCTR-IOR-17012654.

Results: 540 patients were screened, of whom 262 were randomly assigned: 161 to the lifestyle management group, 161 to the control group (30 patients were excluded from analysis). The intervention was started on January 1st, 2016 to December 31st, 2018. 77 (66.4%) patients in the life management group and 78 (67.2%) patients in the control group developed RIT over 48 weeks. Among them, 49 patients (42.2%) and 52 patients (44.8%) had RIT more than twice respectively. The interval of first occurrence of RIT in the life management group was 85.6±5.9 days, which was similar to the control group (84.3±9.0 days). The survival analysis showed that the patients with high frequency of RIT (>3 times within one year before enrollment) in the life management group had a lower risk of RIT than the control group (68 days vs. 65 days). (HR 0.87, 95% CI 0.57-1.31). The level of IgA, C4, C1H0, CD3CD4, CD3CD8/CD21CD8 in the life management group was higher than the control group, suggesting that immunity function of the patients was enhanced after lifestyle management. There was no significant difference in endpoint events, liver and kidney function, PCR and other safety indexes between the two groups.

Conclusions: Lifestyle management shows the effect to reduce the prevalence of RIT in CKD and slow CKD progression.

Funding: Government Support - Non-U.S.
Online Peer Mentoring and Quality of Life Among Patients with CKD
Eric Mark J. Lopez, George C. Ezeji, Jose C. Romeu, Korey Bartolomeo, Vernon M. Chinchilli, Nasrollah Ghalamrani. Penn State College of Medicine, Hershey, PA.

Background: Quality of Life (QOL) is an important medical outcome in patients with chronic kidney disease (CKD). Peer mentoring (PM) is a potentially effective intervention to improve QOL. This study evaluates the differences in the effect of online PM, face-to-face (FTF) PM and usual care on QOL outcomes in patients with CKD.

Methods: A total of 155 patients with stage 4 or stage 5 CKD were randomly assigned to online PM, FTF PM or usual care. Online PM consisted of weekly communication through an interactive online platform, and more frequently through posts initiated by the participants. For the FTF group, the frequency of contact by a mentor was weekly by phone and monthly FTF visit. PM was maintained for at least 6 months. Usual care participants received a printed copy of an information handbook and were encouraged to discuss questions with their care team. All participants completed the Short Form Kidney Disease Quality of Life (KDQOL) tool designed specifically for patients with CKD, at baseline, at 12 months and at 18 months. We used linear mixed effect models to estimate the slope of change of subsets of KDQOL score over time. SAS, version 9.4 was used for data analysis.

Results: A total of 117 patients completed the 18 month assessment. Baseline KDQOL scores and demographic characteristics were similar among the 3 groups. Among the online PM group, there was a significant improvement in the following components of the KDQOL score: Effects of Kidney Disease (EKD) (Slope estimate [SE]:4.13; 95% confidence interval [CI]:[2.75-5.50]); Burden of Kidney Disease (B KD) (SE:5.44; CI: 1.24, 9.66 [P = 0.001]);SF-12 Physical Composite (SE:2.50; CI:10.95, 4.06 [P=0.002]);SF-12 Mental Composite (SE:3.46; CI:1.78, 5.13 [P=0.0001]). In subgroup analyses, the improvements noted among the online PM group were not seen among white patients. There were no statistically significant changes in KDQOL scores among the FTF PM group and the control group.

Conclusions: Online PM was associated with improved scores in subsets of the KDQOL among patients with advanced CKD. This improvement is influenced by race. Funding: PCORI

Funding: Other U.S. Government Support

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Background: Quality of Life (QOL) is an important medical outcome in patients with chronic kidney disease (CKD). Peer mentoring (PM) is a potentially effective intervention to improve QOL. This study evaluates the differences in the effect of online PM, face-to-face (FTF) PM and usual care on QOL outcomes in patients with CKD.

Methods: A total of 155 patients with stage 4 or stage 5 CKD were randomly assigned to online PM, FTF PM or usual care. Online PM consisted of weekly communication through an interactive online platform, and more frequently through posts initiated by the participants. For the FTF group, the frequency of contact by a mentor was weekly by phone and monthly FTF visit. PM was maintained for at least 6 months. Usual care participants received a printed copy of an information handbook and were encouraged to discuss questions with their care team. All participants completed the Short Form Kidney Disease Quality of Life (KDQOL) tool designed specifically for patients with CKD, at baseline, at 12 months and at 18 months. We used linear mixed effect models to estimate the slope of change of subsets of KDQOL score over time. SAS, version 9.4 was used for data analysis.

Results: A total of 117 patients completed the 18 month assessment. Baseline KDQOL scores and demographic characteristics were similar among the 3 groups. Among the online PM group, there was a significant improvement in the following components of the KDQOL score: Effects of Kidney Disease (EKD) (Slope estimate [SE]:4.13; 95% confidence interval [CI]:[2.75-5.50]); Burden of Kidney Disease (B KD) (SE:5.44; CI: 1.24, 9.66 [P = 0.001]);SF-12 Physical Composite (SE:2.50; CI:10.95, 4.06 [P=0.002]);SF-12 Mental Composite (SE:3.46; CI:1.78, 5.13 [P=0.0001]). In subgroup analyses, the improvements noted among the online PM group were not seen among white patients. There were no statistically significant changes in KDQOL scores among the FTF PM group and the control group.

Conclusions: Online PM was associated with improved scores in subsets of the KDQOL among patients with advanced CKD. This improvement is influenced by race. Funding: PCORI

Funding: Other U.S. Government Support

High Incidence of Adverse Drug Reactions in Patients with Advanced CKD
Solené M. Laville, Marie Metzger, Benédicte Stengel, Christian Jacquelinet, Maurice Laville, Luc Frimat, Denis Fouque, Christian Combe, Valérie Gras, Julien Moragny, Izid Massy, Sophie Liabéd, CSEP, Interim U1018, Kidney and Heart Team, Villejuif, France; 2‘Agence de la biomédecine, Saint-Denis La Plaine, France; 3‘Université Claude Bernard, Pierre Benite, France; 4 CHU de Bordeaux, Bordeaux, France; 5 Ambroise Pare University Hospital, Boulogne-Billancourt/ Paris cedex, France; 6 Amiens University Hospital, Amiens, France; 7 Nancy University Hospital, Vandoeuvre les Nancy, France.

Background: The burden of ADRs is high in CKD patients. A low eGFR appears as a risk factor of undergoing ADRs and serious ADRs. Determinants of first serious ADRs were assessed by multivariate Cox regression model.

Results: At baseline, patients’ median age was 69 (IQR, 60-76), median eGFR was 32 (IQR, 23-41) mL/min/1.73m2 and the median number of medications was 8 per day. During a median follow-up of 2 years, 751 ADRs were reported in 536 patients, of which 150 were serious. The incidence rate of ADRs in patients with CKD stage 4 or 5 was 19.5[95%CI,17.6;21.4] per 100 person years (PY), against 10.9[9.7;12.1] per 100 PY in patients with CKD stage 3. We observed the same pattern for serious ADR. This difference was significant among male, but not among female patients and for serious ADR is any event that is fatal, life-threatening, permanently/significantly disabling, requires or prolongs hospitalization or medically important. Determinants of first serious ADRs were assessed by multivariate Cox regression model.

Other U.S. Government Support

Commercial Support - Amgen - Fresenius Medical Care - Lilly - GlaxoSmithKline(GSK) - Otsuka - ViforFresenius - AstraZeneca
Physician-Guided CKD Self-Management via Smartphone App Is Associated with Proteinuria Reduction: A Retrospective Cohort Study

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Background: Smartphone apps are increasingly popular for chronic disease management. However, the feasibility and effectiveness of smartphone apps to manage Chronic Kidney Disease (CKD) are unknown. This study assessed the feasibility and effectiveness of a smartphone app for self-management of CKD.

Methods: The “Kidney online” app is a patient-facing, algorithm assisted, physician-guided, and interactive app in Chinese. Patients with a self-reported diagnosis of CKD used the app to track their symptoms, physical activities, vital signs, and laboratory test results. Participants received automatic recommendations by the proprietary algorithm and consulted their assigned tele-nephrologists on an ad-hoc basis. Patients who were enrolled in this app for more than 3 months between Dec 2016 to Nov 2018 with proteinuria a 500mg/24hr were eligible for analysis. Changes in blood pressure (BP), estimated glomerular filtration rate (eGFR), and 24-hour proteinuria level were evaluated as outcomes between quartile groups, stratified by the total number of patient-physician conversations. Content analysis of the conversations was performed.

Results: Among the 2351 adult app users, 468 patients were identified for analysis. The total number of patient-physician conversations was 26 ± 10, 60 ± 10, 103 ± 16, and 259 ± 4.9 from the 1st to the 4th quartile respectively; and the reduction of 24-hr proteinuria was 162.2 ± 195.3, 859.8 ± 193.6, 164 ± 195.4, and 889.3 ± 194.5mg respectively (p<0.003). The odds ratio of <30% proteinuria reduction in the 4th quartile compared to the 1st quartile was 0.452 (p=0.007) after adjusting for age, sex, clinical parameters, and medications. Compared to the 1st quartile, the 4th quartile received more alerts in hypertension (43.6% vs. 24.1%, p=0.01), and hypotension (2.3% vs. 4.5%, p=0.01). The textual analysis of the patient-physician conversations revealed themes on self-monitoring of BP, awareness of laboratory results, medication optimization and adherence, dietary modification, and education of the app functionalities.

Conclusions: More frequent patient-physician interactions via smartphone app are associated with better proteinuria control. A patient-friendly smartphone app for record keeping and communication is feasible and effective for physician-guided CKD self-management.

Funding: Commercial Support - Beijing Kidney Health Technology Company, China, Private Foundation Support

Timing of Arteriovenous Access Creation in CKD Patients: The French CKD-REIN Study

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Background: Most guidelines on vascular access recommendation create an arbitrary timing (AV) access in eligible patients when estimated glomerular filtration rate (eGFR) is 15-30 ml/min. We sought to assess whether clinical practices align with these recommendations.

Methods: We identified participants undergoing a first AV access creation in CKD-REIN, a ongoing prospective cohort study that includes 3033 adult patients under nephrology care for CKD in 40 clinics in France. We assessed the timing of AV access creation according to eGFR within a period of -90 to +30 days from surgery. We described patient characteristics and cumulative incidence of hemodialysis start and death according to the timing of AV access creation.

Results: Of the 335 participants who underwent a first AV access during a median follow-up of 2.6 years, 270 (81%) had contemporaneous information on eGFR level and were included in this analysis. Median eGFR at AV access creation was 13 ml/min (IQR 10, 19) and creatinine 187 (15, 360) μmol/L. More frequent in men then in women (78% vs 65%, p=0.03), and in patients with then without diabetes (63% vs 47%, p=0.02), cerebrovascular disease (26% vs 15%, p=0.04) and coronary artery disease (42% vs 24%, p=0.003). Conversely, participants with AV access creation <15 eGFR <15 had more nephrology visits over the last 6 months prior to surgery (29% vs 13% with ≥3 visits, p=0.001). The 2-year cumulative incidence of hemodialysis initiation was 79% in participants with eGFR 15-30 and 89% for participants with eGFR <15, with a median time from surgery of 11 (IQR 6-20) and 3 (2-11) months, respectively (p<0.001). Thirteen patients died before requiring hemodialysis. Cumulative incidence of death tended to be higher in the 15-30% (<15% (4%) eGFR group, but this difference was not statistically significant (p=0.23).

Conclusions: In patients under nephrology care in France, later AV access creation seems to be favored over the recommended earlier creation. This practice may limit unnecessary AV access creation (i.e. patients dying before requiring dialysis), but its impact on transitory catheter use is to be assessed.

Funding: Private Foundation Support, Government Support - Non-U.S.
Patients’ Reliance on Non-Nephrologists for CKD Treatment and Advice

Methods: We conducted a cross-sectional study of adults receiving nephrology care and enrolled in the PREPARE NOW trial to assess their reliance on their nephrologist, primary care provider (PCP), another specialist, or all their providers equally for CKD treatment and advice. We also asked participants about the frequency and patient-centeredness (range 0 [least] to 12 [most]) of their nephrology care. We assessed participants’ kidney function and comorbidity (Charlson Comorbidity Index, range 0-37) using data from their electronic health records. In multivariable analyses, we quantified associations between participants’ reliance on their nephrologists (vs. others) for their CKD treatment and demographics, comorbidity, kidney function, and perceived patient centeredness (range 0 [least] to 12 [most]) of their nephrology care. We assessed associations between participants’ reliance on their nephrologists (vs. others) for their CKD treatment and advice.

Conclusions: Many nephrology patients rely on non-nephrologists for CKD treatment and advice. Establishing longitudinal, patient-centered nephrology care and partnerships with patients’ other physicians may help ensure patients adhere to nephrologists’ CKD treatment and advice.

Clinical Context for RBC Transfusions in CKD Patients: Results of the START-CKD Trial

Background: Erythropoiesis-stimulating agents (ESA) have been used in CKD patients to reduce the need for Tx. The START-CKD trial evaluated an ESA treatment (darbepoetin) on the incidence of RBC Tx in anemic CKD subjects using either a hemoglobin (Hgb)-based titration algorithm (TD) or a fixed dose (FD). This study collected prospectively Tx data.

Methods: This was a US phase 3, multicenter, randomized, double-blind, parallel group study. 377 participants with stage 3-5 CKD were treated in the TD and in the FD arms for a period of up to 2 years. Tx per protocol, were performed as deemed necessary by the treating physician and were prospectively adjudicated with the reasons and context for Tx recorded.

Results: The average age of the subjects, baseline Hgb and estimated GFR were balanced between the arms: 69 yrs, 9.0 g/dL and 22 ml/min/1.73m2. The primary endpoint of the study was similar between the TD and FD, 24% in both arms with an average Hgb at the time of first Tx of 7.4 vs 7.3 g/dL respectively. All Tx events are shown below:

Conclusions: The main reason for Tx was symptoms which were principally constitutional. Bleeding accounted for approximately 20% of Tx. The Hgb at the time of Tx was consistent with transfusion practice guidelines.

Funding: Commercial Support - Amgen

FR-PO337

Clinical Context for RBC Transfusions in CKD Patients: Results of the START-CKD Trial

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Background: Erythropoiesis-stimulating agents (ESA) have been used in CKD patients to reduce the need for Tx. The START-CKD trial evaluated an ESA treatment (darbepoetin) on the incidence of RBC Tx in anemic CKD subjects using either a hemoglobin (Hgb)-based titration algorithm (TD) or a fixed dose (FD). This study collected prospectively Tx data.

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Conclusions: The main reason for Tx was symptoms which were principally constitutional. Bleeding accounted for approximately 20% of Tx. The Hgb at the time of Tx was consistent with transfusion practice guidelines.

Funding: Commercial Support - Amgen

FR-PO338

Kibow Multisite Hope Study-CKD IV Randomized Clinical Trial Protocol: A Unique Double-Blind Placebo-Controlled Cross-Over Design Using Renadyl™ with Standard-of-Care Therapy (n=500-600, 20-25 sites in the United States)

Natarajan Ranganathan,1 Usha N. Vyas,1 Pari Ranganathan,1 Anthony Irvin,1 Alan D. Wemberg,2 Kibow Biotech, Inc., Newtown Square, PA; 2Mount Sinai, Hackensack, NJ.

Background: CKD patients experience poor quality of life due to high levels of uremic toxins in the blood. Treatment options for CKD patients are restricted diet and medications for primary comorbidities like hypertension and diabetes. Outcomes like fatigue pain and anxiety though major concerns and critically important to patients and clinicians may not be reported in clinical trials (Kid Int 2019; 95:1200-1283). The Standardized Outcomes in Nephrology (SONG) initiative 2014 established core outcome sets for its policy trials (https://songinitiative.org/). An alternative regime to address some of these issues would benefit all stages of CKD patients. Renadyl™, a Pre/Probiotic dietary supplement is proven to reduce several uremic toxins in 3 pilot clinical trials with no reports of adverse outcomes. We propose to carry out large scale RCT to validate it as a Live Bio-Therapeutic (LBT) drug with US FDA approval.

Methods: One-year RCT cross over design in an outpatient setting. Renadyl™ will be orally given at 90 CFU/day.

Results: Measured end points: 1: eGFR, Quality of Life (QOL). 2: Uremic metabolite panel, CBC, liver function test 3: Biomarkers including KIM-1, NGAL, TMAO, IL-6 and CRP.

Conclusions: This is the first-ever RCT proposed using Renadyl™ as a Live Bio-Therapeutic (LBT) drug for CKD IV patients. Being noninvasive the intervention avoids any possible infection. As a rare unconventional crossover design, patients will be their own control for prudent data analysis. Secondly, every patient gets the interventional product, thus accelerating better patient recruitment. Significance of p-value alone does not help in the decision of the application of results to clinical care and its policy (Kid Int 2019; 95:28-30). P < 0.05 and P > 0.05 can affect interpretation and lead to bias. The study design, quality of measurements, and the logical basis of assumptions are also important. (Kor J Pain 2017; 30(4): 241-242). Addition of Renadyl™ with standard care of therapy may possess excellent potential towards CKD treatment worldwide. Seriously interested clinical PI’s please contact: rangan@kibowbiotech.com

Funding: Commercial Support - Kibow Biotech Inc.
FR-PO340
Evolution of Patient Partner Roles in a Canadian, Patient-Oriented Kidney Research Network: A Qualitative Study
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Background: Engagement of patients as partners in health research is a mandate of the patient-oriented kidney research network, Can-SOLVE CKD. However, how patients assume and integrate their unique roles within the Network has not been examined. The aim of this study was to explore how researchers and patient partners characterize the roles and responsibilities of patients in the context of their individual projects and broader Network governance.

Methods: This study used a qualitative descriptive methodology informed by Role Theory. We purposively sampled across all research teams within Can-SOLVE CKD and conducted interviews and focus groups with researchers (i.e. project leads, co-investigators, and research coordinators) and patient partners (i.e. persons living with chronic kidney disease and informal surrogates) formed by 8 cross-cutting projects. A total of 22 interviews and 4 focus groups were conducted (N=10 researchers, N=12 patients). We analyzed transcript data using an inductive, thematic analysis approach. Coding was done in duplicate (MJE, NF), and themes were developed in relation to the objectives.

Results: With increasing familiarity and comfort engaging together in research partnership, participants described an evolution of perspectives on patient partner roles within the Network and patient-oriented research more generally. We identified 3 themes to support this: 1) Receptivity to novel engagement opportunities – patient partners increasingly engage in knowledge translation and moving research into practice.

Conclusions: The perceived roles of patient partners within the Can-SOLVE CKD Network have evolved since the Network’s inception, as has participants’ receptivity toward patient-oriented research. Future work will further characterize unique opportunities for patients to engage in kidney health research and the perceived impact of this engagement.

FR-PO341
Establishment of a Virtual Slide System Linking to the Japan Renal Biopsy Registry
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Background: A virtual slide is a high-resolution digital image created from scanning specimen on glass slides. Digital images are saved in a storage system and accessed on a computer screen using slide viewing software that is accessed via a web browser. These images can be assessed in the same way as with microscopy. The Japan Renal Biopsy Registry (J-RBR) has been operated since 2007 by the Japanese Society of Nephrology’s Kidney Disease Registry Committee. As of December 2018, 143 facilities have joined the registry and data have been registered for more than 40,000 patients who underwent renal biopsy. The J-RBR is now one of the largest national registries in Japan and provides a wealth of information for examining actual conditions, conducting secondary research, and developing clinical practice guidelines. We attempted to establish a virtual slide system to connect to the J-RBR conducted 4 focus groups (2 patient and 2 researcher groups; N=26) and 28 interviews (N=12 patients, N=16 researchers). We analyzed transcript data using an inductive, thematic analysis approach. Coding was done in duplicate (MJE, NF), and themes were developed in relation to the objectives.

Methods: Installation of a server computer was made possible by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The server computer was constructed at Niigata University, image view software was installed (Aperio eSlideManager®, Leica Microsystems K.K.), and the server was connected to the J-RBR server. When logged into their J-RBR accounts, users can access the J-RBR server to view the histopathology images via a web browser.

Results: The virtual slide system was linked to the J-RBR in March 2019, and virtual slides from more than 100 patients were registered during the first 2 months of operation. The virtual slides are available to all researchers with a J-RBR account.

Conclusions: The virtual slide system enables renal biopsy specimens to be viewed and diagnoses made via teleconsultations, and it can help pathologists establish a clinical consensus for diagnosis. The system should also increase the reliability of J-RBR data, which in turn will promote more secondary research, including machine learning, to be undertaken and provide precise information for guideline development.

Funding: Government Support - Non-U.S.

FR-PO342
Electronic Health Record Based Population Health Management for Improving CKD Care: The Kidney-Coordinate Health Management Partnership (CHAMP) Study
Manisha Jhamb,1 Jonathan Yabes,2 Gary Fischer,3 Chung-Chou H. Chang,1 Bruce L. Rollman,1 Thomas D. Nolin,1 Khaled Abdel-Kader.1 University of Pittsburgh, Pittsburgh, PA; 2Fanderbilt University Medical Center, Nashville, TN.

Background: Primary care providers (PCPs) care for most CKD patients but report limited knowledge, familiarity with guidelines, and time, leading to suboptimal care and clinical outcomes including progression to end-stage kidney disease (ESKD). CKD population health management (PHM) using electronic health records (EHRs) can be a sustainable, resource-efficient strategy to overcome clinician- and system-level barriers in the delivery of CKD care. The Kidney CHAMP study will test the effectiveness of a multifaceted EHR-based PHM intervention to improve evidence-based CKD care in patients with high-risk CKD (NC1038323955, www.kidneychamp.pitt.edu).

Methods: This is a 42-month pragmatic, cluster randomized controlled trial comparing an EHR-based PHM intervention versus usual care in 1,650 high-risk CKD patients. Patients are recruited using an opt-out approach from the University of Pittsburgh’s PCP network (3,330 PCPs; 840,000 patients). The CKD PHM dashboard uses risk prediction models to identify patients at high risk of CKD progression. The intervention combines timely PCP-targeted nephrology guidance (primarily as E-consults), pharmacist-led medication reviews, and patient-targeted CKD education. This builds on our prior work using EHRs to identify gaps in CKD care (e.g., suboptimal HTN control and RAASi use, unsafe medication use, late nephrology referrals). Primary outcome is a composite of 40% reduction in eGFR or ESKD.

Results: The CKD dashboard has been developed and includes the validated Kidney Failure Equation, patient demographics, dates of PCP visits, lab values, and active medications. Additionally, an internal CKD risk prediction model has been developed and validated. The dashboard will be used to identify eligible patients, track the intervention components, and monitor CKD progression. Study enrollment began in May 2019. We have partnered with 80 practices and randomized the first 8. Enrollment will continue for 18 months, with 4 practices randomized each month.

Conclusions: Our study tests a novel approach to deliver CKD care that minimizes patient and PCP burden. This will inform efforts to use health IT, risk prediction modeling, and PHM to augment evidence-based CKD care.

Funding: NIDDK Support

FR-PO343
Using Lean-Six Sigma Principles to Develop a Telenephrology Dashboard to Monitor Rural Veterans at Risk of Kidney Disease Progression
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Background: Chronic kidney disease (CKD) affects about 14% of Americans, with a 34% greater prevalence in Veterans than the general population. Although early identification and consultation improves outcomes and lowers costs, access is challenging for rural Veterans. To improve access, we developed a telenephrology dashboard to monitor Veterans with CKD and intervene accordingly. This informed the “Measure” and “Analyze” phases, where the voice of the customer, current and future state maps, and process observation were utilized. In the “Improve” phase, PDSA (Plan-Do-Study-Act) cycles refined dashboard design. The “Control” phase is ongoing.

Methods: A telenephrology dashboard was created to monitor patients with kidney disease within the Iowa City VA Health Care System. Voice of the customer (primary care providers and case managers) revealed 3 objectives: (1) timeliness of identification of CKD risk and progression, (2) rapid access to specialty care, and (3) improvement of patient satisfaction. Process observation and mapping revealed opportunities for early identification and intervention for CKD using telenephrology protocols (Figure). From April 2018 to March 2019, 1080 charts were flagged and reviewed by the telenephrology team.

Results: A telenephrology dashboard was created to monitor patients with kidney disease within the Iowa City VA Health Care System. This enables real-time access to nephrologists, thereby reducing wait-times to the next appointment and allowing for active surveillance of renal problems, and may improve overall quality of care.

Funding: Veterans Affairs Support
FR-PO344

Effect of Virtual Patient Simulation at Improving Management of Chronic Hyperkalemia
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Background: We sought to determine if an online, virtual patient simulation (VPS)-based continuing medical education (CME) intervention could improve performance of nephrologists to identification of patients with hyperkalemia, and chronic management of hyperkalemia.

Methods: The intervention comprised two patients presenting in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments in a manner matching the scope and depth of actual practice. Tailored clinical guidance (CG), based on current evidence and expert recommendation, was provided following each decision, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user’s baseline (pre-CG) decisions using a 2-tailed paired t-test to determine P values. The activity posted April 30, 2019; data for initial abstract submission was collected through May 22, 2019.

Results: To date after being live for 3 weeks, 37 nephrologists have participated (larger sample size expected by ASN conference). Significant improvements were observed after CG: Case 1: Initiate a loop diuretic: 24% absolute improvement (41% pre-CG vs 65% post-CG: P<.05) Order nutritional counseling: 19% absolute improvement (41% pre-CG vs 60% post-CG, P=.05) Initiate a potassium binder: 41% improvement (8% pre-CG vs 49% post-CG: P<.01) Discontinue spironolactone: 22% improvement (41% pre-CG vs 43% post-CG: P=.05) Case 2: Diagnose chronic kidney disease stage 3a: 43% absolute improvement (5% pre-CG vs 48% post-CG; P<.01) Diagnose heart failure, NYHA (WHO) Class II: 38% absolute improvement (14% pre-CG vs 52% post-CG; P<.01) Order nutritional counseling: 19% absolute improvement (41% pre-CG vs 60% post-CG; P=.05) Initiate potassium binder therapy: 57% absolute improvement (19% pre-CG vs 76% post-CG: P<.01)

Conclusions: VPS that immerses and engages specialists in an authentic and practical learning environment can improve evidence-based clinical decisions related to patient identification and management of hyperkalemia.

FR-PO345

Renal Hemodynamic Effects of Soluble Guanylyl Cyclase Activation vs. ACE Inhibition in a CKD Model in Conscious Rats
Karen A. Griffin,1 Geoffrey A. Williamson,2 Perriannan Sethupathi,3 Agnes M. Benardeau,4 Tibor Schomber,5 Frank Etinet,6 Anil K. Bidani.1
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Background: BP control using renin-angiotensin system (RAS) blockade is the current standard of care for CKD. However, outcomes remain suboptimal in part because adequate BP reductions are difficult to achieve in the volume expanded CKD states with RAS blockade even with additional antihypertensives. Given that endothelial dysfunction and/or NO loss accelerate the progression of diabetic and non-diabetic CKD, soluble guanylate cyclase (sGC) activators represent potential novel therapeutic interventions in CKD.

Methods: Two wks after 3/4 nephrectomy, male rats were instrumented for chronic BP radiotelemetry and RBF recordings and started on a 4% NaCl diet. Conscious BP and RBF recordings (1-2 hr; 2-4 wks) were initiated 1 wk later and continued over 3 wks while they were sequentially receiving: vehicle only by gavage (5 ml/kg), a low and a high dose of either the sGC activator (BR-11257) (3.10 mg/kg), enalapril (20.50 mg/kg) or the combination (3-4 days/wk with a 3-day washout period). Effects on mean arterial pressure (MAP), RBF, renal vascular resistance (RVR) and the autoregulatory (AR) ability to buffer spontaneous BP fluctuations were assessed using a methodology developed in our lab.

Results: Table (mean ± SEM) In this CKD model with volume (salt) dependent hypertrophy (HTN), BR-11257 but not enalapril significantly reduced BP and RVR (high dose), but in combination the two were synergistic. Effects on RBF were more variable. No adverse effect on AR ability to buffer spontaneous BP fluctuations was observed with any of the regimens.

Conclusions: These data suggest that sGC activators may have significant therapeutic potential in CKD states with volume dependent and/or RAS blockade resistant HTN that merit further investigation.

Funding: Commercial Support - Bayer AG

FR-PO346

Increased Urinary Prostaglandin E2 (PGE2) Precedes Overt Albuminuria in Hyperfiltration-Induced Renal Injury in Children with Solitary Functioning Kidney (SFK)
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Background: Children born with SFK are at risk for end stage renal disease from hyperfiltration-induced injury. Urinary albumin and epimidal growth factor (EGF) are established biomarkers of glomerular and tubular injury, respectively. A biomarker to detect glomerular changes preceding microalbuminuria will be valuable in defining early effects of hyperfiltration. A new model of hyperfiltration as a continuum of glomerular changes caused by biomechanical forces, namely fluid flow shear stress (FFSS) and tensile stress, we showed that FFSS upregulates PGE2, cyclooxygenase-2 and PGE2, receptor EP2 in cultured podocytes as well as in unilateral nephrectomized mice. We hypothesized increased urinary PGE2, in children with SFK.

Methods: Urine samples from children with SFK and controls were analyzed for PGE2, by LC-MS/MS autoanalyzer and EGF by ELISA. Patient characteristics of age, gender, Z-scores for height, weight, BMI, and BP were obtained. A 2-sample t-test or Mann-Whitney test was used group for comparisons and Spearman analyses for correlations.

Results: Children with SFK were comparable to controls except for having lower weight and BMI Z-scores. The median and interquartile range in control vs. SFK children were 9.1 (4.4, 16.7) n=57, p=0.009 vs. EGF [18637 (15298, 25622) n=44 vs. 20088 (13238, 30263) n=44, p=0.746] pg/mgCr. Urine albumin was within the normal reference range. A significant increase in urine PGE2 (p=0.024) and albumin (p=0.019) but not EGF (p=0.412) was observed in SFK when sex, age, weight z-score, height z-score, DBP z-score, and SBP z-score were controlled for in regression modeling. Patient characteristics did not correlate with urine PGE2, albumin or EGF. Urinary PGE2, and albumin, PGE2, and EGF and albumin were not correlated.

Conclusions: Urinary PGE2, and albumin, but not EGF, were elevated in children with SFK compared to controls, and were independent of each other distinguishing pathophysiologic mechanisms. Urinary PGE2, is a potential biomarker for early glomerular injury caused by hyperfiltration associated increase in FFSS prior to overt microalbuminuria.

Funding: NIDDK Support

FR-PO347

Adaptive and Maladaptive Kidney Repair Models Reveal Distinct Pathways of Myocardial and Lymphoid Cell Recruitment and Activation
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Background: Incomplete repair after acute kidney injury (AKI) can lead to progressive fibrosis and development of chronic kidney disease (CKD). We have previously shown that unilateral ischemia-reperfusion kidney injury with contralateral nephrectomy (IRI/CL-NX) results in significantly less fibrosis in the injured kidney than does unilateral IRI with contralateral kidney intact (U-IRI). Here, we investigated the mechanism of this difference by comparing an identical time of ischemic injury between mice subjected to U-IRI and those subjected to IRI/CL-NX.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Methods: Male wild-type mice were subjected to warm U-IRI or IRICLX (27 min). The injured kidneys were removed on day 7, 14 and 30 after IRI (n=10/group). Renin function was assessed by serum creatinine and BUN. Renal fibrosis and macrophage accumulation were assessed by Sirius red staining and IHC staining for F4/80. Kidney injury, inflammation, accumulation of myofibroblasts and lymphoid cells, chemotactic and survival factor expression were assessed by qPCR at each time point.

Results: This analysis revealed that initial recruitment and activation of macrophages, dendritic cells and T cells as well as myofibroblast activation and profibrotic gene expression were equivalent through day 7 in these two models. However, in the IRICLX model macrophage numbers declined after day 7 with tubule regeneration and only modest interstitial fibrosis on day 30. In contrast, macrophages persisted and expressed significantly higher levels of profibrotic growth factors Pdgfa and Tgfβ1 while dendritic cells and T cells significantly increased in numbers and expressed greater amounts of Tgfβ1 and F4/80. These sustained immune responses correlated with progressive expression of collagen and fibroconnectin, sustained expression of Havel1 and Len2, less tubule regeneration and greater kidney atrophy. The persistence of macrophages, dendritic cells and T cells in injured U-IRI kidneys highly correlated with sustained expression of the chemokines Ccl2 and Ccl12.

Conclusions: Abnormal accumulation of macrophages, dendritic cells and T cells may lead to progressive interstitial fibrosis, sustained inflammation and kidney injury in the setting of maladaptive kidney repair following IRI. Blocking homing chemokines may serve as a therapeutic target to attenuate CKD progression.

Funding: NIDDK Support

FR-PO348
Expression of an Anti-Fibrotic Molecule Smad Anchor for Receptor Activation (SARA) is Significantly Regulated in Epithelial Cells and Fibroblasts at a Translational Level

Vidhi Dalal,1 Xiaoyan Liang,2 Xinyue D. Hao,2 H. William Schnaper,2 Tomoko Hayashida,2,1 Pediatrics, Lurie Children’s Hospital of Chicago, Chicago, IL; 2Northwestern University, Chicago, IL

Background: We reported last ASN meeting that overexpression of SARA specifically in pericytes prevents them from differentiating into fibroblasts, hence mitigates fibrotic changes in a mouse model of interstitial fibrosis. These findings suggest that SARA is a key molecule that regulates cellular phenotype. Here, we aimed to explore the mechanism by which SARA levels are regulated.

Methods: SARA protein and mRNA expression levels were evaluated in cultured epithelial cells and fibroblasts derived from rat kidney (NRK52E and 49F, respectively), with or without transfection of a plasmid expressing human SARA cDNA or HA-tagged focal adhesion kinase (FAK). RNA from NRK52E and 49F was subjected to RNA sequencing.

Results: SARA protein was abundantly expressed in NRK52E, while it was barely detected in NRK49F. In contrast, SARA mRNA levels were similar in NRK52E and 49F. When a plasmid expressing human SARA driven by a constitutive promoter was transfected, SARA protein overexpression was apparent in NRK52E cells, but not in 49F, while HA-FAK protein expression used as a control was equivalent both in NRK52E and 49F, indicating that the difference in S2E and 49F are not due to transfection efficiency. Indeed, human SARA RNA driven by SARA overexpression plasmid was significantly and equally increased in both NRK52E and 49F. RNA sequencing revealed 107,000 genes expressed both in NRK52E and 49F, and 922 and 754 genes were unique to NRK52E and 49F, respectively. KEGG enrichment analyses revealed that genes associated with metabolic pathways were most commonly differentially regulated (N=630), followed by those associated with PI3K-Akt signaling pathways (N=197) and endocytosis (N=176).

Conclusions: SARA is a key molecule that regulates cellular phenotype. Here, we aimed to explore the mechanism by which SARA levels are regulated. It is suggested that, in fibroblast, SARA expression is downregulated whereas, in epithelial cells levels are kept high through regulation of certain metabolic pathways.

FR-PO349
Par1a Deletion Protects Against Focal Acidic and Unilateral Ureteral Obstruction-Induced Fibrosis in Mice

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Background: We recently identified Par1 serine threonine kinases as regulators of Notch signaling in the developing kidney: dual loss of Par1a/b led to impaired Notch activation and glomerular and proximal tubular development. Par1a expression increases following unilateral ureteral obstruction (UUO) and acidic urine (FA) induced injury. However, the effect of Par1a deletion on renal regeneration is not known. We hypothesized that loss of Par1a would attenuate Notch signaling activation and renal fibrosis. We demonstrated that Par1a was required for tubule regeneration and Notch signaling activity.

Methods: Immunofluorescence staining was used to examine the expression of Par1a and Notch signaling components. To test effect of Par1a deletion on fibrosis in vivo, FA (250 mg/kg dissolved in 300 mM NaHCO3) or vehicle was injected in 5 week old male Par1a +/- (Par1a KO) and Par1a +/- (Par1a KO) Wt littermates. Kidney phenotype was assessed at 4 weeks post injection. UOO was performed in adult (10 week old) male Par1a KO and Wt littermates; phenotype was examined at 7, 6-8 mice/group were studied. To detect renal red staining of whole kidneys, perfusion with carboxyfluorescein sodium was performed. Podized liver and kidney sections were stained with antibodies against Par1a and Par2. The expression of profibrotic growth factors was assessed in kidneys and liver by qPCR.

Results: UUO significantly increased profibrotic growth factors Pdgfa, Tgfβ1, and Il1b expression in control primary tubular cells, Par1a knockout cells had preserved E-cadherin expression following TGFβ treatment. These results suggested that reduction of some profibrotic molecules which induce renal damage could have beneficial effects on CKD.

Conclusions: Lipidomics analysis revealed that ALOX15-mediated lipid metabolites were significantly decreased in kidneys of mice with subtotal nephrectomy in comparison with those of control mice. Therefore, we examined two CKD models of ALOX15 knockout mice, subtotal nephrectomy and adenine-induced nephropathy. Renal functions of ALOX15 knockout mice were more preserved than those of wild type mice in both CKD models. Aldo-SMA and NGAL were also suppressed in ALOX15 knockout mice. Quantitative-PCR revealed that mRNA level of alpha-1 type collagen in kidneys of ALOX15 knockout mice was reduced compared with that of wild type mice in both CKD models. Mason’s trichrome staining revealed decreased interstitial fibrosis of ALOX15 knockout CKD mice in comparison with wild type mice. These results suggested that reduction of some ALOX15-mediated lipid metabolites which induce renal damage could have beneficial effects on CKD.

Funding: NIDDK Support

FR-PO351
Erythrocyte SphK1 Activation Coupled with P2PA Inhibition: A Missing Component to Counteract CKD

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Background: Hypoxia drives chronic kidney diseases (CKD) and promotes end organ damage. The erythrocyte is the only cell type delivering oxygen (O2) and O2 releasing capacity is finely regulated by hypoxia. However, its role and regulatory mechanisms in CKD remain unknown.

Methods: Untargeted metabolomics screening in the plasma and erythrocyte of mice infused with or without angiotensin II (Ang II) at 500ng/kg/min up to 14 days was performed. Mice with specific ablation of SphK1 in erythrocytes and patients with CKD were used to determine its function in CKD, potential mechanisms and human relevance. We demonstrated that genetic depletion of SphK1 in specific Sphingosine Kinase 1 (SphK1, the only enzyme to generate SIP in erythrocytes) leads to severe renal hypoxia, persistently active Hif-1α, sustained inflammation, imbalanced vasoactive factors and fibrosis comparing to the Ang II-infused controls. Mechanistically, using untargeted erythrocyte metabolic profiling, we found that Ang II-infused controls but not erythrocyte SphK1 knockout mice show highly active glycolysis, which fuels erythrocyte energy supply and O2 release mediator. These studies led us further discover that SphK1 activation induces AMPK-mediated activation of BPG mutase and thus the production of 2,3-diphosphoglycerate (2,3-DPG), which increases the O2 affinity of Hb and thereby facilitates O2 delivery to tissues.
of 2,3-bisphosphoglycerate (2,3-BPG), an erythrocyte specific glycolysis metabolite negatively regulating hemoglobin oxygen affinity (Hb) and 2,3-BPG production sites close to KLF6. Moreover, 2,3-BPG and Hb activity were significantly induced in the erythrocytes of CKD patients compared to control samples, indicating a potential role for KLF6 in erythrocyte function.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.**

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**FR-P0352**

Complete Pik3c3 Deletion in Renal Proximal Tubule Cells Causes AKI Leading to CKD

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**Background:** Renal proximal tubules form the bulk of the kidney and are particularly sensitive to ischemic, toxic, and metabolic stress contributing to the pathogenesis of kidney disease. Class 3 phospholipidinositol 3-kinase (Pik3c3) is the only PI3-kinase sensitive to ischemic, toxic, and metabolic stress contributing to the pathogenesis of kidney disease. Our study focused on patients with nephrotic syndrome due to primary focal segmental glomerulosclerosis (FSGS), immunoglobulin A nephropathy (IgAN), and idiopathic membranoproliferative glomerulonephritis (MPGN). In particular, enhancers are distal non-coding DNA elements that are critical in driving PT injury. In particular, enhancers are critical in driving PT injury.

**Methods:** To overcome this issue, our group devised a simple and novel NET-CAGE technology, in which nascent RNA is used as input.

**Results:** We apply this NET-CAGE technology to describe active cis-regulatory landscape across renal aging and analyze differentially regulated enhancers and genes.

**Conclusions:** We identify a number of kidney-specific enhancers.

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**FR-P0353**

Proximal Tubule-Specific Klf6-Mediated Amino Acid Metabolism Is Critical for the Progression of Kidney Injury

Sian Piret, Yiqing Guo, Sandeep K. Mallipatni. Stony Brook Medicine, Stony Brook, NY.

**Background:** Transcriptional regulators of DNA-damage pathways leading to renal fibrosis are not well characterized. The p53 tumor suppressor gene lines up proximal tubular cells and results in the expression of genes involved in fibrosis.

**Methods:** To overcome this issue, our group devised a simple and novel NET-CAGE technology, in which nascent RNA is used as input.

**Results:** We apply this NET-CAGE technology to describe active cis-regulatory landscape across renal aging and analyze differentially regulated enhancers and genes.

**Conclusions:** We identify a number of kidney-specific enhancers.

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**FR-P0354**

Genome-Wide Identification of Active Enhancers in Renal Aging

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**Background:** Aging is one of the major risk factors for acute kidney injury and chronic kidney disease. The aging kidney undergoes complex changes that predispose people to renal diseases. However, the regulatory circuitry governing the transcriptional network in renal aging is unclear.

**Methods:** To overcome this issue, our group devised a simple and novel NET-CAGE technology, in which nascent RNA is used as input.

**Results:** We apply this NET-CAGE technology to describe active cis-regulatory landscape across renal aging and analyze differentially regulated enhancers and genes.

**Conclusions:** We identify a number of kidney-specific enhancers.

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**FR-P0355**

Follistatin-Like Protein 1 (FSTL1) Expression Is Correlated with Measures of Kidney Injury in the Nephrotic Syndrome Study Network (NEPTUNE) Cohort

Nicholas Maksimowski,1 York P. Pei,1 Heather N. Reich,1 James W. Scholey.1 University of Toronto, Toronto, ON, Canada;2 University Health Network and University of Toronto, Toronto, ON, Canada;3 Toronto General Hospital, Toronto, ON, Canada.

**Background:** The pathogenesis of progressive kidney injury has not been fully elucidated in chronic kidney disease (CKD). Gene expression profiling of renal cortical mRNA samples was performed in male Col4a3−/− and Col4a3+/+ mice at 4 and 7 weeks of age. Our microarray analysis showed that FSTL1 was one of three genes upregulated at 4-weeks of age. FSTL1 is expressed in interstitial fibroblasts. It activates NFκB and increases COL1α mRNA.

**Results:** Analysis revealed FSTL1 was one of the three genes upregulated at 4-weeks of age. FSTL1 is expressed in interstitial fibroblasts. It activates NFκB and increases COL1α mRNA.

**Conclusions:** We comprehensively analyze of enhancers will provide key biological insights into cis-regulatory mechanisms in renal aging.

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**FR-P0356**

Expression arrays of human CKD biopsies showed similar downregulation of BCAA genes with increasing histological stage. The authors concluded that suppression of BCAA genes may be responsible for the histological stage.

**Conclusions:** Loss of PT KLF6 was associated with preserved BCAA metabolic enzymes that may help maintain the TCA cycle and increase glutathione, thus reducing injury after AAI. The potential role of transcriptional regulation of amino acid metabolism in driving PT injury has not been previously described.

**Funding:** NIDDK Support

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Impacts of Periostin in Aging Kidney
Jiwon Ryoo,1 Yun Jae Kwon,2 Hyung Duk Kim,2,3 Eun Nim Kim,1 Yongjie Jin,1 Ji Hee Lim,1 YaeKi Kim,2,3 Cheol Whee Park,2,1 Burnssoo Choi,3,1 1The Catholic University of Korea, Seoul, Republic of Korea; 2Seoul St. Mary’s Hosp, Catholic Univ of Korea, Seoul, Republic, of Korea; 3Division of Nephrology, Department of Internal Medicine, Seoul, Republic, of Korea.

Background: Periostin is a matricellular protein which plays important role in tissue adaptation to injury. In kidney disease, periostin is known to be highly expressed in tubulointerstitial fibrosis and correlated with renal function inversely. In this study, we investigated the effect of periostin in aging process and progressive renal interstitial fibrosis.

Methods: 1. UUO model We conducted unilateral ureteral obstruction (UUO) surgery in wild type (WT) mice and periostin knockout (KO) mice. And compared interstitial fibrosis and pericyte changes. 2. Aging model We compared interstitial fibrosis and changes of pericytes in 4 groups; WT young age group, WT old age group, periostin KO young age group and periostin KO old age group.

Results: In UUO model, periostin KO mice shows less interstitial fibrosis and increased number of pericytes. And periostin KO aging mice shows attenuated fibrosis and abundant pericytes compared to WT aging mice.

Conclusions: Periostin inhibition ameliorated renal interstitial fibrosis in UUO model and aging process. It is thought that it affects pericyte and shows a renoprotective effect.
receptors alone or in combination in cardiodrenal diseases is dependent on the presence of congestion and/or kidney hypoxia.

**Funding:** Commercial Support - Bayer AG

**FR-PO358**

Hypoxia Reduced Renal Injury and Inflammation in Rats with Chronic Nitric Oxide Inhibition


**Background:** Chronic NO inhibition by Nω-nitroarginine methyl ester (NAME) leads to hypertension (HT) and Chronic Kidney Disease (CKD). Tissue hypoxia (HYP) has been postulated as a pathogenic factor in CKD, but we showed recent evidence that it may instead be reprotective. We investigated whether this detrimental effect would also be observed in NAME rats and whether it would involve NLRP3 and/or NFκB inhibition.

**Methods:** Male Munich-Wistar rats received NAME, 80 mg/kg/d in tap water. Ten Control (C) and 10 NAME rats were kept under 21% O₂ (NOR), while 12 C and 12 NAME rats breathed 12% O₂. After 4 wk, we assessed hemoglobin (Hb, g/dL), tail-cuff pressure (TCP, mmHg), urine albumin/creatinine (UAC, mg/gCr), urinary albumin/creatinine (UAC, mg/gCr), glomerulosclerosis (GS, %), % ischemic glomeruli (% IG), cortical density (mm²), nuclear p65 and IL6.

**Results:** HYP reduced HT, inflammation, oxidative stress, renal injury, and the content of NLRP3, IL6, Casp1, HO1 and SOD2 (WB), and IL1β (IFN-ω/IFN-γ) in NAME rats and whether it would involve NLRP3 and/or NFκB inhibition.

**Conclusions:** Tissue HYP exerted a protective effect in NAME, suggesting that it may influence a common pathogenic mechanism, which may relate to downregulation of the NLRP3 inflammasome/Casp1/IL1β and NFκB/IL6 pathways, and to limitation of oxidative stress. FAESP/CNPq.

**Funding:** Government Support - Non-U.S.

**FR-PO359**

INO80 Inhibits Tubulointerstitial Apoptosis Under Hypoxia

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**Background:** Chronic kidney disease (CKD) is known to be caused by various kinds of factors including epigenetic factors. Among them focused on the role of INO80. INO80 is an ATPase and nucleosome spacing factor. Biological function of INO80 is known to be ATP-dependent chromatin-remodeling, and it regulates transcription, DNA repair and replication. Our aim of this study is to clarify the pathophysiological role of INO80 in the kidney.

**Methods:** In order to investigate the expression levels of INO80 in the impaired kidney, we utilized 5/6 nephrectomy rats. To clarify the biological function of INO80 in the kidney, we performed *in vitro* experiments using HK2 (human kidney-2) cells in which INO80 was knocked down by using siRNA. In addition, genome-wide analysis using RNA-seq was performed to identify the downstream target genes of INO80 under hypoxia. Furthermore, we examined the effects of INO80 on apoptosis of tubular cells.

**Results:** In 5/6 nephrectomy rats, we found that the expression of INO80 was significantly suppressed at the mRNA level compared to sham rats. When HK2 cells were cultured under 1% hypoxic conditions for 24 hours, the expression level of INO80 significantly decreased. Genome-wide analysis by RNA-seq identified 32 downstream target candidate genes whose expressions decreased less than half compared with control siRNA when INO80 was knocked down by siRNA. While, knockdown of INO80 in HK2 cells promoted tubulointerstitial apoptosis by 24 hours, the expression of mRNA of tumor suppressor gene p53 and transcription factor E2F1 was significantly increased.

**Conclusions:** INO80 plays an important role in suppressing apoptosis in renal tubular cells, and it is considered that E2F1-mediated regulation may be involved in the apoptosis suppression pathway by INO80.

**FR-PO360**

Direct Inhibitory Effect of Sodium on Nrf2 Expression in Collecting Duct Cells

Mi-Lu Liu. *Southern Medical University Shunde Hospital, Foshan, China.*

**Background:** High salt is associated with the progression of CKD. High salt also contributes to oxidative stress in renal tissue and cells. However it remains unclear if high salt is involved in the pathogenesis of CKD through the regulation of oxidative stress. Nuclear factor E2-related factor 2 (Nrf2) is a transcriptional factor which regulates the expression of downstream antioxidant and detoxifying genes. The study was aimed at clarifying whether high salt will affect Nrf2 expression and Nrf2-dependent pathway.

**Methods:** Mice was treated with acute salt loading. Nrf2 expression in the kidney were detected by western blotting and immunostaining. mpkCCD cells were cultured in high osmolarity medium by adding NaCl. We measured the expression of Nrf2 and Nrf2-dependent genes via western blotting and qRT-PCR. Pretreatment with NAC, spironolactone or NS-398 in mpkCCD cells were performed and Nrf2 mRNA expression were monitored.

**Results:** Nrf2 protein levels in the kidney were markedly downregulated after acute salt loading. Nrf2 was remarkably downregulated in mpkCCD cells after NaCl treatment. Sodium gluconate had a similar effect on Nrf2 expression as NaCl, whereas neither Choline-C1 nor mannitol changed Nrf2 protein level. The mRNA levels of Nrf2-dependent genes were downregulated by NaCl mainly dependent on the effect of Na⁺. The expression of Nrf2-dependent genes of Nrf2 was not affected by NAC, spironolactone or NS-398.

**Conclusions:** Sodium has a direct inhibitory effect on the expression of Nrf2 and Nrf2-dependent genes.

**Figure 1. Nrf2 protein expression in kidneys after acute high salt loading.**

**Nrf2 expression in mpkCCD cells after NaCl, Na-Glu, Choline-Cl and mannitol treatment**

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Abnormal Cytokine-Induced Responses in IgA1 Subpopulations Enhance Production of Galactose-Deficient IgA1, the Main Autoantigen in IgA1 Nephropathy

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Background: IgA nephropathy (IgAN), the most common primary glomerulonephritis in the world, is characterized by glomerular IgA1 immune deposits enriched for galactose-deficient IgA1 (Gd-IgA1). Patients with IgAN have elevated blood levels of Gd-IgA1. Gd-IgA1 blood levels also predict disease progression. IgAN patients often present with sympathtic hematuria, and have elevated serum levels of IL-6, indicating ongoing inflammation. Some cytokines increase Gd-IgA1 production by IgA1-secreting cells from IgAN patients. We hypothesized that Gd-IgA1 overproduction induced by a cytokine stimulation may involve only a subpopulation(s) of IgA1-producing cells and used single-cell transcriptome analysis of cells from IgAN patients and controls to test that hypothesis.

Methods: A mixture of cytokines mimicking those of T-follicular helper (Tfh) cells (IL-4, IL-6, IL-21, CD40L; 50 ng/ml) was used to activate immortalized Ig-producing cells from IgAN patients and healthy controls (HC) for 30 min before single-cell transcriptomic analysis. IgA1-secreting cells were identified using a splice-variant analysis to differentiate membrane vs. secreted isoforms. Resultant data were normalized using Seurat v2.4 and the curated data were analyzed with Alteryx. Gd-IgA1 overproduction was assessed after cytokine stimulation for 72 h.

Results: Gd-IgA1 production increased in Ig-producing cells from IgAN patients but not HC after stimulation with Tfh cytokines. Several subpopulations of IgA1-secreting cells from IgAN patients exhibited substantial repression of genes associated with regulation of cytokine responses (e.g., PTPN11, SOCS3, PTPN2) due to Tfh cytokine stimulation (N=3, p<0.05). The same subpopulations also exhibited abnormal changes in glycosyltransferase genes implicated in Gd-IgA1 production.

Conclusions: We identified subpopulations of IgA1-secreting cells from IgAN patients that exhibited differential regulation of expression of glycosyltransferases due to abnormal Tfh-cytokine signaling. These data suggest that there are subpopulations of IgA1-producing cells that may be primarily responsible for Gd-IgA1 overproduction.

Funding: NIDDK Support, Private Foundation Support

Effects of Bone Marrow Mesenchymal Stem Cell-Derived Exosomes on Renal Fibrosis by Regulating Macrophage Phenotypic Transformation

Xiaolan Chen. The Affiliated Hospital of Nantong university; Nantong, China.

Background: In recent years, bone marrow mesenchymal stem cells (BM-MSCs) have received extensive attention due to their biological characteristics such as self-replication, high proliferative potential and multi-directional differentiation. This hinders the clinical transformation of MSCs in the treatment of kidney disease. Recent studies have shown that homing of MSCs to the injury site in the circulatory system is not the main mechanism for their continued therapeutic effects.

Methods: Establishment of unilateral ureteral obstruction (UUO) model in mice and random grouping: (1) sham operation group; (2)U/O group; (3)U/O+PBS group; (4)U/O+MSC (1×10^6/animal); (5)U/O+ exosomes (30μg/animal) group. Stem cells and exosomes were injected intravenously in the caudal vein on the day of modeling. Specimen collection and detection: HE staining and Masson staining were used to detect the pathological changes of renal tissue in each group of mice. Western Blot was used to detect the expression of α-SMA protein. Immunohistochemistry was used to detect renal interstitial fibrosis, macrophage infiltration and phenotype in each group. Flow cytometry was used to detectmacrophage subtypes.

Results: In vivo: Compared with U/O group, the renal pathology of the two groups of mice involved by MSC and exosomes tail vein injection was significantly improved. The expression level of CD68 was significantly decreased after MSC and exosomes intervention, while the expression level of CD206 was increased; the ratio M2/M1 of macrophage subtypes in MSC and exosomes intervention groups was significantly increased. In vitro: the proliferation ability of macrophages in LPS group was significantly decreased, the secretion of IL-12 by macrophages in LPS group significantly increased, but the secretion of IL-10 did not change significantly (P>0.05); the expression of iNOS and ARG1 mRNA in LPS group increased. Compared with LPS group, the proliferation ability of macrophages after exosomes intervention, the expression of IL-12 decreased and the expression of IL-10 increased after exosome intervention. \( \text{NO}_{\text{S}} \text{tRNA expression was down-regulated} \) and \( \text{ARG1 mRNA expression was up-regulated} \) after exosomes intervention.

Conclusions: Exosomes derived from bone marrow mesenchymal stem cells can regulate macrophage phenotypic transformation, thus improving renal fibrosis.

The Expansion and Phenotype of HLA-DR Intermediate Monocytess in CKD


Background: A chronic microinflammatory state occurs in CKD, one aspect of which is monocyte subset dysregulation. Monocytes are comprised of one major (“classical”) and two minor (“intermediate” and “nonclassical”) subsets. The intermediate monocyte (IM) subset is pro-inflammatory and numerically increased in CKD. Having recently reported that human IM may be further subdivided into HLA-DR^{+} and HLA-DR^{−} subpopulations and that IM increase in CKD is specific to the HLA-DR^{+} IM subset, we aimed to determine whether HLA-DR^{+} IM display distinctive expression of surface proteins required for endothelial adhesion and transmigration in health and in CKD.

Methods: Adult outpatients with CKD or healthy controls (HC) provided blood samples by informed consent. Peripheral blood mononuclear cells (PBMC) were isolated and analyzed by multi-colour flow cytometry for monocyte subpopulation numbers and surface protein expression levels (CD45, CD14, CD16, HLA-DR, CCR2, CCR5, CXCR7, CXCR1, CD11a, CD11b, CD11c, CD206, CD49d and CD162).

Results: Consistent with prior results, higher numbers of total IM (p<0.03) and HLA-DR^{+} IM (p=0.015) were present in PBMC from CKD vs HC. IM had higher expression of CCR5 than classical and non-classical monocytes (p<0.0001). Among the IM, high CCR5 was specific to HLA-DR^{+} IM (p<0.002). Surface expression of the integrin chains CD11b and CD11c was also highest among the HLA-DR^{+} IM subset, we aimed to determine whether HLA-DR^{+} IM display distinctive expression of surface proteins required for endothelial adhesion and transmigration in health and in CKD.

Conclusions: Adult outpatients with CKD or healthy controls (HC) provided blood samples by informed consent. Peripheral blood mononuclear cells (PBMC) were isolated and analyzed by multi-colour flow cytometry for monocyte subpopulation numbers and surface protein expression levels (CD45, CD14, CD16, HLA-DR, CCR2, CCR5, CXCR7, CXCR1, CD11a, CD11b, CD11c, CD206, CD49d and CD162).
FR-PO365
Comparative Analysis of Regulatory T Cell Subpopulations in CKD Outpatients and Healthy Controls
Neema Negi, Sarah Cormican, Eanna O Coileain, Matthew D. Griffin. National University of Ireland Galway, Galway, Ireland.

Background: Regulatory T cells (T-reg) suppress autoimmune/inflammation and allo-antigen-specific immune response in transplantation. Consequently, ex vivo-expanded T-reg are a promising immunomodulatory therapy. In CKD/ESRD, circulating T-reg numbers are preserved and can be culture-expanded. Nonetheless, T-reg sub-phenotypes and their relevance to CKD pathophysiology are not fully characterized. We aimed to compare relative proportions and surface phenotype characteristics of circulating T-reg subpopulations in adult CKD outpatients and healthy adults.

Methods: Blood samples and clinical information were provided by CKD outpatients without immune-mediated disease (n=35, eGFR<11-64) and by healthy volunteers (HV, n=20). Multi-color flow cytometry was performed on fresh PBMC for CD4, CD25, CD127 and FoxP3 (to identify T-reg) and for CD45RA, HLA-DR, TNFR2, CCR7, CD62L and CD39 (to define subpopulations and their functional markers).

Results: Peripheral blood CD4+ CD25+ CD127+ T-reg (confirmed to be FoxP3+) were identified and subdivided into 3 subpopulations based on expression of CD45RA and HLA-DR (RA+ DR-, RA- DR+, RA- DR-). No difference in T-reg frequency (expressed as % of total CD4+ T-cells) was seen between CKD and HV. However, RA- DR- T-reg were proportionately increased and RA+ DR- T-reg were proportionately decreased in CKD (p<0.0001), consistent with a relative expansion of "antigen experienced" T-reg. In regard to surface proteins of potential functional importance, the selectin CD62L was proportionately increased and RA+ DR- T-reg were proportionately decreased in CKD (average MFI 665 vs 6936, p<0.0001) and was present on lower proportions of RA- DR+ expressed at higher level on total T-reg of CKD vs. HV (average MFI 3810 vs 1299, p<0.0001) in CKD vs. HV. Expression of CCR7 and TNF receptor 2 (TNFR2) did not differ for T-reg and T-reg subpopulations of CKD and HV.

Conclusions: Although adults with CKD had comparable blood T-reg numbers compared to HV, they differed in the relative frequencies of CD45RA/HLA-DR-defined T-reg subpopulations and in expression of proteins that could reflect alterations in migration patterns (CD62L) and specific regulatory functions (CD39).

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO366
Klotho Restrains RIG-1/NF-κB Signaling Activation and Monocyte Inflammatory Factor Release Under Uremic Conditions
Ting He. Department of Nephrology, Xinqiao Hospital, Chongqing, China.

Background: Systemic inflammation is a main hallmark of chronic kidney disease (CKD). However, the mechanisms underlying the pathogenesis of CKD-associated systemic inflammation are unclear. Our study aimed to investigate the relationship between indoxyl sulphate (IS) and CKD-associated systemic inflammation, and the protective effect of Klotho against IS-induced systemic inflammation in CKD.

Methods: Serum Klotho was measured by ELISA. Heterozygous kl/kl (kl+) mice or WT mice were treated with 5/6 renal damage and then injected with recombinant Klotho protein.

Results: It shows that in 286 CKD patients, the serum levels of inflammatory factors are positively related with IS, but negatively related with Klotho. Klotho can significantly inhibit IS-induced retinoic acid-inducible gene 1 (RIG-I)/NF-κB activation and the productions of IL-6 and TNF-α in cultured monocytes. In vivo, RIG-I/NF-κB activation is observed in monocytes in both CKD mice and patients. Notably, higher levels of IL-6 and TNF-α are detected in kl-/- mice with CKD. Klotho administration can evidently attenuate RIG-I/NF-κB activation in monocytes and systemic inflammation in CKD mice.

Conclusions: These results suggest that Klotho can suppress CKD-associated systemic inflammation through inhibiting IS-induced RIG-I/NF-κB activation and monocyte inflammatory factor release.

The basic information of 286 CKD patients

<table>
<thead>
<tr>
<th>CKD stage</th>
<th>CKD (t+50)</th>
<th>CKD (t+50)</th>
<th>CKD (t+50)</th>
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<td>Age, years</td>
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<tr>
<td>Male (gender)</td>
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<td>IS (umol/L)</td>
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<td>GFR (mL/min)</td>
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<td>Urea (mg/dL)</td>
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FR-PO367
Single-Cell Genomics Applied to Unilateral Ureteral Obstruction Kidneys with Lymphatic Vessel Knockdown Identifies the Key Role of Adaptive Immunity in Renal Fibrosis
Jianliang Wu, Zhimei Ma, Jing Guo, Gang Xu, Rui Zeng, Tongji Hospital, Huazhong Univ of Science and Technology, Wuhan, China; Wuhan Biobank Co., Ltd., Wuhan, China.

Background: Lymphangiogenesis in chronic kidney disease has been reported in a large number of literatures. However, it is still unclear how the lymphatic vessels (LVs) act as a transport channel regulating the infiltration of immune cells in the kidney. The purpose of this study was to clarify the mechanisms by which LVs regulate the infiltration of immune cells and the following chronic kidney disease and fibrosis.

Methods: We constructed four lymphatic knockdown mouse models. The new-born proliferated LVs were knockdown by injection of Ganciclovir after unilateral ureteral obstruction (UUO) in Lyve-1-tk and Prox-1-tk mice, and resident LVs were knockdown by injection of DT in Lyve-1-DTR and Prox-1-DTR mice. Then, we performed RNA-Seq and single-cell transcriptomics on the kidneys of lymphatic knockdown group and control group.

Results: It showed that the UUO kidney had less LVs, less inflammatory cell infiltration and reduced fibrosis after new-born proliferated LVs or resident LVs knockdown. The ischemia reperfusion injury model yields the similar results. Both differentially expressed genes (DEGs), GO and KEGG pathway analysis identified that DEGs are mainly enriched in chemokine related genes. The heat map showed that chemokines and renal extracellular matrix deposition related genes were significantly down-regulated after lymphatic knockdown. The single-cell transcriptomics showed that lymphatic knockdown attenuated UUO induced intrarenal inflammatory infiltration (from 60% to 25%) and preserved renal tubular epithelial cells (from 40% to 75%). The main reduced inflammatory cells were T cells and DCs. Interestingly, the reduction in T cells included all subpopulations, while the subpopulation reduced in DCs was lymphoid DCs, but not myeloid DCs. The other immune cells, such as macrophages, B cells, and neutrophils, were not altered. In addition, we found that B cells expressed more abundant genes associated with cell senescence such as p21cip1 and p16ink4a after lymphatic knockdown.

Conclusions: We verified that lymphatic knockdown alleviates renal inflammation and fibrosis in UUO kidneys. The decreased immune cells after lymphatic knockdown are T cells and lymphoid DCs, accompanied with B cell senescence, suggesting the adaptive immunity participates in UUO induced renal inflammation and fibrosis.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Heritability Enrichment Analyses in Kidney Function Genome-Wide Association Study Identifies Trait-Specific Kidney Cell Types

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Background: Identifying relevant tissues and cell types underlying kidney function and disease informs experimental follow-up studies to understand disease biology. Novel statistical methods allow for unbiased identification of trait-relevant cell types by incorporating RNA-seq data with GWAS summary statistics.

Methods: We used LD score regression for specifically expressed genes (LDSC-seq) to partition heritability in GWAS summary statistics of European ancestry participants from the CKDGen Consortium of estimated glomerular filtration rate (eGFR, n=567,460), urinary albumin-to-creatinine ratio (UACR, n=547,361), blood urea nitrogen (BUN, n=243,031) and serum urate (n=288,666). GWAS of asthma (UK Biobank, n=452,264), and schizophrenia (CLOZUX-PGC Consortium, n=105,318) were used as negative controls. Publicly available kidney single-cell RNA-seq datasets (human, 24 cell types; mouse, 16 cell types) were used to construct the top 10% specifically expressed genes per cell type followed by testing heritability enrichment in each trait. For examination at tissue level, the same procedure was applied using GTEx v7 data.

Results: Across tissues, we found significant enrichment of heritability in trait-associated loci containing genes that are highly expressed in kidney (eGFR: 2.2-fold enrichment, p=9.1e-8; urate: 2.1-fold enrichment, p=1.2e-6); liver was also enriched. Within the kidney, enrichment was observed in regions containing genes specifically expressed in proximal tubular cells in human (eGFR: 2.3-fold, p=8.2e-5; BUN: 1.7-fold, p=0.005; urate: 2.3-fold, p=7.8e-6) and mice (eGFR 2.3 fold, p=0.003; BUN 1.8 fold, p=0.02; urate: 2.3-fold, p=0.0002), as well as in human podocytes (UACR 1.7, p=0.009). Both asthma and schizophrenia did not show significant enrichment of heritability in regions with genes that are highly expressed in kidney cell types, but instead in brain tissues (schizophrenia, smallest p=9.8e-16).

Conclusions: GWAS signals of kidney function traits are enriched for genes that are highly expressed in relevant tissues and cell types such as proximal tubular cells for eGFR, BUN and urate, and glomerular cells for UACR. These results allow for identifying relevant cell types for experimental research to translate GWAS loci into a mechanistic understanding.

The Antioxidant Activity of Neurotropin Contributes to the Kidney Protective Effect

Masaki Fukunaga,1 Akemi Uchida,2 Miyu Sueyoshi,1 Hitoshi Maeda,1 Yuki Narita,1 Hiroshi Watanabe,1 Toru Maruyama,1 Hakaru Seo,2 Sumio Hirata,3 Daisuke Kadowaki.2 1Faculty of Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan; 2Faculty of Pharmaceutical Sciences, Sojo University, Kumamoto, Japan.

Background: Neurotropin (NTP) is an extract from inflamed cutaneous tissue of rabbits inoculated with vaccinia virus and contains various non-protein components. NTP has long been used for the treatment of neuropathic pain such as postherpetic neuralgia. Recently, NTP have been reported that various organ protective effects by its antioxidant action. Furthermore, it is also suggested that NZ-419, which is one of the components of NTP, has the direct radical scavenging effect but also the antifibrosis.

Conclusions: In this study, it is considered that NTP has the direct radical scavenging activity and alters intracellular signal transduction to suppress oxidative stress. In conclusion, NTP may contribute to the renoprotective effect not only by the antioxidant effect but also the antifibrosis.
Nishan Protein Regulates Apoptosis in HK-2 Cells via Caspase-Dependent Pathway

Shi Ji, Jianwen Wang, Jishu Liu, Hao Zhang. The Third Xiangya Hospital of Central South University, Changsha, China.

Background: To investigate whether Niban protein plays a role in renal interstitial fibrosis by regulating apoptosis of renal tubular epithelial cells.

Methods: Unilateral ureteral obstruction (UUO) model was established by using 24 C57B/6J mice, which were divided into sham operation group, UUO 3 day group, UUO 7 day group and UUO 14 day group. Renal pathological changes were observed by HE staining and Masson staining. Immunohistochemistry was used to detect the expression of Niban, α-SMA, E-cadherin, p47phox and Chop, and co-staining with Hsc70 was also observed. In UUO 3 day group, the expression of Niban was significantly decreased, and the expression of p47phox, Chop and α-SMA was significantly increased.

Results: The renal interstitial fibrosis was significantly increased in the UUO 3 day group compared with the sham operation group. The expression of Niban was significantly decreased, and the expression of p47phox, Chop and α-SMA was significantly increased in the UUO 3 day group.

Conclusions: Niban protein is involved in the regulation of renal interstitial fibrosis by regulating apoptosis of renal tubular epithelial cells.

Funding: Government Support - Non-U.S.
FR-PO377

Oligomerization of APOL1 Risk Variants After Mitochondrial Damage

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Background: Inheriting two copies of APOL1 risk variants (G1 and G2) increases susceptibility to chronic kidney disease in African Americans. G1 and G2 are toxic, gain-of-function variants despite their recessive mode of inheritance. APOL1 multimerization has been proposed as an explanation for recessive gain-of-function.

Methods: Immunoprecipitation experiments were performed in HEK293 cells with co-transfection of constructs expressing APOL1 (G0, G1, or G2) tagged with FLAG or MYC. Oligomerization of untagged APOL1 was assessed in tetracycline inducible APOL1-expressing HEK293 cells using blue native PAGE. Mitochondrial-enriched and cytosolic fractions were prepared by differential centrifugation. TOMM20 was knocked down with siRNA 48 hours prior to induction of APOL1 expression. APOL1-induced cytotoxicity was determined using the Multi-Tox Fluor Multiplex cytotoxicity assay kit from Promega. After co-transfection of FLAG and MYC-tagged APOL1, immunoprecipitation of FLAG followed by Western blot for MYC demonstrated APOL1-APOL1 binding. Blue native PAGE of APOL1 expressing cell lines revealed that G1 and G2 tend to form large oligomers whereas G0 remains mostly monomeric. When we fractionated cells via differential centrifugation, we found that the oligomers were present mostly in the mitochondrial-enriched fractions. Knockdown of the mitochondrial outer membrane protein TOMM20 blocked APOL1 mitochondrial import and eliminated both APOL1 oligomer formation and APOL1-induced cytotoxicity.

Conclusions: APOL1 oligomers can interact with other APOL1 molecules and risk variants have a greater tendency to form large oligomers. The oligomers are mostly located in the mitochondrial-enriched cell fraction and inhibiting mitochondrial import of APOL1 dramatically reduces the formation of oligomers, suggesting that mitochondrial import of APOL1 is necessary for subsequent oligomerization of G1 and G2. Whether these APOL1 oligomers directly cause cytotoxicity remains to be answered.

Funding: NIDDK, Support, Other U.S. Government Support

FR-PO378

Energy Production System Is Suppressed in Kidneys of Low-Birth-Weight Rats, Which Develop FSGS

Toshiyuki Imasawa, National Hospital Organization Chibahigashi National Hospital, Chiba, Japan.

Background: Intraglomerular hypertension is associated with the pathogenesis of FSGS lesion of low-birth-weight (LBW) related nephropathy, because LBW is significantly associated with a decreased number of nephrons. However, there is a possibility that other mechanisms participated in the pathogenesis of LBW-related nephropathy. We purposed to investigate innate factors which should be involved in the pathogenesis of LBW-related nephropathy at adulthood.

Methods: Low-birth weight rats (N = 7) were obtained by intra-peritoneal injection of dexamethasone into pregnant rats. Normal-birth weight rats (N = 7) were obtained by salin injection. At 4 weeks of age, left kidneys were removed. After that, until 9 weeks of age, rats were fed with high salt diet. Results: At 9 weeks of age, serum creatinine levels of LBW rats were significantly higher than NBW rats (p<0.03). Furthermore, at 9-week-age, focal segmental sclerosis (FSGS) lesions were observed in 7.43% of glomeruli in LBW rats, but only 0.48% in NBW rats. On the other hand, at 4 weeks of age, there were no sclerotic lesions and any other pathological changes both in LBW rats and in NBW rats. A quantitative proteomics by using histologically normal cortexes at 4-week-age revealed marked suppression of energy metabolism in kidneys of LBW rats. For example, 15 proteins related to TCA cycle, 15 proteins of fatty acid metabolism, 14 proteins glycolysis, and 12 proteins of mitochondrial oxidative phosphorylation were significantly suppressed in LBW rats. Bioinformatics analysis by using Ingenuity Pathway Analysis revealed RICTOR should be a regulator of these metabolic changes.

Conclusions: Kidneys in low-birth-weight rats should have suppressed energy production system before the occurrence of histological kidney damage. Not only intraglomerular hypertension, but also such innate defects of energy production, might to form FSGS lesions in LBW-related nephropathy.

Funding: Government Support - Non-U.S.

FR-PO379

Effect of Magnesium on the Processes of Inflammation and Oxidative Stress Associated with CKD

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Background: The development and progression of vascular calcifications (VC) is a prevalent complication in advanced stages of chronic kidney disease (CKD). Previous observations show that magnesium (Mg) may be beneficial in preventing the development of VC. Uremia is considered to be an inflammatory state, and both chronic inflammation and oxidative stress appear to have a causal effect in VC by directly affecting vascular smooth muscle cells (VSMC). The main goal of this work was to assess, through both in vitro and in vivo approaches, the effect of Mg on inflammation and oxidative stress associated with CKD.

Methods: In vitro studies were based on the culture of VSMC in the presence of high phosphorus (P), with or without Mg. In vivo experiments were performed in an experimental model of uremic rats feeding with high P diet and Mg dietary supplementation during 14 days. All experimental protocols were reviewed and approved by the Ethics Committee for Animal Research of the University of Cordoba (Cordoba, Spain) and adhered to the recommendations included in the Guide for Care and Use of Laboratory Animals (US Department of Health and Human Services, NIH) and European laws and regulations on protection of animals, under the advice of specialized personnel.

Results: VSMC incubated with high P exhibited an increase in pro-inflammatory mediators, the inflammatory cytokines and the levels of oxygen reactive species (ROS). The addition of Mg prevented the elevation in inflammatory markers. Uremic rats receiving normal dietary Mg showed elevated levels of ICAM-1 and high oxidative stress blood biomarkers. Furthermore, when the rats received Mg supplementation, the oxidative stress levels decreased. The weight of the kidneys was reduced in the Mg group compared to the control.

Conclusions: Taken together, these results suggest the protective role of Mg in the generation of oxidative stress and inflammation in the context of renal disease.

Funding: Government Support - Non-U.S.
FR-PO381

Marketers of Mitochondrial Mass and Biogenesis Are Reduced in Non-Dialysis-Dependent CKD and Not Restored Following Exercise


Background: Patients with non-dialysis dependent chronic kidney disease (NDD-CKD) exhibit reduced exercise capacity, poor physical function and symptoms of fatigue. The mechanisms that contribute to this are not clear but may involve mitochondrial dysfunction. We investigated the effect of NDD-CKD on mitochondrial mass and the expression of transcription factors involved in mitochondrial biogenesis compared to healthy controls, and the effect of 12-weeks of exercise on these markers.

Methods: Skeletal muscle biopsies were collected from the vastus lateralis of 16 NDD-CKD patients (Stage 3b-5) and 16 matched healthy controls (HC). To investigate the effect of exercise training VL, biopsies were collected from 17 NDD-CKD patients stage 3b-5 pre and post a 12-week exercise intervention. Mitochondrial mass (porin/β-actin ratio) was analysed by western blotting and the expression of transcription factors (PGC-1α, βCKD, NRF-1/2, TFam, mfn2 and SOD1/2) compared to HC (p<0.05). 12-weeks of exercise training resulted in a significant increase in PGC-1α expression only (p=0.04), but no change in mitochondrial mass was observed (p>0.05).

Conclusions: NDD-CKD patients exhibit a reduction of skeletal muscle mitochondrial mass and suppression of mRNA expression of transcription factors that are involved in mitochondrial biogenesis, which may contribute to the detrimental muscle related symptoms experienced in this population. After 12-weeks of exercise training no improvement was observed. Reasons for this lack of improvement warrant further investigation in NDD-CKD.

FR-PO382

PET Imaging of Renal Mitochondria in Acute and Progressive Kidney Disease Models Using a Novel PET Probe 18F-BCPP-BF

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Background: The kidney is a highly energy-demanding organ and rich in mitochondria. In addition to physiological importance of mitochondria as a powerhouse, mitochondrial dysfunction is often associated with overproduction of ROS, which is believed to play a critical role the pathogenesis of kidney diseases. Nonetheless, only a few studies have reported the renal mitochondrial status in the clinical settings partly due to a paucity of methodologies. Recently, Ohba et al. developed a novel PET probe 18F-BCPP-BF specifically binding to mitochondrial complex I (MC-I). 18F-BCPP-BF has a favorable pharmacokinetic property for kidney imaging, which enables us to non-invasively visualize and quantify the amount of MC-I in whole kidneys in vivo (ENMNN Research 2016; 6; 82).

Methods: In this study, we demonstrated high-resolution animal PET analyses for kidneys in glomerulonephritis and AKI model animals using 18F-BCPP-BF.

Results: In anti-GBM glomerulonephritis model rats, the uptake level of 18F-BCPP-BF in kidney showed only slight decrease at the acute phase (74% vs. normal control), while it became more remarkable at the later phase (33% vs. normal control). The significant decrease in the PET signal was accompanied with robust reduction of mitochondrial complex proteins including MC-I, demonstrated by Western blotting analysis. The slight change in PET signals at acute phase despite massive proteinuria may reflect less damage in tubular epithelium. In rat acute renal FR model, the renal uptake of 18F-BCPP-BF was slightly decreased at 3 hours after reperfusion (75% vs. sham), when kidney function was slightly declined accompanying morphological abnormality of mitochondria in S3 proximal tubular cells though the loss of proximal tubular epithelial cells was still minimal.

Conclusions: The novel PET probe opens up new possibilities for studying pathophysiological meanings of mitochondrial status in kidney disease, which may be applicable to new clinical diagnosis for patients with various types of kidney diseases.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Integrative Omics Reveal Molecular Signatures of Endoplasmic Reticulum Stress in Tubular Epithelial Cells

**FR-PO384**

**Background:** Over the past decade, dysregulated and prolonged endoplasmic reticulum (ER) stress has been observed in acute kidney injury and chronic kidney disease (CKD). However, how ER stress contributes to disease pathophysiology in the kidney remains unclear. Here we take an unbiased approach to identify potential modulators of ER stress pathways in human proximal tubular epithelial cells.

**Methods:** We performed bulk RNA sequencing (RNA-seq) and untargeted LC-MS metabolic profiling on HKC-8 proximal tubular epithelial cells cultured with and without 2.5 µM of tunicamycin, an inducer of ER stress. Single-cell RNA-seq (scRNA-seq) was performed on kidney organoids differentiated from induced pluripotent stem cells, grown to day 25, and treated with tunicamycin.

**Results:** RNA-seq revealed 2921 differentially expressed genes after 4 hours and 2436 differentially expressed genes after 24 hours of tunicamycin treatment. These genes were enriched for pathways relevant to inflammatory response (P < 0.001), Wnt signaling (P <0.005), protein processing in the ER (P <0.002), and extra-cellular matrix receptor interaction (P <0.04). A subset of the most highly differentially expressed genes were validated in tubular cells profiled in scRNA-seq of tunicamycin-treated 3D kidney organoids. Thirty genes differently expressed in HKC-8 cell ER stress were also genes at kidney trait loci identified in recent genome-wide association studies; these genes are involved in cellular differentiation (PAX8 and AC10), and are known epigenetic modulators, with implications for differential methylation activated by ER stress. Decreased abundance of these metabolites is also consistent with the commensurate increase in PHGDH expression (FC 2.87, P<0.001).

**Conclusions:** These results demonstrate a possible role for inflammatory injury-related and ER stress induced transcriptional changes in kidney cells, with potential modulation by genetic variation and intermediate metabolites.

**Funding:** Other NIH Support - K08 HL133548

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FR-PO385

Renal Failure Induced by Deletion of the Gene Encoding Canonical Transient Receptor Potential 1 (TRPC1) Channels: A Mouse Model of Normotensive CKD

**Background:** TRPC1 plays a key role in cardiac hypertrophy, vascular smooth muscle proliferation & glomerular mesangial cell contractility. It is reduced in diabetes, but exact mechanisms underlying aging nephropathy (AN) are unclear. Renal angiotensinII (AII) and NF-κB system can contribute to reduce the decline of renal function with age. FAPESP/CNPq Government Support - Non-U.S.

**Methods:** Male Munich-Wistar rats were divided in 4 groups: 12M (n=10), 12-month-old rats; 15M (n=10), 15-month-old rats; 15M+L (n=8) rats receiving L (50 mg/kg/d) and 15M+L+PTDC (n=8), rats receiving L and PTDC (15 mg/kg/d). Both compounds were given orally from day 12 to 15 months of age. We assessed body weight (BW, g), tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/24h), serum creatinine (Scr, mg/dL), glomerulosclerosis (G,S, %), cortical macrophages (MΦ, cells/mm3) and AII (cells/mm3). Renal failure was assessed 14 days before death, by histology and quantification of interstitial fibrosis and tubular dilatation.

**Results:** ATRAP deficiency exacerbated age-associated tubulointerstitial fibrosis. Although the molecular mechanisms by which ATRAP deficiency exacerbates age-associated tubulointerstitial fibrosis has not yet been defined, renal SIRT1 protein expression was more decreased in aged ATRAP-deficient mice compared with aged wild type mice. Further investigations of ATRAP-dependent SIRT1 protein expression are important to resolve aging-associated kidney dysfunction. In this study we aimed to establish an ex vivo model of the proximal tubule to determine the role of ATRAP in SIRT1 protein expression.

**Methods:** We established an immortalised RTEPC line by expressing hSIRT1 and shRNA-targeted CDKN2a. Next, we cloned this immortalized RTEPC and then characterised the cells based on the expression of a proximal tubular marker (SGLT2, DPP4). We call this cloned immortalised RTEPC, cirRTEPC. To analyze the ATRAP function in the proximal tubular cells, we use siRNAs induced ATRAP knockdown in cirRTEPC and CRISPR-CAS9 mediated ATRAP knockout.

**Results:** SIRT1 mRNA expression, which was induced by serum starvation, was unaffected by transient ATRAP knockdown. On the other hand, SIRT1 protein expression was not induced by serum starvation in cirRTEPC cells, although transient ATRAP knockdown induced the expression of the normal and serum-starved conditions. Like ATRAP knockdown, ATRAP knockout did not affect SIRT1 mRNA expression under either the normal or serum-starved condition. However, SIRT1 protein expression was significantly decreased by serum starvation in ATRAP knockout cells, while no significant reduction in SIRT1 protein was observed in control cells.

**Conclusions:** These results indicate that ATRAP mediates SIRT1 protein abundance in cirRTEPC by regulating its synthesis and/or stability but does not affect the level of SIRT1 mRNA transcription or stability.

**Funding:** Government Support - Non-U.S.

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FR-PO387

Combined Treatment with Losartan and an NF-kB Inhibitor Affords Better Renoprotection Than ATIR Blockade Alone in Aging Rats

**Background:** The mechanisms underlying aging nephropathy (AN) are unclear. Renal angiotensinII (AII) and NF-κB activation are important factors in the pathogenesis of Chronic Kidney Disease (CKD). We investigated whether combined treatment with Losartan (L) and the NF-kB inhibitor Pyrroline Dithiocarbamate (PTDC) would attenuate experimental AN.

**Methods:** Male Munich-Wistar rats were divided in 4 groups: 12M (n=10), 12-month-old rats; 15M (n=10), 15-month-old rats; 15M+L (n=8) rats receiving L (50 mg/kg/d) and 15M+L+PTDC (n=8), rats receiving L and PTDC (15 mg/kg/d). Both compounds were given orally from day 12 to 15 months of age. We assessed body weight (BW, g), tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/24h), serum creatinine (Scr, mg/dL), glomerulosclerosis (G,S, %), cortical macrophages (MΦ, cells/mm3) and AII (cells/mm3), Collagen-I (Coll-I, %), as well as renal TLR4 and IL-6 (WB).

**Results:** Group 15M exhibited mild hypotension, creatinine retention, albuminuria, glomerulosclerosis, Coll-1 deposition and cortical infiltration by MΦ. Renal accumulation of TLR4 and IL-6 was also increased, suggesting activation of the NF-kB pathway. L decreased cortical Coll-I and Coll-1, but not TLR4 or IL-6, failing to reduce ALB or GS%. Combined L+PTDC prevented the increase of renal TLR4, IL-6 and MΦ, reduced AII- and strongly attenuated ALB and GS%.

**Conclusions:** Simultaneous inhibition of renal AII and of the NF-kB system can contribute to the reduction of the decline of renal function with age. FAPESP/CNPq Funding: Government Support - Non-U.S.

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Mean±SE; *p<0.05 vs 12M, †p<0.05 vs 15M, ‡p<0.05 vs 15M+L

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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FR-P0388

Progression of Established CKD Is Halted by Metformin Treatment in Rats
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Background: Metformin, the first-line drug for type-2 diabetes mellitus, also exerts multiple benign pleiotropic actions on different organs. Recent preclinical and clinical data point towards a beneficial impact of metformin on the kidney. Chronic kidney disease (CKD) is a worldwide recognized public health problem and represents a progressive loss of renal function over a period of months or years. Current treatment strategies for CKD mainly focus on controlling important risk factors. To date, effective treatment directly targeting the kidney is lacking. Here, the efficacy of metformin to attenuate progression of already established CKD was investigated.

Methods: A rat model of adenine-induced CKD (n=64) was used. Metformin (200 mg/kg) or vehicle (1% carboxymethylcellulose) treatment, by daily oral gavage (7 days/week), was initiated after 4 and 5 weeks of adenine (0.25%); administration; i.e. after CKD had developed. Treatment was continued during 4 weeks until the end of the study (i.e. week 8 and 9, respectively). A constant dose volume of 10 mL/kg was used. The effect of metformin on renal function and histopathology was studied.

Results: Serum creatinine levels dramatically rose in vehicle-treated CKD rats; from 0.6±0.1 mg/dL (week 0) to 1.3±0.2 mg/dL (week 4) and 2.6±1.2 mg/dL (week 5) and further to 5.7±0.6 mg/dL (week 8) and 4.1±1.1 mg/dL (week 9). This increase from week 4 and 5, respectively, was almost completely prevented by metformin treatment as indicated by serum creatinine levels after 8 (2.0±0.5 mg/dL) and 9 (2.9±0.5 mg/dL) weeks respectively (p<0.05 vs. vehicle). Histological examination of periodic acid–Schiff-stained renal sections revealed less tubular dilatation, epithelial flattening, brush border loss and, basement membrane thickening in metformin-treated rats in comparison to vehicle-treated animals. The renal tubulointerstitial area percentage, consisting of both extracellular matrix and infiltrating cells, in metformin treated CKD rats, was significantly lower, as compared to vehicle treated (33% and 23% lower in rats receiving metformin from week 4 and 5, respectively, as compared to vehicle).

Conclusions: Metformin is able to attenuate the progression of pre-existing adenine-induced CKD in rats.

Funding: Government Support - Non-U.S.

FR-P0389

Latent Transforming Growth Factor Beta Binding Protein 4 (LTBP4) Attenuates Tubulointerstitial Fibrosis and Ameliorates Inflammation and Mitochondrial Dysfunction in CKD
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Background: Transforming growth factor beta (TGFβ) signaling has been well-known as a key regulator of fibrosis and inflammation. LTBP4 regulates TGFβ signaling in complicated ways. Disruption and loss of LTBP4 expression is associated with abnormal accumulation of extra-cellular matrix (ECM) and altered TGFβ activity. However, the role of LTBP4 in chronic kidney disease remains largely unknown.

Methods: To investigate the impact of LTBP4 on tubulointerstitial fibrosis (TIF), we generated LTBP4-overexpression and LTBP4-deficiency human renal proximal tubule cells (HK-2), treated with exogenous TGFβ2 and established a fibroblast-HK-2 co-culture system using rat fibroblasts (NRK-49F) and HK-2 cells. Moreover, to create TIF model, we performed unilateral ureteral ligation (UUO) in Ltbp4+/− mice and wild-type (WT) mice to check ECM deposition and phenotypic alterations.

Results: Up-regulation of Lbp4 in fibrotic kidney was noted in TIF model with UrO. Markers and mediators of fibrosis, α-SMA, fibronectin, collagen I, Pdgfrb and TGFβ in gene and protein levels were reduced significantly in Ltbp4-knock down HK-2 cells treated with additional TGFβ2. LTBP4-overexpression enhanced epithelial-mesenchymal transition (EMT) with showing decreased epithelial-cadherin, increased vimentin and collagen I in the co-culture system. In addition, lower expression of Pdgfrb with higher expression of Nrf2 signaling was noted in fibrotic kidneys in Ltbp4−/− mice compared with changes in WT mice, suggesting inflammation condition could be altered by the absence of Lbp4. Lbp4-deficiency also reduced inflammatory gene expression such as IL-6 and altered IL-6-associated mitochondrial biogenesis.

Conclusions: Lbp4 plays a regulator of fibrosis and inflammation. Lbp4 appears to inhibit antioxidant Nrf2 pathway and enhance fibrosis in a TGFβ-related manner in a murine UUO model of TIF and in a cell co-culture system. In addition, LTBP4 deficiency ameliorates mitochondrial dysfunction and alleviates renal fibrosis.

FR-P0390

Tolvaptan and Bardoxolone Methyl Synergistically Activate the Nrf2/HO-1 Pathway
Tamami Fujiki, Fumikazu Ando, Shintaro Mandai, Kiyoshi Isobe, Takayasu Mori, Koichiro Susa, Naohiro Nomura, Eisei Sohara, Tatemitsu Rai, Shinichi Uchida.
Tokyo Medical and Dental University, Tokyo, Japan

Background: Tolvaptan, a vasopressin type 2 receptor antagonist, has been approved for the treatment of autosomal dominant polycystic kidney disease. Furthermore, tolvaptan has been shown to improve proteinuria in patients with chronic kidney disease (CKD); however, the underlying molecular mechanisms remain unknown. CKD is characterized by increased levels of oxidative stress, and an antioxidant transcription factor-nuclear factor erythroid 2-related factor 2 (Nrf2)-has been gaining attention as a therapeutic target. Therefore, we investigated the effects of tolvaptan and a well-known Nrf2 activator, bardoxolone methyl (BARD) on Nrf2.

Methods: We investigated the effect of tolvaptan and bardoxolone methyl on Nrf2 using mouse cortical collecting duct (mpkCCD) cells and mice kidneys.

Results: Tolvaptan led to Nrf2 mRNA translocation and induced mRNA and protein expression of heme oxygenase 1 (HO-1) in mpkCCD cells and the outer medulla of mice kidneys. Phosphorylation of unfolded protein kinase RNA-like endoplasmic reticulum kinase (PERK) by tolvaptan played an important role in activation of Nrf2/HO-1 pathway. Moreover, tolvaptan and BARD synergistically activated Nrf2/HO-1 antioxidant pathway in mpkCCD cells.

Conclusions: We found the novel pharmacological property of tolvaptan that activated the PERK/Nrf2/HO-1 signaling pathway. Nrf2-regulated antioxidant systems were synergistically activated by tolvaptan and BARD. Tolvaptan is a potential therapeutic candidate in renal disease.

Funding: Government Support - Non-U.S.

FR-P0391

Adipose Tissue Macrophage Infiltration in CKD
Goni Katz-Greenberg,¹ Zhao Lin,² Cristina Martos-Ros,² María P. Martínez-Cantarín,² 1Thomas Jefferson University Hospital, Philadelphia, PA; 2Thomas Jefferson University, Philadelphia, PA.

Background: Patients with advanced chronic kidney disease (CKD) present higher levels of inflammatory markers, associated with significant morbidity and mortality. Increased adipose tissue macrophages (ATM) may play an important role in a state of chronic inflammation seen in CKD patients. Historically, macrophages were divided into two main phenotypes, M1 or pro-inflammatory, and M2 associated with tissue repair. The aim of this study is to examine the degree of macrophage infiltration and macrophage characteristics in adipose tissue in patients and mice models with CKD.

Methods: We studied adipose tissue from 4 pairs of control-advanced CKD patients undergoing kidney donation or transplantation the same day. Stromal vascular fractions (SVF) were isolated from subcutaneous (SCF) and visceral (VF) adipose tissue. Macrophage populations were studied by flow cytometry. A model of advanced CKD mice, macrophage populations were studied in adipose tissue SVF and peripheral blood. The same experiment was replicated in a model of advanced CKD in IL-6 knock-out (KO) mice.

Results: Patients with CKD had higher number of macrophages in adipose tissue compared to controls [fold change 1.9 for SCF and 2.7 for VF; p<0.01]. In CKD mice, there was an increase in total number of macrophages in SCF versus control [42.24% ± 5.96%; P<0.01]. SCF of CKD mice also had lower CD31+CD11c+ macrophages [1.5% ± 16.15%; P=0.005] and higher CD31+CD11c+ macrophages versus controls [96.6% ± 3.35%; P<0.001]. No difference was observed between the CKD and controls in VF. When SVF were studied in an IL-6KO mouse model, there were no differences in AAT numbers in SCF or VF. In peripheral blood and despite lower total number of leukocytes [CD4+ 10.5% ± 16%; P=0.05], CD163+, CD11c+ and CD206+ macrophages were significantly increased in CKD mice compared to controls [47% vs 27%; 4.3% vs 2.6%; and 2% vs 1.3% respectively; P<0.05 for all]. There was also a higher number of T-cell sub-populations seen in CKD mice compared to controls [CD4+ 13.6% ± 11.4% and CD8+ 7.5% ± 5.4%; p<0.001 for both].

Conclusions: In humans, there was higher macrophage infiltration in adipose tissue. This was reproduced in a mice model of CKD. The lack of increased AAT numbers in the IL-6-KO mice model, suggest IL-6 may play a role in the recruitment of macrophages to adipose tissue in advanced CKD.

FR-P0392

Kidney Injury Molecule-1 (KIM-1) Promotes Tertiary Lymphoid Tissue (TLT) Development in the Kidney Through LTβ/TLR8 Signaling
Min Yang, Yutaro Mori, Naoko Murakami, Takaharu Ichimura, Joseph V. Bonventre. Division of Renal Medicine, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.

Background: TLTS, inducible ectopic lymphoid tissues formed in chronic inflammatory conditions, have been described in various pathologic kidney diseases. However, the links between activation of the inflammation and the triggering cascade of B/T-cell clusters in the kidney are not understood. Here we investigated the role of KIM-1 on tubular epithelial cells (TECs) in affecting the formation of TLTS and modulation of the immune response in kidney injury. The immune response associated with TLT formation was investigated using a kidney injury model induced by aristolochic acid (AA) in wild-type (WT) or
KIM-1 (functional knockout of KIM-1) mouse. Studies in vitro were also done using renal primary TECs isolated from WT or KIM-1 mice kidney or macrophage cells. Cells were treated with AA and incubated with endothelial cells (ECs, primary mouse kidney endothelial cells and bEND3), followed by measurement of the lymphotxin pathway, lymphoid chemokines and pro-inflammatory characteristics.

**Results:** Under a treatment WT, but not KIM-1, mice developed multiple TLTs in the kidney, morphologically characterized by high endothelial venules (HEVs) PNAβ, germinal centers within B cell follicles and T cells infiltration. These characteristics were associated with higher expression of lymphoprogenetic chemokines (CXCL13-CXCL16/CXCL17/TC17), adhesions (VCAM1, VACAM1, VACAM1.1, VCAM1), TECs also displayed reduced expression of LTN, LTβ and induction of HEV marker PNAβ following AA stimulation, similar to in vivo.

**Conclusions:** KIM-1 plays a critical role in initiation of the inflammatory response by activating HEV through LTN/LTβ signaling, providing inflammatory milieu to enhance kidney fibrosis. These findings provide a new insight that TECs modulate immune reaction in kidney injury and can be a therapeutic target for inflammatory renal diseases.

**Funding:** NIDDK Support

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**FR-PO391**

**Experimental CKD Reduces Tubuloglomerular Feedback Synchronization and Impairs Autoregulation**

Tayyaba Zebra, Heather L. More, Sherreen M. Hamza, William A. Cupples, Branko Braam. University of Alberta, Edmonton, AB, Canada; Simon Fraser University, Burnaby, BC, Canada.

**Background:** Tubuloglomerular feedback (TGF) is an important component of autoregulation of renal blood flow and can prevent transmission of high blood pressure to glomeruli. We have previously shown that the TGF mechanism operates in a network fashion, leading to TGF synchronization. Eventually, this ensures that each nephron receives appropriate perfusion to match the energy-intensive reabsorption of Na+. We have shown that loss of synchronization impairs autoregulation which is implicated in chronic kidney disease (CKD). We hypothesized that structural damage to the nephron-network would impair TGF-synchronization.

**Methods:** Male Lewis rats underwent uninephrectomy followed by partial nephrectomy to induce CKD (6) or underwent sham-operation (n=6). Six weeks later, the rats were anesthetized and mean arterial pressure (MAP), renal blood flow (RBF), and glomerular filtration rate (GFR) were assessed. Renal cortical perfusion was recorded with laser speckle contrast imaging (LSCI; Moor Instruments). After filtering to isolate TGF frequencies, we quantified phase coherence (PC) and used graph analysis to provide information about TGF synchronization between nephrons.

**Results:** Within the control group, RBF (8±0.6 to 6.7±1.0 mL/min) and GFR (0.89±0.33 to 0.37±0.7 mL/min) were decreased compared to controls (7.4±1.3 to 7.0±1.4 mL/min, 0.63±0.38 to 0.55±0.14 mL/min), respectively, although this did not reach significance. MAP showed no differences between CKD (102±7 to 89±5 mmHg) and controls (104±6 to 91±4 mmHg). Strength of TGF-synchronization between nephrons is indicated by higher values for phase coherence (PC). PC values were decreased for CKD (0.03 vs 0.04) versus for CKD rats (0.03) which indicates weaker synchronization (p<0.005). Each pixel in the image is treated as a node and connected to other nodes via edges with significant PC; the CKD group had a lower number of connecting edges (780±532) compared to controls (3693±22589) (p<0.005). The number of synchronized neighboring nephrons for CKD rats (4±0.18) was lower than controls (2±0.18) (p<0.005).

**Conclusions:** In this model of CKD, we demonstrate an impaired ability of nephrons to synchronize TGF in the renal cortex as assessed by LSCI. Since this network synchronization could prevent hypertensive injury further investigations are on improving network function.

**Funding:** Government Support - Non-U.S.

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**FR-PO394**

**CKD of Unknown Etiology (CKDUs) in Sri Lanka (SL): A Tissue Analysis**

Necia Kambham,1 Nishanthana Nanayakkara,2 Karen L. Artilles,1 Vivek Bhalia,1 Andrew Fire,2 Shiuchi Anand.1 CKD Sri Lanka 1 Stanford University, Stanford, CA; 2Teaching Hospital, Kandy, Kandy, Sri Lanka; Stanford University, Stanford, CA.

**Background:** CKD is a leading cause of kidney disease in Central & North Central SL. Based on a prospective renal biopsy study, we hypothesized that higher acuity reflects CKD: Mechanisms - II

**Funding:** Government Support - Non-U.S.

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**FR-PO395**

**Gut Flora-Dependent Metabolite Trimethylamine-N-Oxide Accelerates Kidney Aging through p53/p21/Rb Pathway and Age-Related CircRNAs**

Fanfan Gao, Hongli Jiang. Dialysis Department of Nephrology Hospital, First Affiliated Hospital of Medicine School, Xi’an Jiaotong University, Xi’an, China.

**Background:** Gut microbiota can influence the aging process and may modulate aging-related changes in cognitive function. Trimethylamine-N-oxide (TMAO), gut microbial intermediates, has been shown to be associated with kidney disease and other disease. However, the relationship between TMAO and aging, especially renal aging, has not been fully elucidated.

**Methods:** We analyzed age-related palomas levels of TMAO and circRNAs in 3-month-old and 24-month-old mice. Male CD1 and TCMK-1 cell were incubated with different concentrations of TMAO (0, 1µM, 10µM, 100µM, 1000µM) for 24 hours and 72 hours. western blotting and qPCR was used to detect the changes of related proteins and RNA after exposure to TMAO.

**Results:** In the present study, we found that circulating TMAO increased with age in mice. In vitro, we demonstrated that prolonged TMAO treatment induced senescence in HK2 and TCMK-1 cell, characterized by reduced cell proliferation, increased expression of senescence-associated β-galactosidase (SA-β-gal). Meanwhile, TMAO increased the expression of p53, p21, p16 and decreased phosphorylation of Rb expression. Furthermore, TMAO changed the expression of circRNAs.

**Conclusions:** In summary, these data suggest that elevated circulating TMAO during the aging process may deteriorate HK-2, TCMK-1 cell senescence and renal aging, which is probably associated with the activation of the p53/p21/Rb pathway and the change of circRNAs.

**Funding:** Government Support - Non-U.S.

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**FR-CRC16**

**CircRNA_15698 Exacerbates Folic Acid-Induced Renal Interstitial Fibrosis via the miR-185/TGF-ß1 Pathway**

Dongdong Wang, Junjun Luan, Hua Zhou. The Affiliated Shengjing Hospital of China Medical School, Shenyang/China, China; China medical university, Shenyang, China.

**Background:** Circular RNAs (circRNAs) are a novel type of noncoding RNAs that play important role in the pathogenesis of many diseases. A study reports that circRNA_15698 aggravates the renal mesangial extracellular matrix of diabetic nephropathy via miR-185/TGF-ß1. However, the role of circRNA_15698 in renal tubulointerstitial fibrosis remains unclear. In this study, we aim to investigate whether circRNA_15698 plays an important role in folic acids-induced renal interstitial fibrosis and its corresponding mechanism.

**Methods:** Male CD-1 mice were peritoneally injected 250 mg/kg of FA or its vehicle. We collected kidney tissue after removing blood by PBS perfusion on day 30 after FA injection and evaluated renal interstitial fibrosis by PAS and Masson staining. We measured mRNAs levels of pro-inflammatory cytokines such as interleukin-6 (IL6), tumor necrosis factor-α (TNF-α), and inflammatory cells including T lymphocytes and macrophages in the kidneys. We also examined the expression of pro-fibrosis factors, alpha smooth muscle actin (a-SMA), Collagen 1 (COL-1), and Fibronectin. Finally, we examined the renal expression of circRNA_15698, miR-185, transforming growth factor-beta (Tgfβ) and analyzed the mRNA expression between circRNA_15698 and miR-185 as well as between miR-185 and Tgfb on Targetscan and miRanda.

**Results:** Peritoneal injection of FA induced obvious renal interstitial fibrosis (RF) seen on PAS and Masson staining on day 30 after the injection. Pro-inflammatory cytokines, both IL6 and TNF-α elevated remarkably in FA-injected mice compared to normal control mice. The infiltration of T lymphocytes and macrophages were seen in the kidneys. Pro-fibrosis factors, a-SMA, COL-1, and Fibronectin were increased in renal FA-injected mice on both mRNA and protein levels of the above factors. In addition, the
renal expression of circRNA_15698 was upregulated, renal miR-185 was downregulated and Tgfβ was also upregulated. Finally we found perfect match seed displayed between circRNA_15698 and miR-185 as well as between miR-185 and Tgfβ on TargetScan and miranda analysis.

Conclusions: Our results suggested that circRNA_15698 might play an important role in renal interstitial fibrosis by spatially regulating the expression of TGF-β and increasing production of prollibiotic TGF-β1. This is a novel pathway in pathogenesis of renal fibrosis and circRNA_15698 might be a new therapeutic target for renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO397

Racial/Ethnic Disparities in Atrial Fibrillation Treatment and Outcomes in US Dialysis Patients

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Background: Stroke prevention is a major goal in the management of end-stage renal disease (ESRD) dialysis patients with atrial fibrillation (AF). In the general AF population, racial/ethnic minorities have higher stroke rates, lower rates of anticoagulation and higher anticoagulation complication rates. We describe differential treatment patterns by race/ethnicity and their association with racial/ethnic disparities in stroke outcomes among dialysis patients with AF.

Methods: We used the United States Renal Data System to identify ESRD patients diagnosed with AF who initiated hemodialysis from 2006-2013 with Medicare Part A, B, and D follow-up through 2015. We measured colonoscopy, mortality, and time to initiation of oral medications for AF, and cardiovascular disease procedures (CVD) for AF. We used a causal inference mediation approach that accounts for time varying mediators and confounders to quantify what proportion of excess stroke can be attributed to lower use of AF therapies by race/ethnicity.

Results: The study included 56,587 ESRD dialysis patients with AF. Black, non-Hispanic White, Hispanic, and Asian patients accounted for 19%, 69%, 8%, and 3% of the population, respectively. In adjusted analyses, Black, Hispanic, and Asian patients were 13%, 18%, and 22% more likely to experience stroke within 1 year and 10%, 17%, and 28% times less likely to fill a prescription for warfarin compared to White patients, respectively. Prescription of warfarin was associated with decreased stroke rates (HR=0.82). Mediation analyses suggested that 7%, 10%, and 12% of excess strokes among Black, Hispanic, and Asian patients occurred if the warfarin distributions in these groups were equalized to that in the White population. We did not find racial/ethnic disparities for all-cause mortality or use of CVD procedures. All results achieved p<0.05.

Conclusions: Increased racial/ethnic disparities in stroke rates among ESRD dialysis patients with AF are partially explained by lower use of oral anticoagulants among Blacks, Hispanics, and Asians. The reasons for these racial disparities in practice are unknown, but the results support the development of strategies to maximize stroke prevention in minority populations that address patient, physician, and system barriers to optimal treatment.

FR-PO398

Dialysis Modality and Cardiac Function at the Time of Kidney Pre-Transplant Patients’ Evaluation

Lawrence R. Butros,1 Omar Mallik,2 Mohanad O. Soliman,3 Mohamed Ellyamin,4 Maria Yaseen,5 Eman Elsawally,6 Karolina Viquez,1 Marc Paramanano,8 Belal M. Khatib,1 Arner V. Elrefai,1 Elijah Kakani,1 Roberto Gedaly,1 Xiaonan Mei,3 Andrew Kolodziejcz,4 Maya Guglin,1 David Booth,1 Amr E. Mohamed,1 Ana L. Castellanos,1 Thomas H. Waid,4 9University of Kentucky, Lexington, KY; 10University of Kentucky Medical Center, Lexington, KY.

Background: Hemodialysis (HD), peritoneal dialysis (PD) and pre-emptive kidney transplant are different options at the time of the pre-transplant patients’ evaluation; however, it is not clear how each dialysis modality affects cardiac structure and function. We analyzed the echocardiographic parameters for all patients and correlated them with the different dialysis modality.

Methods: This is a single-center, retrospective and descriptive study for patients who had completed pre-transplant cardiac evaluation in the renal transplant program at University of Kentucky from January 2010 and December 2015. We classified patients into 3 groups according to the dialysis modality. Group 1 included pre-emptive patients (n=74), group 2 included PD patients (n=61), and group 3 included HD patients (n=144). We analyzed the echocardiographic parameters for all patients and correlated them with the different dialysis modality.

Results: There were no differences in demographic parameters between the 3 groups. Pre-emptive patients had a lower rate of diabetes mellitus (p=0.046) and marginally lower coronary artery diseases (p=0.055). There was no significant difference between the three groups in terms of left ventricular ejection fraction or right ventricular systolic function as measured by end diastolic and systolic dimensions, severity of tricuspid and mitral regurgitations and diastolic function as measured by E/e’ . Moreover, the pulmonary artery pressures as measured by velocity of tricuspid regurgitation and pulmonary artery acceleration time were not significantly different between groups. Left ventricular mass index was significantly higher in patients on hemodialysis and lower in patients on peritoneal dialysis (p=0.010).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Incident HD patients suffer from volume overload and electrolyte abnormalities, ECG at the initiation of HD is thought to be a kind of “stress ECG test”.

**Methods:** We performed a retrospective multicenter cohort study of incident HD patients. We collected the latest data just before the initiation of HD. The primary outcome was atherosclerotic and non-atherosclerotic cardiovascular diseases (CVD) after the initiation of HD. Using Cox proportional hazards models, we examined whether ECG parameters (PR, QRS, QT interval, heart rate, and left ventricular hypertrophy [LVH] by voltage criteria) predict the primary outcome.

**Results:** Among the enrolled 683 patients, 21 and 16% of the patients showed LVH and PR interval >200 ms (PR prolongation), respectively. Serum phosphate levels were positively associated with heart rate and PR interval (Figure). Over a median follow-up period of 3 years, 19 and 16% of the patients developed atherosclerotic and non-atherosclerotic CVD, respectively. Backward stepwise multivariate Cox regression models including ECG parameters and baseline characteristics of patients revealed that LVH predicted atherosclerotic CVD (hazard ratio [95% CI: Confidence Interval]): 1.96 [1.24-3.11]). In contrast, PR prolongation was a significant risk factor of non-atherosclerotic CVD (hazard ratio [95%CI]: 2.00 [1.17-3.42]).

**Conclusions:** LVH and PR prolongation were significant risk factors of atherosclerotic and non-atherosclerotic CVD, respectively. Fibroblast growth factor 23 might explain the positive association of serum phosphate levels with heart rate and PR interval.

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**FR-PO402**

**Impact of Electrolytes and Acid-Base Changes During Hemodialysis Session on Incidence of Arrhythmia**

Emi Amo, Keichiro Hori, Ainori Hoshimoto, Makiko Harano, Rina Hisada, So Hagiwara, Yusuke Tsukamoto. Iubashi Chuo Medical Center, Tokyo, Japan.

**Background:** Patients on hemodialysis (HD) have a high incidence of sudden cardiac death. Since we often observed increasing incidence of arrhythmia during and just after dialysis session, drastic changes in electrolytes and/or acid-base may prolong QTc interval and cause arrhythmia. To investigate occurrence and frequency of arrhythmias chronologically and to examine the effects of electrolyte and acid base change on QTc interval during dialysis session.

**Methods:** We recorded ECG by 24-hour Holter and simultaneously measured changes in serum electrolytes and acid-base during a single hemodialysis session in 50 patients (F/M=15/35, 64% were diabetics, 1993 days of mean HD vintage, 70.1 years of mean age). HD parameters were: 3h (n=1), 3.5hr (n=1) or 4hr/3week, dialyzer: polysulfone, Qb=150-200ml/min. Concentration of electrolytes in dialysate were Na+: 140 mmol/l, K+: 2.0 mmol/l, Ca2+: 3.0 mmol/l, Mg2+: 1.0 mmol/l, Cl-: 110 mmol/l, CH3COO-: 8 mmol/l and HCO3-: 30 mmol/l.

**Results:** ECG was recorded from the start of dialysis session. The highest incidence of SVT/VPC and VPC was recorded during 1st 4-hour period (during dialysis; 25%) and 2nd 4-hour (right after dialysis; 26%). QTc did not increase in 18 patients and increase in 32 patients during dialysis session. Between these two groups, mean initial QTc was not different but logistic regression revealed that serum HCO3- (odds=0.64) and pH (odds=1.05×109) were significant determinants among others (Ca2+, K+, Mg2+, Na+ and QTc). Multiple regression analysis revealed not only initial QTc but also QTc change during single dialysis session was affected by initial level or changes in serum Ca2+ (p=0.0001/0.01), K+ (p=0.007/0.007) and HCO3- (p=0.023) among others (Mg2+ and Na+) by weighted least squares multiple regression (p=0.83/0.85).

**Conclusions:** These results suggest that QTc prolongation during dialysis session is caused by not only magnitude of changes in serum Ca2+ and K+ as reported previously but also magnitude of alkalization in our dialysate composition. In order to prevent prolongation of QTc and arrhythmia, changes in acid-base should be minimized specifically.

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**FR-PO403**

**Silent Arrhythmias In Hemodialysis Patients Does Not Increase Major Cardiovascular Events over Short-Term Follow-Up**

Tarun K. Jeloka, Jaymin P. Somani, Manishkumar S. Mali, Gajanana K. Kale. Nephrology, Aditya Birla Memorial Hospital, Pune, India.

**Background:** This study was conducted to know the incidence and outcome of silent cardiac arrhythmias in hemodialysis patients.

**Methods:** A total of 25 patients on regular hemodialysis (HD) were enrolled for studying cardiac arrhythmias. At screening phase, all HD patients were subjected to fluid optimization and adjustment in the BP medicines over a period of 2 weeks. Only those patients, who had no history of or evidence of arrhythmias in baseline electrocardiogram were enrolled. Holter monitoring for evidence of arrhythmia was done for 24 hours, including 4 hours of hemodialysis session on two occasions: long inter-dialytic (LIDP) and short interdialytic period (SIDP). Incidence and types of arrhythmia was noted. Factors associated with arrhythmias and effect of interdialytic period on arrhythmia were studied. All these patients were followed for a period of 12 months to study the impact of cardiac arrhythmias to adverse cardiovascular events.

**Results:** Out of 25 patients studied, 17 patients (68%) developed arrhythmia. Of the all arrhythmias, sinus bradycardia was the most common type, which occurred in 60% of patients. Incidence of supraventricular tachycardia (SVT) was 24% followed by atrial tachycardia 16%, premature ventricular complex 12%, atrial fibrilation 8%, premature atrial complex 4% and ventricular tachycardia 4%. The baseline demographic parameters of patients with or without arrhythmias were similar. In laboratory parameters, serum creatinine was higher in arrhythmia group (9.2 mg/dL vs 6.9 mg/dL, P=0.003). Mean ultrafiltration was higher in arrhythmia group after long inter-dialytic period (2.86 ± 0.68L vs. 2.12 ± 0.93L, P < 0.036). Incidence of arrhythmia was higher after LIDP as compared to SIDP (64% vs. 52%, P=0.004). A total of 4 patients died over 1 year of follow up - three patients died in non-arrhythmia group while one in the arrhythmia group. One patient in arrhythmia group developed heart failure. None of the patients developed symptomatic cardiovascular event over 12 months of short observational period.

**Conclusions:** Asymptomatic silent arrhythmia is a common complication seen in patients on maintenance hemodialysis (68%) with bradycardia being the commonest (60%). Impact of arrhythmia on long term cardiovascular outcome needs long term follow up of these patients.

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**FR-PO404**

**Cardiac Arrest in Hospitalized Maintenance Hemodialysis Patients**

Katherine M. Scovener,1 João Sérgio Neves,2 Simone Corea,1 Samuel Short,1 Zos A. Kibbelbaard,1 Finnian R. McCausland.1 1Renal Division, BWH, Boston, MA, 2Department of Endocrinology, Diabetes and Metabolism, São João Hospital, Faculty of Medicine, University of Porto, Lisbon, Portugal.

**Background:** Sudden cardiac death accounts for half of cardiac-related deaths in maintenance hemodialysis (HD) patients. Data regarding the frequency of shockable rhythms at presentation to or during a hospital stay is limited.

**Methods:** A retrospective cohort study was performed to evaluate the characteristics, laboratory values and treatment of HD patients with a hospital stay due to or complicated by cardiac arrest between 2015-2018. Arrests following continuous renal replacement therapy were excluded (n=4). Differences in predictors of interest according to the use of defibrillation during cardiac arrest were analyzed by chi2 tests or t-tests.

**Results:** Of the 34 subjects included, mean age was 64 years, 83% were male, 29% were black, 53% had heart failure and 44% had atrial fibrillation. 25 arrested during admission, while 9 had out-of-hospital arrests. 71% died during their admission. 29% had ventricular tachycardia (VT) or fibrillation (VF) during their arrest; 70% of these received at least one shock. 50% had asystole/pulseless electrical activity (PEA) without VT or VF. The remaining 21% rhythms were not described; one of these had no documentation regarding whether or not defibrillation was used. The median duration since the preceding HD session was 24 hours (25-75th percentile:12-45) with pre-arrest serum electrolytes as follows: potassium 4.9±0.7mmol/L, bicarbonate 22±4mmol/L, phosphorus 4.6±1.9mg/dL and calcium 8.8±0.8mg/dL. Comparisons according to receipt of defibrillation are presented in Table 1.

**Conclusions:** Asystole/PEA appear to be more frequent than VT/VF in HD patients with a hospital stay due to or complicated by cardiac arrest. Of patients with VT/VF, 30% were not defibrillated. Further studies are needed to better understand the etiology and treatment of cardiac arrest in HD patients during hospitalization.

**Table 1. Characteristics of Defibrillated vs Not Defibrillated Patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Defibrillated (n=20)</th>
<th>Not Defibrillated (n=14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>64±8</td>
<td>64±9</td>
<td>0.82</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>16/4</td>
<td>12/2</td>
<td>0.32</td>
</tr>
<tr>
<td>Race (White/Black)</td>
<td>8/12</td>
<td>10/4</td>
<td>0.45</td>
</tr>
<tr>
<td>Heart Failure (Yes/No)</td>
<td>12/8</td>
<td>10/4</td>
<td>0.45</td>
</tr>
<tr>
<td>Atrial Fibrillation (Yes/No)</td>
<td>11/9</td>
<td>8/6</td>
<td>0.32</td>
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<tr>
<td>Maximum Serum Creatinine (mg/dL)</td>
<td>9.2±2.3</td>
<td>7.9±2.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Median Serum Calcium (mg/dL)</td>
<td>8.8 (7.3-9.5)</td>
<td>8.6 (7.4-9.5)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Effects of Spironolactone (SPL) on Arrhythmias in Hemodialysis Patients: Secondary Results of the SPi-D Trial

David M. Charytan,1 Jesse Y. Hsu,3 Jonathan Himmelfarb,4 Talat Alp Ikizler,5 Dominic S. Raj,6 J. R. Landis,7 Rajnish Mehrotra,8 Sushrut S. Waikar,9 Paul L. Kimmel,10 Alan S. Kliger,11 Finnian R. McCausland,12 Laura M. Dember.13

Background: The Spironolactone in Dialysis (SPi-D) trial evaluated the safety of SPL for 36 weeks at 12.5 mg, 25 mg, or 50 mg vs placebo in maintenance HD patients. We analyzed data from a subset of participants with arrhythmia monitoring for 7 days at baseline (N=35), 6-weeks (N=37), and end of study (N=53). Adjusted Poisson models including treatment, time point and randomization stratification factors were used to analyze associations of SPL, SPL dose, and serum potassium (K) with the incidence rates of arrhythmias during follow-up.

Results: Conduction blocks or bradycardia and atrial fibrillation or flutter (AF) were common while ventricular arrhythmia was infrequent (Table). Conduction defects or bradycardia were more frequent with SPL compared with placebo in unadjusted and adjusted models. Reduction in AF risk with SPL vs. placebo was less robust at higher SPL dose: (adjusted rate ratios [RR], 95% CI) SPL 12.5 mg (0.09, 0.01-0.77), 25 mg (0.40, 0.06-2.72) and 50 mg/daily (0.89, 0.21-3.72), and conduction block or bradycardia was more frequent at higher SPL dose: (adjusted RR, 95% CI) SPL 12.5 mg (1.56, 0.93-2.52), 25 mg (4.15, 1.06-15.93) and 50 mg (3.00, 1.73-5.20). The RR per 1 mEq/L increase in serum K was 1.54, 0.89-2.65 for AF and 1.20, 0.78-1.86 for bradycardia/block.

Conclusions: Arrhythmias occur with a high incidence in maintenance HD patients with AF and bradycardias/conduction blocks occurring more frequently than ventricular arrhythmias. SPL may reduce AF but increase conduction blocks and bradycardia. Additional studies are needed to confirm these findings, evaluate the effects of SPL dose, and determine if K mediates SPL-associated arrhythmias.

Funding: NIDDK Support, Other NIH Support - NCATS

Arrhythmia Rate at Baseline and Follow-Up

<table>
<thead>
<tr>
<th>Arrhythmia Type</th>
<th>Overall Rate at Baseline</th>
<th>Placebo, SPL 12.5 mg</th>
<th>SPL 25 mg</th>
<th>SPL 50 mg</th>
<th>Combined SPL Dosing During Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrilation</td>
<td>5.6</td>
<td>13.2</td>
<td>1.2</td>
<td>5.3</td>
<td>11.7</td>
</tr>
<tr>
<td>Conduction Block or Bradycardia</td>
<td>3.4</td>
<td>15.5</td>
<td>24.6</td>
<td>27.1</td>
<td>46.5</td>
</tr>
<tr>
<td>Ventricular Tachycardia or Fibrillation</td>
<td>0.8</td>
<td>10.9</td>
<td>0.9</td>
<td>0.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Sinus Bradycardia or Atrioventricular Block</td>
<td>0.7</td>
<td>1.4</td>
<td>1.4</td>
<td>0.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Stress Tachycardia, Supraventricular Tachycardia</td>
<td>14.9</td>
<td>13.7</td>
<td>12.5</td>
<td>10.9</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Results are presented as events per 100 patient-days and are shown for combined placebo and spironolactone group at baseline and by randomized treatment group during follow-up.

FR-PO406

Arrhythmia in Chronic Hemodialysis as a Function of Pre-Dialysis Electrolytes and Intertidal Interval

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Background: Sudden cardiac death is a leading cause of death in hemodialysis patients. For patients on thrice weekly dialysis, these deaths are most common before and during dialysis following the three day interdialytic period. Cummulative fluid, electrolyte, and metabolite accumulation during the longer interdialytic interval have been correlated with increased arrhythmias, but the specific inablations that are driving this cardiac instability have not been identified.

Methods: 60 stable patients on chronic thrice weekly hemodialysis with a tendency to hyperkalemia provided informed consent. Cardiac rhythm was continuously monitored for one week starting at the midweek dialysis session (day 1). Pre-dialysis chemistries and 12 leads of EKG were determined at the pre-dialysis and post-dialysis sessions (days 3 and 6).

Results: Frequency of ventricular ectopy, supraventricular ectopy, and bradycardia, and average QTc were reported in 4 hour blocks. Rates of arrhythmias through the week and correlation with individual clinical parameters were analyzed using standard statistical methods. Calcium and magnesium levels were low and did not correlate with any changes in the whole population. Neither ventricular ectopy nor bradycardia correlated with dialysis or interdialytic interval. Supraventricular ectopy showed peaks during dialysis on both days 3 and 6, but these did not reach statistical significance. None of the arrhythmias correlated with pre-dialysis electrolytes, BNP or ultrafiltration volumes. Pre-dialysis PR intervals, QRS duration, and QTc did not correlate with arrhythmias or with electrolytes.

Conclusions: Rates of arrhythmia are expected to increase in the period following dialysis.

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FR-PO409

Association of Functional Outcomes of Sleep and Intermediary Cardiovascular Outcomes in Incident Hemodialysis Patients

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Background: Prior studies show that sleep conditions are associated with an increased risk of cardiovascular (CV) disease and mortality in adults initiating hemodialysis (HD). It is not known whether functional outcomes of sleep (fatigue, concentration difficulty, and memory impairment) are associated with CV morbidity in incident HD patients. We sought to examine whether functional outcomes of poor sleep were associated with intermediary cardiovascular outcomes in incident HD.

Methods: In 228 incident hemodialysis patients from the Predictors of Arrhythmic and Cardiovascular risk in ESRD (PACE) study, Functional Outcomes of Sleep Questionnaire-10 (FOSQ-10), a validated questionnaire that assesses the functional effect of daytime sleepiness through 5 domains (general productivity, activity level, social outcomes, vigilance and intimacy and sexual relationship), was administered within 6 months of enrollment. Baseline comorbidities, including history of CV disease and diabetes, were ascertained by chart review, and baseline cardiac testing, including ECG and echocardiogram, was obtained. Intermediary cardiovascular outcomes included (QTc [ms], heart rate variability [ms²], left ventricular mass index [g/m², LVMI], and left ventricular hypertrophy [LHV]). Associations of log transformed FOSQ-10 scores with intermediary outcomes were examined using linear regression.

Results: Mean age was 55 years, median body mass index was 28 (IQR 24,33), median Charlson comorbidity index was 5 (IQR 4,6), with 68% African American. Lower FOSQ-10 scores, indicating greater impairment from sleep disturbances, were associated with greater QTc duration and lower heart rate variability after adjustment for clinical factors. [Table] There were no significant associations of FOSQ-10 score and LVMI or LHV.

Conclusions: In adults initiating hemodialysis, poor functional outcomes of sleep are associated with increased risk of intermediary CV outcomes. Screening for sleep disturbances in incident hemodialysis patients may identify individuals at increased risk for adverse CV outcomes.

Funding: NIDDK Support

FR-PO411

Hypomagnesemia with High FGF-23 Is a Significant Risk Factor for Cardiovascular Disease in Hemodialysis Patients

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Background: In patients with chronic kidney disease, cardiovascular disease is the major cause of mortality and morbidity. Magnesium has been shown to impact cardiovascular health positively. Most previous cohort studies and their meta-analysis have shown a link between high serum phosphate levels and high FGF23 levels and an increased cardiovascular risk. However, few studies have investigated parameters associated with magnesium levels in hemodialysis (HD) patients. Accordingly, we examined the clinical significance of magnesium (Mg) cross-sectionally, and investigated the relationship between Mg levels and FGF23 levels.

Methods: Eighty-nine HD patients were enrolled. Their mean age was 66.9 ± 11.3 years, and the mean duration of HD treatment was 10.9 ± 8.1 years. Twenty-six patients had diabetes mellitus (DM) and eighteen patients had cardiovascular diseases. We analyzed their medical history, echocardiography, computed tomography, biochemical measurements, cardiovascular morbidity, mortality, etc. We identified prospective studies reporting associations between Mg and FGF23 concentrations and parameters. Statistical significance of the difference between groups was determined by the chi-square test. All statistical analyses in this study were performed with SPSS statistics software 22 for Windows.

Results: The number of cardiovascular disease patients was significantly higher in the group with a serum Mg level of less than 2.5 mg/dl (P = 0.015) but was not correlated to serum Mg level. The serum FGF23 level was related to cardiovascular disease (P = 0.04). There was no relationship between cardiovascular disease and serum P level. Comparing high FGF23 to low FGF23, cardiovascular disease was significantly increased in the low Mg group (P = 0.021) but not in the high Mg group (P = 0.426). The odds ratio for cardiovascular disease in the high FGF23 group compared with the low FGF23 group was 3.38. The association between FGF23 and cardiovascular disease was modified significantly by Mg level.
Conclusions: We suggest that in cardiovascular disease, FGFR3 and serum Mg levels are more influenced by the serum P level. High serum FGFR3 was associated with cardiovascular disease in hemodialysis patients with low Mg level, but not in those with high Mg level. In particular, the combination of low Mg level and high FGFR3 level is a risk factor for cardiovascular disease.

FR-PO412
Fibrate Therapy in Hemodialysis Patients: A Prospective 10-Year Study
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Background: KDIGO guideline suggests that statin should not be initiated in hemodialysis (HD) patients. Fibric acid derivative (fibrate) is another lipid-lowering drug class capable of reducing plasma triglyceride (TG), cholesterol and LDL-cholesterol (LDL-C), but has been rarely used in HD patients due to potential adverse events, namely myositis and transaminitis. Recent study demonstrated that low-dose fenofibrate (LF) and gemfibrozil (G), two most commonly-used fibrates, has not been compared before in patients with advanced CKD. This research aims to study the lipid-lowering effect and safety profiles of LF and G in HD patients with hyperlipidemia.

Methods: This was a prospective study of all HD patients with hyperlipidemia who were initiated on fixed-dose fibrates at Vajira Hospital between January 2009 and December 2018. The data collected were baseline characteristics, kidney function, body mass index and type of fibrate. All patients were followed for 6 months. Changes in fasting lipid profiles were recorded and compared at 3 and 6 months after initiating treatment. Liver function tests and muscle enzyme were monitored at the beginning and two months after starting drug.

Results: There were overall 94 HD patients recruited to receive fibrate therapy (33 LF and 61 G) without additional lipid lowering drug. At 6 month, LF 100 mg effectively lowered both fasting TG and LDL-C (-34% and -21%; p=0.004 and 0.01 respectively) whereas G 600 mg significantly reduced fasting TG (-29%, p=0.003) but not LDL-C level (-11%; p=0.06). Myalgia and myositis were reported in 5 patients (13.7%) in G group and 6 patients (11.3%) in G groups. No patient experienced rhabdomyolysis or severe myositis requiring discontinuation of fibrate. Transaminits occurred in 5 patients from each LF and G group (15.2% and 8.2% respectively). Only 1 patient receiving LF had significant transaminits (ALT>3 x upper limit of normal) that required fenofibrate discontinuation.

Three patients died (2 in F group and 1 in G group) from causes determined not to be fibrate-related.

Conclusions: Both low-dose fenofibrate and gemfibrozil were effective in lowering plasma TG but only fenofibrate could significantly reduce LDL-C in HD patients. Both drugs were well-tolerated and could be useful alternatives to statin in HD patients with hyperlipidemia.

Funding: Government Support - Non-U.S.

FR-PO413
Statin Dose Prior to Dialysis Transition with Post-Transition Hospitalization Frequency
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Background: In a prior study, we demonstrated that statin use prior to dialysis start was associated with lower mortality and hospitalization risk. Although current guidelines advocate for initiation of a moderate dose statin in late stage chronic kidney disease (CKD), we sought to examine whether risk of hospitalization, in particular septicemia, in the year after dialysis start differed according to statin dose in the year prior to transition.

Methods: In a cohort of veterans transitioning from dialysis to transplantation from 2007-2015, we identified 32,439 patients on low-, moderate- and high-dose statin therapy for at least 181 days in the year prior to dialysis start. Poisson models with adjustment for demographics, comorbidities and use of other lipid altering medications were used to examine associations between statin dose of hospitalization incidence.

Results: Cohort means±SD age was 72±10 years old, 4% were female, 21% African American, 6% Hispanic, 40% diabetic and 39% had a prior myocardial infarction. High-dose patients were more likely to be younger, African American and diabetic but less likely to have liver disease or cancer. In unadjusted and adjusted analyses, statin dose had a linear association with hospitalization rates. Compared with moderate statin dose (reference), low- and high-dose statin therapy were associated with higher and lower hospitalization rates, respectively [RRs (95% CIs) 1.03 (1.01, 1.06) and 0.95 (0.93, 0.97), respectively]. Associations were similar for septicemia hospitalizations.

Conclusions: Risk of hospitalization, particularly septicemia, in the year after transition to dialysis was lower with higher statin dose therapy. Statins are known to have anti-inflammatory benefits and further studies are needed to investigate whether the use of higher dose statins confers benefits that outweigh risk of adverse events in patients transitioning to dialysis.

Funding: NIDDK Support, Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

FR-PO414
A Scoring System for Predicting Individual Effects of Statin Treatment in Type 2 Diabetes Mellitus Patients on Hemodialysis
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Background: Randomized clinical trials did not show a benefit of statins in hemodialysis (HD) patients. However, post-hoc analyses of the German Diabetes Dialyse (4D) study indicated that there are subgroups defined by theragnostic markers showing heterogenous treatment effects. We combined the information of multiple markers to a score predicting individual treatment effects.

Methods: We used data from the 4D study, a randomized trial including 1,255 HD patients with type 2 diabetes, randomized to atorvastatin or placebo. We calculated two scores, score 1 (23 predictive markers) and score 2 (17 clinically available markers) and classified patients in groups based on score cut-points indicating changes in effect. In each group we calculated effect estimates with respect to a composite cardiovascular endpoint and all cause death using both trial follow-up (FU) (median: 4 yrs) and long-term FU data (median: 11.5 yrs).

Results: The groups based on score 1 showed completely differential treatment effects: G1 (score < 26, 458 (36%) pts) showed harm: HR=1.54 (95%CI: 1.16-2.03) [Fig. 1a]; G2 (score 26-31, 331 pts (26%) showed no effect: HR=1.03 (95%CI: 0.72-1.48) [Fig. 1b] and G3 (score>31, 466 pts (38%) showed benefit: HR=0.43 (95% CI: 0.30-0.60) [Fig. 1c]. In G3 statins also reduced all-cause mortality: HR=0.63 (95% CI: 0.48-0.83). Results for score 2 were similar with a smaller group G3 (N=360 pts). For long-term FU the effects were less heterogenous among groups.

Conclusions: The effect of statins in patients on HD is heterogenous and can be predicted by markers that relate to plausible effect modifying mechanisms including cholesterol metabolism, atherosclerosis, protein energy wasting or competing risks. The score will be useful in clinical practice not only to select patients that benefit from statins but also to identify those where treatment is harmful.
FR-PO415

The Target Cholesterol Level for Favorable Prognosis in Hemodialysis Patients: 10-Year Outcomes of the Q-Cohort Study

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Background: The prevalence of atherosclerotic diseases is higher in hemodialysis patients. The aim of the current study was to determine the target cholesterol level for the best prognosis in patients undergoing long-term hemodialysis.

Methods: A total of 3,517 participants undergoing maintenance hemodialysis were followed up for 10 years. The outcomes were the incidences of cardiovascular disease (CVD) and mortality. Total cholesterol (TC) in mg/dL was divided into the following quartiles derived from baseline data: Q1 < 131, Q2 ≥ 131 and < 152, Q3 ≥ 152 and < 178, and Q4 ≥ 178. To determine the cholesterol level of the best prognosis, we used a multivariable-adjusted restricted cubic spline model.

Results: During the follow-up period 1,033 patients had CVD, and 1,742 patients died. Compared with Q1, the respective multivariable-adjusted hazard ratios and associated 95% confidence intervals for ischemic heart disease (IHD), peripheral artery disease (PAD), and CVD in Q4 were 1.40 (1.05–1.85), 1.35 (0.93–1.98), and 1.28 (1.07–1.54). The incidences of IHD, PAD, and CVD were significantly positively associated with higher cholesterol levels after adjustment for confounding factors (p for trend < 0.05). Compared with Q4, the respective multivariable-adjusted hazard ratios and associated 95% confidence intervals for CVD mortality, infection-associated mortality, cancer-associated mortality, and all-cause mortality in Q1 were 1.13 (0.89–1.43), 1.09 (0.82–1.45), 1.69 (1.14–2.51), and 1.24 (1.07–1.43). The TC level at which all-cause mortality risk was lowest was 179 mg/dL.

Conclusions: Higher TC predicts IHD, PAD, and CVD events, and lower TC predicts cancer-associated mortality and all-cause mortality in patients undergoing hemodialysis. We determined the favorable value of serum cholesterol level was 179 mg/dL.

FR-PO416

Circulating Levels of CD34+ Cells Predict Long-Term Cardiovascular Outcomes in Patients on Maintenance Hemodialysis

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Background: CD34+ cells maintain vascular homeostasis and predict cardiovascular outcomes. We previously evaluated the association of CD34+ cells with cardiovascular disease (CVD) events over 23 months, but long-term CVD outcomes in relation to levels of CD34+ cells in patients on maintenance hemodialysis are unclear. Herein, we analyzed the long-term predictive potential levels of CD34+ cells for CVD outcomes and all-cause mortality.

Methods: Between March 2005 and May 2005, we enrolled 215 patients on maintenance hemodialysis at Nagoya Kyoritsu Hospital and followed them up to 12.8 years. According to the CD34+ cell counts, patients were classified into the lowest, medium, and highest tertiles. Levels of CD34+ cells were analyzed in association with four-point major adverse CV events (MACES), CVD death, and all-cause mortality.

Results: The mean CD34+ cell count was 0.09 (range, 0.01 to 0.35 for all study patients). Patients in the lowest tertile were more likely to be older, have higher prevalence of cardiovascular disease, and to smoke than patients in the medium and highest tertiles. Age, smoking habit, lower geriatric nutrition risk index, lower calcium phosphate product, and lower intact parathyroid hormone were significantly associated with the lowest tertile. Among 139 (64.7%) patients who died during a mean follow-up period of 8.0 years, 39 (28.1%) patients died from CVD. Patients in the lowest tertile had a significantly lower survival rate than those in the medium and highest tertiles (p < 0.001). Using multivariable analyses, the lowest tertile was significantly associated with four-point major adverse CVEs (hazard ratio 1.80, p = 0.023) and CVD death (hazard ratio 2.50, p = 0.011).

Conclusions: Our long-term observational study revealed that a low level of CD34+ cells in the circulation predicts CVD outcomes among patients on maintenance hemodialysis.

Funding: Private Foundation Support
FR-PO418

Oval Symptoms and Salivary Function and Association with Mortality in Hemodialysis Patients: A Prospective Cohort Analysis (ORAL-D Substudy)

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Background: Oral symptoms and impaired salivary function are frequently reported by adults treated with long term hemodialysis. We evaluated the association of oral symptoms and salivary function with all-cause and cardiovascular mortality.

Methods: We did a planned sub-analysis in the ORAL-D study, a multinational cohort study involving a standardized oral and dental examination among 4276 hemodialysis patients. We assessed oral mucosal self-reported symptoms (thirst and xerostomia) and salivary characteristics (pH, buffer capacity, flow rate pre/post dialysis). The association with all-cause and cardiovascular mortality was estimated using a Cox proportional hazard regression model adjusted for country, age, sex, education, smoking history, prior myocardial infarction, diabetes, and time on dialysis.

Results: In 4205 adults (mean age 61.6±15.6 years), the mean salivary pH was 7.45 (SD 1.35), with more than 60% of patients (n=1621) with high salivary buffering capacity. The mean pre-dialysis salivary flow rate was 0.83 (SD 0.74) ml/min, and slightly decreased at the end of dialysis (0.76 ± 0.80 ml/min). During median follow-up of 3.5 years, salivary flow rate was associated with lower all-cause (adjusted hazard ratio (aHR) 0.85, 95% CI 0.76 to 0.95 for pre-dialysis flow rate and aHR 0.84, 95% CI 0.75 to 0.94 for post-dialysis flow rate) and cardiovascular mortality (HR 0.74, 95% CI 0.62 to 0.90 for pre-dialysis flow rate and HR 0.74, 95% CI 0.61 to 0.90 for post-dialysis flow rate). When considering the risk of mortality associated with Xerostomia Inventory items, requiring to sip a drink to swallow better was associated with all-cause and cardiovascular mortality (HR 1.26, 95% CI 1.07 to 1.48 and 1.30, 95% CI 1.02 to 1.66, respectively). Similarly, Thrust and Angle symptoms were associated with all-cause mortality.

Conclusions: Oral symptoms are prevalent in haemodialysis patients. Salivary characteristics and related symptoms are associated with mortality.

FR-PO419

Development and Application of Sequential Enrichment Approach for ApoL1 Purification

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Background: Apolipoprotein L1 (ApoL1) is associated with either HDL3 or the Trypanolytic Factor (TLF) complex. The TLF complex also includes Haptoglobin-Related Protein 1 (Hr) and hemoglobin Haptoglobin. Both human and transgenic mouse data suggest genotype is insufficient to cause renal disease. We hypothesized that circulating ApoL1 variants undergo PTM that promote renal disease progression or severity. To test this hypothesis, a method for the selective enrichment of ApoL1 containing TLF particles would be essential for ApoL1 characterization by mass spectrometry. Our objective here was to develop an affinity enrichment method that enabled selective TLF purification from dilute solutions. This method may be parallelized for high throughput processing of patient samples. TLF samples were prepared from peripheral bloods of patients with different ApoL1 abundance is decreased in non-diabetic AA ESRD patients versus diabetic AA ESRD patients versus healthy controls. Funding: NIDDK Support.

FR-PO420

Asymptomatic Cerebral Microbleeds in Hemodialysis Patients with a History of Stroke

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Background: T2*-weighted magnetic resonance imaging (MRI) is an extremely sensitive technique for detecting hemorrhagic lesions. It is especially superior for diagnosing previously asymptomatic cerebral microbleeds (CMBs), compared to other MRI methods. T2*-weighted MRI has increased the detection rate of CMBs, and as a consequence, the prevalence of CMBs has attracted attention in various patient populations. Clinically, CMBs are a risk factor for stroke, and especially intracerebral hemorrhage, and are more frequently detected after intracerebral hemorrhage and ischemic cerebrovascular disease. They are also highly prevalent in hemodialysis (HD) patients. In this study, we examined CMBs in HD patients with a history of stroke.

Methods: A cross-sectional study of the prevalence of CMBs and related factors was performed in 309 HD patients (45 with and 264 without a history of stroke) who underwent T2*-weighted MRI at Osaka City University Hospital and affiliated hospitals from 2005 to 2017. The study protocol was conducted in accordance with the Principles of the Declaration of Helsinki and was approved by the ethics committee of Osaka City University Graduate School of Medicine (No. 1415). Informed consent was obtained from all subjects prior to their participation in the study.

Results: CMBs were detected in 103 patients (33.3%). The prevalence of CMBs was significantly higher in patients with a history of stroke compared to those without this history (57.8% vs. 29.2%, p<0.001). In multivariate analysis adjusted for background characteristics, a history of stroke was a significant independent factor related to CMBs (OR: 3.7, 95%CI: 1.7-8.8), as were age and hypertension. A history of intracerebral hemorrhage was more strongly associated with CMBs compared to cerebral infarction (OR: 4.8, 95%CI: 3.4-25.3).

Conclusions: Our results show a high prevalence of CMBs in HD patients with a history of stroke, and indicate that a history of stroke is significantly associated with CMBs in HD patients. In particular, a history of intracerebral hemorrhage has a strong association with CMBs.

FR-PO421

Outcome of Hemorrhagic Stroke in Patients on Hemodialysis

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Background: Patients on maintenance hemodialysis (MHD) on greater risk of hemorrhagic stroke or ischemic stroke. There is paucity of literature on outcome of hemorrhagic stroke (HS) in patients on MHD. Hypertension (HTN) and use of heparin during dialysis could be risk factors. We performed this study to identify risk factors associated with hemorrhagic stroke in patients on maintenance hemodialysis and outcome of such patients.

Methods: This study is a retrospective analysis of patients admitted with acute hemorrhagic stroke on MHD at our center. Study population comprised of 28 patients of hemorrhagic stroke with intracerebral hemorrhage. Study duration was from January 2008 to December 2018. All patients were on MHD for > 3 months. Hemorrhagic stroke was diagnosed with clinical examination and CT scan. Their demographic data, relevant investigations and clinical parameters were recorded. Student t test was used to compare data between survivors and non survivors.

Results: We had 28 patients (15 males and 13 females). Mean age of patients was 56.2 ± 15.4 years. Comorbidities were Hypertension (100%), diabetes (12 of 28),CAD (9 of 28), hyperlipidemia (8of 28) and history of cerebrovascular accidents (5 of 28). Duration of HD was 27± 9.2 months. All patients had severe hypertension at presentation (BP > 200/110). Mean GCS at presentation was 9.8 ± 4.1. Site of intracerebral hemorrhage (ICH) was putamen (11 of 28), Thalamus (7 of 28), brain stem (4 of 28), massive (3 of 28) and others (3 of 28). Mortality was 68% (19 of 28). Mean time to death was 9.2± 5.2 days. Neurological deterioration was cause of mortality. GCS at presentation and serum albumin were factors influencing survival. GCS was 13.8± 3.7 in survivors and 4.7± 1.9 in non survivors. S. albumin was 3.8 ± 0.4 gm% in survivors and 2.7± 5.4 gm% in non survivors.

Conclusions: Patients of hemorrhagic stroke on hemodialysis had dismal outcome with mortality of 68% and survivors had better GCS and s. albumin at presentation.

FR-PO422

Intradialytic Hypoxemia In ESRD Patients on Hemodialysis

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Background: Mortality rates amongst end- stage renal disease (ESRD) patients on hemodialysis (HD) are high and death is most often due to cardiovascular disease. Based on previously published retrospective data, low oxygen levels during HD have been associated with all-cause hospitalization and mortality. We aimed to explore this association in our two university managed HD units.

Methods: We looked at HD patients with central venous catheters (CVC) and those with arterio-venous access (AV). We measured oxygen levels using crit-line monitors (CLM) for 3-4 routine dialysis sessions. For those with CVC, we considered those with more than 60% of session. We then examined the differences in clinical characteristics between
these high-risk groups with hypoxemia and their control cohorts without desaturation. These characteristics include demographic, session-related, laboratory and CLM parameters.

Results: We enrolled 222 patients, of which 35 had CVC and 187 had AVA. Amongst those with CVC, 22 (62.8%) experienced mean SeO2 <63% and they had an average 1.4 g/dl higher hemoglobin (95% confidence interval [CI], 0.3 to 2.5, P=0.014). However, they did not have any other significant differences from those with higher mean SeO2. Amongst those with AVA, 5 (2.7%) experienced PIH and they tolerated 11.2% smaller change in blood volume per hour, (95% CI, 1.1 to 21.3, P= 0.030). No other statistically significant differences were observed. We did however note that amongst patients with either access type, those with intradialytic hypoxemia tended to have higher hospitalization rates in the preceding 6 months and had more C- curve profiles on CLM.

Conclusions: We did identify patients who experienced low oxygen levels during HD. However, the proportion of our AVA cohort with PIH was almost one quarter of that previously reported by Meyring-Wosten, 2016. Desaturation rates among those with CVC were similar to previously published studies. We intend to further determine if the use of supplemental oxygen during dialysis can correct the intradialytic hypoxemia. If this can be successfully accomplished, it may be worthwhile to conduct larger prospective studies to evaluate the impact of this intervention on patient outcomes.

FR-PO423

Feasibility of an Electronic Neurocognitive Battery for Assessing Cognitive Function in New-Start Hemodialysis Patients: A Pilot Study

Melissa Feasibility of an Electronic Neurocognitive Battery for Assessing Cognitive Function in New-Start Hemodialysis Patients: A Pilot Study

Lawson Research, London, ON, Canada; 5Western University, London, ON, Canada

Evaluation of Screening Tests for Severe Cognitive Impairment in Maintenance Hemodialysis Patients

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Background: Detailed neurocognitive testing shows that cognitive impairment is common among patients requiring maintenance hemodialysis. Identification of a well performing and easy to administer test for cognitive impairment could facilitate broader screening in dialysis units.

Methods: In 150 hemodialysis patients, we performed a comprehensive battery of neurocognitive tests (considered the “gold standard” for this study). Participants were classified as having normal cognitive function versus mild, moderate, or severe cognitive impairment by comparing scores in multiple cognitive domains to normative data. We examined the predictive screening ability of the Mini-Mental State Examination (MMSE), the Modified Mini-Mental State Examination (3MS), the Montreal Cognitive Assessment (MoCA), the Mini-Cog, Clock Drawing test, Trails Making B (Trails B), and Digit Symbol Substitution tests to identify participants with severe cognitive impairment using area under the curve analysis.

Results: Mean age was 64 years; 61% were men, 39% were black and 94% had at least a high school education. Of the 150 participants, 21% had normal cognitive function, 17% mild cognitive impairment, 33% moderate impairment, and 29% severe impairment. The MoCA had the best predictive ability for severe cognitive impairment (AUC = 0.81 [0.73, 0.89]). A score on the MoCA of less than 21, which maximized the sum of sensitivity and specificity, displayed a sensitivity of 86% and specificity of 55% for severe impairment. The Trails B and Digit Symbol tests also performed reasonably well with AUC of 0.73 [0.59, 0.87] and 0.78 [0.68, 0.88], respectively. The MMSE, 3MS, Mini-Cog, and Clock Drawing tests had the lowest predictive performance.

Conclusions: Nearly one third of participants had severe cognitive impairment. The MoCA, a widely available, brief assessment that requires relatively simple training to administer, showed high sensitivity and moderate specificity in detecting severe cognitive impairment in prevalent hemodialysis patients.

FR-PO4425

Cognitive Impairment and Mortality in Maintenance Hemodialysis (HD) Patients: A Longitudinal Study

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Background: We examined the transition of the Mini-Mental State Examination (MMSE) results and the mortality rate of maintenance HD patients in our hospital over a 130-week period, in order to compare the cognitive functions and mortality.

Methods: Using the longitudinal cohort of 181 HD patients aged ≥65, we examined the MMSE in March 2016, and a follow-up MMSE was conducted on 112 surviving patients in September 2018. We also tracked the serological data during this period. MMSE score of 28 to 30 was classified as the normal group, 24 to 27 as mild cognitive impairment (MCI) group, and less than 23 as dementia group.

Results: In 2016, 76 patients were within the normal group (41.9%, mean age 72.1), 48 were within the MCI group (26.5%, mean age 77.9), and 57 were within the dementia group (31.5%, mean age 80.2). As shown in figure 1 below, compared to the normal group, mortality rate decreased significantly as the severity of dementia further deteriorated. There was no significant difference in the nutritional status index such as albumin or Cholinesterase among these groups. The pneumonia-associated death in patients with dementia was twice as high as among those without dementia or MCI (64% vs 36%, 39%; p < 0.05).

Conclusions: This longitudinal study indicated that the presence of dementia is an independent predictor of mortality in patients on HD.

FR-PO424

Evaluation of Screening Tests for Severe Cognitive Impairment in Maintenance Hemodialysis Patients

Drew, F; Wild, C; House, C; McIntyre, W; Scherr, M; Zalizniak, C; E. C; Feasibility of an Electronic Neurocognitive Battery for Assessing Cognitive Function in New-Start Hemodialysis Patients: A Pilot Study

Lawson Research, London, ON, Canada; 5Western University, London, ON, Canada

This longitudinal study indicated that the presence of dementia is an independent predictor of mortality in patients on HD.

FR-PO424

Evaluation of Screening Tests for Severe Cognitive Impairment in Maintenance Hemodialysis Patients

Drew, F; Wild, C; House, C; McIntyre, W; Scherr, M; Zalizniak, C; E. C; Feasibility of an Electronic Neurocognitive Battery for Assessing Cognitive Function in New-Start Hemodialysis Patients: A Pilot Study

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FR-PO424

Evaluation of Screening Tests for Severe Cognitive Impairment in Maintenance Hemodialysis Patients

Drew, F; Wild, C; House, C; McIntyre, W; Scherr, M; Zalizniak, C; E. C; Feasibility of an Electronic Neurocognitive Battery for Assessing Cognitive Function in New-Start Hemodialysis Patients: A Pilot Study

Lawson Research, London, ON, Canada; 5Western University, London, ON, Canada

This longitudinal study indicated that the presence of dementia is an independent predictor of mortality in patients on HD.
FR-PO417
Depression Screening Is Associated with Lower Mortality and Hospitalization Among Adults Initiating Chronic Hemodialysis
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Background: Transitioning to chronic hemodialysis (HD) continues to be a vulnerable period for adults with end-stage renal disease (ESRD). Depression commonly develops among these patients and negatively impacts quality of life, treatment adherence, hospitalization, and mortality. Depression screening may be an important tool in identifying depression and improving outcomes. Among a large national cohort of Veterans, we examined whether depression screening in the year prior to chronic HD transition led to lower mortality and hospitalization in the first year of HD.

Methods: Using data from the USRDS Transition of Care in HD study, an observational study that focuses on Veterans who transitioned to chronic dialysis between 2007 to 2015, we identified adults with an outpatient nephrology, geriatric or primary care visit in the year prior to transition to HD. Pre-ESRD depression screening was defined as completion of a Patient Health Questionnaire-2 (PHQ-2) in the 12 months prior to transition. The main outcomes were all-cause mortality and hospitalization in the 12 months post transition. Associations were examined with Cox proportional hazards models (mortality) and Poisson regression models (hospitalization). Hierarchical adjustment models were used to account for sociodemographics, comorbidity and laboratory values, pre-ESRD care intensity, and post-ESRD dialysis characteristics.

Results: After excluding adults with a diagnosis/treatment of depression, bipolar disorder, or dementia prior to the index outpatient visit, the final analytic cohort consisted of 30,013 Veterans who transitioned to HD. Sixty-one percent of patients had PHQ-2 screening during the 12 months prior to HD transition. During the 12 months post-transition, the crude all-cause mortality rate was 32/100 person-year for those screened and 35/100 person-year for those not screened, while the median (IQR) hospitalizations were 2 (2.2) per year for both groups. In fully adjusted models, PHQ-2 screening was associated with a significantly lower risk of mortality (HR 0.94, 95% CI: 0.90-0.98) and hospitalization (IRR 0.97, 95% CI: 0.95-0.99).

Conclusions: Screening for depression among adults with ESRD in the year prior to transition to chronic hemodialysis was associated with improved outcomes after dialysis initiation.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO426
Hemodialysis Can Contribute to Acute Changes in Cerebral Volume and White Matter Structure
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Background: Cerebral atrophy, silent cerebral infarcts, and leukoaraiosis are common brain injuries in chronic kidney disease (CKD) patients undergoing hemodialysis (HD), but their etiology is poorly understood. To elucidate the acute effects of HD on the brain, we used a novel system designed in-house to perform magnetic resonance (MR) imaging during HD. Diffusion tensor imaging (DTI) is an MRI modality used to characterize white matter (WM) structure. Mean diffusivity (MD) is a DTI metric associated with cellularity and edema in WM. We predict that HD will induce a transient increase in MD and cerebral volume, potentially due to osmotic stress and edema.

Methods: 12 CKD patients receiving hemodialysis a3 times/week underwent diffusion and T1 weighted MR scans (Siemens 3T Biograph mMR) prior to and in the last 60 minutes of HD. The MR data were processed to correct for noise, motion, and artifacts prior to tensor fitting. Spatially normalized scalar maps were compared pairwise using tract-based spatial statistics (TBSS) and a general linear model with threshold-free contrast enhancement. Cerebrospinal fluid (CSF), WM, and gray matter (GM) volumes were extracted from T1 maps in CAT12 and compared before and during HD with Wilcoxon paired t-tests (p<0.05).

Results: During dialysis, MD was elevated (p<0.05) in regions of the superior corona radiata (fig. A) and peripheral WM near the cingulate gyrus (fig. B). CSF volume decreased by an average of 50.2 ± 12.2 ml (p<0.05) while the GM volume increased by an average of 28.7 ± 9.1 ml (p<0.05), as shown in figure C.

Conclusions: Increased MD in conjunction with increased brain volume suggests cerebral edema, potentially caused by osmotic stresses associated with HD. Further investigations are ongoing to determine if edema contributes to the brain injury and cognitive impairment observed in HD patients.

Funding: Private Foundation Support, Government Support - Non-U.S.

The regions with significantly increased MD (p<0.05) during HD are shown in red in A and B. C gives the volumes of WM, GM, and CSF before and during HD.

FR-PO428
An Analysis of Delirium in Elderly Patients with ESRD During Hospitalization for Starting Maintenance Hemodialysis
Yohei Arii,1 Hiroyuuki Tanaka,2 Shingo Shiogi,2 Isao Kondo,3 Eri Sakamoto,2 Minami Suzuki,1 Daisuke Katagiri,1 Manami Tada,1 Fumihiro Hiroshita,1 Yohei Arii,1 Hyogo Prefectural and Dental University, Bukkyo-ku, Japan; 2National Center for Global Health and Medicine, Shinjuku-ku, Japan; 3Yokosuka Koyoai Hospital, Yokosuka-shi, Japan.

Background: Delirium is an acute and usually reversible disturbance in mental abilities that causes confused thinking and emotional disruption. It has recently been reported that delirium occurs much more easily in the elderly, it remains unproved whether the occurrence of delirium during hospitalization for starting dialysis is associated with early mortality after the start of dialysis in elderly populations.

Methods: We conducted a retrospective cohort study to investigate the association between delirium and early mortality after starting dialysis in the elderly. The cohort consisted of patients aged 75 years old or older who started hemodialysis for ESRD at the National Center for Global Health and Medicine from 2010 to 2017 and at Yokosuka Koyoai Hospital from 2007 to 2011. Delirium was defined as patients who, during hospitalization for starting dialysis, newly showed confused thinking and reduced awareness of their environment and were prescribed anti-psychotic medications. The primary outcome was death within a year of the start of dialysis. Data were analyzed using Cox proportional hazard models with adjustments for baseline characteristics. To assess underlying characteristics of the patients with delirium, we identified the determinants using a multinomial logistic regression.

Results: We enrolled 264 patients (males, 59%); 34 patients were diagnosed with delirium. The primary outcome was observed in 19 patients with delirium (55%) and 26 patients without delirium (11%) (p < 0.01). In a Cox proportional hazards model, delirium was independently associated with a higher risk of all-cause mortality within a year of the start of dialysis (hazard ratio 6.96, 95% confidence interval 3.84-12.63; adjusted hazard ratio 5.78, 95% confidence interval 2.93-11.41). In a multinomial logistic regression, delirium was positively correlated with “cognitive impairment” and “the use of steroid” and inversely correlated with “the presence of arteriovenous fistula”.

Conclusions: Delirium predicts early mortality after starting dialysis in the elderly.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Patient Treatment Adherence in the ASCEND Trial for Depression in Patients Undergoing Maintenance Hemodialysis

Dialyzer

Robert Costanzo,1 Amelia Scott,2 Daniel Dember,2 Yaminette K. Grote,2 Nancy Heagerty,2 Tessa Dubovsky,2 Tom Young,2 Paul Sondheimer,12

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Methods: We undertook a post-hoc analysis to characterize patient adherence to these treatments and to examine the association of patient treatment adherence with depression scores at the end of the intervention.

Results: The average age of participants (n=120) was 51 ± 13 years, 57% were male, and 43% were white. Patients randomized to CBT, 82% completed at least 7 of the 10 sessions, 72% were rated by the therapist as engaged in at least 7 CBT sessions and 47% of the participants attempted/completed CBT homework > 50% of the time. The general rating of CBT was very high, and the mean attendance was assessed by the Quick Inventory of Depression Scores, Clinician Rated (QIDS-C) at 12 weeks. There was a weak negative association between number of CBT sessions attended and QIDS-C score (R=-0.19) and number of days SER was taken and QIDS-C score (R=-0.27). We examined the association of baseline parameters (demographics, depression diagnosis, severity, and history, participation in a pre-enrollment motivational interviewing session, and initial treatment preference) with treatment adherence separately for CBT and the only significant predictor for CBT adherence was a history of depression; participants with no history of depression attended on average 1.8 more sessions and were 26% more likely to attend a session (p<0.02) than participants with a history of depression. There was no relationship between baseline parameters and SER use.

Conclusions: High levels of treatment adherence for depression, with both CBT and SER, can be achieved in patients on maintenance hemodialysis. Baseline characteristics are generally poor predictors of future adherence to treatment. The identification of patient and treatment level factors that promote adherence to treatments for depression are needed.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO430

Low Proteinuria Is Associated with Increased Mortality in Incident Dialysis Patients: Results from the CRIC Study

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Background: In multiple studies, increased levels of proteinuria are associated with worse outcomes. However, in individuals with glomerular filtration rate <30 ml/min, some studies have reported a J-shaped association of proteinuria and mortality. However, this association has not been examined in incident dialysis patients.

Methods: Among 725 incident dialysis participants in the CRIC Study (mean age 60.1 [SD 11.4] years, 32.4% White, 54.2% Black, 59.0% men), we evaluated the association of proteinuria with mortality. We stratified by eGFR category (PCR) within two years of dialysis initiation (PCR <0.5, 0.5-0.9, 1.0-3.4, ≥3.5 g/g) with mortality (333 deaths during the median follow-up of 3.5 years) using Cox models adjusting for potential confounders (e.g. blood pressure, serum albumin, history of cardiovascular disease including heart failure).

Results: Among incident dialysis patients, there was a J-shaped association between baseline proteinuria and mortality. In the highest PCR category (PCR ≥3.5 g/g) (crude hazard ratio 2.69 [95%CI 1.79-4.04] vs. PCR of 0.5-0.9) followed by the highest PCR category (1.46 [1.01-2.00]) (Table). The excess risk in persons in the lowest PCR level was attenuated but still statistically significant after accounting for potential confounders.

Conclusions: Among incident dialysis patients, there was a J-shaped association between pre-dialysis proteinuria associated risk of mortality; with the highest risk in the lowest PCR category. While the reasons for this association are uncertain, our findings suggest that healthcare providers should be aware that low protein excretion, not just high protein excretion, is a marker for an increased risk of mortality in patients who start dialysis.

Funding: Private Foundation Support

FR-PO431

Retrospective Analysis of Serum Albumin and Other Biomarkers in Chronic Hemodialysis Patients Dialedyzed with the Optiflex F180NR Dialyzer

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Background: Optiflex® dialyzers are commonly used in US ESRD patients. Considering that low serum albumin (sALB) levels are associated with increased risk of mortality, albumin loss during hemodialysis (HD) should be minimized, especially in patients (pts) with hypoalbuminemia. A retrospective analysis was conducted to assess changes in sALB and other biomarkers in pts dialedyzed with the Optiflex F180NR (OPTI). Methods: In-center HD pts (n=284) treated with OPTI dialyzers for 6 months were analyzed. Pts maintained the same vascular access type and were without a diagnosis of liver disease or cancer. Changes in pre-dialysis (Pre-HD) labs at month 1 (M1) and month 6 (M6) were compared using paired t-tests. A sub-analysis of pts with hypoalbuminemia (sALB <3.5 g/dL) was conducted. Results: After 6-months of HD treatments, significant increases in mean sALB (0.07 g/dL), NPRC (0.05), and hemoglobin (0.42 g/dL) were observed with increased mean ultrafiltration volume (UFV) and adequacy (Table). A sub-analysis of 47 pts with hypoalbuminemia at M1 showed increases in sALB (0.36 g/dL) at M6 for 44 pts. Three pts had concomitant decreases in sALB (0.4 g/dL) and nPCR (0.44) during the same period. Conclusions: During a 6-month follow-up, HD patients dialedyzed with Optiflex F180NR dialyzers showed increased levels of serum albumin, sPCR, hemoglobin, ultrafiltration volume, and Kt/V. Funding: Commercial Support - Fresenius Medical Care Renal Therapies Group
exposure times cardiovascular and respiratory readmission risks were also observed but are not shown due to space constraints.

**Conclusions:** Our results show increased risk of hospital admission and 30-day readmission associated with elevated PM$_2.5$ for patients receiving chronic hemodialysis. These findings suggest that daily ambient air quality may impact morbidity and healthcare costs for patients with End Stage Renal Disease. This abstract does not reflect EPA policy.

**Funding:** Other U.S. Government Support, Clinical Revenue Support

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**FR-PO433**

The Predictive Role of Serum MRP8/14 (S100A8/A9) on Mortality in Hemodialysis Patients

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**Background:** The inflammatory mediator myeloid-related protein 8 (MRP8: S100A8), which forms a heterodimeric complex with a binding partner MRPI4 in the bloodstream, plays important roles as an endogenous ligand in various diseases. Serum MRP8/14 reportedly became a potential biomarker in patients with acute coronary syndrome and ANCA-associated vasculitis. The aim of this study was to investigate the predictive role of serum MRP8/14 levels on all-cause mortality in hemodialysis patients.

**Methods:** We conducted a multicenter, observational cohort study of 388 Japanese subjects undergoing maintenance hemodialysis in Kumamoto, Japan. Serum MRP8/14 levels were measured using an ELISA. The potential associations between serum MRP8/14 levels and clinical variables were examined in a cross-sectional study. Multivariable Cox regression was used to estimate the association between serum MRP8/14 levels and mortality, adjusting for possible confounding variables including age, sex, diabetes and others. Median follow-up was 6.6 years.

**Results:** The mean age of the subjects was 65.3 years, 36.9% were female, and the median vintage was 5.8 years. The median MRP8/14 level was 610 ng/ml [normal range for healthy subjects: 500–5500] at baseline. Serum MRP8/14 levels positively correlated with white blood cells (ρ=0.54, P<0.0001) and high-sensitivity C reactive protein (hs-CRP) values (ρ=0.34, P=0.0001). We classified MRP8/14 and hs-CRP into tertile, and estimated the hazard ratios (HR) for all-cause mortality in comparison with the lowest tertile. As for hs-CRP, the middle tertile (HR, 1.90; 95%CI, 1.04–3.61) and the highest tertile (2.97; 1.54–5.54) were each significantly associated with all-cause mortality in the low-phosphate group (cut-off, 6.0 mg/dl), after adjustment for relevant confounding factors. In contrast, elevated MRP8/14 levels were evidently associated with all-cause mortality in the middle tertile (12.3; 1.64–71.6) and in the highest tertile (20.6; 3.49–610) of high-phosphate levels, but not in the low-phosphate group.

**Conclusions:** Serum MRP8/14 levels should give a potential predictive marker on mortality in hemodialysis patients with high-phosphate levels, which characteristic differs significantly from that of a conventional inflammatory marker, hs-CRP.

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**FR-PO434**

Trimethylamine N-Oxide and Cardiovascular Outcomes in Hemodialysis Patients

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**Background:** Trimethylamine-N-Oxide (TMAO) has a definite role in promoting atherosclerosis, which is an independent risk factor of cardiovascular disease. Cardiovascular disease is the leading cause of death in hemodialysis patients. The plasma level of TMAO in hemodialysis patients increases significantly, which is more than 20 times over the non-dialysis patients, but the relationship between TMAO and the cardiovascular outcomes in hemodialysis patients has not been well defined.

**Methods:** A prospective cohort study design was adopted. 252 patients who were eligible for the inclusion criteria were enrolled, and baseline clinical data were collected. Then these patients were followed for 9 years, the primary endpoints were all-cause and cardiovascular death, and the secondary endpoints were cerebrovascular death. The plasma TMAO concentration was determined, the Kaplan-Meier method and Cox proportional risk model were used to analyze the relationship between TMAO concentration and cardiovascular mortality and all-cause mortality.

**Results:** Median follow-up was 73.4 (42.9–108) months. During the follow-up, there were 123 cases of death totally, among them 39 cases of cardiovascular death, 19 cases of cerebrovascular death, 65 cases of other causes death. 20 cases transferred to other dialysis centers, and 15 cases received kidney transplantation. The median plasma TMAO concentration was 63.1μmol/L. Based on the median concentration of TMAO, the patients were categorized as High TMAO group (TMAO > 63 ng/μl) and Low TMAO group (TMAO ≤ 63 ng/μl). Kaplan-Meier analysis found that the incidences of all-cause death (Log-Rank P = 0.001) and cardiovascular death (Log-Rank P = 0.006) in High TMAO group were significantly higher than those of Low TMAO group. Multivariable Cox regression demonstrated that plasma TMAO was significantly associated with all-cause death (TMAO as continuous variable: HR = 1.123, 95%CI[1.067-1.183], P<0.001; TMAO as dichotomous variable : HR = 2.147, 95%CI[2.149-3.117], P<0.001) and cardiovascular death (TMAO as continuous variable: HR = 1.126, 95%CI[1.027-1.235], P<0.01; TMAO as dichotomous variable: HR = 2.752, 95%CI[1.674-4.559], P<0.001). After adjustment of conventional and non-conventional risk factors, the relationship of plasma TMAO and all-cause and cardiovascular death remained significant.

**Conclusions:** Plasma TMAO is an independent risk factor of cardiovascular outcomes in hemodialysis patients.

**Funding:** Government Support - Non-U.S.

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**FR-PO435**

Circulating PCSK9 Level Predicts Risk of Cardiovascular Events and Death in Hemodialysis Patients

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**Background:** The propionate convertase subtilisin/kexin type 9 (PCSK9) is a promising new target for prevention of cardiovascular event (CVE). However, the clinical significance of circulating PCSK9 is unclear in HD patients.

**Methods:** A total of 353 patients were prospectively enrolled from June 2016 to May 2018 in K-cohort study groups. Serum PCSK9 level was measured at the time of study enrollment. Serum levels of high-sensitivity C-reactive peptide (hsCRP), monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6, osteopontin and receptor activator of nuclear factor kappa-B ligand (RANKL) were also measured. The primary endpoint was defined as composite of CVE and death from any cause.

**Results:** Serum PCSK9 level was positively correlated with total cholesterol level, but not with inflammatory (hsCRP, MCP-1 and IL-6) and calcification-related markers (osteopontin and RANKL). Multivariable linear regression analysis revealed that statin treatment, serum albumin and total cholesterol levels at baseline were independent determinants of circulating PCSK9 levels. In multivariate Cox-regression analysis, PCSK9 tertile 3 was associated with 1.99-fold risks for composite event (95% confidence interval [CI], 1.08-3.66), and it was independently associated with 2.26-fold risks for CVE (95% CI, 1.14-4.62). PCSK9 tertile 3 also provides additional prognostic significance to predict composite event in subgroups with higher level of hsCRP and LDL, and no statin treatment.

**Conclusions:** Circulating PCSK9 level independently predicts CVE and death in HD patients, and these results anticipate future studies for the effect of PCSK9 inhibition in HD patients.

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**FR-PO436**

Sex-Specific Association Between Serum Uric Acid and Cause-Specific Mortality in Maintenance Hemodialysis Patients: A Multicenter Prospective Cohort Study

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**Background:** Studies have shown inconsistent results about the association between serum uric acid (SUA) and mortality in maintenance hemodialysis (MHD) patients. Moreover, no studies have explored the possibilities of the relationship between SUA and non-cardiovascular (CVD) mortality.

**Methods:** We conducted a multicenter prospective cohort study among 1039 MHD patients. The blood samples of all participants were obtained prior to the hemodialysis session at baseline. Multivariable adjusted Cox proportional hazards models were used to estimate the HRs and 95%CIs for the risk of all-cause mortality, CVD mortality and non-CVD mortality associated with SUA.

**Results:** Over a median follow-up of 28 months, 230 deaths were recorded, of which 140 (60.9) were due to cardiovascular disease. overall, a U-shaped relationship was found between SUA and all-cause mortality. Moreover, the patients in the lowest SUA showed a higher risk of CVD mortality (HR: 3.57; 95%CI: 1.03–2.40), whereas no significant association was found with non-CVD mortality. By contrast, the patients in the highest SUA group showed a higher risk of non-CVD mortality (HR:1.82; 95%CI: 1.04-3.17) and no significant association was found with CVD mortality. The association between SUA and all-cause mortality were consistent across different subgroups.

**Conclusions:** There was a U-shaped relationship between SUA and all-cause mortality. Furthermore, lower SUA had an increased risk of CVD mortality and higher SUA had a higher risk of non-CVD mortality. Whether SUA reduction therapy is beneficial to the MHD patients should be the subject of the future research work.
The association between sex-specific serum uric acid levels and mortality

<table>
<thead>
<tr>
<th>SUA (mg/dL)</th>
<th>No. events (%)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1</td>
<td>100 (28.0%)</td>
<td>1.45 (1.04, 2.03)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>67 (17.6%)</td>
<td>1.00 (0.6)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>60 (19.9%)</td>
<td>1.46 (1.01, 2.11)</td>
</tr>
</tbody>
</table>

FR-PO437

Erectile Dysfunction Is Associated with Increased Coronary Artery Calcification But Not Mortality in Incident Dialysis Patients

Neil Roy, Danwen Yang, Sylvia E. Rosas. Joslin Diabetes Center, Boston, MA.

Background: Erectile dysfunction (ED) is prevalent among the hemodialysis population. Increasing age, diabetes and nonuse of ACE inhibitors has been associated with a higher incidence of ED in our previous work. ED predicts mortality in the general population likely through its association with CVD risk factors.

Methods: Objective: To determine the relationship between ED, coronary artery calcification and mortality in incident dialysis patients without prior coronary events using the Dialysis, Heart and Bone Study.

Methods: Sixty-three male participants were enrolled in this prospective study and completed the fifteen-item validated questionnaire, the IFIE-15 as well as MSCT to measure coronary artery calcification. Subjects having a score of 25 or less in the self-administered questionnaire were considered to have ED. Detailed information regarding demographics, medical history, and medication usage was obtained by self-report.

Results: The mean age of participants was 49.2 (±13.1) years and two-thirds were AA. Forty-four percent of participants had severe ED, 23.8% had moderate ED, 15.8% had mild ED and 15.8% had no ED. The median (IQR) Agaston score was 56.8 (0.4-606.5) for those with ED and 0 (0-0) for those without ED [p=0.007]. Twenty-three percent of the participants died during an average follow-up of 5 (1.5) years. Twenty-one percent of the participants with ED died compared to ten percent of people without ED (p=0.4). Using a proportional hazard model with covariate adjustment by propensity score, ED was not significantly associated with mortality (p=0.64).

Conclusions: ED is common in new to dialysis patients. ED was significantly associated with increased CAC score. However, it was not associated with increased mortality in incident dialysis patients.

FR-PO438

Relationship Between Serum Uric Acid and Vascular Calcification in Patients Treated with Hemodialysis

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Background: Vascular calcification (VC) is highly prevalent among hemodialysis (HD) patients and predicts cardiovascular mortality. The level of serum uric acid (SUA) may be related with endothelial dysfunction, which may involve in VC. However, whether uric acid concentrations are associated with VC in HD patients is unknown. The aim of our study was to assess the association of SUA and VC in HD patients.

Methods: This was a cross-sectional study including 313 patients receiving HD therapy for at least 3 months between January 2014 and December 2018. The simple linear vascular calcification score (SVCS) in plain X-rays of the pelvis and hands was used to evaluate VCs.

Results: Mean age was 57.1±14.0 (SD) years, and 32.2% had diabetes. Mean uric acid level was 476.06 (±99.99) mg/dL, and 73.8% had hyperuricemia. The SVCS detected VC in 179 (57.1%) patients, including 160 patients presenting VC of pelvis arteries and 95 patients presenting VC of hands arteries. In total of patients, a SVCSa 3 was present in 104 (33.2%) patients. By binary logistic regression, age (P<0.001), HD duration (P<0.001), diabetes (P<0.001) were independently associated with a SVCSa 3, the levels of SUA was not associated with a SVCSa 3. Adjusted logistic regression models showed that the ORs per 1umol/L higher uric acid level for VC of pelvis arteries was 0.996 (95% CI, 0.994-0.998) while no saturin status (P=0.015) in total patients and 0.995 (95% CI, 0.991-0.999) (P=0.010) in non-diabetic HD patients. However, there was no association between SUA and VC of hands arteries.

Conclusions: Higher uric acid levels were associated with lower risk of VC of pelvis arteries in patients treated with HD.

FR-PO439

Atheromas and Peripheral Vessel Physiology in Relation to Culinary Habits in ESRD: Diversion Between Peritoneal Dialysis and Hemodialysis Population by Adopting the Mediterranean Diet Regime

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Background: End stage renal disease (ESRD) relates to atheroma formation and typically amplifies cardiovascular risk. Patients on hemodialysis (HD) impose strict dietary restrictions. On the contrary, patients on peritoneal dialysis (PD) may consume a wide variety of alimentary goods.

Methods: 92 male ESRD patients, 52 of them on HD and the rest 40 on PD without apparent cardiovascular disease were matched to enroll the study. The 2 groups did not differ statistically in age, (64.9 ± 15.2 vs 64 ± 11.4) prevalence of hypertension, diabetes mellitus, smoking and lipid profile. All underwent common carotid ultrasound examination for detecting plaque formation and intima–media thickness (IMT) evaluation as indices of subclinical atheromass. Peripheral vessel rheology was assessed by the SHIM-5 score that grades erectile potency. A lower score indicates severe erectile dysfunction unmasking thus endothelial dysfunction. Dietary habits were evaluated through a special diet score (Med-Diet score, range 0-55), which assesses adherence to the Mediterranean diet. Lower values indicate poor adherence to this alimentary pattern.

Results: Patients on HD had statistically higher IMT (1.5 ± 0.7 vs 0.85 ± 0.2), lower SHIM-5 score grading (8.8 ± 6.9 vs 12.8 ± 4.5) and lower Med-Diet score(22 ± 4 vs 29 ± 3) as compared to PD patients (all P<0.05). Carotid IMT and carotid plaque formation were inversely associated (r=-0.32, P=0.001) and SHIM-5 was positively correlated (r=0.29, P<0.01) to the Med-diet score. The associations remained significant in linear regression analysis after adjustment for age, body mass index, presence of hypertension, diabetes mellitus, tobacco use and statin therapy (all P<0.01).

Conclusions: ESRD male patients on peritoneal dialysis may exhibit lower atheromatic load and enhance peripheral vessel rheology by adopting the Med-diet regime. Healthy dietary choices may improve quality of life and cardiovascular outcome in this specific ESRD population.

FR-PO440

Association of Serum Indoxyl Sulfate Level with Peripheral Artery Occlusive Disease in Patients with Hemodialysis

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Background: Indoxyl sulfate (IS) can be considered as a cardiovascular toxin and a nephrotoxin that has been associated with intima media thickness, vascular disease, coronary artery disease, progression of kidney disease and increased mortality. Peripheral arterial occlusive disease (PAOD) is associated with an increased risk of death in hemodialysis (HD) patients. The aim of this study was to evaluate the relationship between IS level and PAOD by ankle-brachial index (ABI) in HD patients.

Methods: Blood samples were obtained from 80 chronic HD patients. Serum total IS level was performed with high-performance liquid chromatography and mass spectrometry. ABI values were measured using the automated oscillometric method (VaSeva VS-1000). ABI values that were <0.9 were included in the low ABI group.

Results: Among the 80 HD patients, 12 of them (15.0%) were in the low ABI group. Compared with patients in the normal ABI group, the patients in the low ABI group had higher prevalence of diabetes (P=0.010), higher serum C-reactive protein (P<0.001), and IS (P<0.001) levels, while lower had statin used (P=0.042). In addition, the multivariable logistic regression analysis showed that serum IS (Odds ratio [OR]: 1.115, 95% confidence interval [CI]: 1.015-1.225, P=0.023) and CRP levels (each increase 0.1 mg/dL, OR: 1.187, 95% CI: 1.046-1.346, P=0.008) were the independently associated with PAOD in HD patients. The area under the receiver-operating characteristic (ROC) curve predicting PAOD by serum IS level in HD patients was 0.800 (95% CI: 0.696-0.881, P=0.0002).

Conclusions: In this study, serum total IS level was found to be associated with PAOD in HD patients.
increases activity of endothelial nitric oxide synthetase. Sodium thiosulfate is believed to decrease the amount of calcium in serum, and nephrologists recommend a course of dialysis 5–7 days per week for the first couple of weeks of treatment, with the duration of this intensified dialysis therapy depending on clinical response. Sodium thiosulfate is a chelating agent that has antioxidant activity and increases activity of endothelial nitric oxide synthetase. Sodium thiosulfate is believed to act by dissolving insoluble tissue calcium salts to form calcium thiosulfate, which is many thousand times more soluble than many other calcium salts.

**FR-PO441**

**Tumoral Calcinosis in Hemodialysis Patient**

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**Introduction:** Uremic tumoral calcinosis is an uncommon but serious complication of end-stage renal disease. It is characterized by massive extrarenal calcification in peritubular tissues, leading to limited range of joint movement, pain, and skin ulceration.

**Case Description:** A 52-year-old man developed a progressively enlarging painless mass on the posterior surface of the right leg and on the back surface of the right shoulder with limited range of flexion following 5 years of hemodialysis. Magnetic resonance showed amorphous, cystic, and multilobulated calcification. Pathology report revealed tumoral calcinosis. We started intensifying hemodialysis program (5 days per week, 4 hours each session), low calcium bath, aggressive control of hyperphosphatemia, initiation of cinacalcet, antibiotics and administration of sodium thiosulfate 25 mg i.v per each session. After 6 weeks we noticed significant reduction in the magnitude of the masses and in 8 weeks complete resolution. We turned hemodialysis schedule to 3 times a week and continued to have close monitoring of the patient.

**Discussion:** Effective treatment options for tumoral calcinosis remain elusive. The primary focus of therapy should be to optimize calcium and phosphate homeostasis. Avoidance of a positive calcium balance should be a high priority. Experienced nephrologists recommend a course of dialysis 5–7 days per week for the first couple of weeks of treatment, with the duration of this intensified dialysis therapy depending on clinical response. Sodium thiosulfate is a chelating agent that has antioxidant activity and increases activity of endothelial nitric oxide synthetase. Sodium thiosulfate is believed to act by dissolving insoluble tissue calcium salts to form calcium thiosulfate, which is many thousand times more soluble than many other calcium salts.

**FR-PO442**

**Effectiveness and Safety of Modified Sodium Thiosulfate Therapy for Calciphylaxis in Chinese Patients**

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**Background:** Calciphylaxis is a generally fatal condition without acknowledged effective treatment. Some case reports and clinical studies have described intravenous sodium thiosulfate (STS) prevent the progression of calciphylaxis. Nevertheless, this therapy for individuals presented serious complications resulting in withdrawal of treatment in our experience. Based on the ethnic diversity, we modified the usage of STS and evaluated the effectiveness and safety of modified STS therapy for calciphylaxis in Chinese patients.

**Methods:** 20 patients who were diagnosed calciphylaxis and treated with STS in our center were enrolled. Evaluation of effectiveness and safety was based on items including demographics, clinical data and laboratory measurements. Therapeutic schedule were named Zhongda Therapy with 5 course of treatment and 2-3weeks of interrupt between 2 courses. STS from the initial dose (3.2g) were administered intravenously in 100 mL once a day gradually increasing day by day up to the highest dose (6.4g). Patients maintained the condition of highest dose for 2-3 weeks and finished one course of treatment.

**Results:** The Mean age of the cohort was 45.50±14.95 years, 75% of patients was male and the median time span was 87 (52, 120) months from entering the dialysis to diagnosed as calciphylaxis. In our research, 90% patients got improved and 12/20 patients were follow-up more than 12 months with 100% one-year survival rate. Of these patients, lesions involved different body parts such as torso, limb, fingertips or compound type and throughout the body were 20% with powerful pain. The therapy relieved pain and promote early healing of skin lesions, even help one avert amputation. Reduction of phosphorus (P=0.035) and the NPRS (P<0.001) correlated significantly with STS treatment courses. Although adverse events occurs up to the 35% (nausea/vomiting 10%, hypotension 10%, infection 5% and multi-complication 10%), no one interrupted treatment due to mild discomfort. And if the incidence rate were calculated according to frequency divided by the total course, it will reduced to 14%.

**Conclusions:** Chinese patients need to modified the usage of STS to treat the calciphylaxis. And Zhongda Therapy offered a safe and effective treatment.

**FR-PO443**

**Impact of Hemodialysis on the Concentrations of Sodium and Potassium During Infusion of Sodium Thiosulfate Using An In Vitro Hemodialysis Model**

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**Background:** The purpose of this study was to evaluate the impact of hemodialysis on the concentrations of sodium and potassium in the blood when a 25 g dose of sodium thiosulfate injection is infused over 60 minutes in combination with hemodialysis.

**Methods:** Sodium thiosulfate (25 g) was prepared by diluting 100 mL of 250 mg/mL Sodium Thiosulfate Injection with 800 mL of 5% dextrose. This was added to the circulating blood surrogate solution at a rate of 15 mL/minute using an infusion pump of an in vitro model of dialysis machine [Figure]. Serial samples were collected before the administration of the sodium thiosulfate solution, after 15 minutes, 30 minutes, and 60 minutes of infusion from pre-and post-dialyzer ports in both the dialysate circuit and the extracorporeal circuit.

**Results:** The concentration of sodium thiosulfate in pre-dialyzer and post-dialyzer samples of the circulating blood surrogate solution peaked at 30 minutes and 15 minutes, respectively and then remained relatively unchanged during the remainder of the infusion. Mean sodium concentrations (mEq/L) in the circulating blood surrogate solution collected after exposure to a dialyzer were 103.2 ± 12.2, 114.2 ± 18.8, 117.2 ± 7.5, 93.5 ± 5.9 at 0, 15, 30, and 60 minutes, respectively (p=0.248). Mean potassium concentrations (mEq/L) in the circulating blood surrogate solution collected after exposure to a dialyzer were 1.4 ± 0.3, 1.6 ± 0.3, 1.5 ± 0.1, 1.2 ± 0.1 at 0, 15, 30, and 60 minutes, respectively (p=0.365). Sodium and potassium concentrations in dialysate increased marginally after exposure to the dialyzer.

**Conclusions:** Our study demonstrates that neither potassium nor sodium accumulated in a circulating blood surrogate solution when a dose of sodium thiosulfate was infused in conjunction with hemodialysis.
FR-PO444

Avoidance of the Third Amputation with Remission of Intolerable Pain by Sodium Thiosulfate Administration in a Severe Calciphylaxis Patient

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Introduction: Calciphylaxis is a rare but fatal vascular calcification disease characterized by ischemic skin damage and severe pain, often leading to amputation. Currently, there is no specific therapy, but sodium thiosulfate (STS) shows potential curative effects in many related reports. We report a calciphylaxis patient with recurrent skin necrosis which seems the third amputation is inescapable. STS significantly relieves the sharp pain and delays deterioration of skin ulcer.

Case Description: A 64-year-old Chinese male with 23-year hemodialysis history had recurrent and progressively worsen acro-skin ulcer accompanied by extremely pain. His highest pain score for numeric pain rating scale (NRS) was 9, which made him behave suicidal tendency. He had twice amputations of left fingers and right lower limb, there is still an emerging ulcer on his left heel (Fig.1) with unmanageable pain. His previous amputating wound was also poor-healed after half a year of surgery. X-rays showed the large vessel calcification (red arrows) which suspected of supplying blood at the necrotic site(Fig.2). A skin biopsy on his amputated right lower leg showed extensive calcium deposition in small vessel walls(Fig.3). He was diagnosed as severe calciphylaxis and we conducted a comprehensive therapy based on intravenous STS with the daily increasing dose from 3.2 g/d to maintain with 6.4 g/d after 5 days. After one-week treatment, the patient felt pain significantly relieved (Table) and 3 months later, his amputating wound gradually crusted so that a third amputation was avoided.

Discussion: Although there is no large randomized clinical trial to confirm the effect of STS in calciphylaxis patients, the use of STS significantly reduces pain and the patient avoids the third amputation. It is suggested that STS also has a certain therapeutic effect on severe calciphylaxis, which mainly relies on relieving pain and delaying the progression of skin ulcers.

FR-PO445

Dialysis Initiation Improves Calcification Propensity

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Background: Cardiovascular morbidity and mortality is high in patients starting dialysis and could be related to modifications of calcification inducers and inhibitors by dialysis, promoting cardiovascular events. The impact of dialysis initiation on serum calcification propensity evolution and arterial stiffness is however not well known. We therefore, prospectively determined the evolution of the $T_{Ca}$ value and its main determinants, as well as pulse wave velocity (PWV) over the first three months of dialysis initiation.

Methods: We analyzed the evolution of $T_{Ca}$, fetuin-A and phosphocalcic parameters before dialysis initiation (M0), and monthly until month three (M3) of incident patients starting hemodialysis (HD) or peritoneal dialysis (PD) in two tertiary Swiss University Hospitals. Arterial stiffness was assessed by pulse wave velocity at M0 and M3, and biological parameters were compared between M0 and M3 and before/after HD.

Linear mixed models were used as parameter estimation models over time taking into account repeated measures and other influencing variables.

Results: Forty-six patients on HD and 12 on PD were followed. Among them, 45 were male (78 %) with median age of 67 years (25%-75%: 54-77). $T_{Ca}$ significantly increased between M0 and M3 from 183 (120-266) to 246 (175-330) minutes, $p<0.001$. Fetuin-A, calcium and magnesium also increased while phosphate decreased. Factors associated with $T_{Ca}$ changes over time were fetuin-A, phosphate and magnesium ($p<0.001$). Fetuin-A changes were associated with inflammation-related factors (albumin, crp) but not phosphocalcic parameters. Arterial stiffness was not significantly modified over 1 month. PD and HD initiation followed similar trends.

Conclusions: Dialysis initiation significantly improves calcification propensity and fetuin-A levels. These modifications do not explain the high mortality related to dialysis initiation. The clinical relevance of using T50 values to initiate dialysis awaits further studies.

Funding: Government Support - Non-U.S.

FR-PO446

Acid-Base Dynamics in Allo-Hemodialysis Treatments: Quantitative Insights from a Novel Physiology-Based Mathematical Model

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Background: In some areas of the world access to conventional hemodialysis (HD) is elusive, resulting in millions of premature deaths every year. Allo-hemodialysis (alloHD) is a substantially simplified and less costly dialysis modality, in which the blood of a healthy subject ("buddy") flows counter-current to the patient’s blood through the dialyzer. Solutions, including bicarbonates, are transferred across the membrane. In this study, we proposed a physiology-based mathematical model to explore the impact of alloHD on the patient’s and buddy’s acid-base status.

Methods: A dynamic model of physiological regulation of HCO₃⁻/CO₂ buffering system with Henderson-Hasselbalch mass-action kinetics is used to describe a coupled transfer between patient and buddy via alloHD. The model incorporates production of CO₂ and H⁺, loss due to non-bicarbonate buffering, and ventilation. In addition, we assume a normal renal function and regulation of HCO₃⁻/CO₂ in the buddy, but not in the patient. The patient model is parameterized to yield various degrees of metabolic acidosis, while the buddy model is parameterized to physiological values.

Results: Figure 1 shows an example of acid-base dynamics. AlloHD is able to correct patients’ acid-base status. Interestingly, there are only minimal changes to the buddy’s acid-base status. The buddy’s kidney function affects the extent to which the patient’s acid-base status is corrected. Furthermore, since buddy’s renal function is fully intact, we observe a secondary compensation where HCO₃⁻, pCO₂ and pH initially decrease before regulatory compensations restore the buddy’s acid-base status.

Conclusions: Our findings indicate that an alloHD session can restore the patient’s acid-base status. Our modeling suggests that there is minimal disturbance in buddy’s acid-base status while providing substantial corrective regulation of patient’s acid-base homeostasis. Although our modeling results are promising, there is a need for further empirical investigation to verify the predictive power of the model.

FR-PO447

Cardiac Stunning During Haemodialysis: The Therapeutic Effect of Intradialytic Cycling

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Background: Cardiac risk is elevated in end stage renal disease (ESRD). Left ventricular dysfunction is linked to repetitive transient ischemia occurring during maintenance haemodialysis (HD); cardiac stunning can subsequently occur defined as myocardial regional wall motion abnormalities (RWMA). Ischemic RWMA have been documented during HD resulting in maladaptive cardiac remodelling and increased risk of heart failure. Intra-dialytic exercise is well tolerated and can improve quality of life and physical function. It may also attenuate HD induced cardiac stunning. The aim of this exploratory study was to assess the effect of intra-dialytic cycle ergometry on cardiac stunning.

Methods: Twenty exercise naïve participants on maintenance HD (59 ± 11 yrs) underwent resting echocardiography and maximal cardiopulmonary exercise testing.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

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Subsequently, cardiac stunning was assessed with myocardial strain derived RWMAs at four timepoints during standard HD, and 2) HD with 30 mins of sub-maximal, intra-dialytic cycle ergometry at a workload equivalent to 90% of oxygen uptake at the anaerobic threshold (VO2AT).  

**Results:** Compared to HD alone, HD with intra-dialytic exercise significantly reduced RWMAs at 2.5hrs of HD had elapsed (Total 110 ± 4, mean 7 ± 4 segments vs total 77 ± 3, mean 5 ± 3 respectively; p = 0.008). Global cardiac function, intra-dialytic haemodynamics and left ventricular volumetric parameters were not significantly altered with exercise.

**Conclusions:** Intra-dialytic exercise, completed after one hour of maintenance HD, significantly reduced cardiac stunning. Thirty minutes of sub-maximal exercise at 90% VO2AT was sufficient to elicit this acute cardio-protective response.

**Funding:** Commercial Support - Coventry University PhD funded project

Regional wall motion abnormalities during haemodialysis. At 2.5h-HD, the number of regional wall motion abnormalities was significantly reduced with intra-dialytic exercise (HD+CLE).

**FR-PO449**

**Predictors of Hypophosphatemia and Outcomes During Continuous Renal Replacement Therapy**

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**Background:** Hypophosphatemia occurs in up to 80% of patients undergoing continuous renal replacement therapy (CRRT) and is associated with poor outcomes. Whether pre-emptive phosphate supplementation is warranted in select patients has not been adequately explored. This single-center, retrospective cohort study evaluates predictors of hypophosphatemia and characterizes treatment approaches in adult patients undergoing CRRT.

**Methods:** Patients requiring CRRT for at least 12 hours were divided into two groups based on the presence or absence of hypophosphatemia as defined by serum phosphorus <2.5 mg/dL. Select laboratory values at baseline and during CRRT, medications and nutritional sources affecting phosphorus, and CRRT parameters were compared. Patient outcomes including acute kidney injury (AKI) resolution, freedom from renal replacement therapy (RRT) at hospital discharge, duration of intensive care unit (ICU) and hospital stay, duration of mechanical ventilation, and ICU mortality were evaluated.

**Results:** Seventy-two patients were included. The group was 43% female and 51% African American. CRRT was ordered for AKI in 83% and for end-stage renal disease in 15% of patients. Hypophosphatemia occurred in 45 patients (63%). Mean time to development of hypophosphatemia was 34 ± 22 hours. Patients who developed hypophosphatemia received a longer duration of CRRT (p = 0.001), were more likely to have a diet ordered (p = 0.005), less likely to have received calcium infusions (p = 0.045), and had lower phosphorus (p = 0.017) and potassium levels (p = 0.038) and higher calcium levels at baseline (p = 0.048). Development of hypophosphatemia was associated with an increased duration of ICU stay (p = 0.014) but not with the other patient outcomes evaluated. Twenty-seven of the 45 patients (60%) who developed hypophosphatemia received phosphate supplementation with near equal use of intravenous, oral, and combination routes. Only 16 patients (36%) achieved resolution of hypophosphatemia while on CRRT.

**Conclusions:** Hypophosphatemia is common, difficult to correct, and contributes to longer ICU stays in patients requiring CRRT. A pre-emptive approach to address hypophosphatemia including aggressive supplementation strategies to correct phosphorus is warranted in patients requiring CRRT.

**FR-PO450**

**Development and Validation of a Predictive Model for Delivered Dose in Continuous Renal Replacement Therapy**

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**Background:** Continuous renal replacement therapy (CRRT) has become one of the most relevant therapies for acute kidney injury and critical patients. Since the beginning there has been controversy about delivering, measuring, and defining ideal dose. Measuring effluent volume related to body weight has been the method of choice for the last years. It’s well known that prescribed dose and delivered dose differ significantly, mainly because of down time, the effect of pre-dilution replacement, and the dialyzer capacity to saturate the effluent. A tool that could account for the three main factors that lower the dose and could predict the delivered dose, could be of great help for the daily prescription of CRRT. The objective of this study is to validate the results of the proposed model in our Institution.

**Methods:** We developed an app-based model programed in Xcode® for iOS, with a prescription step method, and patient based format, that considers: down time, pre-dilution replacement, and effluent saturation. The model is given a desired therapy and then calculates the simulated delivered dose. For validation we evaluated since March 2019, 5 treatments of CRRT in CVVHDF mode, and run 15 dose evaluations by measuring simultaneously: BUN pre-filter pre-dilution, BUN pre-filter post-dilution, and of the effluent solution. We then compared the delivered dose with the results of the predictive model.

**Results:** We found good correlation compared to the delivered dose. We conducted a Pearson correlation that showed: r = 0.91, 95% CI= (0.74 - 0.97), R2 =0.82, and a P value of <0.0001. To evaluate agreement we conducted a Bland Altman plot we demonstrated that 100% of results where between the 11% error: (Bias= -2, SD of Bias 4.2% Limits of agreement (-11 - 5.5).  

**Conclusions:** Even though the sample was small, the delivered dose predictor computes accurate results as compared to the delivered dose. The App based tool can help predict delivered dose given to a patient, it can be of great utility to simulate different therapies with different prescriptions, and compare different results. At present new focused therapies and treatments are being continuously evaluated to strengthen even further the results.
FR-PO451
Prognostic Potential of Calcitriol in the Patients Requiring Postoperative Continuous Renal Replacement Therapy After Liver Transplantation
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Background: The mortality of the patients with End-Stage Liver Disease and renal dysfunction is high. It is important to know and correct the predicting risk factors of mortality in the patients requiring continuous renal replacement therapy (CRRT) after liver transplantation (LT). Immunomodulatory and anti-inflammatory effects of calcitriol, produced by liver and kidney, improved survival rate in the animal experiment under went solid organ transplantation. We investigated whether lower calcitriol level is associated with the mortality in the patients requiring CRRT after LT.

Methods: We conducted a retrospective study consisted of 65 patients requiring CRRT after LT. Their demographic data and biochemistry parameters were obtained at the initiation of CRRT by reviewing electronic medical records. The deficiency of calcitriol was defined as its plasma level < 10 pg/ml. Primary end point was 180-day mortality from the initiation of CRRT after LT.

Results: The subjects were divided into calcitriol deficient group (CDG, n=36) and calcitriol non-deficient group (CNDG, n=29). There were no significant differences in demographics between two groups. Compared with CDG, hematocrit (26.3 ± 2.3 vs. 20.5 ± 5.1 %), p=0.045) and 25(OH)D3 (7.2 ± 2.8 vs. 2.8 ± 1.2 ng/ml, p=0.011) were higher in CNDG at the initiation of CRRT. In contrast, 180-day mortality in CDG (30/36, 83.3%) was higher than that of CNDG (3/29, 10.3 %, p=0.005). By Cox regression analysis, calcitriol deficiency (OR 25.9, 95% CI 2.72-246.9, p=0.005) and Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification (OR 0.4, 95% CI 0.16-0.99, p=0.04) were significant risk factors of mortality after adjusting Model for End-Stage Liver Disease (MELD) score, RIFLE and 25(OH)D3.

Conclusions: Calcitriol deficiency is associated independent risk factor with the mortality in the patients requiring CRRT after LT. In the future, randomized interventional trial is necessary to confirm whether calcitriol is a correctable risk factor to improve the survival in them.

FR-PO452
Accelerated Venovenous Hemofiltration (AVHV): Piloting a Transitional Renal Replacement Therapy in the Intensive Care Unit
Paul Endres,1 Tyler Parris,2 Sophia Zhao,3 Megan F. May,2 Mary H. Sylvia-Bezreh,4 Nicole Bezreh,2 Roberta L. Culbert-Costley,2 Lillian Ananian,2 Russell J. Roberts,2 Natasha Lopez,2 David M. Charytan,3 Tina E. Tolkoff-Rubin,2 Andrew S. Allegretti.1 1Massachusetts General Hospital, Boston, MA; 2BH/MGH, Boston, MA; 3New York University School of Medicine, Bronx, NY.

Background: The need for continuous renal replacement therapy (CRRT) is associated with high mortality and resource use in the ICU. There are no guidelines established that blood transfusion transition from CRRT to intermittent hemodialysis (iHD) as AVHV is a form of CRRT that allows for higher blood flows, increased hemofiltration rates, no anticoagulation, and a 10 hour treatment period, as a transition between CRRT and iHD, and assessed treatment characteristics.

Methods: Quality improvement pilot aimed to achieve a safe and effective transition between CRRT and iHD using AVHV at large academic medical center between October 2017 and August 2018. A VVH treatment doses, blood flows, clearances, filter clotting, and patient outcomes were recorded.

Results: 51 patients received a total of 142 complete AVHV treatments. 11 (8%) patient treatments were not completed due to inadequate blood flows (3), filter clotting (7), and change to comfort measures (1). Average prescription was: treatment time 9.3 ± 1.6 hours, blood flow 350 ± 22 mL/min, replacement fluid rate 4.1 ± 0.3 L/hr, ultrafiltration volume 2.0 ± 1.1 L/treatment, urea reduction ratio 28 ± 17%,10 hrs. 32.5/61% patients received sequential daily treatments (range 2-13 treatments). In-patient mortality was 31%, length of stay 53 ± 49 days. 36/51 (70%) patients successfully transitioned to iHD, 10/51 patients (20%) recovered renal function after AVHV, and 4/46 (8%) patients required readmission to the ICU after developing hypotension on iHD.

Conclusions: AVHV was successfully integrated into our ICU program as an innovative transition therapy between CRRT and iHD. It has tremendous potential to reduce ICU readmission and healthcare costs. Further study is needed to determine its impact on resource utilization and patient outcomes.

Patient Characteristics

| Characteristic | AVHV | AVHV
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>ICU Cases</td>
<td>44</td>
<td>44</td>
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<tr>
<td>Apache Score</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Use of vasoopressors</td>
<td>41 /97</td>
<td>41 /97</td>
</tr>
<tr>
<td>In-Hospital Mortality</td>
<td>16 /37</td>
<td>16 /37</td>
</tr>
<tr>
<td>Plasma BV/Vg (mg/dL)</td>
<td>44 /17</td>
<td>44 /17</td>
</tr>
<tr>
<td>Plasma AVHV BUN (mg/dL)</td>
<td>51 /1-3</td>
<td>51 /1-3</td>
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FR-PO453
Efficacy and Safety of High-Volume Hemofiltration (HVHF) in Patients with Septic Shock and AKI: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Sherida N. Edding, Brian Michael I. Cabral. Department of Medicine, St. Luke’s Medical Center - Global City, Taguig City, Philippines.

Background: Septic Shock is among the most common causes of death in the intensive care unit (ICU). The underlying pathophysiology involves an overactive immune response. It has been theorized that transition from blood purification techniques that reduces the levels of inflammatory cytokines and/or bacterial toxins could mitigate this response. High-volume hemofiltration (HVHF) is a blood purification technique that has been studied to improve outcome associated with septic shock. Our aim is to do a systematic review of randomized controlled trials that assessed the use of HVHF in septic shock.

Methods: A comprehensive literature search from the PubMed, Embase, Cochrane Library, and Ovid was performed with the following search terms: Hemofiltration, Septic Shock, Acute Kidney Injury. The search was limited to randomized-controlled trials that compared HVHF to Conventional (as dictated by the Surviving Sepsis Guidelines) and/or Standard-Volume Hemofiltration (SVHF). Six prospective clinical trials were selected and analysed using Cochrane Revman v5.3. The primary outcome was 28-day mortality. Other outcomes assessed were dialysis dependence, length of ICU and hospital stay, vasopressor requirement and adverse events.

Results: Six trials comprising 745 patients were selected. 373 patients treated with HVHF and 372 patients in the control group were included. Pooled analysis of the 6 trials for 28-day mortality did not show a statistically significant difference between HVHF and conventional participants, OR: 0.90, 95% CI 0.67-1.21. There were no noted significant difference between groups for any of the secondary outcomes. Adverse events, including electrolyte abnormalities and secondary infections, were more commonly observed in HVHF-treated patients, although reporting was inconsistent across studies.

Conclusions: There is the need for more evidence to support the therapeutic benefit for routine use of high-volume hemofiltration in patients with septic shock. Larger trials are needed to fully assess clinically relevant outcomes as well as cost-effectiveness.

Figure 1. Forest Plot for 28-Day Mortality

FR-PO454
Effectiveness of Implementation of Hemodiafiltration and Achieving Target Convective Volume: Results from HDFit Trial
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Background: Hemodiafiltration (HDF) is associated with better outcomes compared to hemodialysis (HD), provided adequate convective volumes (CV) are achieved. Implementation of protocols targeting optimal CV have not been well described.

Methods: HDFit was a randomized controlled trial studying the impact of postdischarge high-volume online HDF versus high-flux HD on measured physical activity (NCT02787163). HDFit included stable patients (Kt/V ≥1.2, permanent access, vintage ≥3 to 24 months). Clinic staff were trained to use Fresenius 5008 CorDiax® HDF machines the day before/morning of randomization visit. HDF was performed in 6-month follow-up with a CV target of 22L/treatment. We assessed implementation of HDF with a median achieved CV ≥22L across treatments.

Results: HDFit randomized 195 patients (HDF n=97, HD n=98) at 13 clinics with mean age 53±15.1 years and 11% used a permanent catheter. There was an 8% and 11% dropout rate in HDF and HD groups. HDF group had 95 patients with CV data recorded (median=75 treatments/patient, OR: 0.90, 95% CI 0.67-1.21). Median treatment time was 235 (IQR 232 to 240) and 235 (IQR 233 to 240) minutes for HD and HDF. Median CV ≥22L was achieved in 86% (82 of 95) of HDF patients during follow-up. Monthly mean CV ranged from 24L to 25L (Figure 1). At 3-5 months, distinctions were found in mean Ki/HDF=1.8±0.4, HD=1.6±0.4, p<0.001) and postdialysis (POD) (HDF=4.8±1.3, HD=5.1±0.4, p=0.022). Distinctions were maintained at 6-months in mean Ki/HDF=1.8±0.5, HD=1.7±0.4, p=0.028), yet not po4.

Conclusions: HDF was successfully implemented in the HDFit trial with 86% of participants achieving goal CV of ≥22L/monthly mean CV. HDFit provided higher Ki/HDF throughout follow up and more PO4 removal at 3 months. HDF appears to be an easily implementable technique with brief training required.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Propensity Score-Matched Cohort Study

Improved Survival with High-Volume Hemodiafiltration in Argentina: A Propensity Score-Matched Cohort Study

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Jochen G. Raimann,
Peter Kotanko,
Marcelo H. Puddu,
Cristina Marelli,
Adrian M. Guinsburg,
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Background: While hemodialysis (HD) is the current standard of care, hemodiafiltration (HDF) adds high convective volume to remove middle molecules. We compared all-cause mortality in Fresenius Medical Care Argentina patients treated with either HDF or high-flux HD.

Methods: Data were extracted from Fresenius EuClID® database and comprise treatments between 11/2011 and 05/2018. Pts were divided patients into those treated with HD (control group), high-volume (HV) HDF (>70% of treatments with >23 L substitution volume), and low-volume (LV) HDF (< 23 L substitution volume). The baseline period comprised 3 months before the HD-to-HDF switch, it was followed by 1 month washout period. Pts were for 1 year, death, or lost to follow-up. To minimize bias by indication, HDF pts were propensity score matched to HD pts by age, gender, diabetes, vintage, fluid status (determined by bioimpedance), vascular access, systolic blood pressure, phosphate, albumin.

Within the known limitations of observational trials (patient selection bias, residual confounding) our propensity score matched multicenter study shows a survival benefit of HV-HDF vs. HD (11.46 vs 22.5 deaths/100 pt-years, p=0.039, figure 1), but not for LV-HDF (23.4 vs 22.5 deaths/100 pt-years).

Results: We selected 12,911 pts from 73 centers (11,111 HD; 1,800 HDF). Propensity score matching resulted in 537 HD and 545 HDF patients (Table 1). Kaplan-Meier analysis showed a survival benefit of HV-HDF vs. HD (11.46 vs 22.5 deaths/100 pt-years, p=0.039, figure 1), but not for LV-HDF (23.4 vs 22.5 deaths/100 pt-years).

Conclusions: Within the known limitations of observational trials (patient selection bias, residual confounding) our propensity score matched multicenter study shows a survival benefit of HV-HDF, but not LV-HDF, over HD in Argentinian patients.

Table 1: Survival Analysis of HD and HDF

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>HD Mean (SD)</th>
<th>HDF Mean (SD)</th>
<th>p</th>
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<tbody>
<tr>
<td>57.9 (15.9)</td>
<td>56.2 (15.7)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Male %</td>
<td>60</td>
<td>70</td>
<td>0.03</td>
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<tr>
<td>DRT %</td>
<td>30</td>
<td>30</td>
<td>0.75</td>
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<tr>
<td>Vintage (months)</td>
<td>20.5 (14.8)</td>
<td>20.6 (23.0)</td>
<td>0.00</td>
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<tr>
<td>Hydration</td>
<td>3.2 (2.4)</td>
<td>1.8 (2.1)</td>
<td>0.07</td>
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<tr>
<td>Catheterization %</td>
<td>20</td>
<td>10</td>
<td>0.04</td>
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<td>SBF (nmol/L)</td>
<td>128.4 (18.0)</td>
<td>129.4 (19.5)</td>
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<tr>
<td>P (mg/dl)</td>
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<td>5.2 (1.2)</td>
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<tr>
<td>Alb (g/dl)</td>
<td>3.9 (0.4)</td>
<td>3.9 (0.5)</td>
<td>0.30</td>
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</tbody>
</table>

FR-PO456

Safety and Efficiency of Low-Molecular-Weight Heparin (LMNH) Administered in the Venous Line of Patients Treated by Online Hemodialfiltration and High Flux Hemodialysis

Hebibi Hedia,
David Attal,
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Background: Removal of low molecular weight heparin (LMWH) occurs during high flux hemodialysis (HF-HD) and online hemodiafiltration (OL-HDF) if administered before the dialysis session in the arterial line of the extracorporeal HD circuit. It is recommended to administer (LVMH) through the venous line to improve anti-coagulation efficacy. The goal of our study is to evaluate efficacy, and safety of LMWH administered through the venous line in OL-HDF and HF-HD patients.

Methods: We enrolled 49 OL-HDF and 48 HF-HD patients from February to October 2018 (mean age 66 yrs, arteriovenous fistula 90%, the average dialysis time 240 min). Three consecutive 6-week periods (i.e. 5400 dialysis sessions) were analyzed according to the path and dose of (LMWH) administration: Phase I (arterial line), phase II (venous line), phase III (reduced dose). Phase I and II involved HF-HD + OL-HDF patients, and phase III involved only OL-HDF patients. In each session we evaluated filter and chamber clotting (semi-quantitative visual scale), venous pressure, KT/V, volume infused in OL-HDF. The 3 periods were done with FX membranes (90%), BK, BG

Results: 34 %, 63 % and 66% of membranes were scored as “clean” during phases I, II, III respectively (p<0.05). 9%, 6.6% and 0% of membranes clotted during phases I, II, III respectively (p=0.05). 1%, 0.6% and 0% were clotted with loss of circuit during phases I, II, III respectively (p=0.5). Average LMWH doses were: 0.45 ml (0.2-0.6) and 0.3 ml (0.2-0.6) of Nadroparin during phases I, II respectively (p<0.001). During phase III, LMWH dose decreased from 33 to 50% for 58% of patients with an anti-Xa target ~ 0.4ui/ml. Between phases I-II, KT/V improved from 1.71 to 1.83 (p<0.005). Infused volume from 20.7 to 23.7 l. Bleeding time was identical during Ph I - Ph III. In the HF-HD sub-group during phases I and II, venous LMWH administration decreased the average LMWH dose from 0.55 ml to 0.34 ml respectively and improved the quality of blood restitution.

Conclusions: Venous line administration of LMWH at the start of dialysis allows a dose reduction and improvement of dialysis adequacy parameters.
FR-PO457
Hemodialysis (HD) Using Super High-Flux Dialyzer Provides Comparable Efficacy with High-Volume Post-Dilution Online Hemodiafiltration (ol-HDF): A Prospective Crossover Randomized Controlled Trial
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Background: Although high volume post-dilution online hemodiafiltration (ol-HDF) that could remove large toxin such as beta-2 microglobulin (B2M, MW 11.8 kDa) as well as protein-bound toxins especially indoxyl sulfate (IS) and subsequently improve survival of HD patients is now accepted as the best modality for chronic HD patients, the procedure is sophisticated and expensive. The present study was conducted to compare the efficacy in term of large and protein-bound uremic toxin removals between HD using novel super high-flux (SHF) dialyzer which has large pore size close to albumin, PES 17D alpha (Nipro, Japan) and ol-HDF in a non-inferiority fashion.

Methods: A prospective cross-over randomized controlled trial included twelve prevalent HD patients who were randomly allocated into 2 sequences of treatment period of SHF-HD treatment and later ol-HDF period or vice versa. Each treatment period took 12 weeks and divided by wash out phase of 4 weeks of HD using regular high-flux (HF) dialyzer. The primary outcome was removal of B2M in term of reduction ratio (RR). Other small, protein-bound and large uremic toxin removals, albumin loss, and nutritional parameters were also compared.

Results: SHF-HD provided comparable B2M RR with ol-HDF (78.8±4.7 and 76.8±4.1, respectively, p=0.152). In addition, B2M clearance, alpha-1 microglobulin (A1MG, MW 33 kDa) RR, A1MG clearance, and IS RR were also comparable. The spKt/Vurea was not different. Although the albumin loss in dialyze was higher in SHF-HD than ol-HDF(4.2±2.8 and 0.6±0.9 g/session, respectively), the serum albumin levels at baseline and after 12 weeks of SHF-HD treatment were significantly from 3.71±0.38 to 3.83±0.22 g/L (p<0.001) while they did not change during ol-HDF period. In addition, normalized protein catabolic rate was significantly increased in SHF-HD compared to ol-HDF (p=0.012) with no significant change of lean tissue index after 3-month period of the study.

Conclusions: SHF-HD that lower cost and accessibility was non-inferior efficacy to ol-HDF in term of large, protein-bound and small uremic toxin removals without adverse effects on serum albumin potentially improve long-term survival.

Funding: Private Foundation Support

FR-PO458
High-Volume Postdilution Online Hemodiafiltration Is Possible Even at Low Blood Flow Rates
Young-II Jo,1 Ki sung Kim,1 Kyung-Hee Chung,2 Mi-Jung Seo.3 1Nephrology, Konkuk University Medical Center, Seoul, Republic of Korea; 2Dialysis center, Konkuk University Medical Center, Seoul, Republic of Korea.

Background: Recent evidence suggests that high-volume hemodiafiltration (HDF) improves patient survival. However, in patients with low blood flow rate (BFR), it is not easy to obtain a high convection volume (CV) with postdilution online HDF. The aim of this study was to investigate whether it is possible to achieve high CV, defined as “convection volume that provides survival benefits among patients on online hemodiafiltration.” This study included patients with low BFR (less than 300 mL/min).

Methods: A total of 33 consecutive patients undergoing thrice-weekly postdilution HDF were included. In order to obtain a high CV, we optimized treatment parameters such as treatment time (TT), BFR, needle size and filtration fraction (FF) in all patients according to a stepwise protocol, depending on patient’s condition. All dialysis machines were equipped with auto-substitution system. Data of 2592 sessions for one month before and after completion of optimization of treatment parameters were analyzed. The mean CV was determined.

Results: The mean age of patients was 62.5±12.5 years, and 45.5% male. Before the initiation of a stepwise protocol, TT was 233±6.10 h, BFR was 267±11.1 mL/min, and 84.8% of needles were 16G and 15.2% were 15G. The mean CV was 23.8±2.4 L/session and 75.8% of patients reached CV of ≥22 L/session. After completion of optimization, 90.9% of patients reached a high CV with mean of 24.4±2.3 L/session. Of note, TT was 241.8±16.1 min, BFR was 293.6±12.5 mL/min, and 69.7% of needles were 16G and 30.3% were 15G. Interestingly, in 96.70% of patients who reached a high CV, BFR was less than 300 mL/min with mean of 293.5±12.5 mL/min. In addition, 90.0% of patients with BFR of less than 300 mL/min reached a high CV. The changes of CV after optimization of parameters is shown in the figure.

Conclusions: The high convection volumes could be achieved by increasing of BFR and treatment time and optimization of FF even if high BFR was not obtained. High-volume postdilution HDF is possible in routine clinical practice even for patients with low BFR less than 300 mL/min.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO461
Impact of Hemodiafiltration on Serum Interferon Levels in Patients with CKD: Results from the HDFIT Study
Ana clara S. Almeida,1 Luiz F. Franco de Lima,1 Murilo H. Guedes,1 Caroline Silva,1 Ana Beatriz L. Barra,2 Maria Eugenia F. Canziani,3 Americo L. Cuvello neto,4 Carlos E. Poli de Figueiredo,5 Giovani Gadonski,5 Roberto Pecois-Filho,5 Andrea N. Moreno-Amaral,1 Pontificia Universidade Católica do Rio Grande do Sul, Brazil; 2Fresenius Medical Care, Rio de Janeiro, Brazil; 3Federal University of Sao Paulo, Sao Paulo, Brazil; 4Hospital Alemão Oswaldo Cruz, Sao Paulo, Brazil; 5Arbor Research Collaborative for Health, Ann Arbor, MI; 6Pontificia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil.

Background: Interferons are cytokines that play an important role in immunomodulatory processes. Hemodiafiltration (HDF) optimizes the removal of medium-sized molecules, and although HDF has been associated with a reduction in pro-inflammatory biomarkers, its effect on serum interferon levels have not been described until the present.

Methods: HDFIT was a multicenter randomized controlled trial comparing HDF to high flux hemodialysis, in which biosamples were collected at baseline and after 6 months (HD n=67; HDF n=63). Cytokines measurement was performed through Milliplex® Human Cytokine Magnetic Bead Panel (IFN-γ and IFN-α2) (EMD Milipore Corporation, USA).

Results: There was no significant difference in patients demographic characteristics between groups regarding age (53 years old in HD vs 53 ± 16 in HDF), gender (68% male in HD vs 71% in HDF) and diabetes (44% in HD vs 28% in HDF). The mean difference (95% confidence interval) between HDF and HD in 6 months was 0.18 (-0.16 — 0.53) vs 0.07 ± 1.08 vs 1.11 ± 1.08) and their maintenance on HDF group (IFN-α2 0.78 ± 1.79 vs 0.78 ± 1.79 and IFN-γ 1.55 ± 1.12 vs 1.46 ± 1.12).

Conclusions: This study demonstrates that after 6 months of treatment, patients on HDF maintained the concentrations of circulating interferons (IFN-α2 and IFN-γ) compared to HD, which concentrations of IFN decreased over time. Based on the knowledge of IFN actions and functions, these findings suggest that HDF may have immunomodulatory effects that could be beneficial to patients with CKD.

FR-PO462
Flexitrate Regional Citrate Anticoagulation in Continuous Venovenous Hemodiafiltration
Ilan Lenger,2 Wilma M. Hopman,2 Adam J. O’Connell,1 Francesca Hume,1 Charles C. Wei,1 Lakеridge Health, Oshawa, ON, Canada; 2Faculty of Medicine, University of Toronto, Toronto, ON, Canada; 3Queen’s University, Kingston, AB, Canada.

Background: This study compared Flexitrate, an innovative regional citrate anticoagulation (RCA) protocol, to traditional RCA (tRCA) and Heparin anticoagulation protocols in intensive care patients treated with continuous renal replacement therapy (CRRT).

Methods: A single-center, retrospective, cohort study, was conducted in a 26-bed ICU in a large community hospital. Consecutive patients from a 6 month pilot of Flexitrate CRRT were compared to consecutive patients from the preceding 9 months receiving tRCA and Heparin CRRT anticoagulation. 80 dialysis sessions (Flexitrate = 2,852 hours, tRCA = 3,580 hours and Heparin = 2,026 hours), performed in 53 patients, were evaluated for filter life, RCA control, and metabolic control.

Results: Filter survival was significantly improved with Flexitrate compared to tRCA (HR 0.24, p = 0.018) and Heparin (HR 0.14, p = 0.004); see attached Figure. Anticoagulation control was superior with Flexitrate with Patient Ionized Calcium out of target a median of 16% of the time, compared to 27% for tRCA (p<0.001). Filter Ionized Calcium was also at target a median of 6.8% of the time, compared to 23% for tRCA (p = 0.03). Flexitrate produced significantly less alkalosis, hypernatremia, and hypocalcemia than tRCA, and was comparable to Heparin anticoagulation. The only adverse metabolic outcome with Flexitrate was more Hypomagnesemia.

Conclusions: The Flexitrate protocol extended filter life, delivered more consistent anticoagulation, and provided superior metabolic control compared to a tRCA protocol. Filter life was also superior to Heparin anticoagulation, with similar metabolic control. A randomized control trial comparing these protocols is recommended.

FR-PO463
Haemodialysis (HD) vs. Online Haemodiafiltration (HDF) and Mixed Haemodiafiltration (MHDf): What Place? Kunigal A. Shivakumar, Renal Medicine, Russells Hall Hospital, Dudley, United Kingdom.

Background: HD has been a gold standard of dialysis. High-efficiency on-line HDF is recognised as an advanced modality of treatment improving patient outcome. Yet post-dilution HDF has limitations like increased blood viscosity, protein concentration, high transmembrane pressure impairing uraemic solute removal. Pre-dilution method can partially overcome this but the price to pay is decreased overall efficiency. Joining both modalities can potentially improve conductive and convective solute removal and maintain patients haemodynamic stability.

Methods: Eighteen ESRD adults were established on HD for at least one year were chosen. They received 6 months conventional HD, followed by 6 months HDF (with 1.2 HDF factor), then 6 months MHDf. Fresenius 5008 machines were used with FXCorDiax/1000 dialysers and therapy monitoring system (TMON). A central delivery system supplied 3 types of fluid and ultrapure water direct to the machines. All patients had cardiovascular instability. Various parameters were measured monthly as per standard UK Renal Association guidelines. SF24 Quality of Life questionnaire was analysed by an independent observer.

Results: Results are summarised in the table with mean values. The increased urea reduction rate on HDF and MHDf over conventional HD was statistically significant, p=0.002 and 0.003 respectively. There was no difference between HDF and MHDf.

Similarly the difference in Kt/V between HD vs HDF and MHDf was significant, p<0.005 and 0.001 compared to HD and MHDf.

Differences in predialysis phosphate level between the 3 modalities was not statistically significant although the post-therapy phosphate value between HD v HDF and MHDf showed a p value of 0.003. The haemoglobin and PTH had no significant differences between modalities. We measured 2 microglobulin and proBNP in the MHDf group, the difference in 6 months was insignificant. HDF and MHDf patients had higher physical and mental component scores. 63 had cardiovascular instability. Various parameters were measured monthly as per standard UK Renal Association guidelines. SF24 Quality of Life questionnaire was analysed by an independent observer.

Conclusions: On-line HDF and MHDf are superior to conventional highflux dialysis, we could not observe additional benefit between HDF and MHDf. Perhaps using a higher HDF factor for dilution and substitution fluid is required to achieve better results.

Funding: Government Support - Non-U.S.
FR-PO464

Removal of Middle Molecules Using Medium Cut-Off Membranes in Hemodialysis Mode vs. High-Flux Membranes in Post-Dilutional Online Hemodiafiltration Mode: The REMOC Study

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Background: Medium-cut-off (MCO) dialyzers were shown to provide better clearance of larger middle molecules compared to high-flux HD and hemodiafiltration (HDF). Whether this results in lower predialysis levels in decreased exposure is not clear.

Methods: In this randomized, open-label, cross over study, 27 HD patients were randomized to either 12 weeks of HD with MCO dialyzers (Theranova 400, Baxter) or online post-dilution HD with high-flux dialyzers (FxCorDiax 800, Fresenius medical care) using maximally achievable substitution volumes. After 12 weeks, patients were crossed-over to the other treatment modality for 12 weeks. Pre-dialysis serum levels of middle molecules (κ- and κ-free light chains [FLC]) were assessed at the beginning and end of each treatment period. The primary outcome was efficiency as assessed by predialysis treatment levels of κ- and κ-FLC, as well as safety (serum albumin levels and frequency of adverse events). A mixed linear model based on the delta value was used to compare the effect of MCO-HD and HDF on FLC levels. Here, treatment modality and randomization order were assumed as fixed effects, the patient as random effect.

Results: Twenty-seven patients were randomized, six dropped out due to inability to receive randomized study treatment. Twenty-one patients completed the study and were included in the analysis (14 [66.7%] males; mean age 56.9±14.9 years; mean BMI 28.2±7.4; median dialysis vintage 16 [8–40] months). For κ- and κ-FLC, the delta to baseline after 12 weeks of MCO-HD compared to HDF (κ-: -8.8±5.2 vs. -8.0±1.0 mg/dL; κ-FLC: 4.2±2.4 vs. -4.2±2.6 mg/dL) was not significantly influenced by treatment modality or order (κ-FLC: p=0.29; κ-: p=0.37) but rather by the patient (κ-FLC: p=0.004; κ-: p=0.02). There was no difference in AE incidence or delta serum albumin levels (MCO-HD vs. HDF: 0.0±0.2 vs. 0.0±0.3 g/dL) between treatment modalities.

Conclusions: Twelve weeks of MCO-HD treatment compared to twelve weeks of HDF did not significantly change predialysis levels of κ- and κ-FLC in prevalent dialysis patients. This suggests that MCO-HD clears larger middle molecules as effectively as high-efficiency HDF, which may allow to extend the benefits of HDF to patients where this treatment modality is not available.

FR-PO465

In Vitro Cytokine Removal: Comparison of Conventional High-Flux Dialyzers and Middle-Cut-Off Dialyzer (Theranova HDx)

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Background: The removal of inflammatory mediators is important for the treatment of acute (ARF) or chronic renal failure (CRF). In ARF and sepsis, attempts is made to achieve removal through the use of high-volume treatments or adsorbers. In CRF, this seems to be possible in both areas. The effectiveness of HDx in the removal of interleukins (interleukin 6, interleukin 10 and TNFalpha) in hemodialysis treatments will be assessed.

Methods: The efficacy of HDx was compared to conventional high-flux dialyzers (Fresenius FX80). The measurements were performed in vitro in a 3 l pool of fresh frozen plasma (citrate and heparin anticoagulation). IL6 (24.5 kDa), IL10 (18.6 kDa, dimer) and TNFAlpha (17.4 kDa, trimer) were added to plasma (1.5 g/gl each). Samples were taken before and after the dialyzer (after 5, 15, 30, 60, 120 and 180 minutes. In addition to cytokines, albumin and total serum protein concentrations were measured (LEGENMAX Human IL-6/L-10TNF-α; Cobas Mira Plus; Roche LT-AB0103, LT-TP253).

Every test was repeated 5 times.

Results: Theranova HDx showed significantly higher removal rates of all tested cytokines over a period of 180 minutes. A comparison of the concentrations at the beginning and end of the measurements showed: IL-6 reduction - HDx about 80% / FX80 about 40%, IL-10 reduction - HDx about 50% and FX80 about 10%. TNF-α reduction - HDx about 25%; FX80 no reduction The concentration of albumin and total serum protein has so far not been sufficiently addressed, but is important for mortality (MIA syndrome). The removal of inflammatory mediators is important for the treatment of acute (ARF) or chronic renal failure (CRF). In ARF and sepsis, attempts is made to achieve removal through the use of high-volume treatments or adsorbers. In CRF, this seems to be possible in both areas. The effectiveness of HDx in the removal of interleukins (interleukin 6, interleukin 10 and TNFalpha in hemodialysis treatments will be assessed.

Conclusions: The removal of inflammatory mediators is important for the treatment of acute (ARF) or chronic renal failure (CRF). In ARF and sepsis, attempts is made to achieve removal through the use of high-volume treatments or adsorbers. In CRF, this seems to be possible in both areas. The effectiveness of HDx in the removal of interleukins (interleukin 6, interleukin 10 and TNFalpha in hemodialysis treatments will be assessed.

FR-PO466

Easy, Simple, and Effective Pressure Control by Pinch Valve in CRRT Directly Connected to Extracorporeal Membrane Oxygenation

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Background: The simultaneous use of continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) is increasing in the patients with AKI coexisting with respiratory or circulatory failure in ICU. However, there are no recommended techniques to combine them. Pinch valve is suitable for handling flow capacity by throttling line without corrosion or contamination. Therefore, we investigated whether the external use of pinch valve on the blood lines of CRRT connected to ECMO is helpful to maintain the pressures of CRRT lines in the acceptable pressure range without modifying ECMO settings or inhibiting pressure alarms of CRRT.

Methods: We conducted a prospective observational study in 14 patients (M:F=8:6, age median 50.5 (range 21–75) years, SOFA score 12 (4–16)) requiring CRRT (blood flow rate 150 ml/min) and ECMO (veno-arterial:veno-venous=12:2, FIO, 60 (40–100) %, cardiac support 90 (70–125) % of normal cardiac index, blood flow rate 3.8 (2.9–5.0) L/min, sweep gas flow 3.0 (1.0–5.0) L/min) between Aug and Oct 2018. The connections of CRRT to ECMO were performed 41 times. Inflow CRRT line is connected after the oxygenator and the outflow CRRT line, before the blood pump in the ECMO circuit. Pinch valve was externally used on inflow and outflow lines of CRRT.

Results: The initial blood flow rate of CRRT was 150 ml/min. Any reduction of blood flow rate in CRRT on ECMO was not necessary. Before the application of pinch valve, the pressures of CRRT were too high or too low to maintain CRRT directly connected to ECMO circuit. However, after the application of pinch valve, the pressures of CRRT were tolerable and significantly different (p=0.05, *p<0.001) from those before the use of pinch valve. CRRT alarms disappeared owing to pinch valve. The changes of CRRT pressures were summarized in Table (Means±SEM). The median life span of CRRT filter was 63 (range 10–72) hours.

Conclusions: Management of line pressures in CRRT connected to ECMO could be easy, simple and effective by the external application of pinch valve without inhibiting CRRT alarms.

FR-PO467

Outside-In Filtration Technology for Prolonged Filter Life

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Background: Maintaining circuit patency is a prerequisite for optimal treatment efficacy and is essential for continuous renal therapies. In currently marketed dialyzers, blood flows in the intra-luminal (IL) space where formation of thrombi inside the fibers leads to filter blockage. This effect limits set life in continuous renal therapies. In currently marketed dialyzers, blood flows in the intra-luminal (IL) space where formation of thrombi inside the fibers leads to filter blockage. This effect limits set life in continuous renal therapies. In currently marketed dialyzers, blood flows in the intra-luminal (IL) space where formation of thrombi inside the fibers leads to filter blockage. This effect limits set life in continuous renal therapies. In currently marketed dialyzers, blood flows in the intra-luminal (IL) space where formation of thrombi inside the fibers leads to filter blockage. This effect limits set life in continuous renal therapies.

Methods: In a simulated extracorporeal circuit we measured pressure drop and filter life using both bovine and donated human blood. Clearance of small and middle solutes were measured in the Outside-In (OI) hemodialyzers using standard methods. Clotting of different zones of the filter was made by depositing the filter and estimating the number of clots in each zone.

Results: In vitro data using a conventional dialyzer in an OI configuration (blood outside-in) reveals significantly lower membrane clogging and extended filter life. OI increases filter life to over 100 h vs ~24 h with standard filter flow with statistically
equivalent clearance[i]. These advantages are due to new hydrodynamics where blood flows in 3-D interconnected flow channels created in the IF space. When a urea-based hemodialyzer is used in the OI configuration, we discovered that stagnant zones are created within the filter. Such zones can be eliminated with a modified filter housing that maintains an optimal blood shear rate and uniform velocity distribution. NovaFlux is developing progressive changes to overcome such limitations. [i] Dulkin SS, Labhe ME, et al. OI HF for prolonged operation. Jour Mem Sci, 464 (2014) 173–178.

Conclusions: Two key refinements are required for completing commercial OI dialyzers, namely: modified membrane and housing design. Current membranes are characterized by an asymmetric membrane structure with a smooth inner lumenal skin (active membrane layer). This membrane structure is reversed for OI so that the blood contacts a smooth active membrane layer on the outer surface of the fiber. We have made progress in developing a hemocompatible OI PES hollow fiber with an outer active hydrophilic membrane layer. OI dialyzers with these modifications should be able to be produced by new production equipment with relatively minor modifications, enabling longer set life and lower anticoagulation.

FR-PO468
Study of Dilution Modes Under Different Operational Conditions in Continuous Venovenous Hemofiltration
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Background: The landmark CRRT dose trial (Rono et al, Lancet 2000) was performed in the post-dilution CVVH mode. The clinical benefits provided by different CRRT modes may influence MM clearance. The purpose of this experimental CVVH study was to measure the clearance of small solutes (urea, creatinine) and MM surrogates (vancomycin, inulin) in different dilution modes, degree of pre-dilution, and flow conditions along with MM sieving coefficient (SC) values over extended periods.

Methods: The Prismaflex (Baxter) machine was used to deliver replacement fluid at a flow rate of 200 mL/min with five different pre-dilution points (pre-pump blood dilution (PPB), pre-dilution (PRE) and post-dilution (POST)). Simulated treatment involved 6 liters of bovine blood (Hct ~ 35%) processed at zero net ultrafiltration for a duration of 240 minutes. A 1.4 m2 hemofilter (HF 1400) was used. The three experimental conditions were: 1) blood flow rate (Qb): 190 mL/min; replacement flow rate (QR): 2 L/hr; 2) Qb: 290 mL/min; QR: 3 L/hr; 3) Qb: 380 mL/min; QR: 4 L/hr. These conditions were chosen to maintain filtration less than 25% in POST. Solute clearance at various times were calculated based on mass balance.

Results: There were significant differences (p < 0.001) in urea & creatinine clearance for the different experimental conditions. There was a significant decrease (p < 0.01) in urea and vancomycin clearance from POST to PRE and from POST to PPB, although there were no significant differences between PRE and PPB for any of the solutes. Neither urea nor creatinine clearance changed significantly over time for any of the operational conditions and dilution modes. There were significant differences (p < 0.001) in inulin and vancomycin clearance in these 3 experimental conditions. No significant differences (p > 0.05) in urea clearance between post-dilution and predilution mode, post-dilution and pre-pump-dilution mode, and pre-dilution and pre-pump-dilution mode were observed. A significant decrease in urea and vancomycin SC occurred over time under all conditions was most evident in POST.

Conclusions: 1) Small MW solute clearance increased as the extent of pre-dilution decreased 2) MM SC decreased substantially (especially in POST) with time, most likely due to increased dilution rate of the patient. 3) The data obtained from varying pre-dilution percentages are predictable for small solutes but are not entirely consistent for MMs.

FR-PO469
Urea Transfer Kinetics in Allo-Hemodialysis: Results from an Ex Vivo Study
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Background: Allo-hemodialysis (alloHD) is a novel, low-cost extracorporeal dialysis modality where the conventional dialysate is replaced by blood from a healthy subject (“buddy”). We are not aware of literature reporting urea transfer across allohemodialysis membranes with counter-current blood flow through the conventional dialysate and dialysate compartments.

Methods: We developed a mathematical model of alloHD setup comprising the patient and the buddy beaker, the extracorporeal circuit, and the dialyzer. To calibrate the model, we conducted an ex vivo alloHD experiment with human whole blood. We dialedyzed a 500-mL patient bucket against a 500-mL buddy bucket for 60 minutes. Heparin (5,000 U/L) was used as anticoagulant. Average blood flow rate of 110 mL/min on both sides was achieved by peristaltic pumps. The patient side was spiked with urea to simulate post-dialysis conditions. Blood samples from both sides were collected at multiple time points into the experiment. Serum urea was measured using automated spectrophotometry.

Results: The urea concentrations on the patient and buddy sides equilibrated rapidly (Figure 1). The estimated urea mass transfer coefficient (K_a) was 853 mL/min. Using this estimated K_a, the model-based urea concentrations predicted the observed concentration profiles very well.

Conclusions: The estimated K_a of 853 mL/min is similar to a typical urea in vivo K_a reported for conventional hemodialysis (~1000 mL/min). The presence of blood on both sides of the channel did not appear to affect the urea mass transfer capacity of the dialyzer in a clinically meaningful way, and rapid urea equilibrium was achieved in this ex vivo alloHD setup. These findings are an important step towards validation of the alloHD concept and planning of future animal experiments.

FR-PO471
Ten Thousand Consecutive Treatments Using the Tablo Hemodialysis System in Hospitals and Clinics
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Background: The Tablo® Hemodialysis System is an all-in-one system indicated for use in clinic and hospital settings. Features include an integrated water purification system, the ability to produce dialysate on demand, a simplified user interface, and two-way wireless connectivity for data transfer. This study reports on the clinical experience using Tablo for 10,000 treatments (txs) in the clinic and hospital settings.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Reuse of Dialysis Reverse Osmosis System Reject Water for Aquaponics and Hydroponics
Fason Chang, Chun Ieong Low, Nephrology Unit, Hospital Sultan Abdul Halim, Sungai Petani, Malaysia.

Background: Hospital Sultan Abdul Halim hemodialysis unit located in the district of Sungai Petani in Kedah, Malaysia has started operation since 1998. The dialysis unit has 19 hemodialysis machines and is located in 2 separate buildings with ratings for about 90 patients. Hemodialysis is provided by single-pass, proportioning dialysis systems paired with reverse osmosis (RO) system water filtration that rejects 60–70% of the presented mains at the RO system membrane. This reject water is discarded to drain almost universally.

Methods: In our unit, the reject water is used for aquaponics and hydroculture since July 2018. The reject water from one of the buildings has been repiped and the reject water is then pumped into fish tanks. The amount of reject water is estimated to be between 1000 – 12000 litres per day. The state fisheries department collaborated with us by providing us with the necessary capacity tanks and equipment. Three 700 litres capacity tanks and one 1000 litres capacity tank were used. The fisheries department performed water testing to determine the suitability of the water for aquaculture. The test revealed water temperature of 31 degrees Celsius (25-35), pH of 7.76 (6.5-8.5), ammonia level of 0.001 (<0.02 ppm mg/l) and dissolved oxygen level of 5.84 (>4 ppm). The species of fishes that were bred is Oxyeleotris marmorata (Marble Goby). The fries released were initially 2-3 inches long and weighed about 20-30 grams in average. After a period of 5 months, the fishes grow. The fishes that were grown included Amaranthus dubius (red spinach), Sissoo (brazillian spinach), Brassica juncea (mustard), Mentha (mint) and Allium schoenoprasum (chives). These vegetables were harvested and given to patients for consumption. It also provides a good biosecurity environment for the fishes to grow.

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Conclusions: Rejection of waste that is actually clean and uncontaminated water can be reused to promote water conservation and used for aquaculture and hydroponic activities with encouraging results. It also provides a good biosecurity environment for the fishes to grow.

FR-PO472

Reuse of Dialysis Reverse Osmosis System Reject Water for Aquaponics and Hydroponics
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FR-PO474

Clinical Study to Assess the Performance of a Novel Dialyzer with Endexo™ in ESRD Subjects
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Background: Surface modifying macromolecules (SMM) may improve the hemocompatibility of hemodialyzers in the development of heparin free hemodialysis (HD). The aim of this clinical trial was to assess the performance and safety of a new dialyzer using a novel fluorinated SMM additive (Endexo™) in ESRD Subjects.

Methods: This prospective, sequential, multi-center, open-label study (NCT# 03536663) was designed according to the FDA's Guidance for the premarket testing of hemodialyzers. Adult subjects, prescribed thrice-weekly HD for at least 180 days, were enrolled in 1087 clinics in the US. After completing 12 HD sessions (4 weeks) with an Optiflux® F160NR dialyzer using a novel fluorinated SMM additive (Endexo™) in ESRD Subjects.

Results: A total of 23 subjects (60.5±15.1 yr., BW 70.9±17.4 kg, 17 males) were enrolled and 17 subjects completed the study, 6 subjects were withdrawn due to missed visits not related to the dialyzers. Mean treatment times (208 vs. 207 min), blood flow rates (447.7 vs. 447.5 ml/min), dialysate flow rates (698.5 vs. 697 ml/min), URR (80% ± 0.43 vs. 1.90±0.31) were comparable for EndX and Opti, respectively. There was no evidence of overt complement activation as C5a and C3a levels remained unchanged from pre-HD, and a slight trend for increase in sC5b-9 levels at 30 minutes postdialysis. Complement activation results were comparable for Opti and EndX, and hemoglobin and platelet count for EndX only.

Conclusions: The novel hybrid conductivity-UKM based method of monitoring hemodialysis adequacy is non-inferior to the standard approach. It has the potential to avoid Kt/V errors related to improper periodic BUN sampling.
and spKt/V. The β2-microglobulin removal efficiency was 67% higher with the dializer with MCO.

Funding: Commercial Support - Fresenius Medical Care North America, Renal Therapies Group, Waltham, MA, United States.

FR-PO475

High-Volume Predilution Online Hemofiltration (HVPO-HDF) Is the Ideal Blood Purification Method from an Amino Acid Nutritional View

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Background: Elderly ESRD patients with sarcopenia and frailty have been recently increased in Japan. It was reported the amino acid losses were up to 6 to 12 g per HD session (Kidney Int. 1994;46: 830-7). It seems to be important to restrain these amino acid losses during dialysis session from the point of nutritional view. We analyzed the amino acid losses that occur on performing high volume pre-dilution on-line HDF (HVPO-HDF) and HD.

Methods: We compared the amino acid and albumin amount into the total waste fluid, reduction rate of β2-microglobulin (β2-MG), and Kt/V (urea) in same 9 patients (7 males, 4 diabetics, mean age: 71.4±2.5 years) when they received HVPO-HDF and HD. The treatment time is 4 hours, respectively. The mean blood flow rate was 200 mL/min, respectively. The dialysate flow rate was 200 and 500 mL/min, respectively. The replacement fluid flow rate was 400 mL/min and total replacement fluid volume was 90 L. The UF rate in HVPO-HDF and HD was 58±739 (7 males, 4 diabetics, mean age: 71.4±2.5 years) when they received HVPO-HDF and HD.

Results: In HVPO-HDF group, the total amino acid, total non-essential, essential, branched-chain amino acid losses (4511±779 mg, 2982±772 mg, 1619±236 mg, 739±167 mg, respectively) were significantly lower than in the HD group (6399±1072mg, 4008±772mg, 2301±414mg, 1058±263mg, respectively) (** p < 0.05). The albumin losses of both methods were almost same and extremely low (HVPO-HDF: 0.15±0.0 g, HD: 0.12±0.0). In the HVPO-HDF group, the β2-MG reduction rate (69±8.5%, ** p > 0.05) was higher than in the HD group (65±3.5%, **) (p > 0.05). The Kt/V(urea) values in the former and the latter were 1.33±0.17 and 1.45±0.23, respectively. The HVPO-HDF can restrain the amino acid loss more effectively than HD. Both of hemodiafilter and dialyzer which were designed to suppress albumin leakage as possible during dialysis session.

Conclusions: In the O-HDF group, the total amino acid, total non-essential, essential, branched-chain amino acid losses (4511±779 mg, 2982±772 mg, 1619±236 mg, 739±167 mg, respectively) were significantly lower than in the HD group (6399±1072mg, 4008±772mg, 2301±414mg, 1058±263mg, respectively) (** p < 0.05). The albumin losses of both methods were almost same and extremely low (HVPO-HDF: 0.15±0.0 g, HD: 0.12±0.0). In the HVPO-HDF group, the β2-MG reduction rate (69±8.5%, ** p > 0.05) was higher than in the HD group (65±3.5%, **) (p > 0.05). The Kt/V(urea) values in the former and the latter were 1.33±0.17 and 1.45±0.23, respectively. The HVPO-HDF can restrain the amino acid loss more effectively than HD. Both of hemodiafilter and dialyzer which were used in this study showed extremely low albumin leakage. In the HVPO-HDF group, the β2-MG reduction rate was higher than in the HD group. The Kt/V(urea) of HVPO-HDF was within favorable range (~1.2).

Conclusions: This method is most powerful method to restrain amino acid and albumin losses in order to keep nutritional condition to avoid sarcopenia and frailty in elderly ESRD patients.

FR-PO476

Variability Between Prescribed and Measured Dialysate Sodium in the Acute Care Hemodialysis: Effects of Additives and Other Electrolytes


Background: Significant variability in ordered versus measured dialysate Na+ has been noted in the outpatient HD setting. We examined this variability in a large hospital acute care hemodialysis program.

Methods: Dialysate electrolyte panels (DEP) were examined with point of care testing. DEP labs included Na+, K+, HCO3, PO4, and Mg, Ordered versus measured values for each electrolyte were analyzed by linear mixed model that included the particular HD machine for random effect. Logistic regression modeling was used to determine factors associated with significant variance between ordered and measured values.

Results: 5415 DEP results identified. Significant differences noted between ordered and measured Na+, HCO3 and Mg, but not K+ (Table 1). We focused on Na+; 94% of HD’s had differences of ± 5 mEq/L between ordered and measured dialysate Na+ levels. Bland-Altman plot showed skew towards a lower delivered versus ordered dialysate Na+ concentration. In 694 HD treatments, dialysate Na was manually corrected based on the measured Na+ level. The measured Na was on average 1.75 mEq/L and 2 mEq/L when performed, corrected this difference 86% of instances when rechecked on the same HD. Additives to the dialysate solution and ordered dialysate Na > or < 140 were associated with out of range measured Na+.

Funding: Clinical Revenue Support

FR-PO477

A 1-Year Study on the Effects of Hemodialysis Using Dialyzer with Medium Cut-Off Membrane


Background: Medium cut-off (MCO) membrane is a dialyzer with enhanced sieving properties and solutes. An internal filtration of MCO membrane facilitated filtration of large middle molecules, and enhanced filtration of small molecules without replacement fluid. A long-term study for several markers after use of MCO membrane is few. We evaluated the various effects related with MCO membrane for 1 year in patients with ESRD.

Methods: Total 40 patients were analyzed for 1 year. The enrolled patients were > 18 years old and were on hemodialysis (HD) using high flux (HF) membrane for ≥3 months before enrolment. We prospectively collected serum samples with 3-month interval for 1 year. All patients were divided into control (HF, n=20) and MCO (MCO, n=20) group. The patients with serum albumin of > 3.5 g.dL⁻¹ and clinical signs, such as uncontrolled hyperparathyroidism or hyperphosphatemia, were included in MCO group. We measured and calculated serum markers, including parathyroid hormone (PTH), C-reactive protein (CRP), phosphate, hemoglobin (Hb), total protein, albumin, and spKt/V with 3-month interval.

Results: Compared to control group, patients in MCO group were younger and showed higher values of serum albumin and phosphate. In MCO group, serum protein and albumin decreased significantly over time (p<0.05), but serum albumin compared with serum protein did not decrease significantly since 6 months (p=0.056). Serum albumin increased significantly after 6 months in MCO group (p=0.012). The spKt/V increased until 6 months, but it did not increase significantly since 6 months in MCO group (p=0.072). Several markers such as serum phosphate, calcium, CRP and Hb except for PTH did not show significant changes in both groups. Unexpectedly, PTH increased significantly in both groups. In analysis of differences between two groups over time, there was a significant difference only in change of serum phosphate (p<0.030).

Conclusions: Baseline levels of serum phosphate and albumin were high in MCO group due to selection bias. Medium cut-off dialyzer showed a reduction in albumin loss in MCO group was not significant after 6 months, and the spKt/V value in MCO group increased until at least 6 months. Moreover, we could recognize the possibility for hyperphosphatemia reduction in MCO group. Thus, HD using MCO membrane may be superior in clearance of small solutes and be not inferior in albumin loss for 1 year.

FR-PO478

Clinical and Operational Results of In-Center Nocturnal Hemodialysis (INHD) Programs in a Large Dialysis Organization (LDO)

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Background: INHD offers a combination of efficacy, safety, and improved treatment tolerability. Recognizing the specific clinical and laboratory results that indicate INHD might be beneficial for a given patient requires an understanding of modality-specific therapeutic differences. Here, we report the operational characteristics and clinical laboratory results of INHD programs in an LDO.

Methods: All patients admitted to LDO INHD programs during 2017 and 2018 were included in the analysis. Patient demographic information, dialysis prescription data, laboratory markers, blood pressure, target weight, and hospitalization rates were assessed and compared to those for in-center hemodialysis (ICHD) patients treated at the LDO during the same period.

Results: Data from 2747 patients treated in 176 INHD programs were assessed. Across the LDO, 19 INHD programs started operation during 2018, 24 closed; the most common closure reasons were transition of patients to the working shift (82%) and staffing constraints (9%). Mean INHD program census was <10 patients, mean operating time was 8.9 hours/shift, and staff retention rate was 85%. Mean age of INHD patients was 562.
52 years; 29.5% were female; access use was 68.9% AVF, 15.1% AVG, 10.6% CVC, and 5.4% other. Laboratory and clinical parameters for INHD vs ICHD patients are shown.

**Conclusions:** INHD was associated with improved solute clearance, lower ultrafiltration (UF) rates, improved nutritional parameters, and lower hospitalization rates compared to ICHD. Patients receiving standard ICHD who are not achieving risk factor control, are experiencing increased organ stunning risk with elevated UF rates, or with hemodynamic instability should be considered for transition to INHD.

**Funding:** Commercial Support - DaVita Inc

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FR-PO479

Controlling High Pre-Dialysis Serum Total Carbon Dioxide Concentration with Low Dialysate Flow Rates During Frequent Nocturnal Hemodialysis

Lee Levpold, Michael A. Kraus, Allan J. Collins. Nalecz Institute of Biotechnics and Biomedical Engineering Polish Academy of Sciences, Warsaw, Poland; NixStage Medical, Inc, Fishers, IN; NixStage Medical, Inc., Lawrence, MA.

**Background:** Although use of low dialysate bicarbonate concentration ([bicarbonate]) during in-center, thrice weekly in-center hemodialysis (ICHD) is a common strategy to control high serum predialysis serum total carbon dioxide concentration ([TCA2]), such an approach is not always possible with commercial lactate dialysates. We used clinical data in patients who transferred from ICHD using bicarbonate dialysate to 6 times per week hemodialysis during the FREEDOM Study and the H+ mobilization model (Sargent et al, Semin Dial 31:468-78, 2018) to calculate the effect of using 30 L versus 60 L of dialysate volume per treatment to reduce [TCA2] during frequent nocturnal hemodialysis (NHD).

**Methods:** The H+ mobilization model was first used to simulate ICHD treatments using dialysate [bicarbonate] of 34, 37 & 40 mEq/L at [TCA2] of 22, 24 & 26 mEq/L to calculate a weekly acid generation rate. Assuming a constant weekly acid generation rate, patients were assumed transferred to NHD with treatment (Tx) frequencies of 3.5 (every other day), 4 & 5 times per week and dialysate volumes per Tx of 30 & 60 L. Blood flow rate was assumed as 300 mL/min, Tx time of 420 min, and dialysate [lactate] was 40 mEq/L during NHD.

**Results:** Summary results are tabulated. Lowering dialysate volume per Tx from 60 to 30 L resulted in lower [TCA2] by approximately 2-3 mEq/L.

**Conclusions:** Patients who may achieve excessively high [TCA2] during NHD using lactate as dialysate buffer can use of 30 L instead of 60 L treatment to reduce [TCA2]. Such reductions in dialysate volume during NHD are not expected to substantially lower dialysis adequacy.

**Funding:** Commercial Support - NixStage Medical Inc. (Fresenius Medical Care)

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FR-PO480

Plasma Viscosity Can Explain the Marked Reduction in Dialyzer Mass Transfer Area Coefficient for Urea and Other Solutes In Vivo Compared with In Vitro Values

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**Background:** The dialyzer area membrane transfer coefficient product (K,A) characterizes the diffusive performance of a dialyzer and is one of the key components to prescribe a dialysis dose. However, in-vivo dialyzer K,A for urea is always much smaller and only 50 to 60% of in-vitro K,A tabulated in dialyzer manufacturer sheets and typically obtained from clearance measurements using crystalloid water solutions. The reason for this reduction has not been clearly determined. We hypothesized that the known effect of viscosity on solute diffusivity might partially or fully account for this reduction.

**Methods:** In-vivo dialyzer clearance of urea and glucose was measured in low- and high-flux dialyzers under different operating conditions using crystalloid solutions as well as bovine blood with different hematocrit and plasma viscosity. Viscosity of plasma, blood, and aqueous solutions was measured at 37°C. Diffusivity and relative K,A values were computed for each solute under these different conditions.

**Results:** Relative K,A was negatively correlated to relative plasma viscosity (p=0.001, r=-0.38) and solute diffusivity (p<0.001, r=-0.48) for urea and glucose (Fig. 1). Plasma was 1.84±0.31 times more viscous compared to crystalloid test solutions with a viscosity of 0.72 mPa.s, suggesting a correction multiplier of 0.54 (=1/1.84) for in-vivo solute diffusivity and K,A relative to the in-vitro value. The average multiplier based on individual measurements was 0.67±0.09.

**Conclusions:** The known effect of viscosity on solute diffusivity is sufficient to explain the reduction of dialyzer K,A for urea and glucose in-vivo compared to in-vitro measurements. The residual scatter in the K,A to viscosity relationship suggest that additional mechanisms may be operative.

**Funding:** Government Support - Non-U.S.
The Proteome of Hemodialysis Membranes: A Discovery Proteomic Pilot Study
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Background: Hemodialysis (HD) membranes have been continuously upgraded during the past decades. Nevertheless, little is known about the real pattern of protein removal among different HD membranes. We aimed to explore the proteome of depuration from a mid-cut-off HD membrane (Theranova, Baxter, IL, USA) and from a high flux membrane in HD and hemodiafiltration (HDF) (FX1000, Fresenius Medical Care, Bad Homburg, Germany).

Methods: 9 HD patients were separated in 3 groups: Theranova, FX1000 in HD and FX1000 in HDF. During their mid-week session, 1 liter of dialysate was sampled and 30 ml were freeze-dried. Additionally, the dialysis membrane was eluted and both dialysate and eluate were prepared for LC/MS-MS analysis (liquid chromatography coupled with a tandem mass-spectrometer). Samples were analyzed using an nano-RSLC (high performance liquid chromatographer, Thermo Fisher, Waltham, MA, USA) coupled on line with a Q-Orbitrap mass spectrometer. Data were processed by database searching using SequestHT with Proteome Discoverer 2.2 software against a human Swissprot database and quantified with a TMT-labeling approach. Semi-quantitative analysis was expressed as a ratio. Proteins were analysed using STRING tool for reactome pathway analysis.

Results: 526 proteins were found in the dialysate samples from all the membranes and 360 onto dialysis membranes. 455 proteins were found in the dialysate from FX1000 HDF group, 437 for Theranova and 410 for FX1000 HD. 360 proteins were also found adsorbed onto the membranes. For Theranova, 45 proteins were found significantly more depurated by diffusion and/or convection than adsorption and 101 more by adsorption than diffusion/convection. For FX1000 HD, 56 and 100. For FX1000 HDF, 61 and 56 respectively. With Reactome pathway analysis, numerous removed proteins were involved in innate immune system, hemostasis, extra-cellular matrix organization, platelet aggregation, lipid metabolism and molecular signaling pathways.

Conclusions: More than 500 proteins were identified in the proteome of depuration from HD and HDF membranes among which a significant number are specific from each membrane and modalities. Further analysis are required to understand the issues of the depuration of these proteins in improving HD patients outcomes.

Funding: Commercial Support - Baxter S.A.

Ex Vivo Validation of Allo-Hemodialysis for Removal of Creatinine and Protein-Bound Uremic Toxins
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Background: Unlike conventional hemodialysis, allo-hemodialysis (alloHD) has a patient dialyzed against a healthy subject (“buddy”). This ex vivo study aimed to explore the feasibility of removing creatinine and protein-bound uremic toxins (PBUTs) with alloHD, where whole blood constitutes the “dialysate”.-1/3

Methods: Two buckets of whole blood (anticoagulated with 5,000 U/L heparin) were designated as “patient” and “buddy” and dialyzed against each other for 2 hours with initial flow rates of 110 mL/min for both circuits using a high-flux cellulose triacetate dialyzer (Nipro Cellentia 17H, surface area 1.7 m²) and targeting zero net ultrafiltration. The “patient” bucket was initially spiked with creatinine, indoxyl sulfate (IS), and p-cresyl sulfate (pCS) to establish a diffusion gradient between patient and buddy. This was followed by a 2nd spike 1 hour into the experiment. After each spike, blood samples from both sides were collected after each spike every 5 min for 30 min, then every 10 min for the next 30 min. IS and pCS were measured via liquid chromatography–mass spectrometry after liquid-liquid extraction, while creatinine was determined via spectrophotometry.

Results: Solute concentration differences between “buddy” and “patient” dissipated rapidly (Figure 1). As expected, creatinine concentrations equilibrated faster (within about 5 min), while PBUT concentrations equilibrated more slowly (within 15 to 25 minutes), presumably due to their high degree of protein binding. No blood clots were present even after 2 hours of ex vivo recirculation.

Conclusions: This bench experiment demonstrates the ability of alloHD to not only remove water-soluble unbound solutes but also PBUTs. These findings support alloHD’s viability as a potential alternative to conventional hemodialysis.

Funding: Commercial Support - Fresenius Medical
**FR-PO484**

**Dialysate Citrate and Mortality in the Dialysis Outcomes and Practice Patterns Study**

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**Background:** Metabolic acidosis is a common threat for hemodialysis patients, managed by alkaline dialysis baths. The main base is bicarbonate, to which small amounts of acetate or citrate may be added. These additives are metabolized to bicarbonate, mostly by the liver. In view of uncertainties about benefits and potential harms associated with citrate-containing dialysate we assess here whether citrate dialysate is associated with mortality in the international Dialysis Outcomes and Practice Patterns Study (DOPPS).

**Methods:** Detailed patient-based information on dialysate composition was collected in DOPPS phases 5 and 6 (2012 to 2017). Cox regression was used to model the association between dialysate containing bicarbonate with versus without citrate and mortality among DOPPS country/phases with at least 15 patients using citrate containing dialysate.

**Results:** Citrate-containing dialysate use was most common in Japan, Italy, and Belgium (25, 23, 21% of DOPPS phase 6 patients) and used in < 10% of patients in other countries. Among 10,618 patients in DOPPS country/phases with at least 15 patients using citrate-containing dialysate, patient demographics, comorbidities, and labs were similar among patients using (14%) vs. not using (86%) dialysate citrate. After accounting for case mix, we did not observe an association between citrate containing dialysate use (any vs. none) and mortality. HR (95% CI) = 1.03 (0.85-1.23). Nor did we find evidence of a dose-dependent relationship when parameterizing dialysate citrate concentrations as 1, 2, and 3+ mEq/L.

**Conclusions:** The use of this emergent practice of citrate-containing dialysate was not associated with the risk of all-cause mortality in hemodialysis patients participating in the DOPPS. Clinical indications for the use citrate dialysate deserve further investigation in future studies.

**Funding:** NIDDK Support, Commercial Support - The DOPPS Program support and additional support for specific projects and countries can be found here: https://www.dopps.org/AboutUs/Support.aspx, Private Foundation Support, Government Support - Non-U.S.

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**FR-PO485**

**Hemodialysis with Citrate Dialysate Does Not Harm Patients: Results from an European NephroCare Cohort**

Charles Chazot,1 Luca Neri,1 Francesco Belloccchio,1 Guillaume Jean,2 Tomas Jirka,3 Fatih Kircelli,3 Martial Levannier,1 David Attal,2 Carlo Barbieri,2 Stefano Stuard,2 Bernard J. Canaud,3 1NephroCare France, Fresnes, France; 2Fresenius Medical Care, Bad Homburg, Germany; 3Fresenius Medical Care Italia, Vaiano Cremasco, Italy; 4Fresenius, Fresnes, France; 5NephroCare Beziers, Beziers, France; 6FMC Deutschland GmbH, Bad Homburg, Germany.

**Background:** Chronic hemodialysis (HD) using citrate dialysate is prescribed for improving dialysis tolerance and reducing heparin needs. Recently the safety of citrate (Ci) has been challenged by a French retrospective study. We report a mortality analysis in incident HD patients treated in the NephroCare dialysis centers in France, Turkey and Czech Republic in which citrate concentrate were prescribed.

**Methods:** This a retrospective study including 10020 incident HD patients between 2014 and 2018. Data were extracted from the EuClID5 database. Patient survival was analyzed from three cohort studies designed to address different potential sources of biases. Patients were considered Ci+ if 70% of dialysis sessions were performed with Ci all along their lifetime (Study 1) or during the first 3 months of dialysis (Study 2). Study 3 included time-varying Ci exposure and time-varying PS score (monthly and 6-monthly averages) in a proportional hazard Cox regression to address variation in dialysate composition and patients’ characteristics.

**Results:** Among 10020 enrolled patients, 435 were classified as Ci+. These patients were older with more severe comorbidities. In Study 1, the mortality was higher in Ci+ patients (p<0.0001). After propensity score matching (PSM; 345 patients Ci+ and Ci-) mortality remained strictly superimposable (Figure 1). In Study 2, no difference in survival was found before or after PSM. The monthly exposure analysis (Study 3), including 3671 patients with 835 deaths, clearly showed that the risk of mortality was related to the propensity score reflecting more severe condition (HR:5.06 (2.05-12.51)) but not with the Ci (HR:0.83 (0.67-1.03)).

**Conclusions:** In the European NephroCare experience, no significant impact on survival was found in chronic HD patients under Ci+ dialysate as compared to standard dialysate treated patients.
Impact of Dialysate Calcium Concentration on Clinical Outcomes in Incident Hemodialysis Patients

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Background: The association between dialysate calcium (DCa) concentration and mortality in hemodialysis (HD) patients is controversial. In this study, we evaluated the impact of DCa concentration on mortality in incident HD patient.

Methods: Incident HD patients were selected from the Clinical Research Center registry—a prospective cohort study on dialysis patients in Korea. Patients were categorized into 3 groups according to the prescribed DCa concentration at the time of enrollment. High DCa was defined as a concentration of 3.5 mEq/L, mid-DCa as 3.0 mEq/L, and low DCa as 2.5 to 2.6 mEq/L. The primary outcome was all-cause mortality and secondary outcomes were cardiovascular or infection-related hospitalization.

Results: A total of 1182 patients with incident HD were included. The number of patients in each group was 182 (15.4%) in high DCa group, 701 (59.3%) in the mid-DCa group, and 299 (25.3%) in the low DCa group. The median follow-up period was 16 months. The high DCa group had a significantly higher risk of all-cause mortality compared with the mid-DCa group [hazard ratio (HR) 3.25, 95% confidence interval (CI) 1.54–6.89, P=0.002; and HR 2.77, 95% CI 1.29–5.94, P=0.009, respectively]. Of these 1182 patients, 163 patients from each group were matched by propensity scores. In the propensity score matched analysis, the high DCa group had a significantly higher risk of all-cause mortality compared with the mid-DCa group (HR 2.52, 95% CI 1.04–6.07, P=0.04) and the low DCa group (HR 4.25, 95% CI 1.64–11.03, P=0.003) after adjustment for clinical variables.

Conclusions: Our data showed that HD using a high DCa was a significant risk factor for all-cause mortality and cardiovascular or infection-related hospitalization in incident HD patients.

A High Magnesium Concentration in Citrate Dialysate Prevents Oxidative Stress and Damage in Human Monocytes

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Background: The use of dialysis fluids (DF) during haemodialysis has been associated with an increased oxidative stress and reduced serum levels of magnesium (Mg), contributing to inflammation and immune system disorders. Since it has been demonstrated the role of Mg in modulating immune function and reducing oxidative stress, in this study we have characterized whether higher Mg concentrations in DF could prevent from oxidative-inflammatory stress in immunocompetent cells.

Methods: The effect of citrate (CDF, 1 mmol/L) or acetate (ADF, 3 mmol/L) dialysates with 0.5 mmol/L Mg (routinely used) or with higher Mg concentrations (1, 1.25 and 2 mmol/L) were assessed in human monocyte culture (THP-1). The levels of reactive oxygen species (ROS), malondialdehyde (MDA) and reduced (GSH) and oxidized (GSSG) glutathione were quantified under basal and/or inflammatory conditions (stimulation with lipopolysaccharide, LPS, 1 µg/ml).

Results: In monocytes, 0.5 mmol/L Mg CDF produced lower basal ROS production in relation to ADF (p<0.05). Moreover, the increase of Mg in CDF resulted in a significant reduction of ROS production under basal and inflammatory conditions, which was extremely marked in 2 mmol/L Mg (p<0.001). These effects were not observed in ADF. Interestingly, in a dose-dependent manner, high doses of Mg in CDF reduced the oxidative stress observed in monocytes under basal conditions. In fact, 2 mmol/L Mg significantly decreased the levels of GSH, GSSG and MDA and the GSSG/GSH ratio in relation with 0.5 mmol/L Mg.

Conclusions: The CDF produces a lower ROS production compared to ADF. Increasing the concentration of Mg in the DF, especially in CDF, could have a positive and protective effect reducing oxidative stress and damage in immune cells.
Primary* and Secondary Outcomes

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<th>Therapy 400</th>
<th>Elixir 178</th>
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<td>Moderate</td>
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<td>Severe</td>
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FF-CR (mg/L)

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Serum Albumin (mg/dL)

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Comparison CRP vs. CR (mg/L)

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RR, reduction ratio

FR-PO497

The Comparison of Vancomycin Removal Between Medium Cut-Off (Theranova®) and Other Dialyzers

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Background: For more perfect treatment of Staphylococcus aureus infection in patients with end-stage renal disease (ESRD) on hemodialysis (HD), the maintenance of the target level of vancomycin (molecular weight 1,448 Dalton), 15~20 mg/L, is very important. Recently developed medium cut-off dialyzer, Theranova®, revealed superior clearance of medium large molecular weight (∼45,000 Dalton). Hence, Theranova® may cause the suboptimal level of vancomycin in HD patients. The aim of this study is to investigate whether the reduction ratio of vancomycin (RRoV) in HD patients on Theranova® is greater than that on low-flux/high-flux dialyzer.

Methods: We analyzed prospectively collected vancomycin levels in HD patients between April 2018 and April 2019. HD dialyzer was randomly assigned to the patients underwent intravenous vancomycin. In the first study (n=31, M/F=21:10, age 66 (55–73) years, dry body weight (DBW) 55.0 (50.6–63.5) Kg), RRoV by Theranova® was compared with that by low-flux dialyzers (FX 10®, Fresinius or Polyflex 17L®, Baxter). In the second study (n=24, M/F=15:9, age 63 (46–75) years, DBW 52.0 (46.0–63.0) Kg), RRoV by Theranova® was compared with that by high-flux dialyzers (FX 80®, Fresinius or Polyflux 170H®, Baxter).

Results: In both studies, there were no significant differences in the total amount of vancomycin, dosing interval, the level of vancomycin just before HD, the time of HD session, and the net ultrafiltration between two groups, respectively. The RRoV by Theranova® was greater than that by low-flux (45.5 (3.6–51.2) % vs. 33.3 (28.8–41.7) %, p=0.001). However, there was no significant difference in RRoV between Theranova® and high-flux dialyzers (64.1 (43.5–54.3) % vs. 46.4 (40.5–53.5) %, p=0.597).

Conclusions: Although the RRoV by Theranova® was significantly greater than that of low-flux dialyzer, there was no significant difference between Theranova® and high-flux dialyzer. Therefore, existing vancomycin dosing protocol on high-flux dialyzer could be valid in treatment of Staphylococcus aureus infection in patients on HD using Theranova®, too.

FR-PO490

Effect of Different Dialysis Procedures on Monocyte Subsets

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Background: In cardiovascular and end-stage kidney disease, monocyte subsets are associated with cardiovascular events and mortality. The aim of the present study was to monitor monocyte subsets over a 6-week period in individuals on different extracorporeal dialysis procedures.

Methods: In a prospective, randomized, controlled, cross-over study enrolling 15 maintenance dialysis patients (DRBSK0001L785), low-flux and high-flux hemodialysis (HD) were compared to high convective volume (a25 L) postdilution hemodiafiltration (HDF). Each patient was subjected three times weekly to each treatment mode for 8 consecutive weeks. Dialysis membrane material was always identical (PUREMA® L and H, resp.). Dialysate flow rates differed in HD and HDF (500 vs. 700 mL/min). Blood flow rates and treatment time were kept identical for individual patients. Monocyte subsets were determined at baseline (0), after 3 (3) and 6 weeks (6) of each treatment period. Monocytopen subtypes were differentiated in classical (CD14+/CD16−), intermediate (CD14+CD16+) and non-classical (CD14−CD16+) by flow-cytometric analysis. In addition, highly sensitive serum CRP was monitored by ELISA.

Results: While there were no differences in monocyte subsets over time within and between treatment modes, ANOVA revealed a lower number of total monocytes at t6 in HDF compared to low-flux HD (885±245 vs. 993±349 cells/μL, p<0.01). Classical monocytes ranged between 677±191 (high-flux HD, 13) and 763±297 (low-flux HD, 16) cells/μL, intermediate monocytes between 91±31 (HD, 13) and 125±69 (HIGH, 08) cells/μL, and non-classical monocytes between 83±39 (HDF, 13) and 100±45 (low-flux HD, 13) cells/μL. Furthermore, no differences in CRP levels were found within and between treatments (range 5.1±2.18 mg/L in HDF at t6, and 11.4±2.19 mg/L in low-flux HD at t6). CRP correlated with total monocytes (r=0.638, P=0.001) as well as with classical (0.608, P=0.001), non-classical (0.216, P=0.017) and intermediate (0.520, P=0.001) subtypes.
FR-PO493
Patient-Reported Outcome Measures (PROMs) and Expanded Hemodialysis (HDs) with Medium Cut-Off Dialyzers in a Large Cohort of Patients in Colombia: The COREXH Study
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Background: Increasing importance and focus have been directed towards quality of life measures (QoL) and patient experience in end stage kidney patients on hemodialysis (HD). A new therapy, expanded hemodialysis(HDx) with Theranova membrane improved clearance of middle molecular uremic toxins but to date its effects on QoL, are lacking.

Methods: Historical cohort, multicenter study in prevalent patients older than 18 years under the HDx therapy with MCO membrane that complete the twelve months of follow up in the COREXH Registry, in Renal Therapy Services (RTS) Colombia network. PROMs were assessed by KDQOL-36, Dialysis Symptoms Index (DSI), and diagnostic criteria for Restless Legs Syndrome (RLS) tools. The ANOVA and Cochran’s Q test was used.

Results: Out of 992, the 619 men (62.4%) with mean age 60.4±15.7 years. For KDQOL-36, domains, symptoms, burden of kidney disease and mental component, significant increase in score at 6 and 12 mos was noted (Table1). ANOVA for DSI shows statistically significant differences in mean severity scores over the follow-up with improvement from 30.7, 29.9 and 28.5 at baseline, six months and one year for DSI shows statistically significant differences in mean severity scores over the follow-up with improvement from 30.7, 29.9 and 28.5 at baseline, six months and one year for DSI

Conclusions: In this large multicenter study, HDx with Theranova resulted in improved patients' related outcomes.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.

Patient Reported Outcome Measures

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline (N=30)</th>
<th>6 months (N=30)</th>
<th>12 months (N=30)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Symptom/Problem Domain</td>
<td>76.0(±5.4)</td>
<td>81.0(±3.5)</td>
<td>81.1(±4.0)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Effect of Kidney Disease</td>
<td>69.9(±22.0)</td>
<td>72.6(±22.0)</td>
<td>75.1(±21.0)</td>
<td>0.001**</td>
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<tr>
<td>Burden of Kidney Disease</td>
<td>64.2(±27.0)</td>
<td>84.9(±29.0)</td>
<td>91.6(±21.3)</td>
<td>0.001**</td>
</tr>
<tr>
<td>SI: Physical</td>
<td>41.1(±13.1)</td>
<td>41.1(±13.1)</td>
<td>41.1(±13.1)</td>
<td>0.922</td>
</tr>
<tr>
<td>SF: Mental</td>
<td>51.3(±11.0)</td>
<td>51.3(±11.0)</td>
<td>53.2(±11.0)</td>
<td>0.006*</td>
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<tr>
<td>RLS</td>
<td>50.7(±23.3)</td>
<td>51.5(±25.3)</td>
<td>52.5(±21.7)</td>
<td>0.008*</td>
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* Anova test
** Cochran’s Q test

FR-PO494
What Is the Most Cost-Effective Strategy to Rinse a Re-Processed Dialyzer Before a Dialysis Session?
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Background: Dialyser reuse is practised in developing countries to reduce cost. The Indian Society of Nephrology (IndSN) Hemodialysis Guidelines recommend using 2L of normal saline (NS) to flush the blood compartment of a dialyzer before each reuse to ensure elimination of air and residual sterilant. It is also recommended that the dialyser cleaning step be rinsed for 5 minutes. In this study, we tested several strategies to determine the smallest volume of NS that could lead to elimination of residual sterilant from a reprocessed dialyzer and thereby lead to cost savings.

Methods: We pilot tested combinations of flushing (after draining the dialyser compartment) with different volumes of NS (2L, 1L and 500 mL) and 0 or 10 minutes dialyzer compartment rinsing in 5 sessions each. After determining the smallest flush volume that consistently eliminated the sterilant (4% peracetic acid, 21% hydrogen peroxide and 10% acetic acid), we reduced the rinsing time in decrement of 2 minutes, starting from 15 minutes of residual sterilant recommended with a commercial step (Serem Research Corporation, IN, USA) that detected the presence of >1 ppm of hydrogen peroxide. We also noted the time taken for the entire process and the cost. The final selected strategy was compared with the 'IndSN gold standard' in 150 sessions each.

Results: The first step of the pilot showed us that the smallest volume of NS that was able to consistently get rid of the sterilant from the reprocessed dialyzer was 500 ml. Next, we found that a minimum of 8 minutes of rinsing was needed to eliminate the sterilant completely. Adding 2 minutes as a safety margin, we then compared 500 ml flush + 15 mins with the strategy recommended by the IndSN in 150 sessions each. The final strategy showed no residual sterilant in any session. The cost (INR 30 versus INR 100) and the time taken (15 mins vs 25 min) were less than that with the protocol recommended by the IndSN.

Conclusions: Flushing of the dialyzer blood compartment with 500 ml of NS followed by 10 minutes of rinsing of the dialyse compartment leads to complete removal of sterilant prior to initiating dialysis using a reprocessed dialyser. This strategy results in a significant saving in terms of cost and time taken to initiate dialysis compared to currently recommended protocol.

FR-PO495
Glycosaminoglycan Modified-Dialysis Membranes Improve Blood Biocompatibility In Vitro
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Background: The number of patients requiring renal replacement therapies is increasing with an estimated number of 5.4 million a year in 2030. Most patients use (hemo) dialysis (HD) therapy. Major drawbacks of HD are: (i) poor removal of toxic larger middle-sized molecules and protein-bound uremic solutes; (ii) large fluctuations in water balance and uremic waste, potassium and phosphate of the patients, since it is non-continuous (iii) not fit for prolonged use due to clogging and coagulation of the membranes. Recently, we showed in vitro that combining dialysis and adsorption in one step using mixed matrix membranes (MMM) improves removal of protein-bound uremic solutes from human plasma as compared to conventional dialysis membranes. Although the results with MMMs are promising, for continuous use further optimization is required. Due to the well-known contribution of glycosaminoglycans (GAGs) to the barrier and anti-fouling properties of the natural filtration barrier in the kidney, this work aimed to create bio- and biocompatible membranes of MMM by application of novel GAGs either as coatings post membrane fabrication or by incorporation of the GAG into the membrane polymer via blending.

Methods: Flat MMM were coated or blended with the following GAG sources: Heparin, GAGs from porcine intestine (GPI), heparin sulphate (HS) isolated from cultured glomerular endothelial glyocalyx, HS from bovine kidney (HSBk), and heparinase III digested HSBk. Both GAG coating and blending showed a high stability on the MMM. Water permeance, and a panel of anti-coagulation and platelet adhesion assays were performed.

Results: The new MMM with 3 out of 5 GAGs have higher water permeance in comparison to non-modified MMM whereas heparin and GPI modified MMM were superior in their anti-coagulation and platelet adhesion properties.

Conclusions: GAG-modified MMM have superior biocompatible properties that may improve current dialysis treatment and ultimately enable incorporation into future portable artificial kidney devices.

Funding: Government Support - Non-U.S.

FR-PO496
Discrepancy Between In Vivo and In Vitro (Dialyzer Mass Transfer-Area Coefficient) KoA in Patients on Chronic Intermittent Hemodialysis (Hd): A Retrospective Analysis

Background: KoA is a measure of the dialysis membranes clearance efficiency. Manufacturer KoA values are determined from in-vitro studies. The achieved in-vivo KoA using these membranes in IHD is not known.

Methods: We retrospectively reviewed measured hemodialysis kinetic results in 70 patients receiving IHD at an outpatient free-standing dialysis unit. Over a 2-month period, we reviewed 140 dialysis sessions. Age, Gender, Weight, Height, length of session, blood flow rate (Qb), dialysate flow rate (Qd), pre-BUN, post-BUN, urea reduction rate (URR), type of dialyzer and manufacturer KoA, UF, pre-weight, post-weight and spKt/V were recorded. Specimens were obtained according to specifications of the dialysis unit. We balanced the KoA using Daugirdas 2 equation (D2), body surface area (m2 calculated using Musteau equation (M-BSA), and total body water (L) calculated using Watson’s formula (W-TBW)). MS Excel® was used for mathematical calculations (“what if analysis”) and IBM SPSS® v22 was used for statistical analysis – correlations and t-tests. In-vivo KoA was back calculated from D2 using AS Michaels equation: Clearance (K) = Qb((exp(KoA-1)/(Qd Qd)) -1)/(exp(KoA-1)/(Qd Qd)) -1 -Qd)

Results: There were 70 patients, 39 females, mean age 58.9±13.4 years, mean time on HD 253±18 months, mean Qb 400±44.8 mL/min, mean Qd 800±60 mL/min, mean...
FR-PO497

A Randomised Study Investigating the Effect of Medium Cut-Off Haemodialysis on Markers of Vascular Health Compared with Online Haemodiafiltration (MoDal Study)

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Background: Medium Cut-Off (MCO) Haemodialysis (HDx) provides improved clearance of larger middle molecules (up to 45kda) with high-flux haemodialysis. Inflammation and cardiovascular (CV) disease is driven by endothelial dysfunction (ED) that is intimately linked in this patient group. Expanded solute removal, through HDx could be biologically significant in modifying endothelial function and CV risk.

Methods: A single-centre, pilot, open-label, randomised controlled trial with 1:1 allocation randomisation to 6 months MCO or HDx on existing HDF therapy (NCT03510520). Pre-dialysis EMV (CD144+) was measured at baseline (T0), 3 months (T12) and 6 months (T24). Secondary outcome measures included inflammatory cytokines, a panel of larger middle molecules, body composition monitoring and patient-reported outcomes.

Results: 63 participants were randomised to either MCO or HDF and 50 participants (25 each group) completed the full protocol. Mean age was 62.8±16 years, 70% male, 60% Caucasian, 34% diabetic, 68% AVF as AV access with no significant difference between groups in these domains. Mean substitution volume in the HDF group was 20.8±12.8 l per session.

There was a rise in EMV in the HDF group (change in mean EMV 0.145 logCD144+ EMV/ml at T12 [p<0.05], 0.269 at T24 [p<0.05] and fall in EMV in the MCO group (-0.18 T12 [p<0.05], -0.145 T24 [p<0.05]). Mean albumin change in the MCO group was -1.8±2.3 g/l (p=0.05) vs 0.1±3.8 g/l in the HDF group (p<0.05).

Conclusions: Switching from HDF to HDx therapy is associated with a reduction in plasma EMV levels at 3 months with a sustained reduction at 6 months. This is in contrast with a rise in plasma EMV levels seen within the same time period in those remaining on HDF. A fall in serum albumin is seen with HDx treatment within the limits expected. Mechanisms behind the changes seen require further exploration. In an era where equipoise still exists between dialytic and convective treatment modalities, HDx could be an important future direction.

Funding: Commercial Support - Baxter Healthcare

FR-PO498

The Relationship of Frequency of Hemodialysis Treatments per Week to Improved Clinical Outcomes in Patients in Skilled Nursing Facilities


Background: Dialysis patients residing in a skilled nursing facility (SNF) are characterized by advanced age, frailty, and hemodynamic instability, with multiple comorbid conditions. Based on previous increased frequency studies it was postulated that SNF residents could benefit from frequent hemodialysis (HD) when compared to conventional therapy. Given the potential for less traumatic treatments we compared the effects of HD performed 5 times per week (MF5D) with 4 times per week (MF4D) on mortality and hospitalization rates for patients in skilled nursing facilities.

Methods: We studied patients enrolled in Dialyse Direct staff-assisted, on-site SNF home HD programs in five states: OH, TX, FL, NY, PN, analyzing 1177 patients under care for 260 patient-years. 83% were dialyzed MF5D (77,745 patient-days) and 17% (15,545 patient-days) were dialyzed) using NxStage technology for approximately 2.7 and 3.1 hours per treatment respectively.

Results: Patient characteristics of MF4D vs MF5D were comparable with respect to age (69y vs 70y), gender (49% F vs 45%), HD vintage (3.14 vs 2.79 yrs), and mean blood pressure upon program entrance (135 vs. 133 mmHg). Weekly time on HD differed (3.1 vs 2.7 hrs -> 12.2 vs 13.4 hours per week). Patients were divided into length of stay quartiles: 15, 33, 90, and 1127 days. Mortality: relative risk in MF5D patients was lower for patients per year (0.25 vs 0.34,p=0.03); significant differences were present in quartile one (OR 0.12, 95% CI 0.05-0.28) and two (OR 0.29, 95% CI 0.13-0.62, p=0.021). Hospitalization: relative risk in MF5D was lower per patient year (2.64 vs 4.88;p=0.05); a significant difference in hospitalization was present in quartile one (1.78 vs 4.25). Blood Pressure: MF5D and MF4D pre-hemodialysis systolic blood pressure were (136 vs 132 mmHg), for both groups pre-HD.

Conclusions: Five times a week dialysis significantly reduces mortality and hospitalization rates in patients confined to nursing homes, possibly related to more effective and gentler fluid management strategy, that with better blood pressure control and fewer episodes of intradialytic hypotension may have protected organ systems. Its success in this frail population confirms the importance of volume control.

Funding: Private Foundation Support

FR-PO499

Circulating Angiopoietin-Like Protein 2 Levels and Mortality Risk in Patients Receiving Maintenance Hemodialysis: A Prospective Cohort Study

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Background: Prognosis of patients undergoing hemodialysis treatment is poor, as many of them exhibit premature aging. Systemic inflammatory conditions often underlie premature aging phenotypes of the uremic population. Thus, we asked whether Angiopoietin-like protein (ANGPTL2), a factor that accelerates progression of aging-related and non-infectious inflammatory diseases, was associated with mortality of hemodialysis patients.

Methods: We conducted a multicenter prospective cohort study of 412 patients receiving maintenance hemodialysis treatment and evaluated relationships between circulating ANGPTL2 levels and risk for all-cause mortality. Circulating ANGPTL2 levels were log-transformed to account for skewed distribution, and analyzed as continuous variable.

Results: Of 395 subjects analyzed statistically, time-to-event data analysis revealed high circulating ANGPTL2 levels associated with increasing risk for all-cause mortality after adjustment for age, sex, hemodialysis vintage, nutrition status, metabolic parameters, and circulating high sensitivity C-reactive protein values [HR: 2.04, 95%CI (1.10, 3.77)]. High circulating ANGPTL2 levels were also strongly associated with increased mortality risk, particularly in patients with a relatively benign prognosis [HR: 3.06, 95%CI (1.86, 5.03)]. Furthermore, the relationship between circulating ANGPTL2 levels and mortality risk was especially strong in populations showing less senescent phenotypes, such as younger patients [HR: 7.99, 95%CI (3.55, 18.01)], short hemodialysis vintage [HR: 3.99, 95%CI (2.85, 5.58)], or non-diabetes [HR: 5.15, 95%CI (3.19, 9.32)].

Conclusions: We conclude that circulating ANGPTL2 levels are positively associated with mortality risk of patients receiving maintenance hemodialysis, and that ANGPTL2 may uniquely reflect progression of premature aging and subsequent mortality risk in that population.

Funding: Government Support - Non-U.S.

FR-PO500

Risk Factors and Clinical Impact of Early-Onset Peritonitis in Peritoneal Dialysis Patients

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Background: Peritoneal dialysis (PD) related peritonitis is a serious complication of PD and the leading cause of technique failure. However, the impact of early peritonitis on PD survival is not clearly proven. This study aims to analyze the risk factors and outcomes of early onset peritonitis.

Methods: We retrospectively reviewed 1336 patients who performed PD catheter implantation between 1996 and 2017. Of the 1336 patients, 614 patients who had at least one episode of peritonitis were enrolled. According to time from start of PD to first episode of peritonitis, patients were divided into early-onset (≤6 months) and late-onset (>6 months) peritonitis group.

Results: Among 614 patients, 164 (26.7%) patients developed their first episode of peritonitis within 6 months. The early-onset peritonitis group had more prevalence of diabetes mellitus (P = 0.004), lower serum albumin level at initiation of PD (P = 0.002) and higher peritonitis rate (P < 0.001) than the late-onset peritonitis group. Multivariate logistic regression analysis showed that risk factors associated with early-onset peritonitis were diabetes mellitus (OR 1.510, 95% CI 1.036-2.201, P = 0.032) and a lower serum albumin level at the start of PD (OR 0.629, 95% CI 0.434-0.910, P = 0.014). In multivariate Cox regression analysis, early-onset peritonitis was not an independent risk factor for technical failure and mortality. However, a negative correlation was observed between the time to first peritonitis and technical failure (HR 0.995, 95% CI 0.991-0.999, P = 0.023) and mortality (HR 0.991, 95% CI 0.987-0.997, P = 0.001). In the Spearman analysis, the time to first peritonitis was negatively correlated with the incidence of peritonitis (r = 0.437, P = 0.000).

Conclusions: Diabetes mellitus and a lower serum albumin level at initiation of PD were independent risk factors of early-onset peritonitis. Early-onset peritonitis was associated with higher incidence of peritonitis, technical failure and mortality.
Microbiology Laboratory Practices Influences a Capacity of Pathogen Identification from Peritoneal Effluent in PD Patient with Peritonitis: A Result from the Thailand PDOPPS

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Background: Effective treatment of peritonitis relies mostly on the identification of pathogenic organisms from the PD effluent. However, culture-negative peritonitis is common in Thailand, a country with “PD First” policy.

Methods: This prospective case-cohort study was conducted in 21 PDOPPS centers in Thailand during May 2016 to October 2017. All cloudy PD bag prior to starting antibiotic from consented PD participants who had peritonitis were submitted to local and central laboratories. Facility practices regarding collection technique and microbiology laboratory practices were collected via survey of microbiology laboratory directors in each facility.

Results: During the cohort period, there were 360 peritonitis episodes (241 participants). The crude peritonitis rate was 0.40 episodes/year. Only 202 episodes (169 participants) had specimen submitted to both laboratories. By local laboratory result, Gram-positive bacteria were accounting for 26.2% of episodes followed by Gram-negative bacteria (23.4%), polymicrobial infection (2.5%), and fungal infection (5.0%). Of note culture negative rates was 42.5%. Central laboratory culture additionally identified organisms in 26 episodes whose local laboratory culture was negative, increasing positive culture rate to 70.3%. Central laboratory culture provided additional yield mainly in fungal, mycobacterium, and polymicrobial infections. Only 1 facility had complete equipment, reagents, and media to culture mold and mycobacteria while obligate anaerobe could be isolated from 4 facilities. None but one performed large volume culture.

Conclusions: Microbiology laboratory practices influence a capacity of pathogen identification from the PD effluent in PD patient with peritonitis and should warrant a competency assessment program.

Funding: Other U.S. Government Support

Reduction of Peritonitis in an Integrated Health Care System: Collaboration Between Nephrologists, Dialysis Provider, and Health Plan

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Background: Peritonitis is a serious complication in patients on peritoneal dialysis (PD). Centers for Medicare and Medicaid Services (CMS) has set peritonitis rates as a performance metric for PD clinics. Kaiser Permanente (KP) Northern California is an integrated health care system with 4.4 million members. In 2018, a workgroup was created to monitor and reduce peritonitis rates in 3 non KP PD clinics with high rates.

Methods: A KP workgroup was formed consisting of 3 non KP PD Medical Directors, a RN Clinical Practice Consultant, and a Regional Health Plan Director. The workgroup outlined performance improvement tools: 1. The facility’s P&Ps were aligned with ISPD guidelines and adherence to P&P monitored; 2. Workflow for patient education and training; 3. Root cause analysis for peritonitis. After an initial site visit, monthly conference calls were held with the work group and facility staffs to review all peritonitis episodes and perform a Root Cause Analysis.

Results: The work group identified several factors that had contributed to peritonitis: 1. Patients that experienced peritonitis were not incident patients, but with a vintage of 2+ years; 2. Patient training and retraining was not consistent; 3. The education and training was not done in an organized manner and there was no enforcement and oversight of this process. The following actions were taken by KP in conjunction with the facility team: 1. P&Ps were reviewed, and staff informed of goals; 2. Staff and management buy-in was ensured to empower and drive improvement. As a result, of the initiative, there was a reduction in the peritonitis rates in all the three facilities (Figure).

Conclusions: In an integrated health care system, creating a dialysis provider and health plan partnership to implement a culture of cooperation is a unique approach to improve patient care. The partnership led to collaboration of care for better outcomes.

Influence of Season and Climatic Conditions on Peritoneal Dialysis-Associated Peritonitis in a Subtropical Monsoon Climate Region of China

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Background: Peritoneal infections are a common complication in patients undergoing peritoneal dialysis (PD) and are frequently the cause of the failure of the technique. Knowing the factors that can lead to the appearance helps to establish preventative measures. The aim of this research is to understand the influence of season, temperature and humidity on peritoneal dialysis-associated peritonitis in the subtropical monsoon climate region (Hunan province) in China.

Methods: A retrospective observational study of all peritoneal dialysis-associated peritonitis that occurred in our center over a period of 9 years (2009-2017). Our PD center is located in hunan province, China which has the subtropical monsoon humid climate. Demographic data of patients, biochemical indicators at the time of onset, culture results of dialysate fluid, and data of the humidity and temperature of the months from 2009 to 2017 in hunan province were collected.

Results: There were 448 cases of peritonitis(0.17episodes/patient/year) in 885 patients (47±13 years, 56.4% males, 8.7% diabetics, 50.2±19 months on technique). There was significant seasonal variation in the rate of overall peritonitis and gram-negative bacteria peritonitis, with peak incidence in June. When comparing the incidence of peritonitis in different seasons, we found the incidence rates of overall peritonitis and gram-negative bacteria peritonitis were the highest in summer, respectively(p<0.05). But we did not find this variation upon analysing the incidence rates of peritonitis caused by gram-positive bacteria. There was significant correlation between monthly peritonitis rate and the average monthly temperature (r=0.258, p=0.018). There was significant correlation between monthly gram-negative bacteria peritonitis rate and the average monthly temperature (r= 0.278, p=0.010) either. But we did not find correlation between the incidence rates of peritonitis and average humidity.

Conclusions: The rates of overall peritonitisand gram-negative bacteria peritonitisperitonitis are the highest in summer. The higher the temperature, the higher the risk of overall peritonitis and especially of gram-negative bacteria.

Prophylactic Oral Antibiotics for Post-Endoscopic Peritonitis in Peritoneal Dialysis Patients

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Background: Gastrointestinal endoscopy (GIE), especially lower GIE, is a risk factor for peritoneal dialysis (PD)-related peritonitis. However, there are currently no recommendations regarding preventive antibiotic regimens for GIE-associated peritonitis.

Methods: We retrospectively reviewed the association between prophylactic oral antibiotic administration and GIE-associated peritonitis.

Results: Among 140 patients who received PD treatment in our hospital from April 2008 to March 2018, 91 patients underwent a total of 360 GIEs, excluding patients who received therapeutic antibiotics for exit-site or other infections. None of the 30 GIEs (0%) (1 upper, 29 lower) accompanied by prophylactic oral antibiotic use led to PD-related peritonitis. The oral antibiotics included levofloxacin (n=24, 80%), amoxicillin-clavulanic acid (n=4, 13%), metronidazole (n=4, 13%). In contrast, two of the 33 GIEs (6.0%) conducted without prophylaxis (1/289 upper, 0.3%, 1/41 lower, 2.4%) resulted in PD-related peritonitis, including one upper GIE procedure involving biopsy and one lower GIE involving oral double-balloon enteroscopy for suspected small intestinal bleeding. The incidence of peritonitis following upper GIE with invasive procedures was 1.0% (1/104), similar to past reports, and the incidence of peritonitis following lower GIE with or without invasive procedures was 2.4%, which was lower than previously reported.

Conclusions: Although it was not possible to show any significant effect of prophylactic oral antibiotics on the frequency of total GIE-associated peritonitis because of the small numbers, we could not conclude that prophylactic antibiotics were not beneficial in patients undergoing lower GIE. The administration of prophylactic oral antibiotics covering Enterobacteriaceae may thus be a convenient and promising option for preventing GIE-associated peritonitis.

Dialysate and Plasma Meropenem Concentrations in Continuous Intraperitoneal Regimen During Peritoneal Dialysis-Related Peritonitis

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Background: Peritonitis is a major complication in peritoneal dialysis (PD) patients. Currently, the increase of intraperitoneal (IP) meropenem used regarding the rise in resistant organisms. A single dose of IP meropenem was recommended. However, data on the continuous regimen of IP meropenem is still limited. We examined plasma and dialysate meropenem level in the continuous IP meropenem in PD related peritonitis.

Methods: A prospective, descriptive study was performed in 8 patients with PD related peritonitis. Seven patients received a loading dose of meropenem 500 mg IP followed by meropenem 125 mg/L IP (4 exchanges daily). Another patient received the recommended intermittent IP meropenem 1 g daily. Concentrations of meropenem in plasma and dialysate were measured at specified intervals over 24 h with a high-performance liquid chromatography method.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: In the continuous group, the mean of maximum meropenem level was 340.6 mg/L (standard deviation [SD] ± 21.5) and 28.7 mg/L (SD ± 21.5) in dialyse and plasma, respectively. At 24 hour, mean dialyse drug level was minimum at 45.3 mg/L (SD ± 36.2). Dialyse meropenem concentrations from this regimen exceeded MIC of the pathogenic resistance organism (MIC > 8 mg/L) at every time points. For the intermittent regimen, mean plasma and dialyse meropenem levels were 11.8 mg/L (SD ± 8.2) and 34.2 mg/L (SD ±35.7), respectively. Interestingly, dialyse meropenem concentration at 12 hours after 1 g of meropenem was 4.9 mg/L which may not provide adequate drug level for resistant organisms. Five patients (71%) responded to the treatment, but two patients (29%) developed treatment failure from fungal peritonitis. No major side effect was observed.

Conclusions: Meropenem loading 500 mg and continue with 125 mg/L provide adequate dialyse meropenem concentration and could be considered for effective treatment in PD related peritonitis.

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FR-PO507
Does Single-Dose Conjugated Pneumococcal Vaccine Provide Enough Antibody Response in Peritoneal Dialysis Patients?
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Background: Dialysis patients have 10-100 fold-increased risk of sepsis and pneumonia related mortality. The incidence of pneumonia increased and over half of reported pneumonia cases in dialysis patients are caused by Streptococcus pneumonia. Immunization against infectious diseases is a fairly simple, prevention strategy in dialysis patients. Implementation of polysacharidde pneumococcal vaccination (PPSV23) has led to an considerable decrease in pneumonia incidence. In accordance to PPSV23, conjugated pneumococcal vaccine (PCV13) has an increased and sustainable immunogenic response. In dialysis patients, antibody response to vaccination is decreased. This is the first study that investigates whether PCV13 vaccination provides enough antibody response in peritoneal dialysis (PD) patients.

Methods: Participants received a single dose of 0.5 ml of PCV13 administered intramuscularly. Blood samples were drawn prior to vaccination and at 1 month after vaccination. Serum antipneumococcal antibody level is measured by ELISA method.

Results: 69 PD (39 male, 30 female) patients and 10 healthy volunteers were inrolled in our study. Mean age was 52,6 ± 12,9 years (Image 1). In PD patients and control groups, first month antibody levels were increased statistically significant than prevaccination (p=0,001, p=0,008, respectively). First month antibody levels were higher in control group compared to patients (p=0,013). In PD group, statistically significant relationship were observed between antibody levels and serum albumin, CRP, Kt/V, weekly CrCl, nPCR parameters (Image 2).

Conclusions: In PD patients, PCV13 vaccination resulted enough but lower antibody levels than control group. Malnutrition, inflammation and lower dialysis adequacy were associated with lower antibody response.
Is Peritoneal Dialysis a Good Technique for Patients with Autosomal Dominant Polycystic Kidney Disease?

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most frequent genetic cause of Chronic Kidney Disease, progressing in most cases to End-Stage Renal Disease. Peritoneal Dialysis (PD) was contraindicated in this kind of patients, because it was thought that an already elevated abdominal volume would decrease the tolerance and promote a higher incidence of complications. However, this trend is in reverse and every day there are more patients with ADPKD in PD without showing more complications, with good tolerability and adequacy.

Methods: Descriptive, retrospective, unincentric study design; we selected all the patients with a diagnosis of ADPKD and that entered our PD program between April 1st, 1999 and March 31st, 2018. Every one of these patients was matched with 2 non-ADPKD patients with the same medical status and in the same period of time. We proceeded to compare the incidence of dialysate leaks, evolutions, periostitis, the number of hospitalizations and technique failures, and the PD adequacy in both groups through their Kv/t and nPCR.

Results: Comparing the basal characteristics of both groups, there was only significant difference in the Charlson index score. The ADPKD group had a mean of 2.9 ±1.07, while the non-ADPKD group had 4.2 ± 1.97. The most common cause to enter on PD program was patient choice. The mean technique survival was similar in both groups 969.6 ± 667.4 vs 847.5 ± 666.4 days. The peritonitis was in APD was higher in the ADPKD group, 71 vs 46% (p = 0.1). The means of episodes of periostitis, dialysate leaks and hospitalizations were similar. The most common cause of withdrawal from the program was transplant (50 vs 32%); the frequency of inraddialization was higher in the non-ADPKD group (7 vs 18%). Kv/t mean was > 1.7 in both groups, but it was overall lower in the ADPKD group. A value of p < 0.05 was only achieved when the peritoneal Kv/t was contrasted.

Conclusions: ADPKD patients not show higher risk of PD complications or technique failure when compared with non-ADPKD with similar characteristics. PD is an effective treatment modality for ADPKD patients, and ADPKD should not be taken as an absolute contraindication. PD adequacy thresholds are achievable in ADPKD patients.

Peritoneal Dialysis Outcomes of Patients with Nephrotic Syndrome: A Propensity Matched Study

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Background: Whether or not nephrotic syndrome (NS) patients developed to end stage renal disease (ESRD) stage could be treated by peritoneal dialysis (PD) were not clear. The aim of this study is to investigate the outcomes of PD treatment on ESRD patients with or without NS.

Methods: In this retrospectively cohort study, all incident PD patients with NS who started PD during February 1st, 2006, to December 31st, 2017, were identified and matched with patients who without NS by using propensity scores based on age, gender, diabetes mellitus and serum albumin. Both the mortality and technique failure on PD were compared.

Results: A total of 53 NS PD patients and 53 matched control non-NS PD patients with a median follow-up of 3.320 (5.955) years were included. The median survival of NS PD patients (6.60 years, 95% CI 4.95-8.25 years) was comparable to that of non-NS PD patients (5.20 years, 95% CI 4.05-6.34 years; p=0.261). An interaction effect was observed between survival time and baseline NS status. Thus, patients’ outcomes within 1.5 years and after 1.5 years were analyzed separately. Both the mortality rate (log-rank test, p=0.235) and technique failure (log-rank test, p=0.543) within 1.5 years in the patients with NS were comparable to those of non-NS group. However, after 1.5 years, as compared to patients to patients without NS, NS status at baseline had both lower all-cause mortality (p=0.020) and lower technique failure rate on PD (p=0.008). Multivariable Cox regression analysis showed that as compared to non-NS patients, PD patients with NS (HR 0.38, 95% CI 0.17-0.86, p=0.019) were significantly associated with both lower all-cause mortality adjusting for age (HR 1.05, 95% CI 1.02-1.10, p=0.001) and serum albumin levels at baseline (HR 0.86, 95% CI 0.75-1.00, p=0.047) and lower technique failure rate after adjusting for age (HR 1.05, 95% CI 1.00-1.05, p=0.020) and hypertension.

Conclusions: This study demonstrated that both the short and long-term PD outcomes of ESRD NS patients were not inferior to their matched control, which indicated that PD could be considered as a long-term renal replacement therapy for ESRD patients with baseline NS.

Impact of Obesity in Peritoneal Dialysis Patients

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Background: Some studies reveal that obesity is associated with a decrease in mortality in hemodialysis patients. However, few studies have addressed the association between BMI in patients on PD (PD) and mortality. The aim of the present study was to evaluate the association between BMI in PD patients and mortality in PD patients.

Methods: We performed this longitudinal, retrospective study, to evaluate the impact of obesity on PD patients, using data from the Registry of Renal Patients of Catalonia from 2002 to 2015 (n = 1573). Obesity was defined as BMI ≥ 30; low weight: BMI <18.5; normal range: BMI 18.5-24.99; and pre-obesity: BMI 25-29.99. Varies in BMI were calculated during follow-up. The main variables evaluated were the technique and patient survival.

Results: Obesity was observed in 20% of patients starting PD. We did not find differences in sex or PD modality, being older the obesity group (65.9% versus 55 years versus 59% non-obese p=0.003) and presenting more DM and cardiovascular disease (75.9% obese versus 56% non obese and 41% versus 31.5% respectively). We did not observe differences in hemoglobin, albumin and KTV in obese patients. Concerning peritonitis rate we did not find any difference between groups, presenting more peritonitis patients on CAPD and 6%5 years (subhazard ratio (SHR) 1.75 (p= 0.000) and 1.56 (p=0.001) compared to technique survival, we found higher transfer to HD in obese group in the univariate analysis that was not confirmed in the multivariate analysis (SHR 1.12 (p=0.4), and we did not found differences in mortality rate. In relation to be transplanted, olderweight group, older and patients with cardiovascular disease or diabetic nephropathy presented less probability (SHR 0.63, 0.24. 0.5 and 0.54 p<0.05). Obese patients did not present differences in survival with weight changes, but in non-obese patients, the gain of 7% of the basal weight during the first year supposed a protective factor of dying (HR 0.6 p=0.034).

Conclusions: We did not observe differences in PD adequacy parameters, technique and patient survival or probability of being transplant in obesity group. However, we found that obese patients presented more DM and cardiovascular diseases that are related to higher morbimortality in the multivariate analysis.
Aihua

Case-Control Study

Peritoneal Dialysis: Modality, Catheter, Infections

hospitalizations were least likely (3.4%, 95% CI: 2.4, 4.3%). For the most common index by a related 30-day readmission (11.8%, 95% CI: 11.3, 12.4%), while renal index (95% CI: 25.0%, 27.2%) in patients with 4 or more hospitalizations (relative increase related readmission. For each of the most common index hospitalization diagnoses, we “related” if the principal diagnoses were of the same organ system. Using multinomial innovations and timeliness for basic nursing care in PD follow-up. IoT devices would help

group, had got alterations of hypotensive drugs, p=0.008. Eight patients (53.3%) in IoT higher than that in conventional group, with rate of 60% and 46.7%, p=0.464. Nine

patients was selected by propensity score matching for the gender, age, dialysis age and

patients were categorized into IoT group (15 patients) and conventional group in which

deployed to PD patients in our center for the nursing follow-up.

that would improve access to and compliance in PD patients, has been designed and

deploying to PD patients in our center for the nursing follow-up.

consecutive ambulatory peritoneal dialysis (CAPD) in our center from 2018.09 to 2018.10. The

patients were categorized into IoT group (15 patients) and conventional group in which

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PD to HD pts.

and had data available in Crownweb records before and after switch. Transplant pts and

parameters in end-stage renal disease (ESRD) pts.

in 2011, the prospective payment

home therapies including peritoneal dialysis (PD) & home

The effect of renal disease and the two dialysis modalities (hemodialysis (HD), and peritoneal dialysis (PD)) on metabolic and nutritional parameters has been well-studied. Compared to HD, PD is associated with low parathyroid hormone level, reduced calcium (Ca) levels, low albumin (alb) and increased BMI. In 2011, the prospective patient system dialysis bundle provided incentive for providers to place patients (pts) on PD, leading to more pts switching from HD to PD. To our knowledge, the impact of switching modalities on these parameters has not been described. We aim to elucidate the effect of switching dialysis modalities and the direction of the switch on metabolic and nutritional parameters in end-stage renal disease (ESRD) pts.

Methods: Using USRDS data, we reviewed 2,955,601 pts and analyzed 16,203 pts who switched modalities from 2012 to 2016. Pts were included if they were age >18, were switched from HD to PD or PD to HD after being on the first modality for at least 2 months, and had data available in CROWNWEB records before and after switch. Transplant pts and pts who switched modalities more than once during the research period were excluded. After excluding data for the last 3 months of the first modality and the first 3 months of the second, we used t-test to compare Ca, phos, alb, BMI, and normalized protein catabolic rate (NPCR). We further used linear models to show differences between the two groups, adjusting for demographics and time on first modality.

Results: In both groups, phos and Ca increased after switch. In the HD to PD group, alpha (0.25mg/dL) and BMI increased (0.43kg/m2); NPCR did not change significantly. In the PD to HD group, alpha (0.26) and NPCR (0.06) increased, though BMI decreased (2.1kg/m2). Compared to HD to PD switch patients and after adjusting for demographics and time on initial dialysis modality, PD to HD pts had higher phos (0.15mg/dL), Ca (0.09mg/dL), alb (0.41mg/dL), and NPCR (0.07g/kg/d), and lower BMI (2.23 kg/m2). All results were significant (p<0.001).

Conclusions: Regardless of the direction of the switch, HD was associated with a higher alb and lower BMI. After adjusting for demographic variables and time on initial dialysis modality, switching from HD to PD results in lower phos, Ca, alb, but higher BMI than PD to HD pts.

FR-PO515

The Transition Care Programme: Our Experience in the Last 10 Years

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Background: Home therapies including peritoneal dialysis (PD) & home haemodialysis (HHD) are associated with better outcomes in patients with end stage kidney disease (ESKD) as compared to in-centre dialysis. Home therapies allow patients autonomy and flexibility with proven improved quality of life. Treating end-stage kidney disease at home means less travel & its associated cost. The cost of HHD to the health care system is the lowest of all dialysis modalities while in-centre dialysis is the most expensive. 1

Home, Independent dialysis and Transition Service (HITS) was commenced in July 2009 within the Kidney Health Service. Since its inception, the uptake of home therapies has increased over the 10 years.

Methods: A retrospective analysis of patients referred to HITS and incident patients requiring kidney replacement therapy (KRT) between Jan 2009 and Dec 2018 with 6 months follow-up after their chosen modality. Incident home therapies pre-HITS and all prevalent dialysis patients via HITS were also analysed.

Results: Incident Home therapies increased from 44% in 2006 (pre-HITS) to 69% in 2018 (HITS). In 2018, 71% of patients transitioning from peritoneal dialysis (PD) to HD were managed as outpatient follow-up monthly.

In adults with Medicare receiving PD in the United States from 1/1/2013-12/31/2017, 72% of incident PD admissions followed by peritonitis were due to peritonitis, technique failure, haemodynamic instability rendering HHD unsafe, between 5-15% patients transitioned from home therapies to in-centre haemodialysis.

Conclusions: Home therapies was relocated to the suburbs and away from the main hospital campus in 2006. The transition unit followed in 2015. Since this initiative, the uptake of home therapies has increased which is largely due to the increased availability of pre-dialysis and specific home therapies nurses, medical support and a dedicated multi-disciplinary team. However, KRT modality in home therapies at 6-months are still not being maintained which necessitates stringent patient selection criteria with rigorous and intense education. Our preliminary results had indicated that IoT technology could provide innovations and timeliness of basic nursing care in PD follow-up. IoT devices would help

FR-PO514

Thirty-Day Readmissions in the Peritoneal Dialysis Population Have High Clinical Variability

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Background: Dialysis facilities are evaluated on their all-cause 30-day readmission rate. We investigated the clinical heterogeneity of 30-day readmissions in the peritoneal dialysis (PD) population and the relatedness of readmissions to index hospitalizations.

Methods: In adults with Medicare receiving PD in the United States from 1/1/2013-12/31/2017, we classified 6 week home therapies and 30-day readmission pairs to “related” if the principal diagnoses were of the same organ system. Using multinomial logistic regression and adjusting for the patient, facility, and geographic factors, we studied whether prior hospitalization burden was associated with a higher likelihood of related readmissions. For each of the most common index hospitalization diagnoses, we summarized the most likely reason for 30-day readmission.

Results: The adjusted probability of an unrelated 30-day readmission was 19.2% (95% CI: 18.7%, 19.7%) in patients with 0 hospitalizations in the prior year and 26.3% (95% CI: 25.0%, 27.2%) in patients with 1 hospitalization. The 30-day readmission rate for “related” if the principal diagnoses were of the same organ system. Using multinomial logistic regression and adjusting for the patient, facility, and geographic factors, we studied whether prior hospitalization burden was associated with a higher likelihood of related readmissions. For each of the most common index hospitalization diagnoses, we summarized the most likely reason for 30-day readmission.

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FR-PO517

Prospective Follow-Up of Peritoneal Function in New PD Patients: Comparison Between a Conventional and a More Biocompatible Dialysis Solution

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Background: Preservation of peritoneal membrane function is essential for patients on long-term peritoneal dialysis (PD). Biocompatible dialysis solutions characterized by a higher pH and a lower concentration of glucose degradation products, are hypothesized to prevent or postpone the membrane alterations that result in ultrafiltration failure and consecutive morbidity and mortality. The objective of this study was to make an in vivo comparison between conventional and biocompatible solutions and the time course of peritoneal solute and fluid transport.

Methods: We analyzed prospectively collected peritoneal transport data from 251 incident patients treated between 1994 and censoring in 2016. The maximal follow-up was 5 years. 135 patients were treated with conventional and 116 with biocompatible solutions. Linear mixed models including change point analyses were performed to compare the time course of peritoneal transport between both groups. Adjustment was made for comorbidity.

The interaction with peritonitis was examined.

Results: 67% (conventional) and 64% (biocompatible) of the patients underwent minimal to moderate 3 transport measurements during follow up. Follow-up during the first years was characterized by consistently faster solute transport and lower ultrafiltration in the biocompatible group. After a change point at 3 years in the conventional group an increase in small solute transport occurred in these patients (p=0.01). Thereafter solute transport increased progressively in the conventional compared to the biocompatible group. This was accompanied by a marked decrease in net ultrafiltration, which became lower in the conventional group between 3 and 4 years. Patients with a previous peritonitis in the conventional dialysis group, showed a significant decrease of transcapillary ultrafiltration already by the 2 years on PD (p=0.02) while this was not present in the biocompatible dialysis group or in patients without peritonitis. The decrease in ultrafiltration was caused by both reduced free water transport (p=0.08) and small pore fluid transport (p=0.06).

Conclusions: This study emphasizes the detrimental relationship between conventional dialysis solutions, peritonitis and the acceleration of peritoneal transport abnormalities in long-term PD patients.

FR-PO518

“We Try Not to Let PD Control Us”: Patient and Caregiver Perceptions of Empowerment in Managing Peritoneal Dialysis

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Background: While peritoneal dialysis (PD) can offer patients more independence and flexibility compared with hemodialysis, treatment can impose a burden outside the home undermining it. While some refused to allow PD to control their lifestyle, others found it comforting and a way to coping with illness.

Methods: This qualitative study included 14 focus group interviews. Participants included 35 patients and 20 caregivers from 9 centers in Australia, Hong Kong, and the United States. The interviews were conducted between March 2016 and October 2017. Transcripts were thematically analyzed.

Results: Four main themes were identified: (1) owning the PD regimen; (2) having control; (3) building resilience and enabling positive outlook; (4) personal growth through adjustment.

Conclusions: For patients and caregivers, understanding the rationale behind lifestyle restrictions, practical assistance and family support in managing PD facilitated empowerment, whereas being constrained in time and capacity for life participation outside the home undermined it. While some refused to allow PD to control their lifestyle, others found it comforting and a way to coping with illness. Further research is needed to identify what leads to empowerment.

FR-PO519

Physician-Led CKD Education Improves Quality and Reduces Cost of Care in Patients with ESRD

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Background: Healthcare providers are tasked with reducing costs and improving patient awareness of chronic kidney disease (CKD). Patient educational initiatives may reduce costs and improve outcomes.

Methods: We performed a large-scale physician-led CKD education program. We performed a retrospective review of all dialysis initiatives over a 24-month period and evaluated outcomes based on participation in educational programs.

Results: A total of 1294 dialysis initiatives were analyzed and 621 patients (48%) attended at least one class. No differences in participation were observed based on gender, race, or primary language spoken. Overall participation in educational workshops was associated with decreased intravascular catheter use, increased home dialysis modalities, and decreased hospitalization for dialysis initiation (p<0.001). Attendance by no participation vs. 1-2 sessions vs. ≥ 3 sessions associated with decreased intravascular catheter use, increased home dialysis modalities, and decreased hospitalization for dialysis initiation (p<0.001). Attendance by no participation vs. 1-2 sessions vs. ≥ 3 sessions associated with decreased intravascular catheter use, increased home dialysis modalities, and decreased hospitalization for dialysis initiation (p<0.001).

Conclusions: Patients who attend CKD educational programs are less likely to need intravascular catheters, and hospitalization for dialysis initiation. They are also more likely to utilize home dialysis modalities. Development of patient educational programs could significantly reduce costs and improve outcomes in this population.
FR-PO520
Lower Utilization of Home Dialysis in Non-White and Dual-Eligible Dialysis Patients
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Background: Past studies have associated non-white race with lower utilization of home dialysis. We aimed to assess the joint influence of race and dual eligibility (i.e., concurrent enrollment in Medicare and Medicaid), a surrogate for poverty, on home dialysis utilization in each state.

Methods: Using Medicare Limited Data Sets, we identified all patients with Medicare Part B claims documenting outpatient dialysis from January 2014 to December 2017. For each calendar week (Monday to Sunday), we identified patients with at least one day of either home hemodialysis or peritoneal dialysis treatment. Within each of the 50 states, we modeled utilization of home dialysis with logistic regression, using a generalized estimating equation. Risk factors comprised non-white race, dual eligibility (DE), the interaction of race and DE, age, sex, and calendar year. We applied a Bonferroni correction to the set of tests of race, DE, and the interaction thereof ($\alpha = 0.05/150$).

Results: The cohort comprised 633,286 patients and 61,522,192 patient-weeks. Overall, 1.8% of patient-weeks were marked by home hemodialysis and 8.9% were marked by peritoneal dialysis. Relative to white patients without DE, state-specific adjusted odds ratios (AORs) of home dialysis in non-white patients without DE were centered at 0.58; among 34 states in which the effect of race was significant, AORs ranged from 0.28 to 0.76. State-specific odds ratios of home dialysis in white patients with DE were centered at 0.42; among 43 states in which the effect of DE was significant, AORs ranged from 0.25 to 0.78. Relative to white patients without DE, state-specific AORs of home dialysis in non-white patients with DE were centered at 0.25. However, interactions of race and DE were significant in only 2 states. In 46 states, non-white patients with DE were less likely to undergo home dialysis than both non-white patients without DE and white patients with DE.

Conclusions: Both non-white race and DE are associated with lower likelihood of home dialysis utilization in most states. The effects are generally log-additive, thus placing non-white patients with DE at profoundly lower likelihood of home dialysis utilization. Substantial growth in home dialysis will necessitate identifying and addressing the reasons for these disparities.

FR-PO521
Early Peritoneal Dialysis Start: Is There Room for More?
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Background: Despite educational care, a considerable number of End Stage Renal Disease (ESRD) patients present to Nephrology without a plan for renal replacement therapy. Early PD start in patients with the urgent need of dialysis could be an important step to improve PD worldwide, overcoming the initiation of HD through a catheter and its well known risks.

Methods: Retrospective, single-center study, with 18 ESRD patients without a dialysis care plan, who started PD in the first 14 days after catheter placement (Early start group - ESG) and 34 patients who started PD after planned dialysis care (Late start group - LSG). For each group we collected demographic data, previous nephrology follow up, type of catheter placement and initial PD prescription. We also measured short-term (90-day) clinical outcomes (Kt/V, creatinine clearance, daily ultrafiltration (UF), hemoglobin, ferritin, parathyroid hormone, phosphorus, calcium and albumin), as well as PD related complications (peritonitis, exit-site infections, leaks and catheter dysfunction).

Results: Patients on ESG begun PD in about 4.9 days after catheter placement, mainly due to overhydration. These patients were predominantly of male gender (88 vs 59%, p= 0.025) and without previous follow-up by Nephrologist (67 vs 97%, p=0.001). Although there weren’t any differences in PD modality and type of catheter used, exchange volumes were lower in the ESG (p=0.001). Short term outcomes were equal among groups, except for daily UF (higher in ESG; p= 0.013). Concerning mechanical complications, the number of leaks and episodes of catheter dysfunction were also similar, as well as the rate of infectious complications.

Conclusions: Despite being a single center study, with a small number of patients enrolled, our results demonstrate the safety and feasibility in beginning PD in patients with kidney failure, without a previous plan for renal replacement therapy. Early PD start in patients with the urgent need of dialysis could be an important step to improve PD worldwide, overcoming the initiation of HD through a catheter and its well known risks.

FR-PO522
Evaluation of a Wearable Artificial Kidney for Peritoneal Dialysis in a Uremic Pig Model
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Background: A WEarable Artificial KIDney (WEAKID – H2020 SC1) for peritoneal dialysis therapy was designed that recirculates dialysate via a tidal mode using a single lumen peritoneal catheter. We hypothesize that continuous dialysate regeneration by the WEAKID system containing sorbents, will maintain a high plasma dialysate concentration gradient and increase the mass transfer area coefficient (MTAC). Thereby, WEAKID may enhance clearance while reducing the number of exchanges. Application is envisaged at night as a bedside device (12 kg, nighttime system). A wearable system (1.6 kg, daytime system) may further enhance clearance during the day.

Methods: The day- (n=3) and nighttime system (n=8) were tested separately for 8 h/treatment in a uremic pig model for PD (n=2). Plasma clearance and the MTAC of urea, creatinine and phosphate with the day- and nighttime system were compared with a standard peritoneal membrane permeability analysis (SPA, n=13).

Results: The daytime system caused a 2.0-fold (p=0.01) and 1.6-fold (p=0.07) increase in creatinine and phosphate clearance and 1.9-fold (p=0.01) and 1.6-fold (p=0.04) increase in MTAC creatinine and phosphate, resp. vs a SPA (Table 1). With the nighttime system, creatinine clearance and MTAC increased by a factor of 1.2 (p=0.002) and 1.4 (p=0.01), resp.

Conclusions: WEAKID increases small solute clearance compared with a SPA. This provides a rationale for a first in human clinical trial to evaluate safety and efficacy of WEAKID in PD patients.

Funding: Government Support - Non-U.S.

Table 1. Plasma clearance and the MTAC of urea, creatinine, phosphate during WEAKID red SPA experiences.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Daytime System</th>
<th>Nighttime System</th>
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</thead>
<tbody>
<tr>
<td>Clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>2.0-fold (p=0.01)</td>
<td>1.9-fold (p=0.01)</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1.6-fold (p=0.07)</td>
<td>1.6-fold (p=0.04)</td>
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</tbody>
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FR-PO523
Assessing the Impact of Dialysis Modality on Hospitalization in a Large Population of ESRD Patients
Martin J. Schreiber,1 Brian Van hout, Zachariah W. Peterson, Michelle Cassin. DaVita Inc. Denver, CO.

Background: Hospitalizations and readmissions pose a significant burden to ESRD patients and result in significant costs to the US health care system. There is increasing focus on patient outcomes and cost advantages for patients starting ESRD treatment on a home dialysis modality. Understanding the impact that specific modalities can have on hospitalizations may assist in changing physician behavior regarding initial modality selection.

Methods: Data were derived from adult patients receiving dialysis treatments in a large dialysis organization between 01 March 2016 and 31 March 2019. Hospitalization rates (overall and cause-specific), length of stay, and readmission rates were assessed
separately for in-center hemodialysis (ICH), peritoneal dialysis (PD), and home hemodialysis (HHD) patients. All outcomes were considered monthly and as 12-month rolling averages.

**Results:** As of March 2019, 12-month rolling average hospitalization rates were 1.24, 1.41, and 1.80 admits/year for PD, HHD, and ICHD patients, respectively; 30-day readmission rates were 26.2%, 24.3%, and 32.1% and mean length of stay was 6.62, 6.60, and 6.52 days, respectively. Significant variability was observed across geographic regions, with PD hospitalization rates ranging from 0.95 to 1.42 admissions/year and HHD hospitalization rates ranging from 1.13 to 1.66 admissions/year. Causes of hospitalization differed across modalities and programs: ICHD patients had higher rates of respiratory-related admissions and lower rates of admissions for gastrointestinal- and infection-related causes than patients on home modalities.

**Conclusions:** There is a pressing need to reduce hospitalization rates among ESRD patients to limit rising health care costs and improve outcomes. Here we demonstrate that hospitalization and readmission rates are consistently lower, and length of stay shorter, for patients using home dialysis modalities (PD and HHD) than those receiving ICHD. However, significant variability was observed across home programs, by program size and geographic location. Findings from this study have been used to develop a proactive approach to decrease readmissions and readmissions based on program characteristics.

**Funding:** Commercial Support - DaVita Inc

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**FR-PO52**

**The Effect of Hemodialysis with Central Venous Catheterization on Urgent-Start Peritoneal Dialysis**

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**Background:** Urgent-start peritoneal dialysis (USPD) has received worldwide attention. A number of clinical studies have shown that USPD has great advantages in early complications, technical survival, and medical economics. Due to differences in economic conditions and acceptance, there is no pre-dialysis preparation in most ESRD patients in China. So most patients accept hemodialysis with central venous catheterization (HD-CVC) before deciding on long-term dialysis alternatives. Patients who eventually choose peritoneal dialysis (PD) must have peritoneal dialysis catheterization performed within 2 weeks. The follow-up time was 1 year.

**Results:** A total of 2,151 incident PD patients were enrolled. The number of patients in the HD-CVC and USPD groups was 319, and 1,832, respectively. Compared with the early-start group, the overall CV mortality rates were 0.8% (p<0.05). In the mid-start group (HR=0.90, 95% CI 0.64-1.45 and HR 0.87, 95% CI 0.55-1.11) compared with the early-start group, however, there was no significant difference in overall CV mortality between the 2 groups (p=0.5). Lower eGFR at PD therapy initiation was not associated with lower mortality risk. However, an eGFR < 5 ml/min/1.73m² at the initiation of PD was associated with lower risk of mortality among elderly patients, while not among younger patients.

**FR-PO525**

**FR-PO526**

**Peritoneal Dialysis: Modality, Catheter, Infections**

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only**

**Underline represents presenting author.**

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**FR-PO527**

**Pilot of Assisted PD in an Integrated Health Care System**

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**Background:** Peritoneal dialysis (PD) is a home based modality that has many benefits. However, it can be challenging for patients with physical disabilities and psychosocial barriers, particularly the elderly. Assisted PD can provide support to overcome these barriers and promote PD utilization and retention. Assisted PD programs have been in use worldwide for over 20 years and have demonstrated good results. There are no such programs in the US. Kaiser Permanente Northern California (KPNC) is an integrated health care system that serves over 4.4 million members. Our PD unit in the Greater Southern Alameda Area is an internal PD program in KPNC, serving over 150 patients. In 2018 a pilot program of assisted PD was developed by the our unit to help overcome common barriers to PD and expand it as modality of choice.

**Methods:** A seven month pilot of temporary assisted PD was completed from April to October 2018. Patients were identified using certain selection criteria and assisted PD was offered for a time limited period of 90 days per patient. A single PD RN was designated for performing CAPD exchanges; adding antibiotics; retraining and psychosocial support. Barriers and benefits to exercise were classed as binary variables (i.e. yes and no). Frequency analysis and chi-squared tests were conducted to compare the barriers and benefits perceived by HD and PD patients.

**Results:** The proportion of HD and PD patients who reported barriers and benefits to exercise is displayed in Figure 1. Significantly more HD patients than PD patients reported ‘‘reduced ability to exercise’’ (p=0.013), ‘‘delayed decline in body function’’ (p=0.010), and ‘‘improves quality of life’’ (p=0.033) as benefits. No significant differences in barriers were observed between the groups. Tiredness was the most commonly reported barrier by both groups.

**Conclusions:** The findings suggest that HD patients are more aware of the physical benefits of exercise than PD patients. This may be due to HD patients being better informed about the benefits and more actively encouraged to exercise than PD patients via regular contact with healthcare professionals. However, more evidence is needed to determine factors that may influence HD and PD patients’ physical activity levels prior to developing exercise interventions.

**Funding:** Private Foundation Support
FR-PO528
Comparison of Outcomes Between Percutaneous and Surgical Placement of Peritoneal Catheters in Dialysis Patients: A Meta-Analysis
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Background: The successful insertion of the peritoneal dialysis catheter (PDC) ensures effective catheter function and technique survival. The most commonly used technique is the surgical approach by laparotomy or laparoscopy. Minimally invasive techniques are currently developing and seem to be an alternative. We evaluated the efficacy and safety of the percutaneous insertion methods compared to conventional surgical methods.

Methods: Studies comparing percutaneous and surgical methods of PDC insertion were identified through databases of PubMed, EMBASE, Cochrane and Web of Science. Catheter survival, dialysate fluid leakage, mechanical and infectious complications were analyzed using random effects model and results were presented as odds ratio (OR) and 95% confidence intervals (CI).

Results: Sixteen studies were finally identified. The pooled data demonstrated no differences in catheter survival, dialysate fluid leakage and mechanical complications between percutaneous and surgical way (OR = 1.24, 95% CI = 0.81–1.91, P= 0.33; OR =1.49, 95% CI = 0.98–2.26, P= 0.06; OR = 0.65, 95% CI = 0.39–1.08, P= 0.08, respectively). Infectious complications occurred less in percutaneous group (OR = 0.56, 95% CI = 0.32–0.96, P= 0.04). The malposition incidence was obviously lower in percutaneous method compared with surgical method (OR = 0.32, 95% CI = 0.28–0.82, P= 0.005). The detailed analysis on bleeding, omental wrapping, hernia, exit site infection; peritonitis and tunnel infection did not show difference.

Conclusions: The percutaneous method is a safe and effective alternative to insert peritoneal catheters and could be an optimal choice besides the conventional surgical way.

Funding: Government Support - Non-U.S.

FR-PO530
Point-of-Care Ultrasound in Peritoneal Dialysis Catheter-Related Infection: An Observational Study
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Background: Peritoneal dialysis (PD) catheter-related infection (PD-CRI) is the most common complication of this form of renal replacement therapy. The diagnosis of PD-CRI is made with physical examination (PE), but the physical findings lack sensitivity or specificity. Point-of-care ultrasound (POCUS) is an emerging discipline in the Nephrology community that allows the physician to incorporate real-time information from the ultrasound into his clinical evaluation. POCUS could improve the diagnostic accuracy of PD-CRI and reduce patient exposure to antibiotics. This single-center observational study aimed to compare the accuracy of POCUS and PE for the diagnosis of PD-CRI.

Methods: POCUS was performed by a Nephrology fellow using a linear transducer when PD-CRI was suspected. POCUS was repeated in every patient visit. PD-CRI was defined as purulent discharge with or without inflammatory signs, and a positive microbiological culture collected from the exit-site. We considered a positive POCUS as an anechoic collection around the external cuff, and its largest dimension was recorded. PE findings were coded using a validated clinical score.

Results: A total of 25 patients (58 % male) were enrolled. We also recruited nine patients with no signs of PD-CRI as controls. A total of 13 PD-CRIs were diagnosed, from 22 suspected cases. The most common isolated agent was Corynebacterium spp. In this population, the diagnostic accuracy of PE was low, with an area under the ROC curve (AUROC) of 0.6 (95% CI 0.37–0.84). Purulent drainage alone, although highly specific (100%), showed a low sensitivity (61.9%) for the diagnosis of PD-CRI. In contrast, POCUS had an AUROC of 0.91 (95% CI, 0.75–1) for PD-CRI diagnosis. All the PD-CRI cases had a positive POCUS evaluation, and we did not find this sonographic sign in controls (p < 0.001). The optimal cut-off point of the collection dimension was equal to or greater than 1.4 mm (Sensitivity 100%; Specificity 89%). Suspected PD-CRI cases with negative POCUS and not exposed to antibiotic therapy, had similar PD-CRI rates in one-month follow-up as the control group (p = 0.829).

Conclusions: POCUS is superior to PE for the diagnosis of PD-CRI and should be considered by nephrologists with access to an ultrasound machine. POCUS may decrease unnecessary antibiotic exposure in PD patients due to an increase in PD-CRI diagnostic sensitivity.

FR-PO529
Local Anaesthesia Peritoneal Dialysis Catheter Insertion: A Single-Centre Tertiary Care Renal Unit Experience from the United Kingdom
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Background: Peritoneal dialysis (PD) is one of the modalities for renal replacement therapy and requires inserting a PD catheter[PDC] into the peritoneal space and is traditionally a surgically assisted PD catheter insertion[SPDCI] under general anaesthesia[GA]. CKD5 patients are at high risk for GA. Local anaesthesia PDC insertion [LPDCI] has been done in those without previous abdominal surgery[PAS]. Peritoneal adhesions due to previous surgery can complicate insertions. We share our experience of LPDCI vs SPDCI from a tertiary care renal unit in the UK.

Methods: Retrospective data was collected from April 2017 to April 2018 and retrieved from electronic patient records and peritoneal dialysis unit notes. The analysis was performed using Microsoft Excel 2010.

Results: A total of 86 catheters were inserted in 83 patients. 35% (29) have diabetes. Peritonitis (3) and respite (1). Visits per patient ranged from 1-10. 50% (8) stayed on PD; 13% (2) switched to haemodialysis (HD); 31% (5) expired and 1 relocated.

Conclusions: Assisted PD provides an effective means to support frail or functionally limited PD patients, encouraging them to select it as a modality and/or remain on PD. In our pilot, providing this assistance enabled us retain 50% of our patients on PD, who would otherwise have had to transfer to in center HD. Assisted PD is a valid and safe alternative to in center HD and should be used to expand modality choices, overcome barriers to PD and shift care to home.

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Quality Improvement Strategies to Reduce Peritoneal Dialysis Catheter Insertion Wait Times: A 10-Year Experience

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Background: Bedside peritoneal dialysis (PD) catheter insertions have been effective in reducing wait-times, however laparoscopic insertions are still needed in patients with prior abdominal surgeries, high risk of leaks and hernia repairs. Our study was aimed to assess the impact of local quality improvement initiatives on wait-times for laparoscopically inserted PD catheters over a 10-year period.

Methods: We reviewed our database at the Toronto General Hospital for laparoscopic wait-times for PD catheter insertions between January 1, 2008 to December 31, 2018. Wait-times for catheter removals, manipulations and hernia repairs were reviewed. Buried PD catheters were excluded from analysis. A control chart analysis of mean quarterly wait-times for laparoscopically inserted PD catheters was performed. We captured the effect of three local interventions on wait times: interventional radiology program (fluoroscopic-guided), bedside insertion program and transition to becoming a centre of regional practice, wherein patients from other parts of the province were referred to us for more complex catheter procedures.

Results: A total of 379 new patients had laparoscopically inserted catheters between 2008 and 2018. Quarterly mean wait-time for catheter insertion was between 21.3 to 28.5 days (Figure 1). After becoming a regional centre of practice in 2016, mean wait-time for new insertions increased dramatically to 39.3 days. There was no change in access to operating room (OR) time during this period. After 2016, there was a 56.4% increase in external patients receiving procedures at our institution without increase in access to OR time. 51% of procedures were hernia repairs, catheter manipulations along with removal and reinserter.

Conclusions: Quality improvement strategies may initially help to reduce wait-times for PD catheter insertions. However, long-term success of these improvement strategies must be supported with administrative policies that lead to proportional increases in access to OR time.

Figure 1

Barriers to Peritoneal Dialysis in Saskatchewan Canada: Results from a Province-Wide Survey

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Background: Peritoneal dialysis (PD) offers similar clinical outcomes to hemodialysis (HD) at a fraction of the cost. PD remains underutilized as remote HD patients in Saskatchewan often relocate or travel hundreds of kilometers weekly in order to receive dialysis related care. The purpose of this study was to determine the barriers to receiving PD in our province.

Methods: We conducted a cross sectional survey of in center HD patients across the province of Saskatchewan. 740 in center HD patients at two academic sites and 7 satellite units were approached by study coordinators. 421 patients (n=268 in the main units and n=153 in the satellite units) agreed to participate in the study. A questionnaire using a five-point Likert scale was created to identify barriers to PD with questions addressing PD awareness and knowledge, accessibility, and risks/fears/beliefs surrounding PD. Results were analyzed using statistical analysis tool.

Results: Only 82% of patients were aware of PD as a treatment option. 35% of patients felt they had no understanding of the benefits or risks of PD. Prominent barriers to PD that we identified were: excellent care in the HD unit (62%), proximity to dialysis unit (41%), difficulty to dialyze daily (36%), and unwilling to learn a new technique (34%). Beliefs held by patients that figured prominently in their decision to choose HD over PD included not wanting to take their disease home (32%), fear of being a burden on family (32%), lack of space (28%), risk of infection, issues with self-image while on PD, and PD being an inferior modality to HD (all approximately 24%).

Conclusions: In this study, we identified patient specific barriers to PD in a prevalent cohort of patients. Several barriers were identified with a few consistent themes being identified, including deficiencies in knowledge, patient specific beliefs and poor patient education. The most frequently reported knowledge barrier was a lack of understanding of benefits and risks of PD. While the study does not reflect the views of all patients, the information gained will be valuable in designing an educational program to improve adoption of PD within our province.

Early-Start Peritoneal Dialysis: How to Increase This Modality?


Background: Despite the increasing incidence of end-stage renal disease (ESRD), peritoneal dialysis (PD) is one of the minor subset of patients. In the last decade, PD rates is the early start of technique after catheter placement without the usual break in times but there are concerns with mechanical and infectious complications that could compromise PD outcomes. The aim of this study was to compare the outcomes and safety of early PD start, after 12 and 24 months.

Methods: Retrospective analysis performed in a single-center; 52 patients: 34 started PD after planning (late start group - LSG) and 18 in the first 14 days after catheter placement (early start group - ESG). Demographic data, comorbidities, Charbon comorbidity index (CCI) were collected. PD related complications and dropout cases were identified.

Results: ESG present a male predominance (88.2% vs 58.8%; p=0.025) and higher CCI (35.9 vs 59.4% estimated 10-year survival) with a significantly prevalence of cardiovascular diseases (p=0.03). Average time between catheter placement and PD starting in the ESG was 5 days. LSG stayed longer under PD (913 vs 555 days). Kidney transplantation was the main cause of dropout in the LSG group whereas in the ESG the causes were mechanical issues and death. First episode of peritonitis (FP) occurred earlier in the ESG (478 vs 831 days) but this difference was not statistically significant among the two groups. The unadjusted Kaplan-Meier estimated that the difference in dropout-free survival was statistically significant in both groups (p=0.006, log rank test). Multivariate analysis with Cox regression demonstrated that, even though the risk of dropout was higher during the first 12 months in the ESG (HR=5.503; p=0.041), this decreases after 24 months (HR=2.363, 95% CI=1.036 of PD). The frequency of dropout was higher in the ESG (77.1% versus 61.8%) but this difference was not significant (p=0.242). When comparing the frequency of dropout after excluding patients that were transplanted, results were similar.

Conclusions: Urgent-start PD can be a valid and safe alternative to hemodialysis via central venous catheter and should be offered to patients without contraindication. Other factors not related to the early start of technique (age and higher CCI), can have a negative impact on the morbidity and mortality of those patients influencing the outcomes of DP technique.

International Variation in Outcomes after PD-Related Peritonitis

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Background: Peritoneal dialysis (PD)-associated peritonitis is a major source of morbidity, mortality, and technique failure for patients receiving PD. We sought to understand if there were regional differences in peritonitis outcomes.

Methods: We used Peritoneal Dialysis Outcomes and Practice Patterns Study phase 1 (2014-2017) data from Australia and New Zealand (ANZ), Canada (CA), Japan (JP), Thailand (TH), the UK, and the US to report variation in peritonitis outcomes (up to 50 days after diagnosis) by country and to estimate associations with organism type using logistic regressions adjusted for country, age, sex, diabetes, and serum albumin. Cure was defined as the lack of any outcome except hospitalization. Technique failure (TF) was defined as permanent transfer to hemodialysis or failure to resume PD within 12 weeks.

Results: We observed 2270 peritonitis episodes in 6949 patients during 7816 years of follow-up (crude rate: 0.29 episodes/year). Cure proportion was 64% (range by country: 54-68%), and death occurred in 6% (JP: 2%; TH: 16%; others: 4-5%). Hospitalization was common for both peritonitis-related causes (35%, range: 41-75%) and for any cause (72%, range: 59-93%), with >80% occurring within 14 days. Relapsing/recurrent peritonitis occurred in 9% (range: 7-14%), and concurrent exit-site infection occurred in 12% (JP: 19%; TH: 6%; others: 9-10%). Catheter removal occurred in 21% (TH, JP: UK: 24-29%; others: 18-20%), and TF occurred in 16% (TH: 10%; others: 16-19%). Higher rates of death, TF, or catheter removal were seen for Gram-negative (OR=2-78, 95% CI=2.03, 3.8), culture negative (OR=1.3, 95% CI=0.92, 1.83), polymicrobial (OR=4.43, 95% CI=2.89, 6.79), and missing/unknown peritonitis (OR=2.64, 95% CI=1.89, 3.69), compared to Gram-positive peritonitis.

Conclusions: High proportions of peritonitis resulting in death (Thailand) and TF (all countries) suggest novel interventions to prevent peritonitis are needed. Emphasis on...
FR-PO535
Declining Peritonitis Rates Incompletely Translate into Improved Technique Survival in Australian Peritoneal Dialysis Patients

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Background: Peritoneal Dialysis (PD) peritonitis rates are declining, but not matched by a uniform reduction in technique failure (TF) rates. Understanding the reasons for this disconnect will potentially help identify new targets for intervention.

Methods: 13653 incident PD patients undergoing first PD treatment episodes in Australia between 2003 and 2017 were analysed for TF in 3-year cohorts. Instances of TF were segregated into infective or non-infective causes and cumulative incidences (CI) calculated at 1- and 2-years on death-censored technique failure (transferred to HD or TF >30 days) with death as competing risks. CI calculated using the Fine and Grey method.

Results: The peritonitis rate in Australia halved over the observation period. There were substantial improvements in death rates during PD treatment. However, there were minimal or no changes in death-censored PD technique failure (DCTF). Adjustment for age and diabetes had little impact on TF rates at 1 and 2 years, with a similar fall at 2 years. After adjustment for age and diabetes, there was a suggestion of moderate improvement among the most recent cohort.

Conclusions: PD peritonitis rates have declined substantially over the study period as have death rates, but overall technique survival has changed only modestly. Non-infective causes of DCTF are proportionately higher; identification of modifiable risk factors provide the next target to enhance PD outcomes.

FR-PO537
Interesting Relationship Between Levels of Thioredoxin and Vitamin D on Antioxidant System in Peritoneal Dialysis Patients

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Background: The reactive oxygen species produced continuously during oxidative metabolism are generated at very high rates in chronic kidney failure. Therefore, defending against oxidative stress is an essential task with the patients who suffering from that disease. An important cellular system against oxidative stress is the cysteine mammalian thioredoxin system (TS) which consist of thioredoxin (trx), nicotinamide adenine dinucleotide phosphate (NADPH) and thioredoxin reductase (TrxR) has emerged as a major anti-oxidant which involved in the maintenance of cellular physiology and survival. Vitamin D is also an other strong antiinflammatory molecule and it has a growing of number of studies revealing its pleiotropic roles beyond the bone and calcium metabolism. The aim of this study is to find a significant relation between these two systems.

Methods: We conducted a study of 69 patients with end stage kidney disease who were under the treatment of continuous ambulatory peritoneal dialysis or automated peritoneal dialysis. Serum thioredoxin level were measured. Measurements were corrected according to comorbid diseases, medications, duration and type of peritoneal dialysis and residual renal function. In addition, they were also evaluated for the correlation between hemoglobin, uric acid, CRP, albumin, ferritin, lipid parameters and iPTH levels. Our aim was to prove the effect of the use of Vitamin D supplementation on thioredoxin as an anti-oxidant system. 40 out of 62 patients were already under the vit D supplementation but the rest of the group was not eligible.

Results: There was no statistically significant difference between Thioredoxin measurements according to PD type, etiology and drugs (p > 0.05) but Thioredoxin levels in patients with vit D supplementation were significantly higher than those without vit D supplementation. (p < 0.01). The results were evaluated in a confidence interval of 95% and a significance level of p < 0.05.
Conclusions: This result of study was not suprising but important because it emphasized that Vit D anti-inflammatory effect especially in chronic kidney failure patients except the bone-mineral metabolism and pointed to strict follow-up Vit D level in this group which is already under the inflammatory situation to reduce complications related to oxidative stress by contributing the augmentation of thioredoxin serum level.

FR-PO538
A Case of Scleroderma Renal Crisis in a Patient with Systemic Sclerosis Sine Scleroderma
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Introduction: Scleroderma renal crisis (SRC) typically presents with abrupt onset of accelerated hypertension (HTN) and acute kidney injury (AKI) usually in patients with diffuse cutaneous Systemic Sclerosis (dcSSc). We report a case of SRC in a patient with systemic sclerosis sine scleroderma (ssSSc), a rare form that presents with visceral involvement in the absence of skin manifestation.

Case Description: A 64 year old female with a history of Raynaud’s phenomenon, seronegative rheumatoid arthritis and HTN was admitted to Northwestern Memorial Hospital with shortness of breath, uncontrolled HTN and AKI. Her blood pressure (BP) ranged from 165/94 to 194/100 mmHg. She had bilateral crackles, no lower extremity edema and no skin manifestations of scleroderma. Anti nuclear antibody was positive >1:1280 with a negative serologic work up including anti-SCL-70, anti-centromere and RNA polymerase III antibodies. Urinalysis was without protein or blood. HTN was uncontrolled and captopril was started with good BP response. AKI worsened and a kidney biopsy was performed (Fig). Pathology showed ischemic glomerulopathy, marked arteriolaris with onion skinning and vascular lesions suspicious for thrombotic microangiopathy concerning for SRC. Her clinical course deteriorated rapidly with the development of severe pulmonary HTN, heart and renal failure.

Discussion: ssSSc is a rare form of systemic sclerosis. Two types of ssSSc patients have been described and the course can follow either limited scleroderma or dcSSc. The latter can have delayed scleroderactyly and early vital organ involvement similar to our case. Clinicians need high degree of suspicion to diagnose ssSSc given the lack of skin findings. While serologic testing can help with diagnosis, SRC is a clinical diagnosis that can be enhanced by renal biopsy. This case highlights the difficulty in diagnosing patients with SRC in the setting of ssSSc.

FR-PO539
Scleroderma Renal Crisis in a Patient with Paraneoplastic Syndrome
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Introduction: Scleroderma renal crisis affects 5-10% of patients with systemic sclerosis, with 5-year survival rate of 59%. Anti-RNA polymerase IIIAb are associated with risk of SRC and cancer. We describe a patient with paraneoplastic scleroderma who presented with AKI and HTN after steroid use and diagnosed with SRC.

Case Description: A 55-year-old woman with h/o HTN, Endometrial cancer (3/2017) s/p TAH-BSO, tumor debulking, paraneoplastic scleroderma (diagnosed a month back with autoimmune antibodies to RNA polymerase III) was sent to ER for worsening creatinine(2 mg/dl to 4.6 mg/dl in 2 weeks). Of note patient was noted to have worsening liver enzymes 2 months back and underwent liver biopsy which showed ductopenia and fibrosis. Given suspicion of an autoimmune process treatment was initiated. On admission, patient was in acute respiratory distress requiring intubation, hypertensive (SBP 180mmHg) and in renal failure. Diagnosis of SRC was made, Captopril was initiated and steroid was discontinued. Renal biopsy showed TMA with extensive involvement of arteries, arterioles, extensive (50%) ischemic glomerular alteration, segmental duplication of glomerular capillary wall and moderate tubular injury. No significant interstitial fibrosis/tubular atrophy. She was discharged on dialysis.

Discussion: SRC is characterized by presence of high blood pressure with variable degrees of renal insufficiency:5-20% of patients with diffuse scleroderma are at risk of developing SRC. A positive RNA Pol IIIAb, present in our patient, further increases the risk of developing renal crisis. SRC associated with paraneoplastic scleroderma is even rarer. An extensive review of the literature showed only 4 cases of SRC in patients with ovarian, lung, breast and renal carcinoma. Given that SRC is a potentially life-threatening disease, we should have a high degree of suspicion in patients with scleroderma who present with hypertension and acute renal failure.

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FR-PO542
Low Alanine Aminotransferase in Hemodialysis Patients: A Marker for Pyridoxine Deficiency
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Introduction: Hemodialysis (HD) patients often have lower serum alanine aminotransferase (ALT) levels than those with normal kidney function. There are multiple proposed mechanisms with controversy surrounding the contribution of pyridoxine (vitamin B6) deficiency, a cofactor for liver aminotransferase synthesis. We present a remarkable case of pyridoxine deficiency diagnosed in a HD patient by an undetectable ALT.

Case Description: A 71-year-old woman on HD for 6 years was admitted for an infected hand wound. She also had a duodenal switch surgery for obesity 17 years prior. Home medications included a dialysis multivitamin and pyridoxine 100 mg daily, though she hinted at variable adherence to both due to insurance issues. Admit labs incidentally showed an undetectable ALT level, confirmed on repeated testing. Bilirubin and AST were normal. She had a normal ALT 4 months prior and past imaging showed no cirrhosis. Subsequent pyridoxine testing, measured in its active form of pyridoxal 5'-phosphate, was low at 7.3 nmol/L [Normal 20-125 nmol/L]. Other water-soluble vitamin levels including thiamine and cobalamin were normal. She was given 10 mg pyridoxine IV daily for one week with maintenance 100 mg oral daily. Follow up 4 weeks later revealed improved pyridoxine levels to 29.3 nmol/L and a now detectable ALT level of 9 U/L. She remains on a dialysis multivitamin and oral pyridoxine 100 mg daily.

Discussion: Aminotransferases are often drawn with routine labs in the dialysis population, with elevations signaling concern for pathology such as infectious hepatitis. However, undetectable or borderline levels may not alarm practitioners, particularly as aminotransferases are known to be lower in HD patients. This poses a risk of missing a diagnosis of pyridoxine deficiency, which may ultimately cause progressive anemia, neuropathy, and confusion. Vitamin B supplementation in HD is accepted as routine due to a restrictive diet and dialytic removal, though insurance coverage may be sporadic. Our data also suggests that critical review and awareness of the extent of extrarenal complications following renal angioplasty may prevent or at least hasten the diagnosis of post-revascularization complications.

FR-PO543
Unique Cause of Renal Infarction: A Case of Pheochromocytoma
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Introduction: Pheochromocytomas (PHEOs) are rare chromaffin cell derived neuroendocrine tumors. Common presentations include paroxysmal episodes of headache, palpitation, sweating and hypertension. Life threatening complications including renal artery stenosis, and acute myocardial infarction had been reported from the possible mechanism of catecholamine-induced vasospasm and/or extrinsic compression of renal artery in some reported cases. Here, we report an interesting case of PHEOs associated with renal infarction, unrelated to artery thrombosis/stenosis.

Case Description: A 48 year old male with no significant past medical history presents to the emergency room (ER) with sudden onset headache and blurring of vision. Vital signs revealed blood pressure of 215/120 mmHg. No focal neurological deficits were noted. Laboratory work was unremarkable. CT head and CT angiogram of head and neck obtained revealed no evidence of intracranial hemorrhage. He left against medical advice at that time, but returned two days later to the ER with left flank pain. This time his vital signs showed blood pressure of 100/60 mmHg, and he had left sided abdominal tenderness. Laboratory work revealed troponin of 23.65 ng/mL [normal, <0.04ng/ml]. Abdominal and chest CT scan showed large wedge like non-enhancing region in the lateral mid to upper pole of left kidney and solid heterogeneous 4.9 cm right adrenal gland mass. PHEOs was suspected, and he was started on doxazosin plus atraipan. Cardiac catheterization was deferred. Specific laboratory work revealed high levels of total plasma catecholamine, plasma metanephrine, nor metanephrine, and chromogranin A respectively. Twenty-four hour total urinary metanephrines, normetanephrines, and catecholamines were also markedly raised. The patient underwent uncomplicated laparoscopic right adrenalectomy few weeks after this admission. Surgical pathology confirmed the diagnosis of PHEO.

Discussion: The workup and definitive diagnosis of PHEOs continue to be challenging. We present a case of PHEOs with renal infarction. Renal infarction from renal artery stenosis/thrombosis has been well documented in the literature. Our case is unique in its presentation, in that his renal infarct was independent of renal artery stenosis or thrombosis. We hypothesize, this was most likely from wide variation in blood pressure, and possible hypertensive episode, in the absence of renal artery pathology.

FR-PO544
Renal Artery Aneurysm in Dialysis Patients
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Introduction: Renal artery aneurysms(RAAs) are rare(less than 1% in the general population), with most found incidentally on abdominal imaging. Aneurysm rupture has a high mortality and morbidity if not recognized in a timely manner.

In view of this and resistant hypertension, he underwent B/L renal angioplasty and stenting. Post intervention BP in the clinic was 123/89 mmHg despite a 50% decrease in BP medications. On day 3, he developed diffuse, progressively worse abdominal pain, along with nausea and vomiting. Laboratory tests showed leukocytosis and elevated lactate. Computed tomography scan confirmed diagnosis of subacute mesenteric ischemia due to superior mesenteric artery (SMA) occlusion and progressive stenosis of celiac trunk. He underwent stenting and angioplasty of the latter which resolved his symptoms. At 1 month, his BP was 106/68 on 3 drugs.

Discussion: Renal artery stenting for drug resistant hypertension improved this patient’s BP. However, the decrease in systemic BP made the hitherto non-critical stenoses of aortic branches clinically critical, thus precipitating bowel ischemia. This highlights some of the mechanisms behind the morbidity associated with renal revascularization.

Our data also suggests that critical review and awareness of the extent of extrarenal atherosclerosis prior to renal angioplasty may prevent or at least hasten the diagnosis of post-revascularization complications.

Upper panel-renal artery stenting,Lower panel-stenosis in celiac artery(left), SMA(right)
Case Description: We present two case–both end stage renal disease (ESRD) patients who presented with RAA rupture. The first patient was a 56 year old African American male on intermittent hemodialysis who presented with complaints of right sided flank pain for one day, without associated trauma, fevers, hematuria and hemoglobin of 7.7mg/dl on labs. A CT scan showed a right retroperitoneal hematoma. CT angiogram revealed two small pseudoaneurysms in the right renal artery with active extravasation that was successfully coiled. The second patient, a 72 year old Hispanic male, on peritoneal dialysis, was admitted to the critical care unit after an ischemic stroke. He was found to have Atrial fibrillation and started on a heparin drip for anticoagulation. His anti-hypertensive medications were held to allow for permissive anti-hypertension. However, his hemodynamics worsened shortly afterwards requiring pressor support and stat labs revealed a drop in hemoglobin to 3.6mg/dl from 9.9mg/dl. Point of care ultrasound demonstrated a hypoechoic area around the left kidney. CT angiography showed multiple areas of contrast blush in the left kidney consistent with active bleeding. IR guided coil embolization of the left renal artery was performed successfully and bleeding was stopped.

Discussion: RAA are associated most commonly with hypertension, followed by connective tissue diseases like fibromuscular dysplasia, Ehler–Danlos syndrome, Marfan syndrome, and vasculitis (such as polyarteritis nodosa and chronic granulomatous with polymyalgia rheumatica). Afterthrombosis is also associated with RAA but exact causative mechanism is not known. RAA rupture may present with back pain, abdominal pain, ileus, and hemorrhagic shock with CT showing retroperitoneal hematoma. Patients with chronic kidney disease and end stage renal disease have several risk factors for development of RAA and rupture. Clinicians should have high suspicion for RAA rupture in dialysis patients presenting with abdominal pain, uncontrolled hypertension and sudden drop in hemoglobin. Endovascular treatment is a minimally invasive option available to treat renal artery aneurysm even in setting of aneurysmal rupture and bleeding as is gaining favor over open surgical repair.

FR-PO545
MobiusHD® Device: Controlling Refractory Hypertension in ESRD
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Introduction: We discuss an interesting case of a patient on dialysis with severe hypertension. As a life saving measure we were granted compassionate use of the MobiusHD device, a baroreflex modulator implanted in the carotid artery. We discuss the outcomes and potential benefits of this device seen in this case.

Case Description: The patient is a 22-year old female with history of ESRD due to FSGS. She was diagnosed at a young age and underwent kidney transplantation at 11. She unfortunately went back on dialysis in 2016 at age 19 due to recurrent rejection and obstruction from a ureteric stricture. On dialysis she was noted to have extremely labile BP. In the 12 months prior to MobiusHD implantation, she had 22 admissions. Most were for hypertensive emergency requiring clevidipine. She also had an admission for PRES with the subsequent cycle#3. Current hypothesis of PRES involves two small pseudoaneurysms in the right renal artery with active extravasation that was successfully coiled. The second patient, a 72 year old Hispanic male, on peritoneal dialysis, was admitted to the critical care unit after an ischemic stroke. He was found to have Atrial fibrillation and started on a heparin drip for anticoagulation. His anti-hypertensive medications were held to allow for permissive anti-hypertension. However, his hemodynamics worsened shortly afterwards requiring pressor support and stat labs revealed a drop in hemoglobin to 3.6mg/dl from 9.9mg/dl. Point of care ultrasound demonstrated a hypoechoic area around the left kidney. CT angiography showed multiple areas of contrast blush in the left kidney consistent with active bleeding. IR guided coil embolization of the left renal artery was performed successfully and bleeding was stopped.

Discussion: We analysed all cases of PRES in pediatric renal patients in our hospital in the last 5 years and found only 3 cases. All of them are adolescents with active lupus nephritis (LN) on hemodialysis (HD).

Discussion: All our patients had multiple risk factors for PRES: LN, new onset HD, cyclophosphamide, hypoaalbuminemia, hypertension, immunosuppression. Recurrent PRES and status epilepticus (SE) have rarely been described in children.

FR-PO546
Secondary Hyperoxalemia Causing Cardiac Failure in an ESRD Patient
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Introduction: Secondary hyperoxaluria is a known complication of bariatric surgery due to impaired fat absorption. Oxalate deposition leading to organ dysfunction is poorly defined outside of primary oxalosis. We describe a case of cardiac and renal oxalosis with end-organ failure secondary to gastric bypass surgery.

Case Description: A 65-year-old male on hemodialysis for 3 years with history of heart failure with preserved ejection fraction (EF), jejunal oxalosis at age 18 and right nephrectomy due to cystic mass presented for exertional dyspnea and orthopnea after newly establishing care with us. His ESRD was presumed due to chronic nephrolithiasis after his jejunal bypass surgery. Electrocardiogram demonstrated atrial fibrillation and low QRS voltage. Transthoracic echocardiography (TTE) showed mildly thickened left ventricular wall with granular, sparkling texture to the myocardium, preserved EF, and biatrial enlargement concerning for cardiac amyloidosis. Serum immunofixation revealed an IgA lambda spike of 0.9 g/dl with kappa and lambda serum free light chains of 19mg/dl and 28mg/dl (ratio 0.67). Bone marrow aspiration showed 5%-10% plasmacytosis, a lambda predominance and negative Congo red stain. Fat pad biopsy was negative for amyloidosis. Myocardial biopsy demonstrated diffuse cardiac oxalosis and interstitial fibrosis; Congo red stain was negative. Retrieval and staining of frozen tissue from prior nephrectomy revealed diffuse oxalosis with interstitial fibrosis. Serum oxalate levels before and after dialysis were 27 and 8 mmol/L (normal ~1.6), respectively, with an oxalate reduction ratio of 67%.

Discussion: Cardiac and renal oxalosis may have resulted from jejunoileal bypass, a now uncommon surgery. Oxalate is well cleared by HD, but long-standing hyperoxaluria may be present in ESRD and between dialysis sessions likely led to myocardial deposition. Patients with ESRD due to secondary hyperoxaluria should continue to adhere to a low oxalate diet and regular dialysis sessions to prevent extra-renal oxalate deposition. Our case also illustrates that low QRS voltage in association with increased left ventricular wall thickness and a sparkling, granular appearance of the myocardium on TTE is not specific for cardiac amyloid, but may suggest cardiac oxalosis in the appropriate setting.

FR-PO547
Different Faces of PRES in Adolescent Lupus Nephritis on Hemodialysis
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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a neurologic condition characterized by seizures, altered mental status, headache, visual changes and specific findings on MRI. For pediatric PRES atypical involvement of frontal lobes, basal ganglia or cerebellum is not rare. Risk factors include SLE, renal disease, dialysis, hypoalbuminemia, hypertension, immunosuppression. Recurrent PRES and status epilepticus (SE) have rarely been described in children.

Case Description: We analysed all cases of PRES in pediatric renal patients in our hospital in the last 5 years and found only 3 cases. All of them are adolescents with active lupus nephritis (LN) on hemodialysis (HD).

Discussion: Our patients had multiple risk factors for PRES: LN, new onset HD, cyclophosphamide, hypoaalbuminemia, hypertension. Despite the common predisposing factors, they all had different but atypical course of PRES. Case 1 had PRES one year after an initial lupus cerebritis and had a concurrent pulse therapy following seizure event because of concern for recurring cerebritis. Case 2 had recurrent PRES while she was on nicardipine drip. Case 3 had SE associated with PRES, a very rare condition. Both cases 2 and 3 received the cycle#2 of cyclophosphamide 2 weeks before onset of PRES. However, there was no PRES with the subsequent cycle#3. Current hypothesis of PRES involves vasogenic edema due to an endothelial injury. Hypertension is a consequence rather than the cause of the disorder; and it may be absent in PRES. LDH was suggested as a useful marker for identification of patients before onset of clinical symptoms. Unfortunately, in our cases LDH was not done. Further studies are needed on the role of LDH as a predictive tool for establishing potential preventive measures such as strict BP control, empirical antiepileptic drug, and optimal fluid control in high risk individuals.
Clinical characteristics during the PRES episode with seizures

<table>
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<td>BI-IV</td>
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<td>IV-IV</td>
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Discussion: In contrast to other conditions leading to death in ESRD patients, metastatic pulmonary calcification does not usually cause symptoms, can result in quick respiratory decline and is often identified only at autopsy as routine chest X-rays are mostly negative. MPC may remain undiagnosed and untreated, at times progressing to severe acute respiratory failure. It is of paramount importance that we not only do timely detection and treatment but also explore new diagnostic and therapeutic methods for MPC to decrease overall mortality in ESRD patients.

FR-PO550

The Heart of Calcium

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Introduction: Calciphyaxis or calcific uremic arteriopathy is a rare disorder causing diffuse calcification of arteries in dermis and subcutaneous tissue. We here by present a case of systemic calciphylaxis presenting as non infective endocarditis with stroke.

Case Description: 59 year old Caucasian female with End stage Renal disease secondary to Microscopic polyangiitis (with only renal involvement + PANCA) for 2 years initially on hemodialysis for a year and then switched to peritoneal dialysis, presented to the hospital with subjective fever and shortness of breath concerning for multifocal pneumonia. Echo showed 1.5 x 2 cm mitral valve vegetation and PFO. Her infectious work up was persistently negative including blood cultures for bacterial, fungus and AFB. She did not have fever during hospitalization. Hospital course was complicated by stroke thought to be embolic from valve vegetation. With worsening clinical conditions she underwent mitral valve replacement and mitral valve pathology showed myxoid degeneration, with no inflammation or organism but calcification and cultures remained negative. On presentation patient also complained of painful hard nodules from ankle to knee of posterior bilateral lower extremities for 6 months. Biopsy was diagnostic for calciphylaxis. She had elevated phosphorus to 11 and PTH of 780 on presentation. Her infectious work up was persistently negative including blood cultures for bacterial, fungus and AFB. She did not have fever during hospitalization. Hospital course was complicated by stroke thought to be embolic from valve vegetation. With worsening clinical conditions she underwent mitral valve replacement and mitral valve pathology showed myxoid degeneration, with no inflammation or organism but calcification and cultures remained negative. On presentation patient also complained of painful hard nodules from ankle to knee of posterior bilateral lower extremities for 6 months. Biopsy was diagnostic for calciphylaxis. She had elevated phosphorus to 11 and PTH of 780 on presentation. The mobile masses seen on echocardiography were likely to represent healed vegetations that had calcified as a result of calciphylaxis. She was started on intensive daily dialysis and sodium Thiosulfate with good outcome.

Discussion: High clinical suspicion is warranted to make the diagnosis of calciphylaxis. Despite a multi-interventional approach for calciphylaxis, the disease remains associated with a high morbidity and mortality. To our knowledge this is the first reported case of non infective endocarditis with complication of stroke as the initial manifestation of calciphylaxis followed by further work up showing skin involvement, with ultimate good outcome.

FR-PO548

An Unusual Vaginal Discharge: The First Reported Case of Peritoneal Dialysis Catheter-Fallopian Tube Fistula

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Introduction: Complications of peritoneal dialysis(PD) include obstructions and fistulas. Obstructions can result from various reasons including omental or fallopian tube wraps while communications/fistulas between the bladder and colonic walls are also possible. Vaginal discharge of PD fluid with an anatomically intact pelvis is not yet reported.

Case Description: The patient is a 42-year old African American woman with a past medical history of Lupus Nephritis and End-Stage Renal Disease on Peritoneal Dialysis(PD) for the past 5 years with poor compliance and repeated episodes of peritonitis. The patient reported an episode of abdominal pain and reported intermittent incontinence with painless vaginal discharge. These symptoms were not initially considered to be related to PD. She was treated for repeat peritonitis and vaginitis/cervicitis. She also reported that the discharge happens only during the fills on PD. She was admitted for peritonitis and PD was resumed. Within an hour of resuming dialysis, she had a large amount of fluid leak from the vagina. Obstetrics and Gynecology performed a pelvic examination that did not reveal an overt fistula or any abnormal findings. CT scan with contrast showed PD catheter coiled in the pouch of Douglas. The contrast went through the catheter to the right fallopian tube, entered the uterus and extended through the cervix into the vagina. It appears that the patient had formed collections on the pelvic floor, and one had PD Cath in direct communication with the fallopian tube. The patient underwent an exploratory lap with salpingectomy. She transitioned to hemodialysis electively.

Discussion: This case highlights the differentials of vaginal discharge in a woman on PD. The patient had reported various concerns like possible intermittent incontinence, sudden vaginal discharge. All these symptoms were not considered to be related to PD, thus delaying diagnosis. Her abdominal pain was related to peritonitis and loculating collection in the abdomen. The painless vaginal discharge was happening through natural communications between the peritoneum, fallopian tube, and vagina. Abnormal fistulas are possible with excoriations and infections leading to friable organs, as also through natural orifices. Vaginal discharge in PD patient should lead to detailed exam and imaging.

FR-PO549

A Queer Case of Rapidly Progressive Metastatic Pulmonary Calcification (MPC) in a Patient with ESRD: Are We Doing Enough?

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Introduction: Metastatic pulmonary calcification (MPC) is a metabolic lung disease which can be rapidly under-diagnosed and can prove fatal. Despite its high prevalence, it remains undetected. We describe a case of MPC in a young female patient with ESRD which ultimately led to patient’s demise.

Case Description: A 32 year old female with history of end stage renal disease (ESRD) and having autosomal dominant polycystic kidney disease presented with generalized weakness for 2 months. She had been on hemodialysis (HD) for 3 years but was not compliant with dialysis. Physical exam was grossly unremarkable and vital signs were within normal limits. Relevant laboratory findings included BUN of 73 mg/dl, Cr of 117 mg/dl, phosphorus of 8.2 mg/dl, calcium of 11.1 mg/dl and PTH was 1284 pg/ml. Broad spectrum antibiotics were initiated. Few hours into admission, she rapidly deteriorated, became confused and was subsequently intubated and transferred to the Intensive Care Unit. High Resolution CT scan of the chest showed very dense airspace opacification (measuring a mean attenuation of 329 HU), involving the right middle lobe and left upper lobe (including the lingula) with patchy dense opacification elsewhere. Patient remained afebrile. Blood cultures, sputum cultures, tuberculosis quantiferon and bronchoalveolar lavage were negative for any infection. Technetium (Tc) 99 bone scan disclosed diffuse activity in the pulmonary parenchyma, strongly supporting metastatic pulmonary calcification Despite escalating supportive measures, the patient became increasingly hypoxic and died 4 days later.

FR-PO551

Ostetis Fibrosa Cystica in Renal Osteodystrophy Masquerading as Malignancy

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Introduction: High bone turnover in renal osteodystrophy is a rare clinical entity nowadays to early diagnosis and treatment of secondary hyperparathyroidism. Since it is a diagnosis of exclusion, a formidable diagnostic challenge exists when the likelihood of malignancy is high in an elderly ESRD patient.

Case Description: A 64-year old African American man with a history of HTN, cardiomyopathy with ICD and ESRD on hemodialysis was admitted for pathological fracture of L2 with no neuro deficit. Imaging showed generalized osteopenia, burst fracture of L2, radiolucent foci all over the spine. Preliminary diagnosis of malignancy was made, and cord compression was ruled out. Biopsy from L2 revealed- i. reactive bone with prominent peri-tribacular fibrosis, ii. patchy hemosiderin-laden macrophages and iii. increased number of multinucleated osteoclasts indicative of bone resorption. Skeletal survey was inconclusive for malignancy or myeloma. Contrast CT abdomen and pelvis reported cortical erosion of synphysis pubis by a mass measuring 3.7 cm x 4.3 cm.
Biopsy from the mass revealed focal granulation tissue and hemosiderin-laden macrophages. Blood work for myeloma showed only polyclonal gammapathy on SPEP. Serology for tumor markers was negative and TB was ruled out. Meanwhile, the patient received multiple units of PRBC, periodic filgrastim and darbepeoin injection for pancytopenia. Bone marrow biopsy reported high normocellular marrow, polyclonal plasma cells, hemosiderin-laden macrophages, extensive peri-trabecular fibrosis and brown tumor (both lytic and expansile mass) and/or peri-trabecular bone marrow fibrosis. Clinical and histopathological co-relation is crucial for such a diagnosis.

**Case Description:** This case illustrates the importance of considering secondary hyperparathyroidism as the possibility of a lytic bone lesion in the ESRD population. High bone turnover in hyperparathyroidism can manifest as osteitis fibrosa cystica (lytic lesion), brown tumor (both lytic and expansile mass) and/or peri-trabecular bone marrow fibrosis.

**Discussion:** The case report highlights the diagnostic and therapeutic challenges in managing bone lesions in chronic kidney disease. The patient's history of dialysis and CKD-related anemia necessitated a comprehensive approach to bone health management. The use of zoledronic acid was effective in resolving the lytic lesions and improving anemia, underscoring the importance of early intervention to prevent complications.

**Conclusion:** This case underscores the need for interdisciplinary collaboration in the care of patients with chronic kidney disease and highlights the importance of regular bone health assessments to prevent and manage bone lesions associated with dialysis.
should be removed is a challenge. We present two cases of remote ambulatory pulmonary artery (PA) pressure measurements in dialysis patients with HF using cardioMEMS.

Case Description: Case 1. Heart Failure with Preserved Ejection Fraction

65-year-old Caucasian female, history of type II diabetes, hypertension, and CKD, NYHA class III systolic HF. Echocardiogram LVEF <20%. CardioMEMS was implanted in 2016. Patient had declining kidney function and a right upper arm arteriovenous fistula was placed, iHD initiated in 2018. His PA pressure readings by CardioMEMS gradually declined after initiation of dialysis (Figure 2).

Discussion: Hemodialysis resulted in significant changes in the PA pressure in HF patients. Remote ambulatory monitoring of PA pressures is a promising strategy in dialysis patients with HF since it might guide the management of volume status and allowing early interventions.

FR-PO556

Striking Radiological Findings of Visceral Arteries Calcification in a Severe Calciphylaxis Patient

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Introduction: Calciphylaxis is a rare complication of end stage renal disease characterized by calcification, fibrointimal hyperplasia, and thrombosis in the subcutaneous adipose tissue and dermis. Skin biopsy is the standard method for confirmed diagnose but it’s still controversial for creating new wounds. The imaging characteristics of calcification may help diagnose calciphylaxis. This article reports a severe visceral calciphylaxis patient confirmed by skin biopsy with striking calcification of the visceral vessels.

Case Description: A 45-year-old female with systemic lupic erythematosus have a 14-year medication history of oral glucocorticoids and 10-year maintenance hemodialysis. She had an erythema on toes and deteriorated into painful dry gangrene with infection 1 month before admission (Fig 1). Skin biopsy (Fig.2) confirmed the diagnosis of severe calciphylaxis. Interestingly, her imaging findlings showed striking calcification of visceral blood vessels. Extensive calcification of arteries of pancreas, kidneys and intestinal canal can be seen in the computed tomography scan (Fig.3). Although she doesn’t have symptoms of visceral ischemia such as chronic abdominal pain or gastrointestinal bleeding, it may be a predictor of visceral calciphylaxis and she may show symptoms of visceral ischemia or bleeding one day. Computed tomography angiography (CTA) of the lower limbs shows diffuse calcification the lower extremity arteries and soft tissues. Exactly, bone scintigraphy scan proved abnormal diffuse high uptake of subcutaneous soft tissue in crus that is in consistence with what shown in CTA (Fig.4). The efficacy of therapies based on sodium thiosulfate is still in follow-up.

Discussion: Characteristic histological features of calciphylaxis include medial arterial calcification and thrombosis in arteries. This patient has typical clinical manifestations of severe calciphylaxis and striking imaging features of visceral vascular calcification. Biopsy in visceral arterioles is difficult, so that the combination of multiple imaging methods is valuable to early diagnosis of visceral calciphylaxis.

FR-PO557

Effluent Colors in Continuous Hemodialfiltration

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Introduction: Continuous venovenous hemodiafiltration (CVVHDF) is widely used as a renal replacement therapy modality on patients with acute kidney injury. It usually generates a yellow citrine outflow that is stored as effluent. Bellow we describe 2 cases of unusual effluent color changes due to special clinical situations in our center.

Case Description: Case Report 1- Red effluent fluid: An 38 year- old female patient admitted to the ICU after mitral valve replacement surgery developed Acute Kidney Injury (AKI). CVVHDF was attempted and on the 14th day after surgery, effluent fluid was red colored, concomitant with the spike of CPK and the diagnosis of rhabdomyolysis. Dipstick analysis revealed the presence of hemoglobin (false positive). Microscopic evaluation of the effluent fluid was negative for the presence of red blood cells, thus excluding the possibility of rupture of the filter. Myoglobin concentration on the effluent was 1765 UI/L. Case report 2- Green effluent fluid: An 50 year-old male patient admitted to the ICU after myocardial revascularization surgery developed AKI and CVVHDF was attempted. Due to refractory shock methylene blue was added to the vasoactive drugs arsenal and 30 minutes later the effluent fluid removed by CVVHDF was green colored.

Discussion: Changes on the CVVHDF effluent color to red should alert the nephrologist to the possibility of hemolysis or dialyzer membrane compromise. Because of it’s high molecular weight and a Sieving coefficient of less than 0,1% hemoglobin is not expected in the dialysate. However myoglobin has a much smaller molecular weight and a Sieving Coefficient of 40%, therefore it should be considered as a possible cause of red dialysate. Blue colored effluent occurred most likely due to and additive effect of the methylene blue with the usual citrine yellow effluent color.

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FR-PO558
Acquired Autoimmune Hemophilia A After Initiation of Hemodialysis
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Introduction: Acquired hemophilia A is a rare autoimmune disorder in which circulating IgG antibodies inhibit and deplete coagulation factor VIII. It is common in patients with congenital hemophilia A after factor VIII transfusions but rare without preexisting hemophilia. Presentation in adults is similar to the congenital form, with spontaneous hemarthroses or bleeding in the setting of isolated PTT prolongation. No consistent triggers have been identified, though associations have been suggested with connective tissue disorders, malignancies, and immunomodulators, among others.

Case Description: A 60 yo man was admitted for painful unilateral thigh swelling and severe anemia with hemoglobin nadir 3.5 g/dL. PMH included ESRD due to hypertension, hemodialysis (HD) had been initiated 1-month prior. Family history negative for bleeding or autoimmune disorder. Laboratory values were significant for leukocytosis (17.8 K/µL) and prolonged PTT (107.8 s) with normal PT, INR, platelets, and reticulocytes. Iron studies were consistent with anemia of chronic disease. On hospital day 2 he developed an unprovoked right upper extremity hematoma requiring emergent fasciotomy on the side of his tunneled HD catheter. A naïve left arm AV fistula was unaffacted. Concern for factor VIII inhibitor was raised, and confirmed with circulating anticoagulant screen and undetectable factor VIII level. Recombinant factor VIIa & factor VIII inhibitor bypassing agent were utilized to control bleeding, concurrent with high-dose prednisone, cyclophosphamide, and plasmapheresis to decrease inhibitor activity. After a complicated course, he was discharged on prednisone, cyclophosphamide, and tranexamic acid with a PTT of 45.2s.

Discussion: We suspect that the recent initiation of HD triggered this autoimmune response. The right DJ catheter was the presumed bleeding site. A small series of HD-PTT of 45.2s.

FR-PO559
Hypereosinophilia in Haemodialysis Patients
Kathryn J. Griffiths,1 David Makanjuola,1 Michael J. Austin,2 Corinne F. De lord,2 Hannah Chency Irowe,1 Simon C. Stern,2 Simon K. Winn.1 1Nephrology, Epsom and St Helier University Hospital NHS Trust, London, United Kingdom; 2Haematology, Epsom and St Helier University Hospital NHS Trust, London, United Kingdom.

Introduction: The incidence of hypereosinophilia (>2 x 109/L) in our haemodialysis population in London over the last 13 years is 9.7 per 100 patients per year. We present 9 cases of significant hypereosinophilia which occurred alongside significant haemodynamic instability during haemodialysis (HD) sessions.

Case Description: All the patients survived these episodes; 7 of 9 had prompt reduction in eosinophil counts following high dose corticosteroids. All patients were on haemodiafiltration, with ultra-pure water. There was a high recurrence rate following weight of steroid treatment. Adaptations to the HD circuits including changing the line lock, dialyser type and dialyser surface area were made, but the inconsistent response suggests more than bioincompatibility. We did specific allergy testing for ethylene oxide (ETO), latex and chlorhexidine in 3 patients, 1 of which raised to latex. All 9 patients were ANCA negative, Hepatitis B, C and HIV negative. 1 patient had positive strongyloides serology. Discussion: The reason for the hypereosinophilia is unclear, but it has made HD challenging in these patients. It is possible that there may be other precipitants not related to the HD circuit. Joint management between nephrologists, haematologists and HD unit staff is important for the management of hypereosinophilic patients experiencing severe haemodynamic instability during HD.

FR-PO560
Erythropoietin Stimulating Agent (ESA)-Resistant Vitamin B6 Deficiency Anemia in a Pediatric Patient on Hemodialysis
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Introduction: Vitamin B6 is a water soluble vitamin, the active form of which is Pyridoxal 5'-phosphate, that functions as a coenzyme of erythroid specific 5-aminolevinate synthase (ALAS2) which is involved in the synthesis of heme. Vitamin B6 deficiency is often associated with inflammation as observed in chronic kidney disease, particularly those requiring dialysis. Administration of an ESA has also been shown to be associated with increased erythrocyte consumption of vitamin B6. We report here a pediatric patient who developed an ESA resistant anemia that significantly improved following vitamin B6 supplementation.

Case Description: 16-year-old African American male with end stage renal disease secondary to obstructive uropathy, on chronic hemodialysis, experienced a decrease in his hemoglobin over a 3-month period from 11 to 6.5 g/dL, while receiving darbepoetin alfa (ESA) [0.9mcg/kg/week] intravenously for one month. His transferrin saturation was 41% (iron saturation level 706 [80-383] ng/mL, mean corpuscular volume (MCV) 87 [78-98] fl). His corrected reticulocyte counts was 2.3%.[0.2-1.8%]. Additional laboratory data included the following: Direct antiglobulin testing and stool for occult blood were negative; Vitamin B12, 635 [193-886] pg/mL; folate, 8.4 [3.1-17.5] ng/mL; copper, 1413 [665-1480] mcg/L; zinc, 77 [60-120] mcg/dL and Ceruloplasmin, 31.4 [15-30] mg/dL. PTH was elevated at 258 [9-69] pg/mL. Vitamin B6 level was low at 1.2 [5.3-46.7] µg/L. Bone marrow biopsy was normocellular (65%) with erythroid hyperplasia and rare dyserythropoiesis. Prussian blue staining showed increased iron storage. Supplemental Vitamin B6 (100mg daily) was initiated, at which time his hemoglobin was 7.3 g/dL. Three months later, his hemoglobin was 11.6 g/dL with transferrin saturation of 18%.

Discussion: Vitamin B6 clearance is increased with standard hemodialysis and a further 50% increase in vitamin clearance is noted when receiving high flux high efficiency hemodialysis as seen in our patient. Vitamin B6 deficiency anemia should be considered in any pediatric patient on high flux hemodialysis who is not responding to standard ESA and iron therapy.

FR-PO561
Role of Extracorporeal Treatments in Management of Massive Bee Attack
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Introduction: Bee stings can cause severe allergic reaction which can be triggered by a single sting, prognosis worsening with increasing number of stings. More than half of the victims who experience multiple bee stings develop Acute Kidney Injury (AKI), which is due to multiple factors, such as intravascular hemolysis, rhabdomyolysis, hypotension and direct renal tubular toxicity of the venom components. We present a case of anuric acute renal failure due to massive bee attack, managed by renal replacement therapy and plasmapheresis.

Case Description: 53 year old male with history of hypertension, presented to our facility after an attack from killer bees (reportedly > 2000 bees). Upon initial presentation(16 hours after attack), he was intubated, in shock requiring vasopressors despite fluid resuscitation, and noted to be anuric. Patient was initiated on a high dose of

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FR-PO563

Treating Resistant Mycobacterium abscessus in Peritoneal Dialysis-Associated Infection

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Introduction: Mycobacteria-associated peritoneal dialysis (PD) infections should be considered in culture-negative or refractory cases. Non-tuberculous mycobacteria (NTM) are abundant in soil and water, and can rarely cause PD infections. NTM are associated with fillings and draining, occasionally noting blood tinged PD effluent. She progressed to peritonitis despite antibiotics and PD catheter revision. PD catheter and the catheter was removed due to concern about recurrence, as the patient wished to preserve fertility. The patient converted to hemodialysis.

Discussion: Fallopian tube migration and malposition can often be challenging in areas with limited access to healthcare, and thus, the treatment is anecdotal. T. inkin is also associated with biofilm formation, causing up to a 1000x higher resistance to antibiotics compared to planktonic organisms. We present a rare case and the first reported case of T. inkin infection in a patient on peritoneal dialysis. T. inkin is an emerging opportunistic pathogen that should be considered in the differential diagnosis of peritoneal dialysis patients with atypical peritonitis symptoms, as delays in diagnosis and treatment can lead to serious complications and mortality.

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**FR-PO566**

Actinomyces neuii Peritonitis in Peritoneal Dialysis

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**Introduction:** Actinomyces is a likely underrecognized cause of peritonitis in PD patients due to its fastidious nature, but identification is important because actinomyces infections may be indolent and may not respond to repeated short courses of antibiotics. If left untreated, sinus tracts and abscesses may form, which can lead to secondary infections.

**Case Description:** A 63 year old female diabetic with history of ESRD treated with continuous cycler peritoneal dialysis and prior history of clostridium difficile colitis. She developed cloudy cloudy PD fluid with loose bowel movement. Stool samples were positive for C. diff and gram-positive bacteria were identified in PD fluid. She was prescribed oral metronidazole and intraperitoneal vancomycin. Final fluid cultures were positive for Actinomyces neuii susceptible to vancomycin and have been successfully treated with 2 weeks of vancomycin. We educated her on the importance of hand hygiene and sterile technique.

**Discussion:** Actinomyces is a gram-positive bacillus comprising normal gut flora. It is rarely associated with soft tissue infections, but may occur in those with impaired immunity. Because the peritoneal cavity lacks robust innate immune responses, it is a favored site for infection. We speculate that increased bacterial translocation from the gut due to colitis or contamination of the PD catheter may have contributed to the peritonitis. Actinomyces is a likely underrecognized cause of peritonitis in PD patients due to its fastidious nature, but identification is important because actinomyces infections may be indolent and may not respond to repeated short courses of antibiotics. If left untreated, sinus tracts and abscesses may form, which can lead to secondary infections.

**FR-PO567**

Compounded Amino Acid Peritoneal Dialysate as an Alternative Volume Management Strategy in a Diabetic Patient

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**Introduction:** Volume control in diabetic patients with end stage renal disease (ESRD) on peritoneal dialysis (PD) can be challenging. Common glucose sparing volume control strategies for these patients include dietary sodium restriction, diuretics, and the use of icodextrin dialysate. Another potential strategy is the use of amino acid based dialysate, which may maintain ultrafiltration by avoiding hyperglycemia and loss of the osmotic gradient between dialysate and blood. In the United States amino acid peritoneal dialysate, which may maintain ultrafiltration by avoiding hyperglycemia and loss of the osmotic gradient between dialysate and blood. In the United States amino acid peritoneal dialysate is often not covered by insurance, leading to limited experience.

**Case Description:** A 63 year old female diabetic with history of ESRD treated with continuous cycler PD developed increasing challenges to maintain dry weight with frequent use of 4.25% dextrose along with a 2L icodextrin day dwell. On exam the weight was 86.5 kg (dry weight 83 kg) and blood pressure was 173/59, with bilateral crackles and trace edema in the extremities. Daily peritoneal ultrafiltration was between 500-700 ml with no residual urine output. Labs showed BUN 47, creatinine 12.4 mg/dl, albumin 3.4 g/dl, glucose 104 mg/dl, sodium 136 meq/L, HgA1c 6.0%, total weekly Kt/V 2.45. Given his 24 hour urine collections for creatinine clearance confirmed increase in his blood pressures to 120-130/60-80 on valsartan 160 mg BID and metoprolol succinate 100 mg daily. His 24 hour urine collections for creatinine clearance confirmed increase in urine output, with a urine volume of 508 cc on the final collection pre-angioplasty and 2000 cc on the first collection post-angioplasty. In addition, his weekly Kt/V from residual renal function alone increased from 0.54 before angioplasty to 2.7 after angioplasty. He developed volume overload with a trial off PD which could not be managed with diuretics alone. PD was resumed, with a reduced frequency of four sessions per week.

**Discussion:** Our patient demonstrated significant improvement in blood pressure control, with a substantial reduction in the number of medications and the stabilization of his blood pressure after angioplasty for renal artery stenosis despite being dialysis-dependent. Residual renal function improved, with fewer PD sessions required weekly to maintain adequate clearance and euvaloemia. Particularly in patients with other manifestations of peripheral vascular disease, the possibility of renal artery stenosis should be investigated, and perhaps treated, in ESRD patients with resistant hypertension.

**FR-PO568**

It Is Never Too Late: A Case of Renal Artery Angioplasty for Resistant Hypertension in ESRD

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**Introduction:** Atherosclerotic renovascular disease is an important and potentially treatable cause of secondary hypertension. In patients with end-stage renal disease, common contributors to uncontrolled hypertension include volume overload, sympathetic overactivity, and erythropoietin-stimulating agents. It is therefore challenging to identify ESRD patients who could benefit from angioplasty for renal artery stenosis.

**Case Description:** A 65 year old patient with ESRD due to BK nephropathy on peritoneal dialysis developed uncontrolled hypertension requiring multiple medications, including hydralazine 30 mg qAM and 100 mg qPM, isosorbide mononitrate 30 mg qAM and 60 mg qPM, labetalol 200 mg BID, amlopidine 10 mg daily, valsartan 160 mg BID, torsemide 40 mg BID, and metoprolol succinate 100 mg daily. His 24 hour urine collections for creatinine clearance confirmed increase in urine output, with a urine volume of 508 cc on the final collection pre-angioplasty and 2000 cc on the first collection post-angioplasty. In addition, his weekly Kt/V from residual renal function alone increased from 0.54 before angioplasty to 2.7 after angioplasty. He developed volume overload with a trial off PD which could not be managed with diuretics alone. PD was resumed, with a reduced frequency of four sessions per week.

**Discussion:** Our patient demonstrated significant improvement in blood pressure control, with a substantial reduction in the number of medications and the stabilization of his blood pressure after angioplasty for renal artery stenosis despite being dialysis-dependent. Residual renal function improved, with fewer PD sessions required weekly to maintain adequate clearance and euvaloemia. Particularly in patients with other manifestations of peripheral vascular disease, the possibility of renal artery stenosis should be investigated, and perhaps treated, in ESRD patients with resistant hypertension.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only**
FR-PO570
Peritoneal Dialysate Tamponading a Massive Retroperitoneal Hemorrhage
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Introduction: Spontaneous retroperitoneal (RP) bleeding is a rare but potentially fatal event. Due to its late manifestations, diagnosis is often delayed until blood loss is profound. We describe a patient in whom an RP bleed was suspected due to hypotensive episodes during peritoneal dialysis (PD) drainage.

Case Description: We describe a 47-year-old male with end stage renal disease (ESRD) on PD, on warfarin with a goal INR of 2.5-3.5 for mechanical mitral and aortic valves, who underwent a total hip arthroplasty for a left femoral fracture. Postoperatively he was continued on his home PD regimen (2L dwell, 2.5% dextrose, 5 exchanges per day) and restarted on warfarin. On postoperative day 17 he became unresponsive during PD drainage, with a blood pressure of 62/34 mm Hg. Hemoglobin dropped from 8.4 to 4.3 g/dL, and the INR was 2.2. Packed red blood cells and norepinephrine were administered, and he was transferred to the cardiac care unit, where he had a PEA arrest requiring CPR and intubation. Following return of spontaneous circulation, his blood pressure recovered and vasopressors were discontinued. Subsequent PD exchanges on the same day were complicated by repeated hypotensive episodes requiring vasopressors. This was observed only during PD drainage and resolved when fluid was re-infused. A CT scan showed a large left RP hematoma (14x11x23 cm). Angiography demonstrated a left L3 lumbar artery pseudoaneurysm as the source of bleeding. Coil embolization was performed, bleeding was well-controlled, and subsequent PD exchanges were well tolerate.

Discussion: We report an unusual case of spontaneous RP hemorrhage in a patient with ESRD for whom PD drainage led to life-threatening hypotension. We speculate that the RP bleed was partially tamponaded by PD fluid via transmission of pressure retroperitoneally.

FR-PO571
PD Peritonitis from Cat Mouth Flora: Pasteurella, Not the Only Thing You Need to Worry About
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Introduction: Neisseria weaveri, previously known as CDC group M-5, is an aerobic gram-negative non-motile rod normally found in animal oral flora and associated with infections related to dog bites. We present a case of peritonitis in a patient on peritoneal dialysis (PD) due to this microorganism after a cat bit the PD tubing.

Case Description: A 61-year-old female with end stage renal disease (ESRD) due to diabetes and hypertension on PD presented to the emergency department after her domestic cat bit and punctured the PD tubing while undergoing an exchange. She had no evidence of peritonitis and was discharged with prophylactic doxycycline for Pasteurella multocida peritonitis. Eight days later, she returned to the emergency department with abdominal pain and cloudy effluent. A diagnosis of peritonitis was made after peritoneal fluid studies revealed an elevated neutrophil count of 2,248 cells/mL. The patient received IV loading doses of vancomycin and cefepime and then transitioned to intraperitoneal vancomycin, cefepime, and oral metronidazole. Her peritoneal cell counts and symptoms quickly improved on antibiotics. The peritoneal fluid culture isolated Neisseria weaveri however blood cultures did not yield any bacterial growth. After all cultures finalized, antibiotics were narrowed to a two-week course of oral ciprofloxacin. Resolution of peritonitis was confirmed after completion of antibiotics with negative peritoneal fluid studies.

Discussion: Neisseria weaveri is found in the normal canine oral flora and has been found in wounds from infected dog bites. A previous case report has been documented of peritonitis from Neisseria weaveri but no mechanism of infection was identified. While cats are less likely to carry Neisseria weaveri, the organism has been isolated from feline oral flora. Care and sterility of peritoneal dialysis equipment is paramount to preventing peritonitis as infection can be devastating for patients on home dialysis modalities. Consideration of the multitude of organisms that have been isolated from feline oral flora (Neisseria, Pasteurella, Pasteurellaceae, Moraxella amongst others) must be kept in mind when wet contamination of PD fluid with feline oral flora occurs, with appropriate antimicrobial coverage.

FR-PO572
Anterior Cutaneous Nerve Entrapment in a Patient on Peritoneal Dialysis
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Introduction: Anterior cutaneous nerve entrapment syndrome (ACNES) is a commonly underdiagnosed cause of abdominal pain and has been implicated in 15-30% of cases of chronic abdominal pain. It is caused by the entrapment of the cutaneous branches of the intercostal nerves at the lateral border of the rectus abdominis muscle that supply the abdominal wall. ACNES should always be considered in the differential in patients with chronic unilateral abdominal pain.

Case Description: 55-year-old man with history of end stage renal disease secondary to hypertension on peritoneal dialysis (PD) for ~4 months and diabetes developed 5/10, intermittent sudden onset shooting and burning right sided abdominal pain. It was not associated with nausea, vomiting, fever or changes in bowel habit. PD fluid analysis revealed clear effluent with total nucleated white cells ≤20 and negative culture. Liver function tests were normal except for mild elevation in lipase (120 units). Noncontrast CT of abdomen and pelvis was unrevealing except for persistent defect in the left rectus abdominis muscle with overlying surgical scar. As Liralugludase can cause elevation in lipase in the absence of pancreatitis, it was discontinued with decrease in lipase to 81. However, his pain persisted and Pregabalin was prescribed with some efficacy. He was seen by neurologist where careful history and physical examination yielded the diagnosis of ACNES. Persistent defect in the left rectus abdominis muscle with overlying surgical scar noted on abdominal CT was thought to be the likely culprit of ACNES. He was treated with a compounded lidocaine gel with resolution of his pain and discontinuation of pregabalin.

Discussion: ACNES is commonly overlooked or confused with visceral pain, often leading to extensive diagnostic testing with negative results before an accurate diagnosis is established. Diagnosis of ACNES is based on the presence of well-localized abdominal pain often along the lateral aspect of the rectus abdominis muscle sheath, increase in tenderness to palpation during muscle tensing on examination (Carnett’s sign) and response to trigger point injection of a local anesthetic. Although ACNES can be quite painful and disabling, it is typically nonprogressive with no long-term sequelae. Management of treatment is reassurance, activity modification, physical therapy, and pain relief with analgesics or trigger point injections.

FR-PO573
Peritoneal Dialysis-Associated Peritonitis Presenting as Catheter Dysfunction
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Introduction: Catheter dysfunction is a common complication among peritoneal dialysis (PD) patients. Most common causes of one-way dysfunction include constipation, catheter tip migration, kinks in external tubing, oriental wrapping, intraluminal obstruction from fibrin or a clot, and peritoneal occlusion via adjacent organs. Catheter obstruction presents a major morbidity to PD patients and is a significant risk factor for modality failure. Up to 20% of patients are transitioned at least temporarily to hemodialysis when they experience catheter obstruction. We report an unusual presentation of a usual pathology, a case of peritonitis that presented initially as catheter obstruction.

Case Description: A 69-year-old man presented for clinic because he was unable to drain his PD catheter the night prior. He had no issues with loss dwell or prolonged drain on prior treatments. On presentation he felt weak, fatigued and lethargic. On further questioning he had decreased appetite, crampy abdominal pain, diarrhea and abdominal bloating. On arrival, he was afibrile, had scattered rhonchi on lung exam, no granulation tissue or erythema at the exit site, and mild LLQ tenderness. We were able to freely instill tissue or erythema at the exit site, and mild LLQ tenderness. We were able to freely instill.

FR-PO574
Bite-Induced Pasturella multocida Peritonitis
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Introduction: Peritoneal dialysis (PD) patients are at an increased risk of developing peritonitis, necessitating the importance of proper sterile technique. While, the majority of peritonitis infections arise from skin flora, an important, but often under-recognized

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Underline represents presenting author.
risk factor for peritonitis is pet ownership. This case report will examine an incident of zoonotic infection occurring in a PD patient.

Case Description: A 70-year-old PD dependent female presented with one day of progressively worsening abdominal pain and cloudy peritoneal fluid, without associated fevers. Physical examination revealed diffuse abdominal tenderness with guarding. There were no cutaneous findings at the PD exit site. Initial blood work was unremarkable, except for a mild leukocytosis. A sample of peritoneal fluid was sent for analysis, but returned a nucleated cell count of 0. However, despite a lack of PMNs, the fluid culture grew Pasteurella multocida. This was an unexpected result that prompted further investigation into the patient’s home environment and PD machine. The patient owns 4 cats and 1 dog, but was not restricting pet access to her bedroom with her dialysis machine. Although the fluid cell count was negative, further investigation showed inadequate dwell time in the ED. The patient was ultimately treated with IP Ceftriaxone.

Case Discussion: This case illustrates that early recognition of this complication in patients with ESRD who develop overt secondary polycythemia that led to morbidity and mortality in End Stage Renal Disease (ESRD) patients. We present a rare case of an Autosomal Dominant Polycystic Kidney disease (ADPKD) patient with ESRD on HD who developed overt secondary polycythemia that led to hyperviscosity, recurrent hemodialysis access clotting and hemodialysis failure. The primary purpose of any hemodialysis access is to provide adequate, long-term and repeated access to the circulatory system with minimum complications. Arteriovenous graft (AVG) rarely fails acutely within the postoperative period causing graft loss with the need for subsequent creation of new hemodialysis access. We describe the rescue of the AVG which immediately failed following its creation, there was no hope for its future use, so consequently was abandoned for over three months.

Case Description: The 63 years old woman with end stage renal disease has been on chronic hemodialysis since 2014. Her right distal arteriovenous fistula was functional until November 2018 when it failed. The right elbow brachial-basilic graft was created successfully which also failed within 24 hours following its creation.3 months later after creation, this patient was referred to our centre. Ultrasoundography visualized stenosis at the peripheral draining vein, severe stenosis at venous-graft anastomosis and intragraft stenosis with no flow of blood through the entire graft. Ultrasound guided Percutaneous transluminal angioplasty was performed with immediate restoration of good graft patency, good patency of brachial artery and basilic vein. The next day, patient used the AVG for hemodialysis successfully for the first time. The AVG remained patent and chronically usable for hemodialysis up to 4 months.

Discussion: Our case demonstrates the feasibility of repairing an immediately failed arteriovenous graft following its creation with restoration of good patency allowing patients to have chronic hemodialysis by ultrasound guided percutaneous transluminal angioplasty, even after 3 months since failure.

FR-POS76
Case of Acute Pseudo-Aneurysm Formation in a Clotted and Abandoned Brachial-Cephalic Arteriovenous Fistula

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Introduction: Pseudo-aneurysm formation is a known complication of dialysis arteriovenous access. Pseudo-aneurysms typically form at the site of needle puncture or at the arteriovenous anastomosis. Here we present a case of acute pseudo-aneurysm formation in a clotted and abandoned arterio-venous fistula (AVF).

Case Description: An 88-year-old male on chronic hemodialysis via a right femoral vein catheter presented to the dialysis unit with sudden onset of swelling in his left arm. This was a new phenomenon for this patient who has undergone multiple access procedures. Antibody testing was negative. Ultrasound revealed a large hypoechoic clot in the left axillary vein, but no clot in the left subclavian vein. A Doppler ultrasound of the brachiocephalic system did not reveal any significant flow abnormalities. CT angiography revealed a pseudoaneurysm at the site of the previous needle punctures (AVF) that had not been cannulated in over 6 months. He denied any trauma at the site of the swelling and attributed a significant increase in the size of the swelling over the past 48 hours. On examination the swelling was firm, pulsatile and non-tender. Vascular surgery was consulted, and same day intra-operative findings confirmed the presence of a pseudo-aneurysm which was resected. The histology and cultures of the resected tissue did not reveal any malignancy or infection.

Discussion: Pseudo-aneurysms are hematomas that form due to a defect in the vessel wall. They are devoid of the endothelium or the vessel wall. In other words, they are hematomas communicating with the lumen of the vascular access, and therefore rupture of a pseudo-aneurysm can be life-threatening. Typically, the pseudo-aneurysms form at the site of repeated needle cannulation. Pseudo-aneurysm formation is very rare in a clotted or abandoned AV access. It is not clear what caused the pseudo-aneurysm formation in this patient, but this case highlights the importance of continued monitoring of ‘abandoned and clotted’ dialysis vascular access.
He later developed polymicrobial bacteremia from a driveline infection, and AVG was excised due to concern for seeding. A second brachiobasilic AVG was placed and functioned well, requiring a thrombectomy 147 days after placement.

**Discussion:** AVG can be successfully used for long-term RRT access in LVAD patients. Infection and thrombosis rates need further study in larger cohorts. Outcomes between AVG, AV fistula, and dialysis catheters should be evaluated.

**FR-PO579**

**Treatment of Refractory Hyperammonemic Coma with CRRT in a Patient with Ureterosigmoidostomy**

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**Introduction:** Hyperammonemia is most common in liver disease but other rare causes exist. Serum ammonia (NH3) concentrations >150umol/L is linked to poor neurological outcomes and even death. In severe cases, extracorporeal removal of NH3 can be lifesaving.

**Case Description:** A 64-year-old female was admitted to the ICU with coma & NH3 level of 534umol/L with normal liver & renal function. She had ureterosigmoidostomy as a child for bladder extrophy. The high NH3 was attributed to increased colonic absorption from urine & increased NH3 production from bacterial splitting of urea in the colon. She did not respond to Lactulose & Rifaximin. Urology was consulted for ileal conduit. NH3 level >150 is related to cerebral edema, increased intracranial pressure (ICP) and brain herniation. Therefore, in severe cases, urgent extracorporeal therapy is necessary. CRRT has been reported, but there is no definite guideline. Some reports favor HD over CRRT due to faster clearance, but when the NH3 is continuously produced at a high rate, CRRT may be more beneficial since it offers fewer interruptions, less rebound, & less rapid fluid shifts which can worsen ICP. This case highlights that CRRT can be an effective bridging strategy in patients with severe hyperammonemic encephalopathy.

Figure 1.

**FR-PO580**

**Familiar Hyperkalemic Hypertension Genotype with a Negative Phenotype: A CUL3 Mosaicism**

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**Introduction:** The familiar hyperkalemic hypertension (FHHH) is an inherited disease featuring arterial hypertension with hyperkalemia, metabolic acidosis, and hypercalciuria, that is mainly due to overactivation of the thiazide-sensitive renal NaCl cotransporter in the distal convoluted tubule, as a consequence of mutations in four different genes: two encoding the kinases known as WNK1 and WNK4 and two encoding proteins that are components of a Ring type ubiquitin ligase complex, known as KLHL3 and CUL3. Mutations in CUL3 produce the more severe phenotype that in all 36 reported cases result in a shorter protein due to skipping of exon 9 and has been described as de novo mutation or as autosomal dominant inherited from one parent.

**Case Description:** Here we report on a 12 year-old boy with arterial hypertension (150/100mmHg), hyperkalemia (7 mEq/L) metabolic acidosis (pH 7.0; HCO3- 17.8 mEq/L) and hyperchloraemia (108 mEq/L). Two months after hydrochlorothiazide was initiated the blood pressure was 129/76 and serum electrolyte values were normal (K+, 4.5 mEq/L; Cl- 98 mEq/L; pH 7.37 and HCO3- 25.8 mEq/L). DNA from the proband and his parents were obtained with their consent to evaluate the cause of the FHHH. The proband’s DNA analysis revealed a CUL3 mutation resulting in exon 9 deletion. The mutation was present in the mother’s blood DNA, but not in the father’s. The mother, however, exhibits no FHHH phenotype. Her blood pressure and serum electrolytes were normal. The CUL3 mutation was found in DNA extracted from the mother’s oral mucosa but at lower levels than in the blood. The mother of the proband is a unique occurrence of CUL3 FHHH genotype, with no phenotype, due to a mosaicism.

**Discussion:** Mosaicism refers to the presence of two genetically distinct cell lines with distinct karyotype or genotype in the same individual and results from postzygotic mutational events. Individuals may present gonadal mosaicism (found only in the gametes), somatic mosaicism, or a combination of both. In somatic mosaicism, it is frequent to find different proportions of the two cell lines across tissues, even within the same embryonic lineage (ectoderm, endoderm or mesoderm). In the proband’s mother, the mutation exhibits presumably little to no effect on renal tubular cells, but is present in the oocytes and was inherited by her child.

**FR-PO582**

**Customized Renal Replacement Therapy in a Patient with a Serum Sodium of 97 mEq/L**


**Introduction:** Hyponatremic patients requiring continuous veno-venous hemofiltration (CVVH) offer a unique challenge as commercial replacement solution contain physiologic concentrations of sodium. Use of such fluids may cause rapid correction of hyponatremia resulting in osmotic demyelination. We present a patient with...
Acute kidney injury (AKI) and severe hyponatremia were successfully treated using customized CVVH solutions.

Case Description: A 55-year-old male with no significant medical history was found with AKI and severe hyponatremia. Hemodialysis (HD) was begun on day 3 post-admission. HD was complicated by hypotension, and fever. Blood cultures, QuantiFERON Gold were negative. Serum calcium increased to 10.8-10.2mg/dL and CBC differential showed eosinophilia 0.64. ACTH stimulation test showed poor adrenal reserve indicative of adrenal insufficiency. Repeated questioning on medication and Methylprednisone found in exam pill bottles, which was absent in admission list. After restarting steroids, he clinically improved to baseline, with recovery of normotension. Day 6, HD was discontinued, and he was discharged home with no need for further renal replacement therapy.

Discussion: Hyponatremia has been associated with increased mortality in numerous patient populations. In ESRD patients, it is commonly seen and attributed to poor compliance with fluid restriction, hence may not be investigated. Potentially life-threatening causes such as AI, as in our patient, can be missed. Arreggar et al, noted in their study that 6 of 15 ESRD patients with sustained hypotension on dialysis had secondary AI, and BP normalized with steroid administration. Our patient was found, with more careful history, to have secondary AI from long term corticosteroid use. Our case suggests that a higher index of suspicion is appropriate in hyponatremic hemodialysis patients, especially if dialysis is complicated with other signs such as intra-diastolic hypotension, as diagnosis and treatment may have benefits in mortality reduction.

FR-PO583
Management of Critical Hyponatremia During Continuous Renal Replacement Therapy and Septic Shock
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Introduction: The concept of osmotic stability in the critically ill during continuous renal replacement therapy is insufficient explored. Herewith, we are reporting a case of extreme hyponatremia (serum sodium [SeNa+] 182 mEq/L) by default, when considering the presence of serum protein content, the absolute sodium concentration, and osmolality.

Case Description: A 52-year-old male suffered a motor bicycle accident with subarachnoid hemorrhage and traumatic right below-the-knee amputation[FT1]. On the 17th day of hospitalization he suffered acute decompensation with increased work of ventilation and 3 pressor agents to maintain acceptable BPs. Initial laboratory studies revealed acute kidney injury with serum creatinine (Scr) 3.6 mg/dL (normal baseline), BUN 142 mg/dL and sodium 177 mEq/L. With intravenous fluids, Scr improved to 3 mg/dL while SeNa rose to 182 mEq/L. The patient was later discharged from hospital to use fixed Separesus CRRT replacement solutions.

Discussion: Rapid correction of severe hyponatremia can cause osmotic demyelination syndrome. CVVH to treat oliguric AKI with severe hyponatremia using commercial premixed replacement fluid bags is a challenge. This case illustrates the utility of customized CVVH solutions as a method for the correction of severe hyponatremia in critically ill patients requiring CVVH.

FR-PO585
Loss of NCC Impairs the Outgrowth of the Renal Distal Convoluted Tubule (DCT) During Renal Development
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Background: Gitelman syndrome is an autosomal recessive renal tubulopathy characterized by hypokalemic alkalosis, hypomagnesemia and hypocalcuria. The syndrome is caused by loss-of-function mutations in the NaCl co-transporter (NCC) in the renal distal convoluted tubule (DCT). Data from NCC ko mice suggest that DCT hypertrophy contributes to the pathogenesis of the disease. Since Gitelman patients are usually diagnosed during adolescence or early adulthood, we tested the idea that the late clinical onset of Gitelman syndrome is related to a progressive regression of the DCT during adolescence.

Methods: Immunofluorescence detection of distal tubule marker proteins as well as morphometric analyses of DCT fractional volume and investigation of DCT specific gene expression with real time quantitative PCR were used to analyse the structure and protein expression pattern of the DCT at different ages and stages of development (day 1, 4, 10 and 6 weeks after birth) in NCC wt and NCC ko mice.

Results: Mice of both genotypes developed normal and showed a similar body weight gain. Plasma aldosterone levels and renal renin mRNA expression were higher in NCC ko mice than in NCC wt mice already at day 10. In contrast, plasma ion levels did not differ between genotypes at age 10 days, but a significant hypomagnesemia was observed in NCC ko mice at 6 weeks. Immunofluorescence detection of parvalbumin (an early DCT marker) revealed that the fractional cortical volume of the early DCT is almost similar for mice of both genotypes at day 4, but gets significantly lower at day 10 and is almost zero at 6 weeks after birth in NCC wt and NCC ko mice. The number of DCT marker correlates with a marked reduction in the protein abundance of the DCT-specific Mg²⁺ channel TRPM6 and an increased proteolytic cleavage and hence activation of the alpha- and gamma subunit of the epithelial Na⁺ channel (ENaC).

Conclusions: Thus, after an initial outgrowth of the DCT up to day 4, DCT development lacks significantly behind in kidneys of NCC deficient mice. The impaired DCT development associates already at day 10 with clear signs of volume contraction with elevated renin and aldosterone levels and an activation of ENaC, suggesting that Gitelman syndrome might be present much earlier during life than usually expected. Despite an early downregulation of TRPM6, hypomagnesemia is a rather late symptom.

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FR-PO586
Aldosterone Activates NCC Through the Resulting Hypokalemia and Chloride-Sensing Mechanism of WNK4
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Background: Aldosterone increases the expression and apical localization of ENaC via binding to the mineralocorticoid receptor (MR). However, the underlying mechanism of aldosterone-induced NCC activation is still unclear. Earlier studies have shown that a high potassium diet reversed NCC phosphorylation in aldosterone-treated mice, and vice versa for the NCC dephosphorylation in MR knockout mice. We recently demonstrated that hypokalemia reduces intracellular chloride concentration, which releases WNK4 from chloride-mediated inhibition. We hypothesized that hypokalemia resulting from aldosterone-activates WNK4, via the chloride-sensing mechanism.

Methods: Aldosterone solution (100 g/kg/day) or vehicle control (5% DMSO in physiological saline) was administered to chloride-insensitive L1319/F1321 WNK4 knockout mice and their control littermates using Alzet osmotic pumps. In vivo NCC activity was measured by the inulin clearance of aldosterone-treated mice, and also by thiazide-sensitive urinary sodium excretion rate. Moreover, other plasma and urine biochemistries were compared.
Results: After two-week aldosterone infusion, both wild-type and choride-insensitive WKY rats (KI) showed a similar iNCC increase (ICOI: 25 vs. 25 mM) and hypokalemia (K−: 2.4 vs. 2.6). Compared with wild-type mice, KI mice had higher urine output (21 vs. 3.2 ml/day), urinary sodium excretion (144 vs 221 mmol/day), and blood pressure. Of note, aldosterone increased the total and T58-phosphorylated NCC in wild-type mice. However, aldosterone did not further enhance the already high NCC phosphorylation in KI mice.

Conclusions: In sum, our results support the notion that aldosterone enhances NCC activity via the resulting hypokalemia and chloride-sensing mechanism of WNK4. Moreover, chronic aldosterone infusion increased natriuresis, compatible with aldosterone escape phenomenon, probably related to pressure natriuresis or natriuretic peptides. Moreover, chronic aldosterone infusion induces natriuresis, compatible with aldosterone escape phenomenon, probably related to pressure natriuresis or natriuretic peptides.

Funding: Government Support - Non-U.S.

FR-PO587
Sympathetic Nervous System Regulation of the NCC in Dahl Salt-Sensitive Hypertension
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Background: Studies suggest that sympathetic nervous system (SNS) release of norepinephrine (NE) influences the activity of the sodium chloride cotransporter (NCC) via α1 and β adrenoceptor pathways. Regulation of the NCC involves a complex network of kinases including WNK1, SPAK, and OXS1. Hypothesis: NE stimulates an α1 adrenoceptor pathway to drive increases in NCC activity that contribute to the development and maintenance of Dahl salt sensitive (DSS) hypertension (SSH).

Methods: Groups of naïve DSS rats and DSS rats given a continuous subcutaneous (s.c.) infusion of the α1 adrenoceptor antagonist, terazosin/DMSO (10mg/kg/day) were placed on a 21 day normal salt (0.6% NaCl, NS) or high salt (4% NaCl, HS) diet. Separate groups of DSS rats were fed a 42 day HS diet; and on day 21, rats were treated with s.c. saline or terazosin for the remaining 21 days of the diet. Basal MAP, NCC activity, peak natriuresis to hydrochlorothiazide [HCTZ], 2mg/kg, and the expression of the NCC and its regulatory kinases were assessed by immunoblot on day 21 or day 42 of experimental diet (N=5-6/group).

Results: DSS rats fed a 21 day HS diet develop SSH and show increases in NCC activity, expression, and its regulatory kinases expression compared to rats on a NS diet. DSS rats fed a 21 day HS diet show increased MAP, increased basal and peak natriuresis to HCTZ, a significant decrease in NCC expression, and decreased phosphorylation of α1, β1, and β2 adrenoceptors, but no change in α2 adrenoceptors. In addition, we observed that DSS rats fed a 21 day NS diet develop SSH and show increases in NCC activity, expression, and its regulatory kinases expression compared to rats on a NS diet. DSS rats fed a 21 day NS diet show increased MAP, increased basal and peak natriuresis to HCTZ, a significant decrease in NCC expression, and decreased phosphorylation of α1, β1, and β2 adrenoceptors, but no change in α2 adrenoceptors.

Conclusions: SNS release of NE activates an α1 adrenoceptor pathway to drive the development and maintenance of Dahl SSH. Significantly, α1 adrenoceptor antagonism attenuates the development and maintenance of SSH by evoking downregulation of NCC activity, expression, and regulatory kinase WNK1 expression. Collectively, these findings suggest that NE stimulates an α1 adrenoceptor pathway involving WNK1 signaling to drive increases in NCC activity and the development and maintenance of SSH in DSS rats.

Funding: Other NIH Support - NHLBI

FR-PO588
Fructose Increases the NCC Activity Through the Calcium-Sensing Receptor-WNK4-SPAK Pathway
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Background: We have recently shown that the Calcium Sensing Receptor (CaSR) regulates NCC via the WNK4-SPAK pathway (JASN 2018). It is known that glucose and other sugars behave as positive allosteric modulators of CaSR. The effect of glucose on CaSR is particularly relevant in the apical membrane of distal convoluted tubule (DCT), which is not exposed to glucose, except during diabetic glycosuria. The exposure of DCT to fructose varies from low to high because it occurs in an intake-dependent manner. Thus, we hypothesize that sugar delivery to the DCT, by its allosteric effect on the CaSR, might activate NCC via the CaSR-WNK4-SPAK pathway.

Methods: To test if glucose or fructose induce phosphorylation, we used HEK-293 cells cotransfected with CaSR + SPANK 1/+, WNK4 cDNA. Expression and phosphorylation of WNK4 were assessed using a constant low-calium medium (0.5mM), but varying the glucose or fructose concentration from 0, to 5, or 25mM. The calcimetric effect of glucose and fructose on WNK4 phosphorylation was assessed.

FR-PO589
Regulation of PKC-Dependent WNK4 Phosphorylation by Extracellular Potassium: Insight into Familial Hyperkalemic Hypertension
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Background: Familial Hyperkalemic Hypertension (FHH) is caused by mutations in genes such as KLHL3 and WNK4, which result in higher protein levels of the kinase WNK4 and thus upregulation of the phosphorylated renal NaCl cotransporter NCC (pNCC), increasing its activity. Because NCC activity is inversely proportional to plasma K+ in physiological conditions, it is puzzling that NCC activity is not suppressed by hyperkalemia in FHH. We have shown that WNK4 phosphorylation by PKC/PKA at S64 is important for NCC activity and that it is increased by hypokalemia. Here we investigated how this site is regulated in hyperkalemia and FHH.

Methods: Wild-type (WT) mice were fed with low (LKD-0%), normal (NKD-1.2%), or high (HKD-5%) K+ diets for 7 days. Transgenic KLHL3R528H/+ mice (with FHH phenotype) were fed with LKD or NKD for 4 days. Blood samples were obtained to measure electrolyte levels. Western Blot assays with kidney lysates were performed to analyze total and phosphorylated WNK4 and NCC levels. WNK4-transfected HEK293 cells were cultured in low (1mM), normal (5mM) or high (10mM) K+ media. Ex vivo kidney slices from WT mice were exposed for 30 min to control solutions followed by 30 min to low, normal or high K+ media.

Results: We observed that fasting-induced hyperkalemia (FHH) phosphorylates pNCC in the low- and normal-K+ media but not in high-K+ media. In human kidney slices exposed to low K+ media, WNK4 phosphorylation was enhanced by hyperkalemia, while in those exposed to normal or high K+ media, no phosphorylation was observed. In a similar manner, WNK4 phosphorylation levels increased in mice that were treated with 141.2% or 253.6% of their apical trafficking. In vivo, fructose intake increased pWNK4-S64 phosphorylation (p<0.01). Moreover, fructose intake activated WNK4 and SPAK (p<0.05). In mice, 20% fructose intake resulted in increased NCC phosphorylation (p<0.01). Median arterial pressure (MAP) increased significantly in mice fed a high-K+ diet (p<0.05).

Conclusions: Our results show that glucose and fructose induce WNK4 phosphorylation in cells in a WNK4-dependent manner. In vivo, fructose intake increased NCC phosphorylation via AKT and SPAK, which were in turn activated by CaSR, since the calcilytic compound NPS2143 prevented the effect. Our observations suggest that activation of NCC by glucose or fructose via CaSR could be one of the mechanisms involved in the development of increased salt reabsorption and hence hypertension in diabetes mellitus or during fructose consumption.

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FR-PO590
WNK Bodies Enable WNK4-Dependent Phosphorylation of SPAK/OSR1 for Their Apical Trafficking
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Background: The distal convoluted tubule (DCT) is vital for K+ homeostasis. Low plasma [K+] stimulates the apical Na+, Ca2+-cotransporter (NCC), limiting electrogenic K+ loss in the downstream tubule at the expense of increased NaCl reabsorption and blood pressure. NCC is activated via phosphorylation by Ste-20-related proline/alanine-rich kinase (SAPK) and oxidative-stress-responsive kinase 1 (OSR1), two homologous substrates of no less than 18 different kinases. During hyperkalemic NCC activation, the human and rodent DCT develop cytoplasmic structures containing WNKs and SPAK/OSR1, termed WNK bodies. Their function is unclear. We hypothesized that WNK bodies serve as sites of SPAK/OSR1 activation, followed by trafficking of SPAK/OSR1 towards NCC.

Methods: To explore this hypothesis, we analyzed cellular distribution and phosphorylation of SPAK/OSR1 in different rodent models of hyperkalemia (dietary K+).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
deprivation, genetic WKY4 deletion, and furosemide treatment) using high-resolution immunofluorescence microscopy.

**Results:** Feeding mice (n=5) a K±-deficient diet for 10 days increased abundance of phosphorylated (p) SPASK/SPAK in the apical DCT membrane and induced formation of NKCC in AAN kidney. These observations provide the new insights into TGF-β signaling in the AAN kidney.

To confirm this, we disrupted cellular trafficking using the microtubule assembly inhibitor colchicine in rats receiving furosemide (n=4). Compared to rats receiving only furosemide (n=4), concomitant colchicine treatment resulted in accumulation of pSPASK/OSR1 at the apical NCC membrane, thereby linking plasma [K+] to NCC phosphorylation, NaCl balance and blood pressure.

**Results:** Cortical WNK1 protein expression in cultured cells by reducing the transcription and protein levels of WNK1 in WNK4 knockout (KO) mice. Knockdown experiments in Cos-7 cells transfected with 14-3-3 γ siRNA and RCC were reversed by knockdown of WNK4 in WNK4 knockdown (KD) cells along with reduced reduced abundant of pSPASK/OSR1. Electron microscopy revealed that WNK bodies are membraneless, hypodense structures closely associated with microtubules.

**Conclusions:** In sum, our results indicate that WNK bodies are membraneless organelles performing SPASK/OSR1 activation for their subsequent apical trafficking, thereby linking plasma [K+] to NCC phosphorylation, NaCl balance and blood pressure.

**Funding:** NIDDK, Support, Government Support - Non-U.S.

**FR-PO591**

**Renal TNFα Activates WNK Phosphorylation Cascade and Contributes to Salt-Sensitive Hypertension in CKD**

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**Background:** The inappropriate over-activation of with-no-lysine kinase (WNK)-STE20/SPS1-related proline-alanine kinase (SPAK)-NaCl cotransporter (NCC) phosphorylation cascade increases sodium reabsorption in distal kidney nephrons, resulting in salt-sensitive hypertension. Although chronic kidney disease (CKD) is a common cause of salt-sensitive hypertension, the involvement of WNK phosphorylation cascade is unclear. Moreover, the effect of immune systems on WNK kinase has not been investigated despite the fact that immune systems are important for salt sensitivity.

**Methods:** WNK phosphorylation cascade and its contribution to salt sensitivity was evaluated in three CKD mouse models (aristolochic acid nephropathy (AAN), adenine nephropathy, and subtotal nephrectomy). The regulator of WNK signaling in CKD was also explored focusing on immune systems.

**Results:** Immunoblotting and immunofluorescent study revealed that the protein abundance of WNK1, but not of WNK4, was increased at the distal convoluted tubules (DCT) in the AAN kidney. Accordingly, the phosphorylation of SPAK and NCC was also increased. Moreover, a high-salt diet did not adequately suppress the activation of WNK1–STE20/SPS1–related proline-alanine kinase (SPAK)–NaCl cotransporter (NCC) phosphorylation cascade increasing sodium reabsorption in distal kidney nephrons, resulting in salt-sensitive hypertension. Although chronic kidney disease (CKD) is a common cause of salt-sensitive hypertension, the involvement of WNK phosphorylation cascade is unclear. Moreover, the effect of immune systems on WNK kinase has not been investigated despite the fact that immune systems are important for salt sensitivity.

**Conclusion:** WNK phosphorylation cascade is an important contributor to salt sensitivity in CKD. These data suggest that WNK4 may be a potential target for the treatment of salt-sensitive hypertension in CKD.

**Funding:** Government Support - Non-U.S.

**FR-PO592**

**The Novel Role of 14-3-3 Gamma in the Pathogenesis of Deoxycorticosterone Acetate Salt Hypertensive Mouse Model**

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**Background:** Sodium chloride cotransporter (NCC) plays a key role in the regulation of blood pressure and electrolyte homeostasis. 14-3-3 γ belongs to a family of multifunction regulatory proteins. Previous data have shown that 14-3-3 γ proteins regulate renal NaCl channel and transporter such as ENaC. Our preliminary data showed that 14-3-3 γ inhibits NCC. Thus, we hypothesized that TNFα regulates WNK protein expression. In fact, TNFα increased WNK1 protein expression in cultured cells by reducing the transcription and protein levels of NEDD4-2 expression and upregulation of WNK1–STE20/SPS1–related proline-alanine kinase (SPAK)–NaCl cotransporter (NCC) phosphorylation cascade at DCT in vivo in the AAN kidney.

**Conclusions:** TNFα activates WNK1–STE20/SPS1–related proline-alanine kinase (SPAK)–NaCl cotransporter (NCC) phosphorylation cascade in the kidney, leading to salt-sensitive hypertension in CKD. These observations provide the new mechanism how immune systems regulate salt-sensitivity in CKD.

**Funding:** Government Support - Non-U.S.

**FR-PO594**

**Effects of Extreme Dietary Potassium Restriction and K+ Loading on Blood Pressure and Renal Tubular Na+ Transport**

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**Background:** For almost a century it has been known that dietary potassium intake inversely correlates with blood pressure. Yet, it is unclear how potassium restriction leads to hypertension, or how potassium excess causes a natriuresis despite elevated aldosterone levels. Our goal was to study the effects of dietary potassium on blood pressure, acid/base balance, and ion transport.

**Methods:** Wild-type SY129 mice were fed K+-deficient, control, high K+-basic, and high KCI diets for 10 days. We monitored BP using radiotelemetry probes, urine electrolyte excretion via metabolic cages, and transporter expression via immunofluorescence, western blots, and diuretic challenges.

**Results:** Interestingly, despite the induction of hypokalemia, extreme K+-depletion had no effect on blood pressure. In contrast, K+ loading resulted in a progressive ~10 mmHg increase in blood pressure. To determine whether these effects were dependent on NaCl intake, we challenged mice with 1% saline. The K+ deficient mice developed an increase in blood pressure (~8 mmHg), whereas K+ replete mice exhibited no significant change in blood pressure with saline challenge. Notably, just 10d of K+-restoration was associated with diabetes insipidus, evidenced by polyuria and a decrease in AQP2 expression. This was associated with an increase in sodium transporters in the upstream tubule, likely due to the salt sensitivity. The elevated blood pressure on the K+-loaded diet correlated with elevated aldosterone levels and increased ENaC activation. During KCI feeding, the type of anion (basic vs. chloride-rich) had a considerable effect on key transporters along the tubule, despite no differences on blood pressure.

**Conclusions:** In our model, the effect of dietary K+ on blood pressure was linked to NaCl intake, due to differential effects of K+ loading and restriction on sodium transport pathways along the nephron. The inverse relationship between Pspask/OSR1-NKCC-phosphorylation in the presence of knock-down ERK1, 14-3-3 γ-mediated inhibition of NCC was reversed. Taken all data together, we concluded that 14-3-3 γ plays an important role in NCC regulation through ERK1/2-mediated signaling pathway in DOCA salt hypertension mouse model, which provides a novel mechanism underlying pathogenesis of DOCA salt hypertension.

**Funding:** Veterans Affairs Support
results. Further, the accompanying anionic content should be taken into consideration when measuring the physiologic effect of K+ intake on tubular salt transport and blood pressure.

Funding: NIDDK Support

FR-PO595

Kidney-Specific and Sex-Dependent Action of the Circadian Clock

Protein BMAL1 in the Renal Response to Dietary Potassium Deprivation

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Background: BMAL1 is a core mammalian circadian clock transcription factor responsible for the tissue-specific regulation of thousands of genes. Male, but not female, kidney-specific BMAL1 knockout (KO) mice exhibit lower blood pressure compared to control mice (CNTL). The goal of this study was to determine the BMAL1-dependent response of the kidney to dietary potassium (K) deprivation in males and females.

Methods: We generated the KO using floxed exon 8 BMAL1 mice crossed with kidney-specific catherin Cre+ mice. Floxed Cre-littermates were used as CNTL. Metabolic cages were used for 12 hr urine collections.

Results: There was not a genotype difference in food intake in either sex, however, males displayed a transient decrease throughout the treatment (M: P<0.05) but females had no change (F: P=0.4). Similarly, neither sex had a genotype difference in body weight. Body weight of males did not change from treatment (M: P=0.8) but females increased in weight (F: P<0.0001). K excretion treatment throughout the study was not as high for females at baseline and remained low for the full 5 days (M: 0.65±0.05 to 0.01±0.002; KO: 0.64±0.02 to 0.015±0.004 mmol; P<0.0001). Females exhibited a similar response to KCN excretion rates (CNTL: 0.3±0.09 to 0.03±0.09; KO: 0.4±0.08 to 0.03±0.01 mmol; P=0.0001). After an initial decrease in sodium (Na) excretion in males, rates remained lower than baseline throughout treatment in CNTL whereas KO increased back to baseline levels by day 5 of treatment (CNTL: 29±0.02 to 0.19±0.01; KO: 22±0.02 to 0.12±0.001 mmol). Sex and genotype-dependent differences in K+ and Na+ excretion were not apparent in females, however, there was a transient increase following treatment in CNTL and KO reaching its peak at day 4 (CNTL: 0.21±0.06 to 0.26±0.05; KO: 0.21±0.03 to 0.23±0.03 mmol; P=0.05). Male CNTL had greater cumulative Na+ compared with male KO (P<0.0001) and both female groups.

Conclusions: Male kidney-specific BMAL1 KO mice exhibited a decrease in renal Na+ retention in response to a low K diet. Thus, BMAL1 functions in the sex-dependent response of the kidney to dietary K restriction.

Funding: NIDDK Support, Private Foundation Support

FR-PO596

Role of Ammonia in the Renal Potassium Response to Dietary K+ Deficiency

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Background: Previous studies have shown that glutamine administration simultaneously increases ammonia excretion and decreases K+ excretion. The current studies determined whether increased ammonia metabolism is necessary for the normal kaliuretic response to hypokalemia.

Methods: We used NBCe1-A KO mice, which have decreased ammonia response to K+-free diet similarly in WT and KO mice. Expression increased with K+-free diet similarly in WT and KO mice. NCC phosphorylation, which has a key role in the renal response to hypokalemia, however, was significantly less in hypokalemic KO than in hypokalemic WT mice. In vivo incubation of kidney slices for 1 hour in defined solutions showed that decreased extracellular K+ increased NBCe1-A protein expression over the tested range of 2.8 mM. Addition of ammonia, 2 mM, also increased phospho-NCC expression. Total NCC expression was not altered by changes in extracellular K+ or by ammonia addition.

Conclusions: The renal kaliuretic response to dietary K+-deficiency-induced hypokalemia requires NBCe1-A-dependent increase in cortical proximal tubule segments ammoniagenesis, which then leads to an ammonia-dependent stimulation of NCC phosphorylation that is necessary for normal K+ conservation.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO597

Insulin Stimulates V-ATPase on Renal Proximal Tubules via the Akt/mTORC2 Pathway

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Background: Maintaining an acid-base balance is essential for homeostasis. Acid-base transport in renal proximal tubules (PTs) is mainly sodium dependent and conducted coordinate by apical Na+/H+ exchanger (NHE3), vacular H+-adenosine triphosphatase (V-ATPase) and basolateral Na+/HCO3- cotransporter (NBCe1). V-ATPase on the PTs well-known to play an important role in proton excretion. Previously, we reported stimulation of PT sodium transport by insulin was mediated via Akt2/mTORC2 pathway. However, it is unclear whether insulin is involved in acid-base balance on the renal PTs. We hypothesized insulin may regulate V-ATPase on PTs.

Methods: We measured luminal V-ATPase activity in freshly isolated, split-opened mouse PTs by using a pH-sensitive dye BCECF. To uncover the signaling mechanism, we examined the effect of bafilomycin, Akt1/2 inhibitor VIII, and mTORC1 inhibitor rapamycin and an mTORC1/2 inhibitor, PP242. The measurement of V-ATPase activity was as follows; Freshly isolated and split-opened PTs in the chamber were first perfused in HEPEs, and then the perfusate was switched to Na+-free HEPEs. The intracellular pH recovery rates during perfusing with Na+-free HEPEs were measured, and intracellular pH change was calculated during the initial 30 seconds as V-ATPase activity. To confirm the protein expression, protein phosphorylation was analyzed by Western blotting.

Results: V-ATPase activity in PTs was markedly stimulated by insulin, and this stimulation was almost completely inhibited by bafilomycin, Akt inhibitor VIII, and PP242, but not by rapamycin. In freshly isolated mouse PTs, V-ATPase activity was increased approximately 20% by bafilomycin above insulin baseline and this stimulation was completely suppressed by Akt1/2 inhibitor VIII. While PP242 completely suppressed the insulin-mediated V-ATPase stimulation in mouse PTs, rapamycin failed to affect the insulin effect. Insulin-induced phosphorylation of Akt in mouse renal cortex was completely suppressed by Akt1/2 inhibitor VIII and PP242, but not rapamycin.

Conclusions: Our results demonstrate that stimulation of V-ATPase activity by insulin in PTs is mediated via Akt2/mTORC2 pathway. These results implicate the complex signaling in the proximal tubule acid-base balance, providing treatment targets for renal disease.

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FR-PO598

Secretin Activates Pendrin-Dependent HCO3− Secretion in β-Intercalated Cells

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Background: The secretin receptor is expressed in the intercalated cells (IC) of the collecting duct. Using in vivo mouse experiments, we have recently shown that secretin triggers a pronounced and rapid increase of urinary HCO3− excretion. Importantly, this secretin effect was completely absent in pendrin (SLC26A4) KO mice and strongly reduced in CFTR KO mice. We hypothesize that secretin directly activates β-intercalated cells (β-ICs) of the collecting duct (CD) via stimulation of basolateral secretory receptors. Methods: We used isolated perfused cortical collecting ducts and intracellular pH measurements in β-ICs to quantify the transport rate of pendrin upon fast removal of luminal chloride in the presence of 24 mM luminal HCO3−. Tubules were loaded with the pH indicator dye BCECF-AM from the luminal side to achieve selective IC dye loading. Results: In isolated perfused CD experiments we have demonstrated that IC pendrin (SLC26A4) expression increased with secretin (0.20±0.03 pM/min vs. 0.43±0.04 pH/min 24 cells, 4 CDIs, 4 mice), (P<0.0001). This increase was significantly different from time controls without secretin (p=0.0022, 20 cells, 4 CDs, 4 mice). In freshly isolated, perfused CDβ-ICs. Secretin (10 nM) was applied for 10 min to the basolateral side. Analysis was performed in a strictly paired fashion in the single β-IC before and after secretin and this was compared to time controls with no secretin stimulation.

Results: Mean ApH/i at was markedly increased with secretin (0.20±0.03 pH/min vs. 0.43±0.04 pH/min 24 cells, 4 CDIs, 4 mice), (P<0.0001). This increase was significantly different from time controls without secretin (p=0.0022, 20 cells, 4 CDs, 4 mice). In freshly isolated, perfused CDβ-ICs.

Conclusions: These results show that basolateral secretin directly activates pendrin-dependent HCO3− secretion in β-ICs. Importantly, HCO3− secretion in β-ICs is markedly reduced in CFTR KO mice. Thus, our previously demonstrated in vivo effects of secretin align well with those reported here in the isolated perfused CD. This shows that secretin triggers urinary HCO3− excretion by activating the β-ICs.

Funding: Government Support - Non-U.S.

FR-PO599

The Molecular Chaperone GRP170 Regulates ENaC Biogenesis and Salt and Water Homeostasis in the Kidney

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Background: The epithelial sodium channel (ENaC) is expressed in a variety of epithelial tissues. In the distal nephron, ENaC is responsible for Na+ reabsorption and regulates salt and water homeostasis and blood pressure. ENaC is a heterotrimcr channel composed of α, β, and γ-subunits. Unassembled ENaC subunits are recognized by the

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Low ENaC Expression Abolishes Furosemide-Induced K⁺ Excretion
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Background: In the collecting duct (CD) ENaC-mediated Na⁺ absorption drives K⁺ excretion. Acute K⁺ excretion is dependent on the regulated delivery of Na⁺ to the aldosterone-sensitive part of the distal nephron (ASDN) and acute activation of ENaC. Furosemide is considered a K⁺ wasting diuretic as it greatly enhances Na⁺ delivery to the ASDN. Here, we study the magnitude of acute furosemide-induced kaliuresis under various states of CD ENaC expression.

Methods: C57Bl/6j mice were subjected to different dietary regimens altering molecular ENaC expression levels. The animals were anesthetized and bladder-catheterized. Diuresis was continuously measured before and after furosemide (250µg/gbw) was administered. Flame photometry was used to measure urinary Na⁺ and K⁺ and ENaC expression levels were determined by semi-quantitative Western Blotting.

Results: A high K⁺ and a low Na⁺ diet greatly increased ENaC protein expression and furosemide-induced kaliuresis. In contrast, furosemide-induced kaliuresis was greatly reduced in normal fed a low K⁺ diet and absent in animals on a high Na⁺ diet, conditions with markedly reduced ENaC expression. No significant differences in furosemide-induced in vitro culture experiments were found when comparing the dietary groups but it tended to be lower in the low ENaC expressing groups. The furosemide-induced diuresis was similar in all culture groups.

Conclusions: Acute furosemide-induced kaliuresis greatly and markedly depends on the a priori molecular expression level of ENaC. Remarkably, it can be even absent in animals fed a high Na⁺ diet, despite a marked increase of tubular flow. This study provides auxiliary evidence that acute Na/K/and ENaC dependent K⁺ secretion requires both functional and molecular activation of ENaC.

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FR-PO603
Effect of Loading NH₄Cl in P2Y₂, Receptor Knockout and Wild-Type Mice
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Background: Chronic lithium (Li) administration for bipolar disorder causes renal tubular acidosis. In animal models, Li invokes collecting duct remodeling (CD-R) responses that result in an increased proportion of Na⁺-ATPase positive intercalated cells, presumably resulting in an increased proportion of [H⁺]-ATPase-positive intercalated cells, presumably resulting in an increased proportion of [H⁺]-ATPase-positive intercalated cells. To test this, murine PCs (mpkccd) were grown on snapwells under functional and molecular activation of ENaC.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 KO mouse. A GRP170 allele flanked by LoxP sites ("floxed") was genetically crossed with a mouse molecular chaperone, GRP170, to delete ENaC to the cell surface. Thus, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 knock-out (KO) mouse. A GRP170 allele flanked by LoxP sites ("floxed") was genetically crossed with a mouse molecular chaperone, GRP170, to delete ENaC to the cell surface. Thus, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 knock-out (KO) mouse. A GRP170 allele flanked by LoxP sites ("floxed") was genetically crossed with a mouse molecular chaperone, GRP170, to delete ENaC to the cell surface. Thus, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 knock-out (KO) mouse. A GRP170 allele flanked by LoxP sites ("floxed") was genetically crossed with a mouse molecular chaperone, GRP170, to delete ENaC to the cell surface. Thus, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 knock-out (KO) mouse. A GRP170 allele flanked by LoxP sites ("floxed") was genetically crossed with a mouse molecular chaperone, GRP170, to delete ENaC to the cell surface. Thus, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 knock-out (KO) mouse. A GRP170 allele flanked by LoxP sites ("floxed") was genetically crossed with a mouse molecular chaperone, GRP170, to delete ENaC to the cell surface. Thus, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 knock-out (KO) mouse. A GRP170 allele flanked by LoxP sites ("floxed") was genetically crossed with a mouse molecular chaperone, GRP170, to delete ENaC to the cell surface. Thus, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 knock-out (KO) mouse. A GRP170 allele flanked by LoxP sites ("floxed") was genetically crossed with a mouse molecular chaperone, GRP170, to delete ENaC to the cell surface. Thus, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.

Methods: To test our hypothesis we generated a kidney tubule-specific, inducible, GRP170 knock-out (KO) mouse. A GRP170 allele flanked by LoxP sites ("floxed") was genetically crossed with a mouse molecular chaperone, GRP170, to delete ENaC to the cell surface. Thus, we hypothesized that GRP170 promotes ENaC surface expression in the mammalian kidney.
Conclusions: P2Y2 receptor seems to have an important role in the maintenance of acid-base homeostasis. This role is crucial for kidney function, as indicated by the significant increase in serum creatinine in P2Y2 knockouts compared to WT mice.

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FR-PO606

MAGE-D2 Is Required for a Normal Cell Surface Expression of NHE3 Protein

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Background: We recently showed that mutations in MAGE-D2 cause polyhydramnios leading to preterm birth and a severe but transient form of antenatal Bartter’s syndrome in humans. Reduced expression of the sodium–chloride transporter NHE3, leading to Na+-dependent aldosterone production and NaCl retention, was shown in a transient aBS patient.

Methods: We investigated the role of MAGE-D2 in the regulation of NHE3 subcellular localization and quantitative surface expression.

Results: MAGE-D2 was highly expressed on the cell surface of human renal proximal tubular epithelial cells (hPTEC) and the brush border was positive to MAGE-D2-specific staining. MAGE-D2 was found in the cytoplasm and the endoplasmic reticulum of hPTEC. MAGE-D2 expression in hPTEC was associated with a decrease of plasma K+ and a hypochloremic metabolic alkalosis. This phenotype, induced by salt load, resembles Bartter syndrome, a salt-losing pathology due to thick-ascending limb volume contraction or compensatory activation of other renal Na+ reabsorption pathways. The findings show that the renal transporter AE4 (Slc4a9) is dispensable for Na+ homeostasis during salt restriction, but is essential for the stimulatory effect of NaCl on NHE3 expression.

Conclusions: The role of endogenously expressed MAGE-D2 in NaCl homeostasis is investigated in transient aBS patients and normal controls. MAGE-D2 expression was significantly increased in hPTEC and normal controls compared to aBS patients. MAGE-D2 expression was associated with a decrease of plasma K+ and a hypochloremic metabolic alkalosis. This phenotype, induced by salt load, resembles Bartter syndrome, a salt-losing pathology due to thick-ascending limb volume contraction or compensatory activation of other renal Na+ reabsorption pathways. The findings show that the renal transporter AE4 (Slc4a9) is dispensable for Na+ homeostasis during salt restriction, but is essential for the stimulatory effect of NaCl on NHE3 expression.

FR-PO607

14-3-3 Epsilon Regulates NPT2a Activity in the Renal Proximal Tubule

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Background: 14-3-3s are a family of highly conserved, evolutionarily ancient, cytoplasmic phosphoprotein phosphoregulators. We recently showed that mutations in NHE3 lead to preterm birth and a severe but transient form of antenatal Bartter’s syndrome in humans. We sought to investigate the potential role of MAGE-D2 in the regulation of NHE3.

Methods: We investigated the role of MAGE-D2 in the regulation of NHE3 subcellular localization and quantitative surface expression.

Results: MAGE-D2 expression in hPTEC was associated with a decrease of plasma K+ and a hypochloremic metabolic alkalosis. This phenotype, induced by salt load, resembles Bartter syndrome, a salt-losing pathology due to thick-ascending limb volume contraction or compensatory activation of other renal Na+ reabsorption pathways. The findings show that the renal transporter AE4 (Slc4a9) is dispensable for Na+ homeostasis during salt restriction, but is essential for the stimulatory effect of NaCl on NHE3 expression.

Conclusions: The findings show that the renal transporter AE4 (Slc4a9) is dispensable for Na+ homeostasis during salt restriction, but is essential for the stimulatory effect of NaCl on NHE3 expression.
Non-phosphomimetic NPT2a (ARL) exhibits no membrane expression or co-localization with 14-3-3 epsilon.FI

Conclusions: These studies demonstrate that the phosphorylation state of T635 in the PDZ binding motif of NPT2a is a determinant in the molecular switch between NHERF1 and 14-3-3 epsilon regulation of the trafficking and functional activity of the cotransporter.

Funding: Veterans Affairs Support

FR-PO608

The Diuretic Actions of SGLT2 Inhibitors and Loop Diuretics Induce Different Compensating Mechanisms

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Background: We recently reported that SGLT2 inhibitor irapagliflozin (Ipra) expresses a sustained diuretic and natriuretic tone that activates compensatory increases in fluid and food intake, and solute-free water reabsorption to stabilize body fluid volume (Am J Physiol Renal Physiol 2018, ASN Kidney Week 2018). Here we determined whether loop diuretics activate similar compensatory mechanisms.

Methods: Sprague-Dawley rats were treated by oral gavage with vehicle (Veh), loop diuretic furosemide (FR) [50 mg/kg] or Ipra [5 mg/kg] (n = 4-8) in metabolic cages for 1 week. Bioimpedance spectroscopy (ImpedVent) was used to assess body water changes on day 0 and 7.

Results: FR and Ipra increased urine volume (Veh 18 ± 2, FR 27 ± 3, Ipra 31 ± 2 mL/day [average of 7 days], ANOVA, p = 0.006), but FR did not increase fluid intake (41 ± 4, 37 ± 6, 51 ± 5 mL/day, p = 0.188) and food intake (23 ± 3, 8 ± 3, 23 ± 3 mL/day, p = 0.099). As a result, FR significantly increased fluid balance (fluid intake-urine volume) (23 ± 2, 10 ± 3, 21 ± 4 mL/day, p = 0.01). Urine osmolality (1.5 ± 0.3, 0.7 ± 0.3, 2.4 ± 0.4 mg/day, day 3, p = 0.024) and renal solute-free water reabsorption (84 ± 10, 42 ± 11, 128 ± 7 mL/day, day 7, p = 0.001) were decreased in the FR group and increased in the Ipra group. Serum osmolality was similar among the groups (307 ± 4, 311 ± 3, 305 ± 2 mOsm/kg, O/day, day 7, p = 0.337). The change in total body water (+8 ± 7, -34 ± 8, -5 ± 3 mL, from day 0 to day 7, p = 0.001) and creatinine clearance (5 ± 8 ± 0.3, 2.7 ± 0.06, 5.6 ± 0.2 mL/day, day 7, p = 0.025) were significantly decreased in the FR group.

Conclusions: The SGLT2 inhibitor maintained body fluid volume and renal function. The loop diuretic decreased both parameters with the impaired solute-free water reabsorption unexpectedly being associated with a lack of compensatory increases in vasopressin secretion and fluid intake.

Funding: Government Support - Non-U.S.

FR-PO609

The Stimulatory Role of SPAK Kinase in the Regulation of the Large Conductance Ca2+-Activated Potassium (BK) Channels Protein Expression in Kidney

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Background: SPAK-related proline-alanine-rich kinase (SPAK) and the oxidative stress-responsive kinase 1 (OSR1) have been shown to be the downstream kinases of norepinephrine (WAK). SPAK/OSR1 has been shown to mediate the regulation of WNK kinase activity in cation-chloride cotransporter including sodium chloride cotransporter (NCC) and potassium chloride cotransporter (KCC), etc. In addition, previous studies reported that the WNK4 inhibits BK channel protein expression by enhancing BK degradation through stimulating ERK 1 and p38 signaling pathway. Our previous work also showed that SPAK/OSR1 suppresses BK channel activity in Xenopus oocytes over-expressing SPAK/OSR1. Based on these observations it is hypothesized that SPAK/OSR1 modulate the BK protein expression in kidney tissues. Thus, in this study we have investigated the effects of SPAK kinase on renal BK protein expressions in both mammalian cells and mouse kidney.

Methods: SPAK KO mice, ERK1 global KO mice, western blot analysis, cell culture, and siRNA knock-down experiments were used in this study.

Results: When Cos-7 and HEK 293 cells were over-expressed with SPAK plasmids, BK protein expressions were increased while decreasing ERK 1/2 phosphorylation in a dose-dependent manner, whereas the cells were transfected with SPAK siRNA, BK protein expressions were decreased while increasing ERK 1/2 phosphorylation in a dose-dependent manner. In SPAK mice, BK protein abundance was decreased while increasing ERK 1/2 phosphorylation. In addition, in ERK 1 KO mice BK protein abundance was increased while dramatically increasing SPAK phosphorylation. In addition, WNK4 inhibited BK protein expression while increasing ERK 1/2 phosphorylation.

Conclusions: These data suggested that SPAK signaling positively regulates BK protein expression through negatively modulating ERK 1/2 phosphorylation, potentially by reducing BK degradation.

Funding: Veterans Affairs Support

FR-PO610

The Impact of TRPV-1 Genetic Polymorphisms on Serum Sodium Concentration in Elderly Patients


Background: Disorders of water balance, reflected as serum sodium concentration, are common in clinical practice but their pathophysiology remains incompletely understood. An N-terminal variant of transient receptor potential vanilloid-1 (delta N-TRPV-1) is important for mammalian central osmosensory transduction in hypothalamic magnocellular neurosecretory cells (MNCs) and is activated by hypertonicity, thus stimulating pituitary AVP secretion. Nevertheless, TRPV-1 single nucleotide polymorphisms (SNPs) have not yet been studied in relation to human osmoregulation.

Methods: We genotyped four common TRPV-1 SNPs in 507 acutely admitted elderly patients and 2480 ambulatory elderly patients, who were respectively at high- and low risk for hyponatremia. These SNPs include rs8065080 (I585V), rs224534 (T469I), rs222748 (H167H) and rs222749 (P91S). The effect of TRPV-1 SNPs on serum sodium concentration and the risk of hyponatremia was examined using multiple linear regression analysis and multiple logistic regression analysis. Haplotype analysis was employed to test the effect of combinations of TRPV-1 SNPs.

Results: In both cohorts, carriage of rs8065080, rs224534 and rs222749 did not significantly influence serum sodium concentrations. In acutely admitted elderly patients, univariate analysis demonstrated that serum sodium levels of rs222749 carriers were lower than non-carriers, both in the entire cohort (133.9 ± 6.0 versus 135.7 ± 6.4 mmol/L, p = 0.049) and in Western-European patients (133.7 ± 6.0 versus 135.7 ± 6.1 mmol/L, p = 0.030). Acutely admitted patients rs222749 carriers were more likely to be included in the lowest sodium tertiles (Serum Na < 137 mmol/L; OR 2.54; 95% CI 1.18 - 5.34). In multiple linear regression analysis, carriage of the rs222749 allele was an independent predictor of serum sodium concentration in acutely admitted elderly patients but not in ambulatory patients.

Conclusions: In view of data from previous in vitro studies we hypothesize that rs222749 involves a gain-of-function mutation through enhanced delta N-TRPV-1 expression in MNCs, leading to increased pituitary AVP release and lower serum sodium levels in vulnerable patients.

Funding: Clinical Revenue Support

FR-PO611

ARL15 Regulates CNNM2-Dependent Mg2+ Transport by Modulating Its N-Linked Glycosylation

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Background: A large genome-wide association study identified that ARL15, a small GTP-binding protein, is associated with urinary Mg2+ excretion. Within the kidney, ARL15 is highly expressed in the thick ascending limb (TAL) and distal convoluted tubule (DCT), where Mg2+ reabsorption is tightly regulated. However, the exact function of ARL15 and the mechanism by which ARL15 regulates renal Mg2+ handling are still unknown.

Methods: To identify protein-interaction between ARL15 and Cyclin M (CNNM) proteins, proximity-dependency biotin identification (BioID) and co-immunoprecipitation were performed. Immunohistochemistry were used to investigate co-localization in mouse kidney and human embryonic kidney (HEK293) cells. Furthermore, cell surface biotinylation and 25Mg2+ uptake assays were used to assess cell surface expression of CNNM2 and Mg2+ transport activity. The glycosylation pattern of CNNMs was determined by far lectin Western blot and glycosidase assays.

Results: We identified members of the CNNM family as direct interaction partners of ARL15 by BioID. Immunoprecipitation with truncated CNNM2 proteins indicated that ARL15 interacts with CNNM2 at its carboxyl-(C)-terminal conserved CBS domain. CNNM2 and ARL15 co-localize in the DCT. Interestingly, overexpression of ARL15 in HEK293 cells showed subcellular localization in the Golgi-apparatus and resulted in an increased N-glycosylation of CNNM proteins. This ARL15-mediated glycosylation was Mg2+ sensitive and encompassed hybrid and complex glycosylation. The functional consequences of ARL15-dependent glycosylation were examined by 25Mg2+ uptake experiments. ARL15 increased 25Mg2+ uptake via CNNM2 by increasing its cell surface expression.

Conclusions: ARL15 increases CNNM2 plasma membrane expression by regulating its N-glycosylation pattern. Altogether, our results establish ARL15 as a novel regulatory mechanism of Mg2+ transport within the DCT.

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FR-PO612

Phenotype of Ksp-Cadherin Deficient Mice: Normal Kidney Development but Delayed Maturation of Maximal Urinary Concentrating Ability
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Background: Ksp-cadherin is a largely kidney-specific member of the cadherin superfamily of cell adhesion molecules. Despite ubiquitous basolateral expression throughout the tubular nephron its function remains unknown.

Methods: To address this question we have generated Ksp-cadherin deficient mice (Ksp-null) by introducing a premature stop codon into the second exon of the Ksp-cadherin gene.

Results: Homozygous Ksp-null animals were born at expected frequencies and were not overtly different from age- and gender-matched wild-type (WT) controls. Kidneys from neonate and adult Ksp-null and WT mice had no discernible differences in the ultrastructural organization of nephrogenic progenitors or mature nephrons. Analysis of E-cadherin and Na/K-ATPase indicate that E-cadherin expression is not modified to compensate for Ksp-cadherin loss and that epithelial cell polarity is unaffected. Serum electrolytes, total CO2, BUN, and creatinine levels were not significantly different between the two groups. Under basal conditions 10 week-old Ksp-null animals produced a urine that was significantly less concentrated than that from a matching WT cohort (1463 ± 219 vs 2184 ± 164 mOsm respectively; P<0.0249). After 24 hrs of water deprivation, similarly aged Ksp-null animals were unable to concentrate their urine to the same extent as their WT counterparts (3283 ± 69 vs 3840 ± 112 mOsm respectively; P=0.0017). Expression analysis of NKCC2, UTA-1-3, UTB, AQP1-2, V2R, ROMK, CLCK1, and UMOD indicated that the concentrating defect was not due to altered expression of the principal proteins involved in the generation of the cortico-medullary osmotic gradient. Immunolocalization studies suggested that the defect may be due to misexpression of AQP2 in the IMCD of the Ksp-null mutants. Under both baseline and water-restricted conditions 10 month-old Ksp-null mutants were able to concentrate their urine to the same extent as similarly aged WT animals, suggesting that the defect in urinary concentrating ability in the Ksp-null mice is due to a developmental delay.

Conclusions: In conclusion Ksp-cadherin is not essential for nephron formation of nephron segment delineation. Its null mutation does, however, significantly delay the maturation of maximal urinary concentrating ability.

Funding: NIDDK Support

FR-PO613

Tacrolimus Improved Symptoms of Type 4 Bartter Syndrome Model Mice Yoshiuki Matsura, Naohito Nomura, Wakana Shoda, Eisei Sohara, Tatematsu Ria, Shiinami Uchida. Department of Nephrology Tokyo Medical and Dental University, Tokyo, Japan.

Background: Type 4 Bartter syndrome (BS) is a hereditary tubular disease characterized by salt-losing polyuria, hypokalemia, and metabolic alkalosis. Because barttin (coded by Bsdn gene, which is a disease causing gene of type 4 BS) is expressing from thick ascending limbs of Henle’s (TAL) to collecting ducts, the function of distal nephron is widely impaired and the symptoms of type 4 BS are generally very severe. Although potassium replacement therapy has been mainly used for hypokalemia, there is no fundamental treatment for type 4 BS. It has been reported that calcium-uridine enhancer inhibit phosphorylation of sodium (Na-) potassium (K) -2 chloride (Cl) cotransporter (NKCC2) and Na-Cit cotransporter (NCC), which are key sodium transporters in TAL and distal convoluted tubule, respectively. In this study, we hypothesized that tacrolimus, a calcium-uridine inhibitor, would increase in phosphorylation of NKCC2 and NCC, and improve symptoms of type 4 BS.

Methods: Bsdn-/- mice, which is morphochromic of barttin, were used as a model of type 4 BS. Bsdn-/- mice showed severe polyuria, hypokalemia, and metabolic alkalosis. Tacrolimus was administered subcutaneously once a day. After a week administration of tacrolimus, blood sampling and kidney harvest were performed. Phosphorylation of NKCC2 and NCC was evaluated by Western blotting. For the investigation of urine volume and urinary K excretion, urine was collected in a urine collection cage after a single intraperitoneal administration of tacrolimus.

Results: After a week administration of tacrolimus, serum potassium levels were significantly increased in Bsdn-/- mice. However, improvement of metabolic alkalosis was not observed after tacrolimus treatment. After single administration of tacrolimus, urinary K excretion was significantly reduced, and urine volume also tended to be decreased. Phosphorylation of NKCC2 and NCC was significantly increased in Bsdn-/- mice.

Conclusions: Tacrolimus administration ameliorated hypokalemia in type 4 BS mice by suppressing urinary K excretion. Increase in phosphorylation of NCC and NKCC2 would induces improvement of hypokalemia in type 4 BS. Tacrolimus might be effective for the treatment of type 4 BS.

Funding: Government Support - Non-U.S.

FR-PO614

Different NKCC2 Amino Acid Sequences Between 129Sv and C57BL/6 Mice Affect Analysis of NKCC2 Phosphorylation with Phospho-specific Antibodies
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Background: The furosemide-sensitive Na-K-2Cl cotransporter (NKCC2) of the thick ascending limb is critical for the renal control of electrolyte and fluid homeostasis. The activity of NKCC2 is regulated via phosphorylation of several serine and threonine (T) residues in the N-terminal tail of the co-transporter. To study NKCC2 function, phospho-specific antibodies directed against these phosphorylation sites (e.g. T96 and T101) have been developed and applied in studies on mouse models. The most frequently used mouse strains are 129Sv and C57BL/6 mice. Surprisingly, when we tried to detect phosphorylated NKCC2 (pNKCC2) with anti pT96/pT101 NKCC2 antibodies, we detected a strong pNKCC2 signal only in kidneys from 129Sv mice but not in kidney from C57BL/6 mice. In the latter, only some unspecific cross-reactivity of the pNKCC2 antibodies with the phosphorylated thiadize-sensitive NaCl cotransporter was seen.

Methods: To address this unexpected finding, we compared 129Sv and C57BL/6 mice via database analysis, metabolic cage experiments, quantitative RT-PCR and immunoblotting.

Results: Database analysis revealed that C57BL/6 mice have a five amino acid deletion (ΔT96N100) in NKCC2, which lies in the region of the epitopes recognized by most anti-pNKCC2 antibodies. Although we observed strain differences in urinary Ca2+ and Mg2+ excretion and in the expression of several renal ion transporters and channels between 129Sv and C57BL/6 mice, these differences are likely not related to the five amino acid deletion in NKCC2. When we crossed 129Sv and C57BL/6 mice to obtain heterozygous F2 generation with the deletion (ΔT96-N100 mice) and mice without the deletion (control mice) were phenotypically similar. In particular, there were no differences in NKCC2 mRNA and protein abundances between the ΔT96-N100 and control mice. Nevertheless, pNKCC2 remained barely detectable in ΔT96-N100 mice using the antibodies against the full-length epitope.

Conclusions: Our study reports an important difference between the NKCC2 amino acid sequences of 129Sv and C57BL/6 mice that does not appear to significantly affect NKCC2 function, but strongly interferes with the detection of NKCC2 phosphorylation via phospho-specific antibodies. This needs to be considered when studying NKCC2 regulation in different mouse strains and when cross-breeding mice.
Actinin-4 (ACTN4) interacts with ALMS1 and NKCC2 in thick ascending limbs (TAL) to regulate NKCC2 trafficking.

**Background:** Loss-of-function mutations in the ALMS1 gene cause Alström syndrome, characterized by hypertension, early onset obesity, type 2 diabetes and progressive loss of renal function. Single nucleotide polymorphisms (SNPs) in the ALMS1 gene are associated with decreased renal function (lower GFR) and increased pulse pressure in the general population. However, the role of ALMS1 in the control of renal function is unclear. We recently found that ALMS1 physically interacts with the apical renal Na/K/2Cl cotransporter NKCC2 in the TAL, where it mediates its endocytosis. However, the molecular mechanisms by which ALMS1 mediates NKCC2 endocytosis are unclear. We hypothesized that ALMS1 is part of a protein complex that binds apical NKCC2 and promotes its endocytosis and recycling.

**Methods:** To begin studying these mechanisms we used a targeted proteomics screen to identify new binding partners for ALMS1 in the TAL as well as immune precipitation.

**Results:** GST-pull down with the C-terminus of ALMS1 identified several trafficking proteins. One of them, Actinin-4 (ACTN4), is involved in endocytosis and its mutation causes focal segmental glomerular disease. GST-ACTN4 (full length) pulled down both ALMS1 and NKCC2 from TALs. Immunoprecipitation of NKCC2 followed by mass spectrometry identified ACTN4. The role of ACTN4 in the nephron is unclear so we studied its localization. ACTN4 was abundant in glomeruli but also localized in cells along the nephron in a punctate vesicular pattern. ACTN4 was located in TALs (co-labeled with NKCC2) and co-localized with ALMS1 in the subapical space. To study the role of ALMS1 and ACTN4 we generated a mouse line with doxycycline (Dox) inducible neprhin-specific deletion of ALMS1 (Dox-inducible-Pax8-Cre-ALMS1flo/x). 4 weeks after Dox treatment, ACTN4 expression in medullary tubules was decreased by 78±14% (p<0.05). Interestingly, ACTN4 expression was also decreased by 5±9% (p=0.05) in nephron specific ALMS1 KO, compared to doxycycline treated controls (ALMS1flo/x). In isolated mouse TALs, the surface to total NKCC2 ratio was increased by 55±19% (p=0.05), suggesting decreased retrieval from the surface.

**Conclusions:** We found that ACTN4 binds both ALMS1 and NKCC2 and is required for proper NKCC2 trafficking. Our data suggest that ACTN4 plays a role in tubular Na absorption in addition to its role in podocytes.

**Funding:** NIDDK Support

FR-PO617

**N-Terminal Phosphorylation of Kidney Na-K-2Cl-Cotransporter Attenuates Its Endocytosis**

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**Background:** The renal Na-K-2Cl-cotransporter (NKCC2) of the thick ascending limb (TAL) is critical for renal salt handling. Its activity is stimulated by phosphorylation of conserved N-terminal threonine and serine residues (T96, T101, T114, and S126), although the underlying mechanisms are not entirely clear. We hypothesized that NKCC2 phosphorylation interferes with its clathrin-mediated endocytosis.

**Methods:** Cellular distribution of NKCC2 and its phosphorylated form (pNKCC2) was studied in rat kidney and cultured rat TAL cells by high-resolution immunofluorescence electron microscopy and biochemical tissue fractionation by sucrose gradient. Association of NKCC2 and pNKCC2 with clathrin was studied by binding assays.

**Results:** Labeling of rat kidney sections for NKCC2 revealed its even distribution between the luminal membrane and apical vesicular compartment, whereas pNKCC2 resided predominantly in the luminal membrane. Analysis of NKCC2, pNKCC2 and clathrin distribution in apical membrane fragments obtained from cultured TAL cells using the rip/flip technique showed regular co-localization of NKCC2- and clathrin immunogold signals, whereas pNKCC2 signal localized to clathrin-negative electron-dense membrane domains containing the lipid raft marker flotillin-1. In line with this, isolation of detergent-resistant membrane rafts from rat kidney tissue using extraction with Triton X-100 and subsequent sucrose gradient centrifugation revealed co-distribution of pNKCC2 and flotillin-1 signals in rafts-containing low-density gradient fractions, whereas clathrin signal was present in non-raff high-density fractions. GST pull down assays showed interactions of clathrin with recombiant N-terminal NKCC2 mutants mimicking its dephosphorylated (S/T->A), whereas mutants mimicking the phosphorylated N-terminus (S/T->D) did not bind clathrin. Acute in vivo stimulation by treating vasopressin-deficient Brattleboro rats with desmopressin (1μg/kg body weight for 30 min) attenuated its co-immunoprecipitation with clathrin (-72%, p<0.05) and increased NKCC2 surface expression (+24%, p<0.05).

**Conclusions:** In summary, these results suggest that NKCC2 phosphorylation inhibits its clathrin-mediated NKCC2 endocytosis resulting in increased NKCC2 surface expression and activity.

**Funding:** Government Support - Non-U.S.

FR-PO618

**Role of Vasopressin V2 Receptor Signaling in NKCC2 Regulation in Diabetes Mellitus**

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**Background:** Previous studies have reported that vasopressin V2 receptor is present in thick ascending limb (TAL) of loop of Henle and can regulate the abundance of Na-K-2Cl cotransporter (NKCC2). Nonetheless, the upstream signaling and the pathological significance in a diabetes state remains obscure. We aimed to address the role of vasopressin V2 signaling in TAL in diabetic kidney disease.

**Methods:** We compared the levels of aquaporin 2 and NKCC2 in the membrane fraction of the kidney between db/+ and db/db mice. We then orally administered tolvaptan, vasopressin V2 receptor antagonist, to db/+ and db/db mice for two weeks and evaluated the changes in aquaporin 2 and NKCC2. To test the role of V2 signaling in humans, we obtained urinary exosomes from diabetic subjects treated with tolvaptan and compared the levels of aquaporin 2 and NKCC2 before and after the treatment.

**Conclusions:** The administration of tolvaptan significantly increased expression in db/+ mice. We also found that NKCC2 abundance was reduced by tolvaptan in this model. To evaluate the role of vasopressin signaling in diabetic kidney, we compared their levels between db/+ and db/db mice, and found that both aquaporin 2 and NKCC2 were significantly elevated in db/db mice (1.87-fold increase for aquaporin 2, P=0.03, and 1.90-fold increase for NKCC2; P=0.001). Moreover, these levels were significantly reduced by tolvaptan administration, indicating the contribution of vasopressin V2 signaling in the kidney in db/db mice. To extend these observations into humans, we evaluated NKCC2 levels in urinary vesicles in subjects with diabetic kidney disease who received tolvaptan. Among 15 subjects examined, six showed response to tolvaptan, resulting in reduced aquaporin 2 levels in urinary exosomes. In these cases, NKCC2 levels tended to reduced after the treatment.

**Conclusions:** Vasopressin V2 receptor signaling is involved in the regulation of NKCC2, which can be dysregulated in the kidney of diabetes mellitus.

**Funding:** NIDDK Support

FR-PO619

**Functional Substrates of Vasopressin-Responsive PARylation in Kidney Collecting Duct Cells**

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**Background:** Poly (ADP-ribose) polymers (PARPs) regulate cellular progress, such as cell cycle, cell proliferation and differentiation, through molecular regulation of protein-protein interactions and protein stability. In our previous study, cellular poly-ADP-ribosylation (PARylation) was induced by vasopressin treatment in mpkCCD cells. The present study aims to examine regulation of PARylation as a part of vasopressin signaling in renal collecting duct (CD) cells.

**Methods:** We examined 1) vasopressin-responsive PARylation in mpkCCD cells using pulldown assay of biotin-conjugated NAD+ and immunoprecipitation assay using PAR (poly ADP-ribose) antibody; 2) immunoblotting for PARP1 abundance in nuclei and cytoplasm. Substrate proteins of PARP1 in kidney CD cells were identified from data mining in multiple public databases. Functional enrichment of PARP1 substrates was assessed using Metascape.

**Results:** dDA VP (10^{-9}M, 24 h) remarkably increased abundance of total PARylated proteins in mpkCCD cells in biotin-NAD+ pulldown and PAR immunoprecipitation assays. Interestingly, the cleavage of PARP1 was induced by both short-term (2 h, 6 h) and long-term (24 h, 48 h) dDA VP (10^{-9}M) treatment, suggesting that vasopressin signaling affects PARP1 action. Immunoblot using subcellular fractions of mpkCCD cells confirmed the cleaved form of PARP1 produced by dDA VP treatment was exported to the cytosolic fraction. dDA VP-induced AQP2 mRNA and protein expression was significantly attenuated under siRNA-mediated PARP1 knockdown conditions in mpkCCD cells. From a data mining approach, we identified 72 substrate proteins of PARP1 and 171 proteins interacting with PARP1 in kidney CD cells. Among them, 72 proteins were found across all the matches, suggesting as putative targets of PARP1 in the kidney collecting duct. Functional enrichment analysis revealed that these PARP1 substrates are involved in DNA damage repair, gene transcription, insulator function and DNA methylation, which have been known as cellular functions of PARP1.

**Conclusions:** Vasopressin-responsive PARylation is accompanied with remarkable changes in protein abundance and cleavage of PARP1 in kidney CD cells. Bioinformatic analyses identified putative PARP1 substrates and functional clustering of the identified substrates that could be involved in vasopressin signaling in the kidney CD cells.

**Funding:** Government Support - Non-U.S.

FR-PO620

**SNX27, Interacting with AQ2 in a PDZ-Dependent Manner, Regulates the Stability of AQ2 Protein**

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**Background:** Sorting nexin 27 (SNX27), a PDZ-domain-containing protein, is known to cooperate with a retromer complex, regulating the trafficking and stability of endosomal proteins. The crystal structure of SNX27 and ACTN4 binds both class 1 PDZ-interacting motif (X-T/S-X-Φ), however, interaction between SNX27 and AQ2 has been understudied.
not been studied. We aimed to examine the interaction of SNX27 for the regulation of AQP2.

Conclusions: SNX27-ΔPDZ, directly interacts with AQP2 in a PDZ-dependent manner, is likely to regulate stability of AQP2 protein. It acts as a component of the AQP2 controlling machinery, at least in part, through regulation of autophagy-lysosomal degradation of AQP2.

Funding: Government Support - Non-U.S.

FR-PO621

Possible Involvement of Upregulated Arginine Vasopressin in Fluid Retention on Peritoneal Dialysis


Background: Fluid retention is a typical complication of peritoneal dialysis (PD), and is associated with the safety and long-term delivery of PD. Arginine vasopressin (AVP), which is synthesized in the hypothalamus, is involved in water reabsorption in the collecting ducts and could be involved in fluid retention. Here, we examined hypothalamic AVP synthesis during PD in both basic and clinical research.

Methods: 1) First, after administration of 3% hypertonic saline (HTN) as dialysis solution for a short-term dwell or polyethylene glycol (PEG) as dialysis solution for a long-term dwell, we evaluated the fluorescence intensity of AVP-enhanced green fluorescent protein (eGFP) in the hypothalamus. The intensity of eGFP offers a quantitative indicator of AVP synthesis in transgenic rats. Second, we quantified Fos-like immunoreactive (IR) cells in several brain regions known to be involved in maintaining fluid homeostasis by control of AVP synthesis and/or having interactions with the hypothalamus. 2) We measured plasma AVP levels, plasma osmolality and urinary osmolality in 20 PD patients during visits.

Results: 1) Fluorescence intensities for eGFP were significantly increased in the hypothalamus after administration of HTN and PEG. Immunohistochemistry for Fos revealed activation of several brain areas after administration of HTN and PEG. 2) Plasma AVP levels (5.5 ± 0.6 pg/ml) and plasma osmolality (303.4 ± 1.6 mOsm/kg) increased significantly in PD patients, and these values were correlated (Rho = 0.56, P = 0.02, n= 20). In addition, a positive correlation was observed between plasma AVP levels and urine osmolality (Rho = 0.65, P < 0.03). Given these findings, we considered that the physiological function of AVP remained in PD patients.

Conclusions: To the best of our knowledge, this represents the first report to reveal an upregulation of hypothalamic AVP during PD by performing both basic and clinical research. Upregulation of hypothalamic AVP could induce fluid retention. These findings provide potential insights into fluid management for PD patients.

FR-PO622

WNK1 as a Central Osmosensor for Vasopressin Release and Water Homeostasis

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Background: The brain circumventricular organs (brain vasculature area) includes the hypothalamic supraoptic nucleus, paraventricular nucleus, area postrema, and the subfornical organ (SFO). These areas have a unique barrier function to mediators for fluid and osmotic balance. In particular, the SFO mediates extracellular osmolality via the WNK1/CLC4/CLC2 complex cascade. This cascade is present in the SFO, but not the other brain regions. It has been suggested that the WNK1/CLC4/CLC2 complex is involved in the regulation of vasopressin (AVP) secretion. However, the role of WNK1 in the regulation of AVP release has not been investigated. We aimed to examine the interaction of WNK1 with AVP release in response to changes in extracellular osmolality.

Methods: WNK1*−/− mice were bred with synapsin-Cre mice to generate neuronal-specific WNK1−/− knockout (KO) mice. Under ad lib water intake and food intake, average daily urine output was higher in KO mice (n = 6) than in control mice (n = 8) (1.57 ± 0.17 ml vs 1.03 ± 0.15 ml, p < 0.05). Daily water intake was also higher in KO than in control (4.94 ± 0.25 ml vs 4.14 ± 0.21 ml, p < 0.05). Serum osmolality was increased in KO mice trended higher but not statistically significantly different from control (314 ± 4 vs 307 ± 3 mOsm/kg, p < 0.18). Urine osmolality was lower in KO than in control mice. The pattern of serum and urine osmolality suggests that defects in vasopressin release or action (i.e., diabetes insipidus) rather than primary polyuria is the characteristic cause of polyuria. To further distinguish between these possibilities, mice were water-deprived for 24 hrs. Urine output remained elevated in KO than control mice under water deprivation (1.17 ± 0.13 ml vs 0.63 ± 0.54 ml, p < 0.05). Serum osmolality was increased and the difference between KO and control was larger during water deprivation (329 ± 4 vs 312 ± 3 mOsm/kg, p < 0.01). To support the hypothesis of blunted vasopressin release in neuronal WNK1-KO, work is ongoing to measure serum vasopressin and copeptin levels in KO & control mice.

Conclusions: Our results suggest that WNK1 protein may function as an intracellular osmosensor for regulating vasopressin release.

Funding: NIDDK Support

FR-PO624

Functional Characterization of Gain-of-Function Mutations of the V2 Vasopressin Receptor Leading to Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD) in the Chicken

Mariana Ranieri,1 Grazi Tamma,1 Vanessa Vezzi,1 AnnaRita Di Mise,1 Marienna Venneri,1 Mariangela Centurine,1 Susanna Cotecchia,1 Giovanna Valentí.1 1University of Bari, Bari, Italy; Istituto Superiore di Sanità, Rome, Italy.

Background: Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD) is a chromosome X-linked disease associated to gain-of-function mutations of the V2 vasopressin receptor (V2R). A protein-coupled receptor. NSIAD can be quite severe in young female children. It is characterized by polyuria and polydipsia or osmotic diuresis as the cause of polyuria. To further distinguish between these possibilities, mice were water-deprived for 24 hrs. Urine output remained elevated in KO than control mice under water deprivation (1.17 ± 0.13 ml vs 0.63 ± 0.54 ml, p < 0.05). Serum osmolality was increased and the difference between KO and control was larger during water deprivation (329 ± 4 vs 312 ± 3 mOsm/kg, p < 0.01). To support the hypothesis of blunted vasopressin release in neuronal WNK1-KO, work is ongoing to measure serum vasopressin and copeptin levels in KO & control mice.

Conclusions: Our results suggest that WNK1 protein may function as an intracellular osmosensor for regulating vasopressin release.

Funding: NIDDK Support

FR-PO624

UT-A2-Mediated Water Transport Is Regulated by N-Glycosylation

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Background: Urea transporters (UTs) are transmembrane glycoproteins that facilitate the diffusion of urea across cell membranes, and play a crucial role in the urinary concentrating mechanisms, important for maintaining nearly constant blood plasma osmolality. Renal UTs include: UT-A1 and UT-A3, which are expressed on the apical and basolateral membranes of the inner medullary cell, respectively; UT-A2, localized in the thin descending limb of the inner and outer renal medulla; and UT-B, expressed in the collecting tubules. In the descending vasa recta and collecting duct cells, UT-A2 is present in the basolateral membranes of the cell surface. UT-A2-mediated water transport was assessed by biotinylation and western blot analyses, with and without PNGase F. P. F. was assessed by placing the oocytes in a hypotonic solution and monitoring the rate of cell swelling with time microscopy.

Results: We observed an immunoreactive band at 34 kDa after treating mUT-A2 with PNGase F, a molecular weight consistent with unglycosylated monomer. No bands
were detected in the 45-55 kDa range with mUT-A2N210Q, indicating lack of glycosylation. The P value for mUT-A2N210Q (0.0013±0.0001, n=27) was significantly greater than UT-A2N210Q (0.0005±0.00004, n=25) and H2O oocytes (0.0006±0.00004, n=30).

Conclusions: These results indicate that the oocytes were not only capable of adding N-linked glycans to membrane proteins, but also that this post-translational modification affects activity. This observation is relevant to urine concentration mechanisms.

Funding: Government Support - Non-U.S.

FR-PO625
Drug-Induced Hyponatremia: Vasopressin-2 Receptor-Dependent and -Independent Pathway
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Background: Drugs associated with hyponatremia were traditionally classified into those enhancing vasopressin release and those potentiating the renal action of vasopressin. For the latter mechanism to act, vasopressin-2 receptor would have the pivotal role in activating aquaporin-2 in the collecting duct. However, vasopressin-2 receptor-independent pathways might be activated as well by drugs that induce central water retention. This preliminary study was undertaken to find antidiuretic drugs acting through vasopressin-2 receptor-independent pathways.

Methods: Five drugs or active metabolites were treated in inner medullary collecting duct suspensions prepared from male Sprague-Dawley rats. The intracellular cAMP levels were determined using a competitive enzyme immunoassay kit to compare the responses with and without tolvaptan (100 nM) cotreatment. Also, diDAVP (10 nM) was used as positive control.

Results: As expected, dDAVP induced an increase in cAMP production (20.7 ± 2.0 vs. 11.4 ± 0.6 pmol/mg protein, P=0.05) Similarly, haloperidol (14.7 ± 0.9 pmol/mg protein, P=0.05), sertraline (18.7 ± 0.9 pmol/mg protein, P=0.05), and carbamazepine (17.3 ± 0.7 pmol/mg protein, P=0.05) also had higher levels of CAMP. These responses were almost completely blocked by tolvaptan cotreatment (haloperidol, 8.5 ± 0.5 pmol/mg protein; sertraline, 12.6 ± 1.2 pmol/mg protein; carbamazepine 12.5 ± 0.7 pmol/mg protein, all P=0.05). Notably, the cAMP level was increased by vircristine treatment (16.7 ± 1.6 pmol/mg protein, P=0.05), but not reversed by tolvaptan cotreatment. On the other hand, chlorpropamide did not change in cAMP level without tolvaptan cotreatment.

Conclusions: As known before, chlorpropamide appears to enhance vasopressin release. Contrary to a previous notion, vincristine may induce water retention via vasopressin-2 receptor-independent pathways. Activation of vasopressin-2 receptor has a role in hyponatremia induced by haloperidol, sertraline, and carbamazepine.

Funding: Government Support - Non-U.S.

FR-PO626
Intracellular Sites of AQP2 S256 Phosphorylation in the Plasma Membrane, Cytosolic Vesicles, and the Trans Golgi Network
Identified Using Inhibitors of the AQP2 Recycling Itinerary
Richard Bouley, Pui Susan W. Cheung, Dennis Brown. Program in Membrane Biology Massachusetts General Hospital, Boston, MA.

Background: Vasopressin-regulated trafficking of aquaporin 2 between cytoplasmic vesicles and the plasma membrane of kidney principal cells is essential for body water homeostasis. VP-induced phosphorylation of AQP2 in serine residue S256 is required for its accumulation at the cell membrane, but the intracellular localization(s) where this phosphorylation occurs are poorly understood. Here, we used strategies to block AQP2 trafficking at different cellular locations in LLC-PK1 cells, and we monitored phosphorylation of AQP2 S256 at these sites using anti-phospho S256 antibodies after AQP2 trafficking at different cellular locations in LLC-PK1 cells, and we monitored phosphorylation at these sites using anti-phospho S256 antibodies after AQP2 trafficking at different cellular locations in LLC-PK1 cells, and we monitored phosphorylation of AQP2 S256 at these sites using anti-phospho S256 antibodies after.

Methods: Phosphorylation extent and location were assessed by western blotting and immunocytochemistry, respectively.

Results: Methy-l-b-cyclodextrin (MBCD) treatment blocks endocytosis, and recycling AQP2 accumulates at the cell surface without an increase in S256 phosphorylation. However, VP/FFK applied to MBCD treated cells resulted in a significant increase in S256 phosphorylation, indicating AQP2 can be phosphorylated when present in the plasma membrane. Taxol, an inhibitor of microtubule function, results in AQP2 containing vesicles being scattered throughout the cytoplasm, and inhibits VP-induced membrane accumulation of AQP2. Taxol alone did not affect AQP2 phosphorylation, but VP/FFK treatment of taxol exposed cells caused a significant increase in S256 phosphorylation, indicating that AQP2 can be phosphorylated on scattered cytoplasmic vesicles. Finally, AQP2 trafficking is blocked in the peri-nuclear, trans-Golgi network both by incubating cells at 20°C for 2 h or by using the VAPase inhibitor batimôtycin. VP/FFK stimulated AQP2 phosphorylation significantly under both conditions.

Conclusions: These findings suggest that the VP/FFK induced phosphorylation of AQP2 at S256 can occur at various locations during its recycling itinerary to and from the cell surface at the plasma membrane itself, on cytoplasmic vesicles, or in a retromer (Na+/H+ exchanger)-dependent pathway to the trans-Golgi network. Whether protein kinase A is involved in AQP2 S256 phosphorylation in all these locations is unclear, but the ability to dissect different intracellular phosphorylation stations may help to uncover new strategies to regulate AQP2 trafficking in conditions such as nephrogenic diabetes insipidus and hyponatremia.

Funding: NIDDK Support

FR-PO627 Urinary Net Endogenous Acid Production: A Reliable Predictor of Net Acid Excretion Tanushree Banerjee.1 Lynda A. Frassetto.2 San Francisco General Hospital, San Francisco, CA; 2University of California San Francisco, San Francisco, CA.

Background: High acid production and positive acid balance have been associated with progression of chronic kidney disease (CKD) and degenerative aging processes. Endogenous acid production (EAP) equations that most accurately represent net acid excretion (NAE) and require analyses of diet and stool ammonium are labor intensive and require titratable acids and bicarbonate, a somewhat complicated research protocol.

Being able to evaluate only urinary analytes might be easier. Here, we evaluate the predictive value of urinary measured (EAP) and unmeasured anions (UNEAP) to the measured value of NAE.

Methods: 24 hour urine collections from metabolic balance studies from 15 patients for repeated intervals were performed at the control period (baseline), diet intervention phase, and the recovery phase. Each phase was at least 3 days. NAE was calculated from measured values (= titratable acid + ammonium – bicarbonate). UNEAP was calculated from urinary [(phosphate+chloride)-(sodium+potassium+calcium)] + sulfate (SO4) + total organic acid (OA) production. EAP = urinary SO4+ OA salts.

Results: Using only urine measures, UANEAP was a more reliable estimate of NAE compared to EAP. Measures for estimating UNEAP may be less cumbersome than measuring NAE and help promote research into treatments that affect acid balance, such as alkali treatment for CKD.

Funding: Clinical Revenue Support

FR-PO628 Pseudohyphobacitatonemia Induced by Severe Hypertriglyceridemia Vipin Varghese,2 Juan Carlos Q. Velez.1 Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA; 1University of Queens-land - Ochsner Clinical School, New Orleans, LA.

Background: Reports of falsely low serum carbon dioxide (sCO2) concentration, i.e., pseudohyphobacitatonemia (pHbHCO3) in patients with severe hypertriglyceridemia (hyperTG) have emerged. This phenomenon results from lipid interference in some spectrophotometric analyzers. Our aim was to assess the magnitude and implications of pHbHCO3, in a tertiary care hospital.

Methods: We searched for cases of serum triglycerides (TG) > 1000 mg/dL with a concomitant (measured -24 hrs apart) sCO2, between 2017 and 2018. We extracted those with CO2 ≤ 12 mEq/L to focus on the more clinically relevant cases. Each measured sCO2 was compared with the calculated bicarbonate (HCO3-), from an arterial blood gas (ABG) obtained within 6 hrs of the venous blood draw. pHbHCO3 was defined as: erroneous HCO3- (mHCO3) - gap = (calculated HCO3- - measured sCO2) > 5 mEq/L.

Results: We identified 1698 events (652 patients) of TG > 1000 mg/dL and a sCO2 measured on the same day, TG inversely correlated with sCO2 (R=-0.38, p=0.00001). We found 179 events (59 patients) with sCO2 < 12 mEq/L. In 104 of those, an ABG was either not available or performed > 6 hrs apart from the venous blood draw. The remaining 75 events included 30 instances (11 patients) of true hypobacitatonemia and 45 instances (24 patients) of pHbHCO3. Among those with pHbHCO3, the median values of sCO2, calculated HCO3-, anion gap and eHCO3- gap were 8 (=5.12, 10 (2.9, 13) and 15 (19–21) mEq/L, respectively, whereas the median pH was 7.37 (7.14 – 7.56). True metabolic acidosis was either absent (42%) or spuriously magnified (58%). TG directly correlated with the eHCO3- gap (R=0.39, p=0.00004). Acute pancreatitis (56%) and diabetic ketoacidosis (38%) were the most common concomitant disorders but they did not fully account for the eHCO3- gap in the pHbHCO3 cases. Additionally, unnecessary HCO3- therapy was initiated in 16% and serum lactate was measured in 80% of the pHbHCO3 events (lactate was normal in 72%).

Conclusions: Severe hyperTG can lead to spuriously low sCO2. The degree of hyperTG correlates with the magnitude of pHbHCO3, Clinicians and laboratory personnel should be aware of this phenomenon to prevent incorrect interpretation of acid-base status and medical mismanagement.

FR-PO629 Sporious Low Serum Bicarbonate Level due to Severe Hypertriglyceridemia: A Clinical Challenge Ali Pardis Dang,1 Amir Kazory.1 University of Florida, Gainesville, FL; 1University Of Del Mar Medical Group, Inc, Oxnard, CA.

Introduction: A low serum bicarbonate level (SBL) in the presence of a high anion gap (AG) generally indicates presence of metabolic acidosis secondary to an increase in unmeasured anions. Herein, we report 2 patients with profound hypertriglyceridemia (HTG) who presented with low measured SBL and a high AG. Evaluation revealed that the low SBL was spurious and resulted from extremely high serum triglyceride (TG) levels; once HTG was treated, the reported SBL was corrected.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Case Description: The first patient is a 48-year-old man with a history of chronic pancreatitis secondary to severe HTG. He was admitted for acute pancreatitis and was found to have a serum TG of 3267 mg/dl. He had normal renal function and electrolytes but SBL was reported <5 mmol/l on chemistry panel with an AG of <28. However, arterial blood gas (ABG) revealed absence of acidemia with pH 7.4, PCO2 32, PO2 84, and bicarbonate 23.7. SBL was <5 mmol/l with an AG of >28. She underwent 3 sessions of TPE, which lowered her serum TG to 1420 mg/dl and raised measured SBL to 18 mmol/l within 3 days with no additional intervention. 

Discussion: Accurate assessment of bicarbonate is essential for the diagnosis of acid-base disturbances. Bicarbonate can be “measured” in serum as total carbon dioxide (iCO2) or “calculated” from ABG analysis (Henderson-Hasselbalch equation). In most instances, iCO2 and bicarbonate are closely related due to the constancy of the apparent dissociation constant of blood carbonic acid (pK'). Presence of a marked difference between the two values creates a clinical challenge that should prompt identification of a cause. Severe HTG interferes with laboratory testing in several ways (e.g. turbidity) and should be considered in the settings where there is no clinically apparent reason for low SBL. These 2 cases highlight the need for the clinicians to keep severe HTG in the differential diagnosis of SBL to avoid management errors.

FR-PO630 Medications Containing H+ Salts Are Associated with Lower Serum Total CO2 and Higher Serum Anion Gap in Patients With Non-Acidotic Diabetic Kidney Disease

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Background: Metabolic acidosis (MA) is associated with adverse clinical consequences in CKD. Many medications contain H+ salts which could contribute to development of MA. This study determined the association between H+ load from medications (med-H+ load) and acid-base indices in patients with diabetic kidney disease (DKD) but without MA.

Methods: We conducted this cross-sectional study in 74 US veterans with DKD (eGFR 51±18 ml/min/1.73m2) and serum iCO2 24±2 meq/L. None were treated with alaki. The daily H+ load from medications containing H+ salts was determined using the daily dose, molecular weight, and valence of the agents. Participants were categorized into a low or high med-H+ load group using a threshold of 7.7 meq/d, which is the equimolar amount of HCO3− in one 650mg NaHCO3 tablet required to mitigate this H+ load. We compared serum (iCO2 and anion gap) and urinary (NH3, titratable acids [TA], and pH) acid base indices between groups using linear regression models adjusted for eGFR, ACR, protein intake, and other potential confounders.

Results: 40 of 123 (33%) medications prescribed contained H+ salts. Two agents contributed 1± meq/d of H+, metformin (9.7±3.3 meq/d) and gabapentin (5.9±3.7 meq/d). In the low and high groups, 93% vs 13% received metformin and 55% vs 18% received gabapentin. .Median med-H+ load was 14±2.4 in the high and 1.6±2.4 meq/d in the low group. Those in the high group had significantly lower iCO2 and higher anion gap after adjustment (Table). Metformin use and gabapentin use (irrespective of dose) were moderately associated with lower serum iCO2 and higher anion gap. Med-H+ load did not seem to impact urinary acid excretion.

Conclusions: Medications containing H+ salts, particularly metformin and gabapentin, contribute to meaningful differences in serum (iCO2) and anion gap in patients with non-acidotic DKD, suggesting that these agents may be novel risk factors for MA in DKD.

FR-PO631 A Validated Anion Gap Threshold for High Anion Gap Metabolic Acidosis


Background: The anion gap (AG), calculated by AG = [Na+]−[Cl−]+[HCO3−], is often used to screen for acid-base disorders but cut-off levels used by clinical texts were based on empirical data. We recently sampled 300 healthy volunteers and the mean AG was 13±2meq/L (manuscript in preparation). The proposed reference range (+2SD; central 95% percentile) was 8±1.7meq/L. This study was to define a cut-off value for high AG metabolic acidosis (HAGMA).

Methods: Data from ICU patients from a prior study was used. Blood samples were classified into 2 groups: no HAGMA, or HAGMA present due to lactic acidosis, ketosis, citrate toxicity or severe uremia. The association of AG and HAGMA was tested by the Mann-Whitney U test. ROC analysis of AG was undertaken with optimal cut-off determined by Youden index.

Results: From 1,545 blood samples, 400 had adequate data. The median age was 64.7yrs, weight 60.1kg, 31.6% were females and 170 had HAGMA. With HAGMA, median AG was 19±2meq/L (IQR 17–22) vs 15±2meq/L (IQR 13–17) without HAGMA (P<0.001). AG has an AUC of 0.802 and the optimal cut-off was a 17±2meq/L (Fig. 1). The false negative rate (FNR) was 19.5%; false positive rate (FPR) 32.1%. Other AG thresholds are shown (Table 1). As HAGMA may be life-threatening, a lower FNR is desired. The best FNR of 13.2% was with AG ≥13±2meq/L, corresponding to mean AG of healthy persons, but FPR increased to 53.0%.

Conclusions: The recommended cut-off cut-off for HAGMA is ≥13±2meq/L. This provides the best sensitivity but at the expense of specificity. As false negatives can still occur, acid-base status should be evaluated clinically, aided by repeated measurements of AG.

Table 1: Sensitivity & Specificity of AG Thresholds for HAGMA

<table>
<thead>
<tr>
<th>AG Threshold (meq/L)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False Positive</th>
<th>False Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥13 (Population Mean)</td>
<td>20.0%</td>
<td>53.0%</td>
<td>51.0%</td>
<td>12.2%</td>
</tr>
<tr>
<td>≥15 (Population Mean + 1SD)</td>
<td>44.3%</td>
<td>49.5%</td>
<td>54.7%</td>
<td>12.7%</td>
</tr>
<tr>
<td>≥17 (Population Mean + 2SD)</td>
<td>75.9%</td>
<td>32.1%</td>
<td>45.7%</td>
<td>19.9%</td>
</tr>
</tbody>
</table>

Fig. 1: ROC curve of AG for HAGMA

FR-PO632 Metabolic Acidosis Is Underdiagnosed and Undertreated in Patients with CKD

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Background: Metabolic acidosis is a common complication of chronic kidney disease (CKD) and is associated with adverse effects on physical function, accelerated CKD progression and increased mortality. Although metabolic acidosis can be easily identified using routinely collected laboratory tests, there is limited data on its recognition and treatment.

Methods: We integrated laboratory data from 36 million US adults with de-identified longitudinal claims and prescription data from 280 million de-identified individuals included in the Symphony Health Solutions IDV® (Integrated Dataverse). Patients who met stringent laboratory criteria indicative of CKD and chronic metabolic acidosis were included: ≥2 eGFRs <60 ml/min/1.73m2 with no intervening eGFR ≥60 ml/min/1.73m2; ≥2 serum bicarbonates ≥12 <22 meq/L with no intervening bicarbonate <12 or ≥22 meq/L; qualifying values ≥28 days apart. No patients with a diagnosis of acute kidney injury (AKI) within 28 days prior to either qualifying bicarbonate value were included. A physician diagnosis of metabolic acidosis was based on administrative claims, and treatment of metabolic acidosis was defined as a prescription for oral alkali therapy.

Results: Approximately 2.4 million individuals met laboratory criteria for CKD, 118,620 of those also met laboratory criteria for metabolic acidosis. Claims and prescription data were available for 86,782 individuals with both CKD and chronic metabolic acidosis. In this population, a diagnostic code for metabolic acidosis was present in only 21% of patients (N=19,038). The overall frequency of oral alkali therapy use was 15% (N=13,272) ranging from 10% in those without a diagnostic code for acidosis to 34% in those with the appropriate diagnostic code.

Conclusions: Metabolic acidosis is underdiagnosed and undertreated in US adults with CKD. Disease specific educational efforts as well as development of novel treatments is needed to improve outcomes for this important complication.

Funding: Commercial Support - Tricida Inc.
FR-PO635

Dietary Protein Intake and Urinary Citrate Excretion in Asians
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Background: Dietary protein intake (DPI) is associated with acid loading. We hypothesized that the lower urinary citrate excretion rate (UCER) is lower in patients with chronic kidney disease (CKD) having higher DPI. We examine the relationship between DPI and UCER in a multi-ethnic Asian population in patients with CKD and participants without kidney disease.

Methods: We used data from patients with stable CKD from the Asian Kidney Disease Study and normal participants without diabetes or hypertension from the Singapore Kidney Function Study. Participants fasted overnight, and provided a 24h urine collection, blood sample, and underwent measured glomerular filtration test (mGFR, mL/min/1.73m²) using 99mTc-DTPA. Daily protein intake (DPI, g/day) was calculated from 24-hour urine urea using Maron’s formula. Non-normal data was natural log-transformation for analysis. We performed univariate analysis of Ln UCER against the factors of age, gender, ethnicity, presence of CKD, Ln mGFR, and DPI. A multiple linear regression model was constructed including these variables to assess the association of DPI with UCER after adjusting for kidney disease and function.

Results: Complete data were available from 187 CKD patients (48.7%male) and 89 non-CKD participants (47.2% male) (p=NS). The mean ages were 59±12.8 years and ±14.3 years in the CKD and non-CKD groups, respectively (p<0.001). The median mGFR in the CKD and non-CKD groups were 45 (IQR: 29-63) and 100 (IQR: 88-113), respectively (p<0.001). The median UCER (mmol/day) was lower in the CKD group (46: IQR: 11-106 vs. 303, IQR: 206-446) (p<0.001). No participant was on sodium bicarbonate supplementation. On univariate analysis, lower UCER was associated with increased age, protein intake, and clinical center.

Conclusions: A significant difference in UCER in patients with CKD and participants without kidney disease were identified. The negative correlation with age, DPI, and clinical center suggests a need for further studies.

FR-PO634

A Comparison of the Effect of Sodium Bicarbonate on Acid-Base Indices in CKD Patients with and Without Diabetes: A Secondary Analysis of the BASE Pilot Trial
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Background: Oral alkalinization with NaHCO₃ does not increase ECV more than placebo in CKD patients receiving oral alkalinization without NaHCO₃, composed a control group. The main criterion was the ECV increase as judged on body weight (BW), blood pressure (BP), and edema at first visit.

Methods: From 01/2017 to 12/2018, 20 investigators included 122 patients whom 92 (75%) had at least one follow-up and 74 (61%) received NaHCO₃. If both groups were comparable as judged on demographic data, patients in the NaHCO₃ group had more chronic kidney diseases (74 vs. 28%, p<0.001) where patients in the non NaHCO₃-group (citrate) had more nephro lithiasis (23 vs. 94%, p<0.001). At baseline (incubation), BW, BP, and presence of edema were comparable in both groups. After a mean of 98±48 days of follow-up, 70 patients (76%) had an ECV increase but the repartition was highly similar in both groups (77 vs. 72%, p=0.76), especially BW did not differ (cf. Figure 1).

Conclusions: Oral alkalinization with NaHCO₃ does not increase ECV more than placebo while it is used in a more risky population. These results should be confirmed in a randomized controlled trial.

Figure 1. Evolution of body weight by inclusion (V0) and first follow-up (V1).
FR-PO636

Drug Therapy Choices for Acquired Distal Renal Tubular Acidosis by US Nephrologists and Rheumatologists

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Background: Drivers of drug therapy choices for acquired distal renal tubular acidosis (dRTA) are not well understood. AdRTA, which is linked with Sjogren’s disease, systemic lupus erythematosus (SLE), primary biliary cirrhosis (PBC) and autoimmune hepatitis, is often encountered by rheumatologists and nephrologists. To better understand the drug therapy approaches for AdRTA patients, a quantitative market research study was undertaken.

Methods: Between March 25th–April 15th, 2019, an online survey was conducted with 30 nephrologists and 20 rheumatologists in the USA on the subject of dRTA, with a focus on AdRTA. All screened respondents had direct clinical experience of AdRTA patients.

Results: Sodium bicarbonate (SB) is the most commonly prescribed treatment for AdRTA, prescribed by 80% of nephrologists (Nph) and 56% of rheumatologists (Rhm), followed by sodium citrate (SC) and potassium citrate (PC). In patients depleted patients, however, PC is the most commonly prescribed agent (Nph 55%, Rhm 57%). The majority of Rhms and Nephs consider the Neph is the most likely to prescribe all of the available treatments (range: 56% Flomax to 78% PC). 67% of Nphs report high satisfaction with SB and 53% with PC, fewer than their Rhm colleagues (high satisfaction: SB-90%, PC-100%). However, 70% of Nphs and 46% of Rhms indicate treatments for AdRTA are sub-optimal and only 60% of Nphs and 42% of Rhms considered the available treatments effective and easily accessible. Many nephrologists expressed that: “More effective therapies that are less burdensome to patients.” and “More new treatment options” are needed.

Conclusions: Most nephrologists and rheumatologists have direct experience prescribing drug therapy for AdRTA with sodium bicarbonate being the most commonly prescribed treatment. However, while they express overall satisfaction with available treatments, many believe that they are sub-optimal, not effective or not easily accessible.

Funding: Commercial Support - Advicene S.A.

FR-PO637

Outcomes of Correcting Metabolic Acidosis in CKD with Cirrhosis: A Retrospective Study

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Background: Chronic Kidney Disease complications include metabolic acidosis. There is evidence of mortality benefit to correcting acidosis to bicarbonate levels of about 22 meq/L. Conversely, in chronic liver disease, respiratory alkalosis is the most common acid-base disorder, which manifests as low serum bicarbonate on labs. Physiologically, it appears that correcting metabolic acidosis to a reasonable level may provide benefit to CKD with cirrhosis, however most practices do not get a venous or arterial blood gases to first identify the cause of low serum bicarbonate. The impact of identifying and managing metabolic acidosis in patient with cirrhosis has not been studied well. Correcting acidosis commonly requires using sodium containing salts, which can lead to sodium overload resulting in increased need for paracentesis procedures. Our hypothesis is that adding oral sodium bicarbonate (NaHco3) targeting bicarbonate 22 meq/L would lead to increased ascites and more frequent paracentesis so we should target lower bicarbonate levels in cirrhosis.

Methods: We conducted a single center retrospective chart review of all patients with CKD and Cirrhosis, managed at University of Arkansas for Medical Sciences, over a period of 5 years to study incidence of paracentesis correlated with oral bicarbonate therapy.

Results: Out of 366 patients with the diagnosis of CKD and cirrhosis, 200 patients did not get paracentesis. Out of these 31(15.5%) were on oral bicarbonate.166 patients received paracentesis out of which 41 (24.7%) were on bicarbonate. However, this difference was not statistically significant (P value 0.0035).

Conclusions: KDIGO guidelines recommend correcting metabolic acidosis with oral bicarbonate supplementation to prevent CKD progression targeting serum bicarbonate of about 22 meq/L. However, it is not clear if we can extend this to the population with cirrhosis and CKD. Purpose of our study is to address this question and to study the effects of bicarbonate supplementation with regard to its effect on incidence of paracentesis procedures that can lead to increased complications for these patients. Our retrospective data suggests that patients on oral NaHco3 require frequent paracentesis, but has not met statistical significance. We plan a prospective randomized control study to address this question better.

FR-PO638

A Case of Tubulointerstitial Nephritis Complicated by Primary Biliary Cirrhosis with Renal Tubular Acidosis and Nephrogenic Diabetes Insipidus

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Introduction: Tubulointerstitial nephritis is often caused by drugs, infections, autoimmune disorders. We report a case of tubulointerstitial nephritis associated with primary biliary cirrhosis, which developed renal tubular acidosis and nephrogenic diabetes insipidus.

Case Description: A 50-year-old woman presented with a four-month history of left shoulder pain, back pain, dry mouth, polydipsia, polyuria. She hospitalized for weakness of limbs. Her lab studies revealed serum creatinine 2.72 mg/dl, serum potassium 1.5 mg/dl, and normal anion gap metabolic acidosis which suggested distal and proximal renal tubular acidosis. She had multiple fractures which suggested the presence of osteomalacia. Her urine output exceeded 10L/day, and urine osmolarity was low. After corrected serum potassium weakness of limbs improved, but polyuria did not improve. She was thought to nephrogenic diabetes insipidus because of resistant to antidiuretic hormone. Kidney biopsy was performed to clarify the cause of these findings. The major histologic changes were interstitial infiltration by mainly lymphocytes, tubulitis, and interstitial edema. The presence of antimicotochondrial M2 antibodies suggested primary biliary cirrhosis. She was treated with oral steroids and a thiazide diuretic. Her polyuria resolved, and serum creatinine level improved to 0.9 mg/dl.

Discussion: In conclusion, our patient with tubulointerstitial nephritis and primary biliary cirrhosis had a favorable outcome from oral steroids and a thiazide diuretic. Previous studies have demonstrated Fanconi syndrome in patients with primary biliary cirrhosis, and our patient suggested that tubulointerstitial nephritis complicated by primary biliary cirrhosis could develop renal tubular acidosis and nephrogenic diabetes insipidus.

FR-PO639

Mortality and Magnesium Levels in CKD

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Background: Magnesium disorders are common in Chronic Kidney Disease (CKD) and are typically a consequence of decreased kidney function or use of medications such as diuretics. While hypomagnesemia has been linked with increased mortality, the association between elevated magnesium levels and mortality is not clearly defined. Additionally, associations between magnesium disorders and risk of different types of death have not been reported.
Methods: Using our Electronic Health Record-based CKD registry, we identified patients with eGFR 15 to < 60 ml/min/1.73m2 who had magnesium levels within the prior year. We examined associations between magnesium levels and all-cause, cause-specific mortality and progression of CKD while adjusting for demographic factors and comorbidities using Cox models, Competing Risks regression and mixed models.

Results: Out of 10,568 CKD patients, 12.4% (N=1,314) had hypomagnesemia (Mg < 1.7 mmol/L) while 1.9% (N=205) had hypermagnesemia (Mg > 2.6 mmol/L). We observed a U-shaped association between serum magnesium levels and mortality, with both hypomagnesemia (HR=1.14, 95% CI: 1.04, 1.24) and hypermagnesemia (HR=1.23, 95% CI: 1.03, 1.48) having higher all-cause mortality. Our results showed increased subhazard of non-cardiovascular, non-malignancy deaths for hypomagnesemia (SHR=1.29, 95% CI: 1.12, 1.49), but no significant differences in other causes of death. In a sensitivity analysis excluding patients with malignancy, results were similar. Hypomagnesemia was not associated with stronger eGFR decline (P = 0.10).

Conclusions: Hypomagnesemia and hypermagnesemia were both associated with increased mortality. Hypomagnesemia was associated with increased non-cardiovascular, non-malignancy death.

The association between hypomagnesemia and all-cause mortality for dichotomous variables (hypomagnesemia vs. normal magnesium or hypermagnesemia group) Fig.

The association between hypermagnesemia and all-cause mortality for continuous variables (hypermagnesemia vs. normal magnesium or hypomagnesemia group)

FR-PO641
Impact of Serum Calcium Level Fluctuations on In-Hospital Mortality
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Background: Calcium concentration is strictly regulated at both the cellular and systemic level, and changes in serum calcium levels can alter various physiological functions in various organs. This study aimed to assess the association between changes in calcium levels during hospitalization and mortality.

Methods: We searched our patient database to identify all adult patients admitted to our hospital from January 1, 2009 to December 31, 2013. Patients with ≥2 serum calcium measurements during the hospitalization were included. The serum calcium changes during the hospitalization, defined as the absolute difference between the highest and lowest calcium levels, was categorized into five groups: 0-0.4, 0.5-0.9, 1.0-1.4, 1.5-1.9, ≥2.0 mg/dL. Multivariable logistic regression was performed to assess the independent association between calcium changes and in-hospital mortality, using the change in calcium category of 0-0.4 mg/dL as the reference group.

Results: Of 9,868 patients included in analysis, 540 (5.4%) died in the hospital. The in-hospital mortality progressively increased with higher calcium changes, from 3.4% in the group of 0-0.4 mg/dL to 14.5% in the group of ≥2.0 mg/dL (p<0.001). When further adjusted for age, sex, race, principal diagnosis, comorbidity, kidney function, acute kidney injury, number of serum calcium measurements, and length of hospital stay, the serum calcium change of 1.0-1.4, 1.5-1.9, and ≥2.0 mg/dL were significantly associated with increased in-hospital mortality with OR of 1.67 (95% CI 1.24-2.25), 2.11 (95% CI 1.48-3.01), and 3.96 (95% CI 2.95-5.30), respectively. The association remained statistically significant when further adjusted for either the lowest, highest, or admission serum calcium.

Conclusions: Larger serum calcium changes in hospitalized patients were progressively associated with increased in-hospital mortality.

FR-PO642
Changes in Serum Phosphate Levels Associated with In-Hospital Mortality
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Background: Fluctuations in serum phosphate levels have recently been shown to be associated with coronary calcification and increased mortality in end-stage renal disease (ESRD) patients. However, the impacts of serum phosphate changes in hospitalized patients remain unclear. This study aimed to test the hypothesis that serum phosphate changes during hospitalization were associated with in-hospital mortality.
Methods: We included all adult hospitalized patients from January 2009 to December 2013 that had at least two serum phosphate measurements during their hospitalization. We categorized the hospital serum phosphate change, which was defined as the absolute difference between the highest and lowest phosphate, into 5 groups: 0-0.6, 0.7-1.3, 1.4-2.0, 2.1-2.7, ≥2.8 mg/dL. Using the phosphate change group of 0-0.6 mg/dL as the reference group, the adjusted odds ratio of in-hospital mortality for various phosphate change groups was obtained by multivariable logistic regression analysis.

Results: A total of 28,149 patients were studied. The in-hospital mortality in patients with phosphate change of 0-0.6, 0.7-1.3, 1.4-2.0, 2.1-2.7, ≥2.8 mg/dL was 1.5, 2.0, 3.1, 4.4, and 10.7%, respectively (p<0.001). When adjusted for potential confounders, a larger phosphate change was associated with progressively increased in-hospital mortality with ORs of 1.35 (95% CI 1.04-1.74) in 0.7-1.3 mg/dL, 1.98 (95% CI 1.53-2.55) in 1.4-2.0 mg/dL, 2.68 (95% CI 2.07-3.48) in 2.1-2.7 mg/dL, and 5.4 (95% CI 3.94-6.45) in ≥2.8 mg/dL compared to the phosphate change group of 0-0.6 mg/dL. A similar result was noted when we further adjusted for either the lowest, highest or admission phosphate.

Conclusions: Greater serum phosphate changes during a patient’s hospitalization were progressively associated with increased in-hospital mortality.

FR-PO643
Granger Causality Analysis of Regulatory Network of Phosphate Metabolism in Healthy Individuals
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Background: Basic and clinical studies reveal that the homeostasis of phosphate is maintained by a regulatory network. The aim of our study was to explore the variation of phosphatemin with the change of diet.

Methods: 6 healthy volunteers were treated with regular Pi diet (NPD) and high Pi diet (HPD) for 5 days. Their blood and urine specimens at 10 fixed time points on the 5th day of intervention were collected. In order to reveal the causality relationship in the phosphate metabolism network, this study used the Granger causal analysis to determine time series relationship.

Results: HPD resulted in a significant increase in serum Pi and urinary Pi excretion. There was a significant increase in PTH. FGF23 was upward trend. By using Granger causal analysis, we found PTH was earliest change in RPD, which was the initiation factor. The change of FGF23 appeared at the latest that was the passive factor. In HPD, FGF23 was initiation factor. Serum Ca and Pi were passive factors.

Conclusions: With the traditional comparison, it was difficult to reveal the causality relationship of phosphate network. By Granger causality analysis, we found in RPD kidney was the most significant organ in keeping serum Pi stably. In HPD, FGF23 was the main hormone to maintain homeostasis of phosphate regulatory network.

FR-PO644
Hyperphosphatemia in a Patient with Mucormycosis and AKI
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Introduction: Hyperphosphatemia may arise from ingestion, extracellular shifts (e.g. cell death or alterations in acid-base status), bone resorption, hormonal dysregulations leading to reduced renal excretion, and/or poor kidney function. Pseudohyperphosphatemia has been well-described but may be under-recognized and/or not commonly seen in clinical practice.

Case Description: A 35-year-old 7-week-pregnant woman with type 1 diabetes mellitus was admitted for mucormycosis involving the clivus and cervical vertebrae. On day 1, she was initiated on liposomal amphotericin (10mg/kg) with normal saline support. On day 4, sulfamethoxazole/trimethoprim and ampicillin/sulbactam were added for methicillin-sensitive Staphylococcal Aureus and Prevotella Buccae from her fungating mass. On day 6, patient was noted to have acute kidney injury (AKI) when her creatinine increased from 0.4-0.5 mg/dL to 1.25 mg/dL. Nephrology was consulted for AKI and concurrent multiple electrolyte abnormalities. See Table for laboratory findings. Chart review was notable for a hypertensive episode when her blood pressure dropped from a baseline of 100/80 mmHg to 79/50 mmHg over 4 hours. Physical exam was unremarkable. Primary team replaced her potassium and magnesium and started sevelamer carbonate 2400 mg tidac.

Discussion: While the etiologies of AKI, hypokalemia, and hypomagnesemia were straightforward, hyperphosphatemia was out of proportion to the degree of AKI. A full investigation for contributing factors of hyperphosphatemia other than AKI revealed that she had pseudohyperphosphatemia due to liposomal amphotericin. Methods for measuring Pi may differ among commonly used clinical analyzers, where some may read the organic phosphate contained in the lipid bilayer of the liposomes as Pi. Repeat phosphorus level on a different analyzer revealed a level of 5.8 mg/dL. Erroaneous treatment of pseudohyperphosphatemia would have been detrimental in current case.
FR-PO645
A Simple Equation to Estimate Urinary Flow Rate Using Urine Creatinine
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Background: Accurate assessment of urine flow is critical to clinical care, but challenging to estimate. We hypothesized we could derive an equation that would accurately estimate urine flow rate.

Methods: We derived a new equation to estimate urine flow rate (eV) using the Cockcroft-Gault and the measured creatinine clearance (UV/P) equations. Accuracy was evaluated by comparing eV to measured urine flow rate (V) in persons with CKD who participated in the AASK and COMBINE trials. Participants with concordant estimated and measured creatinine excretion rates were included to define a subset with highly accurate 24 hour urine volumes.

Results: The eV equation required only urine creatinine, age, sex, and weight data. In AASK, we evaluated 570 participants who had mean GFR of 46.7 ml/min/1.73m2 and measured urine flow rate (V) 94.9 ± 34.2 ml/hour over 24 hours. A high correlation was found between eV and V (r = 0.91, p < 0.001), however Bland Altman plots showed that eV was 9.6 ml/hour lower than V, on average, in AASK. Thus a correction factor was added to the eV equation and externally evaluated in COMBINE, wherein 123 participants had mean eGFR of 34 ± 8 ml/min/1.73m2. eV and V were highly correlated (r = 0.91, p < 0.001) and bias was improved (5.3 ml/hr). Overall, 80% of individuals had eV that was within 20% of V.

Conclusions: A simple equation using urine creatinine and demographics can accurately predict urine flow rate and may have clinical utility in situations where the accuracy of measured collections is uncertain.

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Figure 1 shows the correlation of measured vs. estimated flow rate using eV equation (top of graph) in AASK participants who had measured creatinine excretion rates within 20% of estimated excretion rates (N=570). r = 0.91, p < 0.001.

FR-PO646
Insulin Use for the Treatment of Acute Hyperkalemia

Background: Insulin has been the cornerstone of treatment for hyperkalemia (HK) for many decades and remains in wide clinical use. Despite this, there is a paucity of data on the efficacy and safety of this approach. To investigate this, we interrogated a large electronic health record (EHR) dataset to explore the characteristics and consequences of insulin treatment for HK.

Methods: Patients receiving insulin for the treatment of HK were identified from a complete EHR database of all admissions to a UK tertiary hospital over 3.5 years. Variables extracted included demographics, comorbidities, concomitant medications, biochemistry results including all blood potassium values, and all in-hospital prescribing. Factors associated with the need for insulin retrieval were explored using a mixed-effects logistic regression model and odds ratios are reported.

Results: Insulin was administered to 1,284 adult patients (2,541 total administrations). Insulin-treated patients were aged 72 (IQR 59.5-84.5) years and had significant comorbidity (Charlson index 5, IQR 3 to 7). At the end of the follow-up period, only 60.3% remained alive. Potassium concentration immediately (± 60 min) pre-treatment was 6.34 ± 1.2mmol/L. The mean reduction in potassium at 4-hours post infusion was 0.86 ± 0.92mmol/L. Multiple doses were given to 542 patients (42.2%), of whom 209 (16.2%) were retreated within 4 hours of the first infusion. Patients receiving multiple insulin infusions were more likely to have chronic kidney disease (44.5% vs 36.5%, p = 0.002) or heart failure (22.9% vs 17.4%, p = 0.009) and to have been exposed to ACE inhibitors (32% vs 27.9%, p = 0.03) or potassium sparing diuretics (19.4% vs 15.5%, p = 0.04), although only CKD remained significantly associated with retreatment in a regression model adjusted for age, gender and co-morbidity (OR 1.4, 1.1-1.7, p = 0.01). Dysregulation of glucose metabolism occurred in 672 patients (53%) following insulin. Hypoglycaemia (plasma glucose <2mmol/L) occurred in 133 patients (10.4%) within 4 hours of insulin administration, and 16 patients (1.2%) experienced a glucose <2mmol/L.

Conclusions: HK requiring insulin treatment occurs most commonly in a more elderly and comorbid population, is associated with CKD, requires re-treatment in 4 out of 10 patients, and is associated with dysregulated glucose metabolism (either high or low) in 53%. There is an unmet need for improved emergency treatments for HK.

Funding: Commercial Support - AstraZeneca

FR-PO647
Treatment of Hyperkalemia with Insulin: Comparative Evaluation of Patient Characteristics

Background: Hyperkalaemia (HK) is a common and serious medical emergency and current standard of care consists of an insulin infusion. Here, we report characteristics of HK patients treated with insulin in a tertiary hospital in the UK, compared with HK patients not treated with insulin.

Methods: HK patients (at least 1 potassium measurement ≥6mmol/L) were identified from electronic health records of patients admitted to a tertiary hospital between April 2015 and August 2018. All HK patients treated with insulin (K-I) were identified and compared with HK patients not treated with insulin (K-noI). Categorical variables were compared by X²-test and continuous variables by Student’s t-test or Mann-Whitney U-test. Associations with insulin treatment were explored using a mixed effects logistic regression model with insulin use as the dependent variable, odds ratios (OR) are reported with associated 95% confidence intervals.

Results: HK ≥6mmol/L was identified in 5,272 of 211,993 patients (1.9%) attending the Emergency Department. Of these, 1284 received insulin for HK (K-I). Compared to K-noI patients, K-I patients were older (72 years vs 59.5-84.5 years) vs 71(53-83), p<0.001), more likely to be diabetic (35% vs 25.2%, p<0.001) and have chronic kidney disease (CKD) (39.9% vs 18.6%, p<0.001). Median length of hospital stay was longer in K-I patients (11.7 days (4.9-24.7) vs. 6.0 (1.2-17.3), p<0.001). A higher proportion of K-I patients were taking ACE Inhibitors (30.1% vs 23.1%, p<0.001), Angiotensin-2-receptor blockers (12.3% vs 9.2%, p<0.001) or potassium-sparing diuretics (17.1% vs 9.6%, p<0.001). In a mixed-effects logistic regression model, insulin treatment was associated with CKD (OR 2.4, 2.1-2.8), male sex (OR 1.6, 1.4-1.8), potassium-sparing diuretics (OR 1.6, 1.3-2.0) and hypertension (OR 1.3, 1.1-1.5). At the end of follow up, 575/1,284 patients (44.8%) in K-I vs 1,089/2,988 patients (37.5%) had died (p<0.001). In a logistic regression model adjusting for age, gender and co-morbidity, the risk of death remained higher in the K-I group (OR 1.9, 1.6-2.2). Exact cause of death was not assessed.

Conclusions: Patients that receive insulin for HK are older, more likely to be male and have hypertension, CKD, diabetes and exposure to medications that increase potassium than those that do not. Receiving insulin for HK is associated with longer hospital stay and a higher risk of death.

Funding: Commercial Support - AstraZeneca
FR-PO648

Hyperkalemia Progression Rates Among Patients with Mild Hyperkalemia
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Background: To describe progression from mild hyperkalemia (HK) to moderate-to-severe or severe HK among patients with mild HK and pre-specified subgroups.

Methods: Adults with at least one mild HK event (i.e. serum potassium [K+] > 5.0 and ≤ 5.5 mEq/L) were identified using electronic medical records from the Research Action for Health Network (2012-2018). Index date was defined as the date of the first mild HK event. Patients were required to have at least one additional serum K+ lab value during the study period (2 years post-index date). Progression to moderate-to-severe and to severe HK was defined as the first occurrences of a serum K+ lab > 5.5 mEq/L and > 6.0 mEq/L, respectively. Kaplan-Meier analyses were conducted to estimate the rates of HK progression over the study period for the overall population and patient subgroups including those with and without chronic kidney disease (CKD in stages 3-5), heart failure (HF), hypertension, or type 2 diabetes (T2D).

Results: A total of 35,369 patients with mild HK were included in the analysis. Mean age was 65.6 years, and 47.5% were women. At 2 years post-index, 16.9% and 8.7% of patients progressed to moderate to severe HK and to severe HK, respectively (Table). Patients with CKD, HF, hypertension, and T2D experienced higher rates of HK progression compared with patients without those conditions (all log-rank p < 0.001) (Table). HK progression rates also increased significantly as CKD stage increased (p < 0.001) (Table). A total of 16.9% of patients with mild HK experienced HK progression during the 2-year follow-up period. HK progression rates increased significantly with CKD stage and were also higher among those with HF, hypertension, or T2D.

Funding: Commercial Support - AstraZeneca

Table: Progression to Moderate-to-severe and Severe HK Among Patients with Mild HK

<table>
<thead>
<tr>
<th>CKD</th>
<th>HF</th>
<th>Hypertension</th>
<th>T2D</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
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<td>35.0%</td>
<td>21.2%</td>
<td>32.9%</td>
<td>32.6%</td>
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</table>

FR-PO649

Compared Effects of Calcium and Sodium Polystyrene Sulfonate on Mineral, Bone Metabolism, and Acid-Base Equilibrium in CKD Patients with Hyperkalemia
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Background: Hyperkalemia is prevalent in end-stage renal disease patients, being involved in life-threatening arrhythmias. Although polystyrene sulfonate (PS) is commonly used as the treatment of hyperkalemia, direct comparison of the effects between calcium and sodium PS (CPS and SPS) on mineral, bone metabolism and acid-base equilibrium has not yet been studied.

Methods: This study was designed as a prospective, open-labeled, randomized, and crossover study (n=40). Patients were orally administered CPS (ARGAMATE® 89.29% GRANULE 5.6 g; powder 5 g) or SPS (KAYEEXALATE DRY SYRUP 76% 6.5 g; powder 5 g) after each meal. After 4 weeks, each treatment was immediately switched to another PS without washout interval, and followed-up for further 4 weeks. To investigate the cation-absorption capacity of CPS and SPS, we constructed an artificial colon fluid (ACF) based on the data of human diarrhea as described previously. One gram of CPS or SPS was added into the 50 ml of ACF (n=6, respectively). After filtration, the serum K, Mg, and NH3 were not changed, we found that modifying the RUL led to major changes in PS prescribing for HK patients, whereas only 2% led to an order for RUL 5.3, whereas it occurred at 5.4 with RUL 5.3. The maximum absolute difference between the two cumulative curves (D statistic), 0.17, occurs at K 5.3, falling within the “high” range for RUL 5.1, but normal for RUL 5.3. For RUL 5.1, approximately 10% of results between 5.2-5.3 led to a PS order, whereas only 2% led to an order for RUL 5.3.

Conclusions: While the physiologic understanding of K and its serum levels have not changed, we found that modifying the RUL led to major changes in PS prescribing for hyperkalemia. This abrupt and sustained shift suggests a reflexive approach to treatment, whereby providers are ordering PS based upon an abnormal flag or red-colored value, rather than clinical indication. Educating providers and using appropriate nudges or defaults can lead to more thoughtful approaches to management of K and other electrolyte disorders.

The reference upper limit for potassium has a major effect on Kayeexalate ordering

FR-PO650

Reflex Ordering of Polystyrene Sulfonate for “Red-Flagged” Mild Hyperkalemia: A Problem of Perception
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Background: Lab test results, typically reported with reference ranges, are often flagged and red when abnormal. For potassium (K), while treatment recommendations have not changed, reference limits may have. How the reference upper limit (RUL) impacts provider responsiveness to hyperkalemia treatment with polystyrene sulfonate (PS, Kayexalate) is unknown.

Methods: We queried the EHR at 14 hospitals in a large integrated health system, for orders of PS between 2012-2018. The serum K at the time of an order was deemed the result that occasioned treatment. We extracted the RUL for the result, which changed from 5.1 to 5.3 mEq/L in December, 2015. We compared PS ordering based upon RUL using a two-sample Kolmogorov-Smirnov (KS) test. KS is a non-parametric test to determine if two samples are drawn from the same distribution; the null hypothesis is that the distribution of orders by K level remains the same regardless of RUL.

Results: There were 43,497 orders for PS, almost evenly split between RUL 5.1 and 5.3. The two distributions were statistically different (D = 0.17478, p-value < 0.0001). For results with RUL 5.1, the initial peak in PS ordering occurred at K 5.2, whereas it occurred at 5.4 with RUL 5.3. The maximum absolute difference between the two cumulative curves (D statistic), 0.17, occurs at K 5.3, falling within the “high” range for RUL 5.1, but normal for RUL 5.3. For RUL 5.1, approximately 10% of results between 5.2-5.3 led to a PS order, whereas only 2% led to an order for RUL 5.3.

Conclusions: While the physiologic understanding of K and its serum levels have not changed, we found that modifying the RUL led to major changes in PS prescribing for hyperkalemia. This abrupt and sustained shift suggests a reflexive approach to treatment, whereby providers are ordering PS based upon an abnormal flag or red-colored value, rather than clinical indication. Educating providers and using appropriate nudges or defaults can lead to more thoughtful approaches to management of K and other electrolyte disorders.

The reference upper limit for potassium has a major effect on Kayeexalate ordering
Results: A total of 56 Japanese patients were randomly assigned: 28 received SZC, and 28 received placebo. 95% CI for the 0% and 100% in the BPO group. Patients in the SZC and BPO groups had a mean age of 60.7 and 64.4 years, respectively; all baseline characteristics were balanced between groups. 71.4% (n=20) and 0% were responders (nominal p<0.001) in the SZC and placebo group, respectively. Further, SAEs and AEs were reported, one in SZC group (gastrointestinal hemorrhage) and one in placebo group (arteriovenous fistula site complication); both events were deemed unrelated to the study drug. IDWG was similar in both groups.

Conclusions: This exploratory analysis showed that the safety and efficacy profile of SZC in the Japanese subgroup is in line with that observed in the global study population.

Funding: Commercial Support - AstraZeneca

FR-PO652

Additional Benefit of Patiromer Under Real-Life Conditions
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Background: Patiromer was placed on the market in Germany in April 2018. Additional Benefit was not affirmed by regulatory authorities (GBA-Gemeinsamer Bundesausschuss). In the OPAL-HK trial, in patients that were treated with Patiromer, mean serum potassium levels declined by 1.01±0.03 mmol/L and after 4 weeks 76% of the patients reached potassium levels below 5.1 mmol/L. We sought to evaluate, whether these promising results can be achieved under real-life conditions outside of clinical trials.

Methods: We analysed potassium levels in all patients treated with patiromer in a large chronic kidney disease cohort including patients with and without renal replacement therapy. In addition, the number of patients that reached the target range below 5.1 mmol/L was evaluated. Data extraction and analysis were performed using an multi-factorial Algorithm-based approach.

Results: 7222 Patients that were treated between 1.1.2018 and 15.4.2019 were screened. 49 Patients (20 females) were treated with Patiromer (24 hemodialysis, 25 peritoneal dialysis, 2 peritoneal dialysis, 2 peritoneal dialysis). For 37 patients at least one potassium value was available before and after initiation of Patiromer. Mean potassium levels were 5.8±0.56 mmol/L before and 5.4±0.77 mmol/L on treatment with Patiromer (p<0.01). However, only 13 out of 37 patients (35%) reached a potassium level in the target range below 5.1 mmol/L.

Conclusions: With only 35% of patients in the potassium target range below 5.1 mmol/L, additional benefit of Patiromer under real-life conditions was small compared to OPAL-HK where 76% reached the target range.

Funding: Commercial Support - AstraZeneca

FR-PO653

Long-Term Healthcare Cost and Resource Use in Patients with Hyperkalemia
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Background: Few studies provide information on economic burden of hyperkalemia (HK) especially regarding long-term healthcare cost and resource use.

Methods: A retrospective cohort study was done with a Japanese hospital claims database, Medical Data Vision. We extracted data for patients aged ≥18 years with ≥2 serum potassium (S-K) values ≥5.1 mmol/L from April 1, 2008, to September 30, 2018 for patients with HK, and normokalemic patients without any record of S-K ≥5.5 mmol/L or ≥5.1 mmol/L. Direct healthcare cost and resource use over 1 year after the first HK episode and during follow-up after 1 year were separately assessed.

Results: 27,534 HK cases and 233,098 normokalemic controls were identified from a detection of hypoglycemia incidents after hyperkalemia treatment with dextrose 50% and insulin.

Methods: We conducted a retrospective study of hospitalized adult patients at a large academic medical center, New Orleans, LA.

Results: Patients with HK (n=9,220) vs. those without HK (n=36,764) (mean age 72.3 vs. 72.7 yrs) had higher rates of CKD stage 4 (33.9% vs. 9.7%), heart failure (31.7% vs. 15.0%), and AKI (33.8% vs. 11.5%), and a higher ACR value (393.9 vs. 154.4 mg/g). In the 5-year study period, 16.7% of HK patients and 3.5% of those without HK progressed to CKD stage 5, and 31.7% and 17.0%, respectively, had an eGFR decline ≥10 units (both log-rank p<0.001). In Cox models, patients with vs. without HK had a statistically significant higher risk of CKD progression to stage 5 (adjusted hazard ratio [aHR] 2.20, 95% confidence interval [CI] 2.02-2.38) and eGFR decline (2.40; 2.28-2.52) (both p<0.001). Cox model results were consistent when adjusting for ACR, stratifying by baseline CKD stage, or excluding AKI patients.

Conclusions: Even after adjusting for relevant comorbidities and treatments, HK was significantly associated with higher risk of progression to CKD stage 5 and eGFR decline among patients with CKD stage 3-4. Associations were robust in all sensitivity analyses.

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FR-PO654

Hyperkalemia and Progression of CKD
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Background: To compare rates of chronic kidney disease (CKD) progression between CKD patients with and without hyperkalemia (HK).

Methods: Adult patients with CKD stage 3-4, with or without HK, were selected from electronic medical records from the US Research Action for Health Network (2012-2018). HK status was defined by diagnosis codes or estimated glomerular filtration rate (eGFR). HK was defined as having a serum K+ lab value >5.0 mEq/L and confirmed by another HK event. Index dates were defined as 30 days after the first K+ lab >5.0 mEq/L for HK patients and after a randomly selected K+ lab ≤5.0 mEq/L for patients without HK. Patients were required to have ≥1 eGFR value in both the baseline (6 months pre-index date) and study period (up to 5 yrs post-index date). Two outcomes were evaluated separately: 1) progression to CKD stage 5; 2) a ≥10 unit decline in eGFR. Kaplan-Meier analyses and multivariable Cox models adjusted for baseline eGFR, demographic characteristics, relevant comorbidities, and treatment use were performed. Sensitivity analyses were performed adjusting for albumin-creatinine ratio (ACR), stratifying by baseline CKD stage, and excluding patients with baseline acute kidney injury (AKI).

Results: Patients with HK (n=9,220) vs. those without HK (n=36,764) (mean age 72.3 vs. 72.7 yrs) had higher rates of CKD stage 4 (33.9% vs. 9.7%), heart failure (31.7% vs. 15.0%), and AKI (33.8% vs. 11.5%), and a higher ACR value (393.9 vs. 154.4 mg/g). In the 5-y study period, 16.7% of HK patients and 3.5% of those without HK progressed to CKD stage 5, and 31.7% and 17.0%, respectively, had an eGFR decline ≥10 units (both log-rank p<0.001). In Cox models, patients with vs. without HK had a statistically significant higher risk of CKD progression to stage 5 (adjusted hazard ratio [aHR] 2.20, 95% confidence interval [CI] 2.02-2.38) and eGFR decline (2.40; 2.28-2.52) (both p<0.001). Cox model results were consistent when adjusting for ACR, stratifying by baseline CKD stage, or excluding AKI patients.

Conclusions: Even after adjusting for relevant comorbidities and treatments, HK was significantly associated with higher risk of progression to CKD stage 5 and eGFR decline among patients with CKD stage 3-4. Associations were robust in all sensitivity analyses.

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FR-PO655

Detection of Hypoglycemia Incidents After Hyperkalemia Treatment with Dextrose 50% and Insulin
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Background: Hypoglycemia is a potential complication following hyperkalemia treatment with insulin. Most of the previous studies tried this risk in patients with decreased GFR. Our study assessed the incidence of hypoglycemia and its associated risk factors in patients with normal and decreased kidney function.

Methods: We conducted a retrospective study of hospitalized adult patients at a large community hospital who had hyperkalemia [potassium ≥5.4mmol/L] and were treated with intravenous insulin and dextrose 50%. We identified the incidence of hypoglycemia [blood glucose<70mg/dL] within six hours of insulin administration.

Results: 142 patients were eligible for analysis. 25 patients (17.6%) developed hypoglycemia. Hypoglycemia was detected at a median of 105 minutes after insulin administration. Factors associated with a higher risk of hypoglycemia included lower body mass index mean(25.2±9.2) vs. normal body mass index mean(25.9±10.5), no history of diabetes OR 5.16, 95%CI:1.67-16.0≥, p=0.002, and patients who didn’t receive co-treatment with Polystyrene sulfonate [p=0.047]. Patients with hypoglycemia had lower pre-treatment glucose levels compared to patients who did not mean(96.9±50.5xvs.154.7±87.8)p=0.0001. Previous studies showed a lower risk of hypoglycemia in patients who received co-treatment with...
albuterol. Our study showed a non-significant trend toward higher risk of hyponatremia in patients who received albuterol co-treatment (p=0.19 (20.3%) vs.p=0.10 (14.7%); p=0.384). There was no difference in hyponatremia incidence in patients with normal kidney function versus patients with decreased kidney function, [normal kidney function vs. acute kidney injury p=0.98; normal kidney function vs. ESRD p=0.93]. There was no significant difference in sNa in hyponatremic versus non-hyponatremic patients (24.7±3.4 vs.24.8±3.06;p=0.98).

Conclusions: Patients with lower BMI and no history of diabetes were at a significantly higher risk for hyponatremia. This is maybe explained by a lack of insulin resistance associated with low BMI and non-diabetic status. Lower pretreatment glucose levels were associated with hyponatremia. Hyponatremia was most likely to develop within 1-3 hours of treatment. This study supports the recommendations of frequent blood glucose monitoring following hyperkalemia treatment with intravenous insulin. Identifying risk factors is crucial.

FR-PO656
Tolvaptan in Portal Hypertension: Real-Life Experience
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Background: Tolvaptan (TVP) is an antagonist of V2 ADH receptors, used for hyponatremia in SIADH, congenital heart failure (CHF) and cirrhosis.

Methods: Retrospective review of TVP use between 2012 and 2017 to study the use of TVP in real life in patients with portal hypertension (PHT) (past history of non-malignant ascites or variceal bleeding).

Results: 81 patients received TVP. Of them, 19 had PHT. CHF was more frequent in patients with PHT (53 vs 26%; p=0.03). There were no differences in natremia at the start of treatment (126±1.3 vs 128±0.6mEq/L). There was a delay in correction of hyponatremia in the PHT subgroup over the first month, being the final serum sodium concentration 135±1.6 vs 139±0.8mEq/L (p=0.02). We found no difference in survival. In the PHT subgroup, 8 had confirmed cirrhosis and 11 severe CHF. The cause of cirrhosis was hepatitis C (n=3), alcohol (n=4) and unknown (n=1). 4 had hepatocellular carcinoma. Mean MELD score at the time of receiving tolvaptan was 12±2.3. Only one patient received a liver transplant 4 months after treatment with TVP. Cirrhotics had significant comorbidities (13% CHF; 13% microcytic lung cancer; 75% squamous cell carcinoma; 25% SIADH) and polypharmacy (13% antidepressants; 38% diuretics; 13% antiepileptics; 38% benzodiazepines; 13% cytostatics; 13% antipsychotics). Cirrhotics had fewer episodes of hyponatremia (8.4±1.0 vs 10.6±2.8), although not statistically significant. There was a trend for TVP treatment to be longer in cirrhotics (23±2.7 vs 7±3.2±6 days, p=0.07). We studied the delay in hyponatremia correction observed in patients with PHT: it was attributable to patients with CHF, in whom the mean increase in serum sodium concentration over the first month was 1.4±1.9 vs 7.2±1mEq/L in cirrhotic patients (p<0.03). Median survival time was 105 weeks (C95% 0-239) in CHF vs 5 weeks (C95% 3-7) in cirrhotics, but was not statistiically significant.

Conclusions: Even though TVP is approved for its use in hyponatremia associated to advanced cirrhosis as a bridge to liver transplant, in our experience and those of other authors in hospitalizations for significant comorbidities that can contribute to the development of hyponatremia and worsen its prognosis. Presence of ascites in CHF as a surrogate for PHT complications management, delaying the correction of hyponatremia.

FR-PO659
Use of Selective Serotonin Reuptake Inhibitors and Risk of Hyponatremia in a Large Health Care System
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Background: Selective serotonin reuptake inhibitors (SSRIs) use may increase the risk of hyponatremia. We aimed to quantify hyponatremia risk associated with SSRIs compared to that of serotonin-norepinephrine reuptake inhibitors (SNRIs) and determine whether it differs by eGFR and thiazide diuretic use.

Methods: Among primary care patients prescribed SSRIs between January 1, 2004 and January 30, 2017 in the Geissering Health System, we defined mild and moderate hyponatremia as outpatient blood Na<135mEq/L and ≤130mEq/L in the 3 months after medication initiation. We then used propensity score matching to pair patients prescribed SSRIS with those prescribed SNRIS and evaluated differences in hospitalizations for hyponatremia (defined by ICD-9 and -10 codes) during the entire course of medication use, overall and stratified by demographic factors, level of eGFR, and thiazide diuretic use.

Results: 69,551 patients prescribed SSRIS, 25% had a blood sodium measurement within 3 months of medication initiation. The risk of mild and moderate hyponatremia was 11% and 3%. In comparison, 25% of the 30,089 patients prescribed SNRIS had monitoring, and the risk of mild and moderate hyponatremia was 7% and 1% (p<0.01 for both comparisons to SSRISs). In the propensity matched cohort, there was no difference in the risk of hyponatremia.
3 days after being reported missing. On presentation, he was dehydrated, lethargic with first degree sunburn over his body. He was tachycardiac (heart rate of 118 bpm), BP 104/74mmHg. His weight was 88kg and height 170cm. His sodium was 174mmol/L, chloride > 140mmol/L, bicarbonate 10.3mmol/L, Creatinine 118micromol/L, urea 14.8mmol/L, glucose 5.5mmol/L, and serum osmolality of 357mOsm/kg. His urine sodium 221mmol/L, urine potassium 69mmol/L, and urine osmolality 1100mOsm/kg. His urine output ranged between 40-50mL/hour. He was managed initially at the emergency department with Dextrose 5% drip and kept nil by mouth. His sodium drops from 174mmol/L to 168mmol/L over the next 6 hour. Due to risk of unpredictable changes in sodium level, decision was made to initiate CVVHDF with citrate anticoagulation. His dialysis prescription was as follows: Q5 of 150mL/min, Qd of 1L/hour, QR of 1.6L/hour via a left femoral dialysis catheter. Customization of dialysate and replacement fluid was performed by adding 3% sodium chloride solution. His serum levels decreased as expected, and achieved normal sodium level over 4 days. He was weaned off CVVHDF on day 5. (Figure 1) Patient subsequently was transferred to a private hospital for further management.

Discussion: Extreme hypernatremia is rare and changes in sodium level with conventional treatment can be unpredictable. Correction of severe hypernatremia with CVVHDF provide a slow reduction of serum sodium in a controlled manner with positive outcome.

Figure 1: Serum sodium trend prior, during and after CVVHDF

FR-PO662
Acid-Base Disturbances in Multiple Myeloma
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Introduction: Multiple myeloma (MM) can be associated with several acid/base abnormalities that may not be as frequently appreciated as other clinical manifestations such as renal insufficiency, anemia, hypercalcemia, lytic bone lesions.

Case Description: A 62-year-old man with relapsed IgA kappa monoclonal MM presented with confusion and malaise. Labs showed: serum bicarbonate 13 mEq/L, serum chloride 102 mEq/L, anion gap (AG) 19, albumin 1.6 g/dL. Beta-hydroxybutyrate and lactic acid were not elevated. Additional labs included: blood urea nitrogen 29 mg/dL, creatinine 1.1 mg/dL, eGFR 72 mL/min/1.73m2. Arterial blood gas demonstrated pH 7.50, pCO2 18 mmHg, pO2 95 mmHg. Head imaging and infectious work-up were unremarkable. Although renal function normalized with supportive care, symptoms did not improve and these acid/base abnormalities persisted. Despite no history of liver disease and normal liver function tests, serum ammonia was elevated at 142 umol/L. MM-associated hyperammonenmic encephalopathy leading to hyperventilation was felt to be the cause of his respiratory alkalosis. In addition, the elevated AG was attributed to presumed negatively charged IgA. Ultimately, plasma exchange was started, and he received carbenoxolone, pantoprazole, and dexamethasone. His acid-base abnormalities subsided with treatment of his MM, and mental status returned to baseline.

Discussion: This case demonstrates unusual acid/base disturbances associated with MM. Respiratory alkalosis from hyperammonemnic encephalopathy is thought to be due to excess ammonia production by myeloma cells. Several cases report failure with standard treatments for hyperammonemnia but response to chemotheraphy. In addition, patients mortality is reduced in patients who received MM-targeted therapy compared to those who did not. The AG metabolic acidosis is presumed due to negatively charged IgA immunoglobulins. An increased AG has been reported in up to 30% of patients with IgA monoclonal gammapathy, in contrast to a decreased AG that is more commonly seen in IgG gammapathy. Of note, however, the magnitude of AG elevation does not correlate with monoclonal protein concentration, and AG abnormalities are not a sensitive test for screens for monoclonal gammapathies. It is important for clinicians to recognize and understand these potential acid/base disturbances in MM, as early identification may expedite proper therapy.
was started and serum Na\textsuperscript{+} only increased to 126 mM, so the dose was increased to 30 g placed on NaCl tablets 2 g tid, KCl 20 mmoles twice daily, and furosemide 40 mg twice days later but then decreased again to 117 mM. Tolvaptan was discontinued and he was since maintained isotonicity on twice daily use of urea 30 g, NaCl 2 g, KCl 20 mmoles, and over the next 4 days serum Na\textsuperscript{+} increased to 140 mM. The patient has since maintained isotonicity on twice daily use of urea 30 g, NaCl 2 g, KCl 20 mmoles, and furosemide 40 mg daily.

Discussion: This case illustrates that a patient with severe SIADH may be resistant to a maximal dose of tolvaptan yet still respond to traditional measures. Therefore, while aquaretic therapy aimed at the underlying free water permeability defect may be more physiologically elegant, maneuvers that modify the driving force for electrolyte-free water reabsorption may be more practical.

FR-PO664
Dysnatremia and Crude Mortality Rates: Evidence from the Sodium Metabolism and Management Experience (SoMME) Study

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Background: Few studies have evaluated the association of dysnatremia with mortality among hospitalized patients. It is unclear if there is a reduced mortality rate among hospitalized patients with deranged sodium levels. We evaluated the association between sodium levels on admission with in-patient mortality, 30 day mortality and long term mortality. We hypothesized that mortality rates will vary by sodium levels with worse mortality outcomes at both extremes of sodium levels.

Methods: We obtained data from 39261 patients admitted between 2012-2016 who had a serum sodium on admission at a tertiary referral hospital in Central Wisconsin. We classified the patients into five categories based on their admitting serum sodium: as severe low (<125), moderate low (125-129), mild low (130-134), normal (135-145) and high (>145). We obtained their vital status (alive or deceased) at end of hospital stay, within 30 days of admission and at the end of study period on December 31, 2017. Data were stratified by age and sex.

Results: There were 39261 patients (53% males, 97% whites) with age groups: <45 (12%), 45-64 (30%), 65-84 (44%) and >85 years (14%). A shaped distribution of mortality is associated with serum sodium levels with mortality associated with high sodium levels being the greatest. Mortality associated with moderate low sodium levels almost approximate that of severe low sodium levels. These results were consistent across age and sex.

Conclusions: Higher crude mortality was seen in all patients with dysnatremia. Hypo-osmolality was associated with the worst mortality. The underlying mechanisms that contribute to death in dysnatremia, and researching if correcting sodium levels may prevent further deaths in the future.

FR-PO665

Hypernatremia Induced by Treatment for Hypokalemia in a Patient with Sjögren Syndrome and Renal Tubular Acidosis

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Introduction: Hyperkalemia and metabolic acidosis are severe complications of renal tubular acidosis (RTA). In Sjögren’s syndrome. The concentration of sodium in the plasma water should equal the concentration of sodium plus potassium in the total body water. The sodium concentration is not always considered when treating hyperkalemia.

Case Description: A 60-year-old women presented with general weakness, hypotension, hyperkalemia, metabolic acidosis, and acute kidney injury. Her blood pressure was 60/44mmHg, and her heart rate was 89/min. Na\textsuperscript{+} 144 K\textsuperscript{+} 1.5, Urea 65.9 mEq/L, BUN 2.34 mmol/L, pH 7.052, P\textsubscript{CO2} 36.2 P\textsubscript{O2} 331, and HCO\textsuperscript{3} 9.6 mEq/L. Urinary electrolytes Na\textsuperscript{+} 41 mEq/L, K\textsuperscript{+} 12.2 mEq/L, Cl\textsuperscript{-} 32 mEq/L, pH 6.5, Osmolality 244 mosm/kg. The patient was intubated because of respiratory muscle weakness from severe hyperkalemia. She was treated with intravenous potassium chloride (KCl 400 mEq) and isotonic fluid for the treatment of hyperkalemic shock. This solution was actually hypertonic because of its high potassium concentration: Na\textsuperscript{+} 110 mEq/L, and K\textsuperscript{+} 147 mEq/L, in a total of 2.6 liters. After 18 hours the patient developed hypernatremia (Na\textsuperscript{+} 161 mEq/L), but her serum potassium had normal sized (K\textsuperscript{+} 4.6 mEq/L). Her urine measurements were as follows. Na\textsuperscript{+} 40 mEq/L, K\textsuperscript{+} 52.7 mEq/L, Cl\textsuperscript{-} 82 mEq/L, and osmolality 405 mosm/kg. After the hypertonic fluid was changed to a hypertonic type, she recovered. She was also found to have Sjögren’s syndrome after a positive screen for anti-La, and anti-Ra antibodies. A positive Schirmer’s test and a renal biopsy also suggested Sjögren’s syndrome. She was discharged without complications. There is no physical examination or other vital signs.

Discussion: This case indicates that serum sodium concentration should be carefully monitored in patients with hyperkalemia and acute kidney injury induced by distal RTA receiving intravenous potassium chloride therapy and hypertonic fluid, which contain high levels of potassium. We should keep this complication in mind when treating severe hyperkalemia.

FR-PO666
Symptomatic Hyponatremia: SIADH or NSIAD): Diagnostic Challenge, Surprise Diagnosis, and Successful Management with Tolvaptan for 6 Years

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Introduction: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of euvolemic hyponatremia. In the absence of any identifiable cause after extensive investigations, and especially in the presence of low or undetectable serum ADH level, diagnoses such as nephrogenic syndrome of inappropriate antidiuresis (NSIAD) caused by gain-of-function mutations in the V2 vasopressin receptor (V2R) have to be entertained. Chronic management of symptomatic hyponatremia can also be a challenge.

Case Description: A 17 year old previously healthy girl presented with dizziness, and somnolence. Blood tests revealed serum sodium 128 mEq/L. Clinical picture was suggestive of SIADH (euvolemic state, low serum osmolality, increased urinary osmolality, and increased urinary sodium level) but extensive investigations/imaging studies failed to delineate any underlying cause for SIADH. Review of old medical records revealed normal serum sodium (142 mEq/L) over a decade ago. She was managed as possible SIADH, with water restriction that resulted in modest improvement in her serum sodium level. A month later her symptoms recurred with recurrence of hyponatremia. Serum ADH levels returned undetectable on both occasions and were confirmed to be low 3rd time from two different labs. Later, her serum sodium acutely dropped to 119 mEq/L when she drank water prior to a renal ultrasound. She was suspected having NSIAD but DNA sequencing of V2R gene did not show any mutation. She was managed with combination of moderate fluid restriction and daily Tolvaptan. Five years later, she had features with severe hyponatremia (109 mEq/L) after taking SSRI for depression. 1½ year later she had another episode of unexplained hyponatremia (118 mEq/L), and a head MRI was repeated for headache after correction of hyponatremia which revealed a small enhancing mass in the right osteomeatal infundibulum. The mass turned out to be small blue cell tumor ethionoeburoblastoma, a relatively rare nasal tumor that is rarely associated with SIADH. She underwent complete tumor resection with clear margins, and now has normal serum sodium without any fluid restriction or medications.

Discussion: Patients with chronic unexplained hyponatremia should be followed very closely and reevaluated periodically with high index of suspicion for unusual tumors.
FR-PO667

Is There a Role for Concomitant Administration of Albumin and Diuretics? A Meta-Analysis

Background: Diuretics are the cornerstone of volume management in patients with disease states such as heart failure, nephrotic syndrome and cirrhosis. Diuretic resistance is commonly encountered in such patients and is often attributed to hypoalbuminemia. Although this has sometimes empirically used to increase diuretic efficacy in these patients, we sought to systematically study the effect of albumin combined with diuretics on urine volume and urine sodium in patients with hypoalbuminemia.

Methods: Systemic search of electronic databases from inception until June 2018 was performed. We included clinical trials in patients with hypoalbuminemia that included more than 5 subjects, comparing co-administration of albumin and diuretics versus loop diuretics alone. A total of 754 records were screened independently by two investigators. 26 full text articles were assessed for eligibility. Synthesis of data was done using meta-analysis techniques using Revman Software.

Results: There were 9 eligible studies which met the criteria and had the required data. All of them were cross over studies. 6 of the studies were done exclusively in nephrotic syndrome patients, one of which included pediatric subjects. There was a statistically significant increase in urine volume of 315 ml (95% CI 183.04, 448.33) and urine sodium of 27 meq (95% CI 7.46, 46.59) at 8 hours with co-administration of albumin and furosemide compared to furosemide alone.[fig]. There was no statistically significant increase in the 24 hour urine output 385 ml (95% CI 141.92, 911.68).

Conclusions: Our results suggest that in patients with hypoalbuminemia, co-administration of albumin and furosemide increases urine output and sodium excretion at 8 hours. There were no differences in urine volume at 24 hours, but most of these studies used single doses or few hours of diuretic infusions. Randomized controlled trials in patients with defined diuretic resistance is required to confirm the efficacy of co-administration of albumin and furosemide.

FR-PO668

A Case of IgG4-RD Manifesting as Kidney Disease: Idiopathic or Multilineage Hematopoiesis?
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Introduction: IgG4-RD is a systemic inflammatory disorder characterized by infiltration of IgG4+ plasma cells into affected tissues. When IgG4-RD involves the kidneys it manifests most frequently as tubulointerstitial nephritis and/or membranous nephropathy. Imaging often demonstrates bilateral cortical nodular lesions.

Case Description: A 61-year-old male with hypertension presented for evaluation of elevated serum creatinine to 1.89 mg/dL. He noted NSAIID use 2-4 times/week for back pain for much of the year prior, and home systolic BP readings 140-150mmHg. Additional workup revealed 378mg protein on 24-hour urine, and elevated free kappa and lambda light chains. SPEP showed hypergammoglobinemia, with immunofixation electrophoresis showing narrow monoclonal bands. Bone marrow biopsy demonstrated multilineage hematopoiesis and 3% polytypic plasma cells without evidence of clonality; Congo red stain was negative for amyloid. Spine MRI showed no lytic lesions, but did identify a 2cm L thyroid nodule. PET/CT revealed markedly enlarged and hypermetabolic kidneys bilaterally. A diagnosis of plasma cell disorder was made. Renal biopsy showed severe lymphoplasmacytic tubulointerstitial disease with abundant IgG4+ plasma cells. Molecular analysis of the plasma cell infiltrate detected a clonal IgH gene rearrangement in a polyclonal background. Thyroid tissue from a left hemithyroidectomy for the above nodule was negative for IgG4, but an included adjacent lymph node was diffusely IgG4+.

Discussion: The patient’s serum creatinine demonstrated a stable improvement to 1.3-1.4 mg/dL since initiation of workup.

Discussion: This is an unusual presentation of an uncommon disease, IgG4-related disease. Immunohistochemical staining indicated a polyclonal plasma cell infiltrate on renal biopsy, while molecular testing identified a clonal cell population with IgH gene rearrangement, raising the possibility of multiple populations of plasma cells: one polyclonal, another IgG4+, and a third that is clonal and producing paraprotein. Further workup is needed to determine the etiology.
Infiltrating lymphoma and glomeruli with capillary wall thickening.

FR-PO671
Unique Presentations of Post-Renal Transplant Gamma Delta T Cell Lymphoma
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Introduction: Post-transplant lymphoproliferative disorder (PTLD) is severe complication occurring in up to 10% of solid organ transplant recipients (R). In monomorphic PTLD, the majority of cases arise from B cells (good prognosis) and rarely from T cells. Less than 5% of T-cell lymphomas express gamma delta T-cell receptors. Gamma delta T cell lymphomas (GDTL) are outlined into two groups: hepatosplenic (HSGDTL) and primary cutaneous (PCGDTL). We present 2 recipients that developed PCGDTL and HSGDTL.

Case Description: R1 was a 67-year-old male who received a living, unrelated renal transplant, induced with Simulect. He was EBV IgG+ and mismatched CMV IgG-. He presented 1-year post transplant with 20 lb weight loss, pruritic skin rash, no EBV DNAemia, and diffuse lymphadenopathy on body PET CT. Biopsy of left axillary lymph node, skin, and bone marrow revealed a mature stage 4 T-cell lymphoma (CD2-, CD3-, CD4-, CD5-, CD7-, CD8+, TCR-gamma-delta TCR+, and alpha-beta TCR-). This case of PCGDTL had an unusual phenotype of CD4 positivity with presentation (R). R2 was a 44-year-old male who received a deceased donor renal transplant, induced with Thymoglobulin. He was EBV IgG+ and non-mismatched CMV IgG-. He presented 7 years post transplant with abdominal pain, abnormal liver function tests, no EBV DNAemia, and moderate hepatosplenomegaly on abdominal CT. Peripheral blood flow cytometry and bone marrow biopsy revealed HSGDTL (CD2+, CD3+, CD4-, CD5-, CD7+, CD8 (dimly positive), CD25+, gamma/delta TCR+, and alpha/beta TCR-). Immunosuppression was discontinued. He was treated with 2 cycles of CHOP regimen with treatment failure and 3 cycles of salvage therapy (Gencatibizide, Decadron, Carboplatin) with complete resolution. He relapsed with leukemia conversion 2 months later and died with a functioning allograft within 1 year of diagnosis.

Discussion: Our cases demonstrate that GDTL is an aggressive neoplasia with rapid onset and poor prognosis. Despite initial response, both recipients died within 1 year of diagnosis. PCGDTL seems to clinically present earlier than HSGDTL. Also, neither of our patients had CMV/EBV viremia, suggesting GDTL development is potentially independent of virology.

FR-PO672
Renal Microangiopathy and Tubulitis Following Haploidentical Stem Cell Transplant with c/c T Cell and CD19 B Cell Depletion

Introduction: Selective depletion of c/c T-cells and CD19 B-cells in haploidentical (haplo) hematopoietic stem cell transplantation (HSCT) is being investigated as a strategy to avoid graft versus host disease (GVHD) while preserving immune reconstitution. We describe 4 cases of renal dysfunction following haplo-HSCT.

Case Description: All cases were Caucasian males who underwent non-myeloablative peripheral blood haplo-HSCT using fludarabine, cyclophosphamide and total nodal irradiation (7Gy). All reached engraftment and received mycophenolate (MMF) for GVHD prophylaxis (30 days). All are living at follow up. The table summarizes their presentations.

Discussion: All patients had endothelial injury and most (3/4) had inflammatory tubulopathy. Given the setting of haplo-HSCT with selective T-cell depletion, timeline and degree of renal insult, as well as response to IS, renal complications were most concerning for alloimmune response (GVHD). Chemotherapy and pre-IS infections may also have contributed to endothelial/tubular injury in early post-HSCT period. Our series highlights (1) GVHD is likely an important factor in post haplo-HSCT endothelial injury and direct/indirect tubular injury; (2) This condition is difficult to treat due to high risk of infections post-HSCT. Renal risks in haplo-HSCT need further investigation.

FR-PO673
Crystalglobulinemia in Multiple Myeloma: A Rare Case of Survival and Kidney Recovery
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Introduction: Crystalglobulinemia is a rare complication of monoclonal gammopathy wherein crystallised immunoglobulins deposit in various organs causing occlusive vasculopathy, endothelial damage and thrombosis. The reported mortality in this disease is extremely high.

Case Description: We report a case of a 74-year-old female presenting with polyarthralgia, chest pain, petechial rash and rapidly progressive oliguric acute kidney injury requiring dialysis. The serum creatinine on admission was 368 µmol/L, which peaked at 763 µmol/L on day 5 of admission. Troponin-T was 447 ng/L (normal <14 ng/L), peaking at 1,223 ng/L 7 days later. There were no ischemic changes on ECG. Serum protein electrophoresis showed IgG kappa paraprotein of 25.7 g/L and k/λ ratio 21.8 (normal 0.26-1.85). Kidney biopsy revealed crystalline eosinophilic casts in the lumens of medullary tubules. Similar crystalline deposits were present in some interlobular arteries with luminal occlusion. Several glomeruli showed similar mainly crystalline deposits in glomerular capillary loops occluding lumens. Ultrastructure showed widening of subendothelial spaces of glomerular capillary loops with subendothelial flocculent material consistent with a thrombotic microangiopathy. Tubular crystal deposits had an organised parallel linear ultrastucture. Bone marrow biopsy confirmed immunoglobulin G (IgG) κ plasma cell multiple myeloma. This patient was successfully treated with 5 sessions of plasmapheresis and clone reduction chemotherapy with 11 cycles of cyclophosphamide, bortezomib and dexamethasone. This resulted in complete resolution of her symptoms, normalisation of troponin-T, reduction of paraprotein levels to <1 g/L and overall excellent kidney and hematological recovery. In 2 months, she was no longer dialysis dependent and in 32 months her latest creatinine had improved to 100 µmol/L.

Discussion: Crystalglobulinemia is a rare and life-threatening illness that should be suspected in patients with rapidly progressive acute kidney injury and monoclonal gammopathy. It can mimic other clinical entities, such as acute coronary syndrome, vasculitis and rheumatological disease due to the deposition of crystalglobulins in various organs. Our case demonstrates that timely investigation with appropriate treatment can lead to remission of multiple myeloma and excellent recovery of kidney function.

FR-PO674
Is This the Real Lyse? Is This Just Fantasy? Pseudohyperkalemia with Concurrent Tumor Lysis Syndrome in Extreme Leukocytosis
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Introduction: Hyperkalemia is a potentially dangerous electrolyte imbalance encountered in hematological malignancies, often seen in tumor lysis syndrome (TLS) and renal failure. It is increasingly recognised that potassium can be spuriously elevated in severe leucocytosis.

Case Description: A 74-year-old Chinese gentleman presented to the emergency room with 3 days of giddiness and was diagnosed with Chronic Myeloid Leukemia with blast crisis. Notable serum laboratory results included marked leucocytosis of 710 x 10⁹/L, platelets of 680 x 10⁹/L, hemoglobin of 5.5 g/dL, creatinine of 289 µmol/L, potassium of...
7.2 mmol/L (unsed), phosphate of 1.69 mmol/L and markedly elevated uric acid and lactate dehydrogenase levels of 11.572 mmol/L and 767 U/L respectively. Laboratory abnormalities were attributed to spontaneous TLS with KDIGO Stage 3 acute kidney injury (AKI). Emergent medical therapy was instituted with insulin/dextrose, intravenous hydration and hydroxyurea. Rashburcise was withheld pending insulin-glucose-phosphate depletion status. Urgent renal consult was obtained for the consideration of renal replacement therapy (RRT) in view of oliguria. Simultaneous serum and whole blood potassium sample analysed via direct potentiometry subsequently revealed significantly discordant results of >8.0mmol/L and 4.7mmol/L respectively. Pseudohyperkalaemia was noted by the absence of typical FGF23 and IgG4, suggesting secondary membranous nephropathy. Interestingly, electron microscopy showed deposits along glomerular basement membranes and also paramesangial areas. There were few deposits in the subepithelial areas. He was finally diagnosed with metastatic renal cancer to the lung and brain and chemohapry with sunitinib was begun. Thereafter, the serum creatinine did not change and MPO-ANCA decreased to 32.6 U/ml without using corticosteroids.

Discussion: Although ANCA-GN accompanied by MN has rarely been reported, the present case showed atypical membranous lesions suggesting unique etiology of immune complex formation.

FR-PO675
Solitary Renal Mass in Waldenström Macroglobulinaemia
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Introduction: Waldenström macroglobulinaemia is a rare B-cell lymphoproliferative disorder characterised by the presence of an IgM paraprotein and bone marrow infiltration by lymphoplasmacytic lymphoma. He was commenced on the dexamethasone, rituximab and cyclophosphamide regimen.

Case Description: A 68 year old Caucasian man was referred with a persistent anaemia and weight loss. On examination, there was no evidence of palpable lymphadenopathy, or organomegaly. Initial investigations revealed a normocytic anaemia with a haemoglobin of 11g/dL, while white cell count of 4 x 10^9/L, platelet count of 314 x 10^9/L and normal renal function. He was referred to haematology as serum protein electrophoresis detected an IgM paraprotein band. Computed tomography of his thorax, abdomen and pelvis revealed a renal mass with diffuse nodular sclerosis having polyclonal IgG and IgM lambda deposits, and EM antibody, anti dsDNA, low C3 and C4 levels. A kidney biopsy confirmed MPGN pattern driven by fibroblast growth factor 23 (FGF23) production is a paraneoplastic phenomenon. We present a liver tumor with demonstrated FGF23 expression, a previously unreported site.

Case Description: A 58 y/o female with a history of lupus and osteoarthritis presented with fatigue, weight loss and joint pains. Medications include alendronate, plaquenil and vitamin D. She was found to have 3.6g of 24 hour urine protein and low phosphorous for four years. Fractional excretion of phosphate ranged between 40-65% (normal 10-20%). Other causes of secondary hyperparathyroidism were excluded. Renal biopsy was performed and revealed proximal tubule vacuolation, without evidence of lupus activity. C-terminal FGF23 levels were tested at multiple points and elevated to 97 and 770 RU/mL at a serum phosphorous of 1.7 and 3.4 mg/dL respectively on high dose supplementation. Parathyroid hormone levels were normal. FGF23 levels remained elevated. Ga-67 citrate PET scan revealed an irregular enhancing liver mass which upon resection was a spine, a liver cell tumor with clear margins. Immunohistochemical staining of the pathologic tissue was positive for FGF23 when compared to normal liver. Cell culture of tumor cells versus the patients normal liver cells showed two-fold higher FGF23 expression. The intra-op & post-op period was uneventful except worsening of hypophosphataemia as expected with increase in FGF23 to 800-1400 RU/mL. 3 months post-op, she had a minor fall with an avulsion fracture of the 5th metatarsal bone. 5 months later the patient remains hypophosphataemic, but requires less oral supplementation. Symptoms have improved significantly, however her FGF23 remains elevated.

Discussion: While the liver has been shown to express FGF23, TIO has not been previously described as a consequence of a liver neoplasm. TIO is a potentially curable paraneoplastic etiology of symptomatic hypophosphataemia. Symptoms usually remit quickly in tumors in which resection is possible. This adds to potential sites to explore when evaluating for TIO. Repeat PET scan will be required to evaluate our patient for residual disease given continued FGF23 elevation. Recombinant FGF23 antibody is another potential intervention if other methods of cure are impossible.

FR-PO676
A Case of ANCA-Associated Glomerulonephritis Accompanied by Membranous Lesions During the Course of Recurrent Renal Cancer
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Introduction: ANCA-associated glomerulonephritis (ANCA-GN) has been classified as a pauci-immune type of crescentic renal vasculitis, since smooth muscle cell antibody, antidsDNA, low C3 and C4 levels. A kidney biopsy confirmed MPGN pattern with diffuse nodular sclerosis having polyclonal IgG and IgM lambda deposits, and EM showing focal organized deposits. There was also a diffuse interstitial lymphoplasmacytic infiltrate. Based on the IF findings, the diagnosis of mixed cryoglobulinaemia-associated GN was made, but a paraproteinemia related disease could not be ruled out. A Hepatitis C PCR was negative. Since the kidney disease was related to the rheumatologic findings, steroid were initiated. Despite steroids, her creatinine worsened over 6 weeks and proteinuria increased to over 8gm/24 hours. A repeat kidney biopsy was diagnostic for gamma-3 heavy chain deposition disease, with a nodular sclerosing glomerulonephritis and strong (4+) IgG and C1q reactivity in the mesangium and along glomerular and tubular basement membranes; no significant reactivity for kappa and lambda light chains or C3 was noted on routine IF microscopy. IgG subclass staining showed strong (4+) gamma-3 reactivity, in the same areas corresponding to the IgG staining. Electron microscopy reveals diffuse bowting of the mesangial and also along the GBM. The diagnosis of HCD was discussed. The treatment was changed to anuranic AKI, was suspected and corroborated by the absence of typical hyperkalemia changes on electrolyte analysis. Serum creatinine increased to 2.4mg/dL and was corrected with dialysis.

Case Description: A 70-year-old male was referred to our hospital because of worsening renal function and persistent hematuria and proteinuria of around 0.5-1 g/Gfr. He had undergone nephrectomy for renal cancer at the age of 49 and also left lung cancer. Laboratory examination revealed elevated serum phosphate of 1.48 U/mL and an elevated serum creatinine level (1.5 mg/dL). There were no other findings that suggest organ involvement of systemic vasculitis. CT and PET-CT scans showed nodular lesions of the right lower lung and mediastinal mass suspected of malignancy. A renal biopsy revealed necrotizing extracapillary proliferative glomerulonephritis with fibrous crescents, compatible with ANCA-associated glomerulonephritis (ANCA-GN). However, immunofluorescent study showed granular deposits of IgA along the glomerular capillary walls, with IgG subclass being positive for gamma-3 heavy chain deposition disease. The differential diagnosis of a renal mass and the necessity of prompt biopsy.

Discussion: This case illustrates the importance of consideration of WM and other lymphomas in the haematogeneous dissemination. Our review of the literature identified only six previous cases of renal lymphoma, all presenting with symptomatic hypophosphataemia. Symptoms usually remit quickly in tumors in which resection is possible. This adds to potential sites to explore when evaluating for TIO. Repeat PET scan will be required to evaluate our patient for residual disease given continued FGF23 elevation. Recombinant FGF23 antibody is another potential intervention if other methods of cure are impossible.
showed no change in percent of plasma cells. Regardless, she was started on bortezomib based therapy. Four months later, she still remains dialysis dependent.

Discussion: Diagnosis of HCDD is challenging. In this case, the initial pathology of an autoimmune process causing kidney disease masked a chronic HCDD related kidney disease. High index of suspicion is required for diagnosis of HCDD. Prognosis remains guarded.

FR-PO679
AKI from Polytypic Plasma Cell Interstitial Infiltration in Sjogren Syndrome
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Introduction: 57-year-old woman with a history of extensively treated Marginal Zone Lymphoma diagnosed with concomitant pulmonary AL Amyloidosis on lung biopsy in 2011 as well as remote history of Sjogren Syndrome, referred for acute kidney injury (AKI).

Case Description: During initial evaluation (1/22/19), she was found to have a relatively brisk worsening of creatinine (Cr) from 0.9 to 2mg/dL over a 2-week period. She had new onset microscopic hematuria, glycosuria and pyuria with proteinuria quantified as 1.3g (albumin/cr of 66mg/g). Ultrasound showed edematous bilateral kidneys with serial CT imaging highlighting an insidiously worsening loss of corticomedullary differentiation over the last year. Ancillary studies showed a stably abnormal k/l ratio of 3.5 and IgG-k M-spike of 0.1g/dL, with these serologies showing chronic and fluctuating elevated titers since the diagnosis of Lymphoma. There was also a gradually worsening total serum protein of 11.1g/dL and IgG titer of 5925mg/dL (normal <1610). Native kidney biopsy was undertaken on 2/19/19 that showed extensive interstitial infiltration with polytypic plasma cells with no morphologic or immunophenotypic evidence of lymphoma. Just prior to kidney biopsy, Cr peaked 2.96mg/dL and prednisone 1mg/kg was initiated for empiric management. Given absence of lymphomatous renal involvement, chemotherapy was not entertained. Renal function improved with Cr dropping to 0.7mg/dL following a tapering course of prednisone. This was accompanied by resolution of pyuria and stabilization of IgG titer to 3725mg/dL on last check. She tested positive for serum ANA (positive ss-A and ss-B) with negative double-stranded DNA.

Discussion: Patient experienced AKI from a non-lymphomatous polyclonal plasmacytic interstitial infiltration in the native kidney with a severe hypergammaglobulinemia that responded briskly to prednisone. In the context of worsening sicca symptoms over the last 6 months and positive serologies, the plasmacytic infiltration was deemed a manifestation of Sjogren syndrome, which was first diagnosed in 2005 following biopsy of minor salivary glands. This presentation of renal failure from Sjogren syndrome is a rare occurrence and even more intriguing in a patient with extensive history of lymphoma. KIN has an autosomal recessive form, as well as interstitial fibrosis and tubular atrophy. KIN has an autosomal recessive form, and ss-B) with negative double-stranded DNA.

FR-PO680
Karyomegalic Interstitial Nephritis in a Woman with Hodgkin Lymphoma on Brentuximab Therapy
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Introduction: Karyomegalic interstitial nephritis (KIN) is a rare form of chronic interstitial nephritis that can lead to end stage renal disease. It is characterized histologically by hyperchromatic, abnormally enlarged nuclei of tubular epithelial cells, as well as multinucleated giant cells. KIN is an autosomal recessive form, associated with mutations in the Fan1 gene. Other potential etiologies include toxins (e.g. oxotrenol A), heavy metals (e.g. bismuth, lead), alkylating agents (e.g. ifosfamide), and viral infections. We present a case of KIN in a woman with Hodgkin’s lymphoma on brentuximab vedotin (trade name: Adcetris) therapy. To our knowledge, this is the first case report of KIN associated with this medication.

Case Description: A 50-year-old Hispanic female was diagnosed with anaplastic high-grade Hodgkin’s lymphoma with metastasis to the liver, large intestine, and adrenal gland. She had poor response to 4 cycles of ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine) and 3 cycles of ICE (Ifosfamide, Carboplatin, Etoposide). She then received two doses of Brentuximab vedotin. She had a normal renal function prior to the infusion of Brentuximab vedotin, which declined rapidly afterwards. Urinalysis showed 3+ glucose, 3+ protein, 1 WBC, 0 RBC and 6-10 granular casts/LPF. Urine protein to creatinine ratio was 2.6 g/g. Kidney biopsy showed KIN. Despite discontinuation of brentuximab vedotin, her kidney function continued to worsen, and she was prepared for dialysis.

Discussion: Brentuximab vedotin is an antibody-drug conjugate (ADC) which targets tumor cells expressing CD30, followed by internalization and release of monomethyl auristatin E (MMAE), which binds to tubulin and disrupts the microtubule network. This results in cell cycle arrest, and may explain the markedly enlarged and hyperchromatic nuclei seen in renal tubular epithelial cells, which did not undergo apoptosis as tumor cells do. The present case is the first report of KIN association with brentuximab vedotin. While there is the possibility that KIN may be a late consequence of ifosfamide administration, the temporal relationship between treatment with brentuximab vedotin and the onset of kidney injury suggests that brentuximab vedotin was the most likely responsible agent in this case.

FR-PO681
A Unique Case of Hyponatremia
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Introduction: Immune check point inhibitors (ICI) have revolutionized cancer treatment. They promote activation of T cells causing programmed death of tumor cells. However they can cause life threatening immune related adverse events (irAEs) including autoimmune endocrinopathies, such as hypophysitis, thyroiditis, adrenalsitis, insulinitis, and parathyroiditis. We present a case of hypophysitis caused by the use of ipilimumab and nivolumab, presenting with severe hyponatremia.

Case Description: A 60 y.o. lady with metastatic renal cell carcinoma was started on treatment with ICI- Ipilimumab and Nivolumab. After two cycles of treatment, patient developed thyromegaly, was diagnosed with immune thyroiditis manifesting as hyperthyroidism followed by hypothyroidism, requiring levothyroxine. Two months into ICI therapy she presented to the hospital with complaints of left-sided flank pain. A CT scan of abdomen revealed increase in growth of the left renal mass. Laboratory data revealed serum sodium (Na) level of 127 mmol/L (Na was 142 a week prior). She was placed on fluid restriction of 1.2 liters per day and salt tablets 1 gram 3 times daily. Yet Na level continued to drop to 118 by 3rd day of hospitalization. Urine osmolality was 504 mosm/kg with urine sodium of 24 mmol/L. Her TSH level was low at 0.023 (0.400 - 4.000 mcU/mL) with free T4 levels of 0.69 (0.70 - 1.90 ng/dL). A.M. cortisol level was very low at 1 mcg/dL (6.0 - 18.4 mcg/dL). Patient was diagnosed with adrenal insufficiency and central hypothyroidism thought to be secondary to immune related adverse effects resulting from the use of Ipilimumab and Nivolumab. She was started on methylprednisone 70 milligrams IV daily, her serum Na improved from 119 to 126 mmol/L in 24 hours and normalized over 3 days. She was switched to oral tapering dose of hydrocortisone.

Discussion: The combined treatment of ipilimumab (anti-CTLA4 Ab) and nivolumab (anti-PD-1 Ab) increases the tumor efficacy but also increases the risk for autoimmune hypophysitis, which can cause secondary adrenal insufficiency through complement deposition, mononuclear cell infiltration and production of antibodies to adenohypophysial endocrine cells resulting in adrenal insufficiency induced hypothyreutism. In this case, hypothyroidism did not respond to steroid therapy and she was started on oral hydrocortisone. Hyponatremia induced by ICI should be recognized and treated promptly.

FR-PO682
Mantle Cell Lymphoma Resulting in Paraneoplastic Immune Complex Mediated Glomerulonephritis
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Introduction: Glomerulonephritis (GN) can result from paraneoplastic effect of certain malignancies. Here we report a case of a gentleman with Mantle cell lymphoma (MCL) who developed GN necessitating treatment of his cancer that otherwise did not meet hematological criteria for treatment.

Case Description: A 63-year-old Caucasian male with a newly diagnosed MCL, not on treatment, came in for evaluation of lower extremity edema within two weeks of diagnosis. His edema was associated with a weight gain of ten pounds, and acute kidney injury with a creatinine rise from a baseline of 1.08 to 1.72, peaking at 3.14 mg/dL over the next few weeks. Initial evaluation consisted of a normal renal ultrasound, a urinalysis with 3+ blood, positive leukocyte esterase. A microscopic evaluation of his urine sediment showed dysmorphic red blood cells (RBCs), 5 white blood cells, and no bacteria. A spot urine protein to creatinine ratio of 5.3g/g creatinine of which 3.3g was albumin. Serological work up demonstrated a normal or negative serum and urine electrophoresis, serum free light chains, complements, anti-neutrophilic cytoplasmic antibody, anti-double stranded DNA, anti-glomerular basement membrane antibody, erythrocyte sedimentation rate, C-reactive protein, hepatitis serologies, lactate dehydrogenase, haptoglobin and cryoglobulin. His anti-nuclear antibody was weakly positive. He underwent a kidney biopsy showing acute tubular necrosis with immune complex GN with a focal proliferative and mesangio proliferative pattern of injury. There was no paraprotein deposition or parenchymal infiltration with the lymphoma cells. His GN was attributed to a paraneoplastic process resulting from his underlying MCL. His GN prompted treatment with high dose steroids, bendamustine, and rituximab with improvement in creatinine to 1.2 mg/dL, and complete resolution of proteinuria. A subsequent positron emission tomography scan showed marked regression of his MCL.

Discussion: Renal involvement in mantle cell lymphoma is a rare complication. Mantle cell lymphoma is often an indolent condition that does not require treatment. However, organ-threatening GN such as that reported in our case can only respond to treatment. Serological studies are often insufficient and kidney biopsy is required for definitive diagnosis. Rituximab-based regimens are effective for treatment of paraneoplastic GN resulting from MCL.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO683

Hypophosphatemia and Fibroblast Growth Factor 23 Producing Metastatic Breast Cancer
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Introduction: Fibroblast growth factor-23 (FGF23) is a key regulator of phosphate metabolism and downregulates expression of cotransporters in the kidney essential for phosphate reabsorption. FGF23 mutations cause inherited renal phosphate wasting diseases leading to osteomalacia in adults. In the paraneoplastic setting, FGF23 over secretion leads to tumor-induced osteomalacia (TIO) also known as oncogenic osteomalacia.

Case Description: 47-year-old woman with metastatic breast cancer was evaluated for persistent hypophosphatemia. First diagnosed with left mammary duct carcinoma in 2013, she underwent partial mastectomy followed by chemotherapy. She had a recurrence in 2016 and failed multiple lines of chemotherapy with new metastasis to the liver and several osseous lesions. Patient was initiated on monthly denosumab one year prior to current visit, with last dose one month ago, for metastatic bone involvement. Phosphorous level on consultation was <0.9 (2.5-4.5) mg/dl due to hypocalcemia in the setting of recent denosumab administration. Phosphorous levels remained low despite aggressive oral calcium and phosphate repletion and oral calcitriol. Given persistent hypophosphatemia, FGF23 was checked and levels returned strikingly elevated at 2450 (< ~180) RU/mL suggesting an FGF23 secreting tumor as the most likely cause for severe hypophosphatemia. Oral phosphate supplementation was continued, though unfortunately, given progression of disease, palliative measures were chosen with a focus on comfort care.

Discussion: TIO is a rare paraneoplastic syndrome, but when present, downstream effects of phosphaturia can lead to profound weakness and skeletal collapse. Though prior consideration for secondary hyperparathyroidism, stopping plasma exchange, the patient has been followed up in the renal clinic, with focus in the ongoing reoccurrence in 2016 and failed multiple lines of chemotherapy with new metastasis to the liver and several osseous lesions. Patient was initiated on monthly denosumab one year prior to current visit, with last dose one month ago, for metastatic bone involvement. Phosphorous level on consultation was <0.9 (2.5-4.5) mg/dl due to hypocalcemia in the setting of recent denosumab administration. Phosphorous levels remained low despite aggressive oral calcium and phosphate repletion and oral calcitriol. Given persistent hypophosphatemia, FGF23 was checked and levels returned strikingly elevated at 2450 (< ~180) RU/mL suggesting an FGF23 secreting tumor as the most likely cause for severe hypophosphatemia. Oral phosphate supplementation was continued, though unfortunately, given progression of disease, palliative measures were chosen with a focus on comfort care.

Discussion: TIO is a rare paraneoplastic syndrome, but when present, downstream effects of phosphaturia can lead to profound weakness and skeletal collapse. Though prior reports have identified bone or soft tissue as the primary site, the case above is unique since the syndrome occurred in metastatic disease with a primary breast cancer. Recognition of TIO in these patients may be critical since lesions may undergo resection which may be curative. In patients with several lesions or metastatic cancer, medical therapy can be attempted to improve the quality of life.

FR-PO684

Vascular Renal Amyloidosis with Waldenstrom Macroglobulinemia (WM)
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Introduction: Several kidney diseases have been associated with WM; they include lymphoplasmacytic lymphoma infiltration, immunoglobulin light chain (AL) amyloidosis and cryoglobulinemic glomerulonephritis. AL amyloidosis classically presents with nephrotic syndrome. We present a rare case of renal vascular AL amyloidosis in a patient with WM.

Case Description: A 82-year-old white woman with history of WM presented with worsening kidney function. Nine years prior, she was diagnosed with WM and was treated with Bendamustine and Rituximab for 6 monthly cycles and then Rituximab maintenance for 2 years. She remained stable for six years. Over the last year, she was noted to have worsening anemia, rising serum creatinine from 1.3 mg/dl to 1.8 mg/dl and new onset of subnephrotic range proteinuria (1 gm/day). Her urinalysis did not reveal any blood or dysmorphic RBC. In addition, for several months, her blood pressure was harder to control. At baseline, her serum immunoglobulin free light chain ratio (Kappa/Lambda) was close to 9 and had risen to 45 at the time of presentation. Her immunofixation was positive for IgM and IgG kappa. Physical exam was remarkable for a BP of 170/90 mm hg and trace lower extremity edema. Her serological work up was negative except for a low C4 (8 mg/dl). A kidney biopsy was performed which revealed significant non-segmental glomerulosclerosis with mesangial expansion and some tubular atrophy. Immunofluorescence was positive for IgM and IgG kappa. Electron microscopy was non-diagnostic. As a result, a diagnosis of AL amyloidosis with his WM had been made and the patient was reclassified to stage IV. She was then treated with three cycles of Y90-Dotatate therapy (4.0 GBq). Four months later she started to complain of fatigue and new onset of gouty arthritis. A repeat serum creatinine was remarkable at 1.5 mg/dl. A kidney biopsy was performed which demonstrated morphological features compatible with a TMA. Since stopping plasma exchange, the patient has been followed up in the renal clinic, with focus on good blood pressure control but renal function appears to be declining slowly.

Discussion: TMA has been described in association with Y90-Dotatate therapy and this case demonstrates this rare complication which carries a poor renal prognosis.

FR-PO685

Thrombotic Microangiopathy Following Y90-Dotatate Treatment
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Introduction: Gastro-entero-pancreatic neuroendocrine tumours are rare; the expression of somatostatin receptors enables treatment with radiolabelled somatostatin analogues such as Yttrium labelled octreotide (Y90-dotate). Patients are routinely consented for non-specific renal toxicity prior to treatment.

Case Description: We present the case of a 49 year old woman with a well differentiated neuroendocrine tumour. She was treated with lanreotide (long acting somatostatin analogue) but follow up scans demonstrated progressive disease and she was then treated with three cycles of Y90-Dotatate therapy (4.0 GBq). Four months later she presented with shortness of breath with a haemoglobin of 69 g/L, platelet count of 132 x 10^9/L and creatinine of 145 umol/L. She had previously normal renal function. Over the following days the platelet count fell further to 55 x 10^9/L at the lowest and she was hypertensive. A blood film demonstrated fragments. Three stool cultures were negative for shigella toxin and e.coli. An ADAMST13 demonstrated >10% activity. She was commenced on plasma exchange, receiving five 1.5L cycles with fresh frozen plasma. A renal biopsy was performed which demonstrated morphological features compatible with a TMA. Since stopping plasma exchange, the patient has been followed up in the renal clinic, with focus on good blood pressure control but renal function appears to be declining slowly.

Discussion: TMA has been described in association with Y90-Dotatate therapy and this case demonstrates this rare complication which carries a poor renal prognosis.
kidney, lung, parotid, and breast cancers. Because of elevated PTH, hypercalcemia in IgG4-RD could be mistaken for primary hyperparathyroidism, which could lead to an unnecessary neck exploration as an attempt to identify a parathyroid adenoma. Hypercalcemia in the setting of elevated PTH and non-parathyroid malignancy should thus raise suspicion for this entity.

FR-PO687

Lung Cancer Before and Acute Myeloid Leukemia (AML) After the Diagnosis of IgG4-Related Disease

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Introduction: IgG4-related disease (IgG4-RD) is a multi-organ immune mediated fibro-inflammatory condition. The common diagnostic features of IgG4-RD are tumefactive lesions of involved organs, lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells and storiform fibrosis. Elevated serum concentrations of IgG4 are present in 70% of cases. Glucocorticoids are first line therapy. Recurrent and refractory cases are common and may benefit from steroid sparing maintenance therapy. This case illustrates the association of IgG4-RD with an increased risk of malignancy.

Case Description: A 53 -year old woman with history of epithelial neoplasm of the lung s/p wedge resection in 2016 presented 10 months later with dyspnea. Diagnostic work up was significant for an exudative pleural effusion without malignant cells and bilateral hydrothorax. Imaging showed lesions in the thyroid, right lung, right hepatic lobe and both kidneys. Bone marrow biopsy with flow cytometry was negative for malignancy. Oral cyclophosphamide plus prednisone taper did not help. PET scan showed hypermetabolic activity in the cervical and chest lymph nodes, thyroid, right lung, right hepatic lobe and both kidneys. Bone marrow biopsy with flow cytometry was negative for malignancy. Orally administered cyclophosphamide plus rituximab and prednisone were trialed without success. While on this regimen, she continued to deteriorate and was readmitted with fever and worsening shortness of breath. The plan was to exclude infection and consider a plasma cell inhibitor for refractory IgG4-RD. Repeat work up including bone marrow biopsy was notable for AML for which she is now being treated.

Discussion: Malignancy is associated with subsequent development of IgG4-RD. Some studies also suggest that prior IgG4-RD is associated with increased risk of developing malignancy. Our patient had cancer pre- and developed a different cancer post-IgG4-RD diagnosis. This case sheds light on the importance of cancer screening in IgG4-RD.

FR-PO688

Severe Hypophosphatemia in a Patient with a Relapsing Lymphoma

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Introduction: Hypophosphatemia in cancer patients is commonly ascribed to chemotherapy, renal wasting or malnutrition from anorexia and poor oral intake. We report a case of hypophosphatemia caused by rapid cancer cell proliferation.

Case Description: Hypophosphatemia was observed in a 61-year-old woman with history of marginal zone lymphoma diagnosed in 2017 presenting with fatigue and undetectable phosphate (phos) levels. Her symptoms started 5 days prior with reported decreased oral intake, but no other gastrointestinal symptoms. Blood work showed phos <1 mg/dl; iPTH level was 17. Her medications included Acyclovir 400mg daily and Allopurinol 100mg daily. Her phos further dropped to <0.3 mg/dl on admission. This severe hypophosphatemia required aggressive intravenous phos treatment and simultaneous oral phos supplementation thereafter. 24 hr urinary fraction excretion of phos was only 1.8%, ruling out renal loss of phos, including acyclovir induced phos wasting. Initial white blood count (WBC) was 41 B/L, phos was <0.3 mg/dl, compared to phos of 3.3 mg/dl with WBC of 0.7 B/L a week prior to this admission. She then developed hypophosphatemia, leakage of chemotherapy, after repeated computed tomography scan and flow cytometry confirmed lymphoma relapse. She received 4 days of Dexamethasone where the hypophosphatemia correlated with hyperproliferation of cancerous cells. Therefore, hypophosphatemia might be a surrogate biomarker of recurrence of rapidly proliferating hematological malignancy. Phos levels can serve as an excellent adjuvant, widely available, non-invasive and cost-effective biomarker.

Discussion: The hypophosphatemia correlated with hyperproliferation of cancerous cells in our patient. Hypophosphatemia might be a surrogate biomarker of recurrence of rapidly proliferating hematological malignancy. Phos levels can serve as an excellent adjuvant, widely available, non-invasive and cost-effective biomarker.

FR-PO689

Recurrent Laryngeal Cancer with Uncommon Kidney Metastasis

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Introduction: Laryngeal cancer is the fourteenth most common malignancy worldwide, where squamous cell carcinoma (SCC) is the most prominent subtype. Distant metastases occur in less than ten percent and involve the lung, liver, and bone but kidney metastases are seldomly reported. We report a rare case of recurrent laryngeal cancer with infiltrative kidney metastases.

Case Description: 64-year-old man with recurrent metastatic laryngeal cancer was evaluated for worsening kidney function. First diagnosed with laryngeal carcinoma in 2011, managed with radiation therapy, with recurrence in 2017 requiring laryngectomy. Follow-up scans showed new metastatic lung disease treated with left upper lobe resection and cisplatin chemotheraphy. Creatinine rose to 2.5 (0.7-1.3)mg/dl (baseline of 1.0mg/dl) over 3 months. He denied use of nonsteroidal anti-inflammatory drugs, and had not received intravenous contrast. He was recently started on ramipril for hypertension. Urinalysis showed no protein, with bland urine sediment. Renal ultrasound revealed enlarging kidneys, right 12.3cm (increased from 9.8cm 4 months prior) and left 11.9cm, without hydronephrosis. Positron emission tomography (PET) revealed several new areas of increased uptake by both kidneys, pulmonary nodules and diffuse hilar and retroperitoneal lymphadenopathy. Renal biopsy showed diffuse infiltrative moderately to focally well differentiated SCC replacing most of the cortical and medullary tissue. Four of 29 glomeruli were globally sclerosed, minimal changes in remaining glomeruli, with diffuse tubular atrophy and interstitial fibrosis. Immunofluorescence microscopy was not performed due to diffuse renal tissue infiltration. The patient’s creatinine remained elevated at 2.5mg/dl with plan by head and neck oncology for combination carboplatin, taxol, and cetuximab given the rapidly progressive nature of the disease.

Discussion: Kidney dysfunction in the setting of malignancy is often attributed to nephrotoxic chemotherapy as a potential cause. It is important to recognize that kidney infiltration is also possible where treatment can be aimed at addressing the underlying malignancy. The above case is unique in that it highlights the rare entity of laryngeal carcinoma metastasizing to the kidneys and should be considered in patients presenting with kidney dysfunction and large kidneys.

FR-PO690

Hyponatremia Secondary to CTLA-4 Inhibition-Induced Hypophysitis

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Introduction: Ipilimumab is a cytotoxic T-lymphocyte associated antigen 3 (CTLA-4) inhibitor which is used in therapy of multiple types of cancers, including malignant melanoma. One side effect of ipilimumab, reported in nearly 17% of patients receiving it in clinical trials, is autoimmune hypophysitis. We present a case of a patient with a history of melanoma treated with ipilimumab and hypophysitis, who presented with symptomatic hyponatremia after being treated with CTLA-4 inhibitor therapy.

Case Description: This is a 73 year old man with history of hypertension, DM, invasive melanoma of the right earlobe requiring wide excision and sentinel lymph node biopsy, ptT4a NO MO Stage IIIA. He completed 3 cycles of adjuvant ipilimumab and nivolumab. He presented to the hospital with dizziness and weakness. He was fully oriented on presentation, normotensive and euolemic on exam. The serum sodium was 119 meq/L and calculated serum osmolality was 246 mOsm/kg, BUN 3 mg/dl and SCR 0.4 mg/dl, with a normal uric acid. UA was unremarkable, with urine sodium 29 mmol/L and osmolality 134 mOsm/kg. Further workup showed low TSH, low morning cortisol, and brain MRI showed signs of hypophysitis, confirming the diagnosis of CTLA-4 inhibitor-induced hypophysitis. He was treated with thyroid hormone and adrenocorticoid
replacement, his hyponatremia improved. He was discharged from the hospital few days later with serum sodium 130 meq/L.

Discussion: In cases of hypophysitis, hyponatremia has been shown to occur due to secondary adrenal insufficiency with loss of ACTH-secreting corticotrophs. While the cause of hypophysitis is suspected as treatment-induced autoimmune lymphocytic hypophysitis, which results in anterior hypophysial necrosis, this can only be definitively determined on postmortem. The present case illustrates that the hypophysitis which occurs may be permanent, and requires lifelong adrenal hormone replacement. Physicians and nephrologists should be aware of the diagnosis of CTLA-4 inhibitor-induced hypophysitis and include it in the differential diagnosis of hyponatremia when there is relevant chemotherapy history.

FR-PO691
Intravascular Lymphoma of the Kidney and AKI
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Introduction: Intravascular lymphoma of the kidney (ILK) is an extremely rare condition characterized by malignant infiltration of small vessels.

Case Description: A 66-year-old woman presented with fatigue, altered mental status, and acute onset diarrhea. On exam, she was pale with abdominal tenderness. CBC showed leukocytosis, anemia, and thrombocytopenia. Basic chemistry showed creatinine: 2.1 mg/dL (baseline: 0.8), BUN:15 mg/dL, Na:122 mmol/L, HCO3:17 mmol/L, markedly elevated LFTs, and lactic acid levels. Urinalysis showed: hematuria, mild proteinuria, and granular casts. Multiple studies including cancer work-up from blood, CSF, and BAL was only notable for high ESR. Par CT scan revealed no lymphadenopathy. Bone marrow biopsy, flow cytometry, and genetic studies were also unremarkable. Despite the treatment with fluids and broad-spectrum antimicrobials, her clinical status continued to be poor with encephalopathy and acute kidney injury requiring dialysis.

A kidney biopsy revealed heavy neoplastic cell infiltration of the renal cortex (nests surrounding renal tubules with marked interstitial hemorrhage) and prominent small vessel infiltration. Immunohistochemical staining showed that all malignant cells expressed CD45, PAX5, CD20, BCL6, and CD79a, whereas staining for CD3, CD5, CD10, Tdt, CD4, AE1/AE3, CAM 5.2, and MART1 was negative. Diagnosis of ILK was made. The patient was emergently treated with Rituximab, Cyclophosphamide, Etoposide, and steroids.

Discussion: ILK is a devastating condition with a median survival of less than a year. Antemortem diagnosis is often missed due to the lack of detection of malignant cells in peripheral blood. Biopsy is mandatory whenever possible. Renal hemorrhage, and acute tubule-interstitial nephritis may be a presentation of this condition.

FR-PO693
Use of Anti-FGF-23 Monoclonal Antibody for the Treatment of Severe Hypophosphatemia Secondary to Tumor-Induced Osteomalacia
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Introduction: Hypophosphatemia in patients with cancer may be due to poor oral intake or more commonly from drug-induced tubulopathies leading to renal phosphate wasting. Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic cause of hypophosphatemia and hyperphosphaturia, as a result of constitutive release of fibroblast growth factor-23 (FGF-23). Here we present a case of primary hyperphosphatemia: hypophosphatemic Fanconi syndrome that improved with administration of burosumab, a monoclonal IgG1 antibody against FGF-23.

Case Description: A 68-year-old man with history of metastatic prostate cancer s/p prostatectomy, presented with several months of generalized weakness, worsening fatigue, muscle cramps and paresthesia. A whole-body bone scan showed extensive osseous metastatic disease. Imaging revealed serum phosphorus levels of 0.6 mg/dl and inappropriately elevated random urinary phosphate (125 mg/dl; FFP04 70%), indicative of renal phosphate wasting. His renal function was normal (serum creatinine 0.9 mg/dL) and ionized calcium was 1.07 mmol/L (normal 1.15-1.32mmol/L). Further work up revealed 25(OH)D-Vitamin D level of 40 ng/mL and 1,25 (OH)2Vitamin D level of 28 pg/mL. His serum FGF-23 levels were remarkably elevated (812 RU/mL, normal <180 RU/mL). Patient was diagnosed with oncogenic osteomalacia and was initially treated with oral phosphate and active vitamin D supplementation, which was unsuccessful due to the patient’s refractory osteomalacia.

Burosumab is a human IgG1 monoclonal antibody directed against FGF-23 that has been approved for X-linked hypophosphatemia. By decreasing levels of FGF-23, burosumab increases both renal reabsorption and gastrointestinal absorption of phosphorus. Although burosumab is not yet approved for the treatment of hypophosphatemia in oncogenic osteomalacia, our case reveals another application for burosumab in this setting, especially in patients with refractory and symptomatic hypophosphatemia.

FR-PO609
Early-Stage IgG4-Related Tubulointerstitial Nephritis Incidentally Detected with a Tumor Lesion of the Ureteropelvic Junction
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Introduction: Histological examination of IgG4-related kidney disease (IgG4-RKD) is typically performed when kidney function decreases or when multiple low-density lesions are found in enhanced computed tomography (CT) images; thus, advanced-phase rather than early-phase IgG4-TIN is often detected. Here, we report a case of a very early-stage IgG4-related tubulointerstitial nephritis (TIN) incidentally detected with imaging of the ureteropelvic junction (UPJ).

Case Description: A 72-year-old Japanese man was admitted to our hospital for progressive renal dysfunction. He had been followed-up for 18 years after surgical resection of a bladder tumor. Six months prior to presenting at our hospital, periodic CT showed a mass lesion on his right UPJ. He was clinically diagnosed with right ureter cancer and received neoadjuvant therapy followed by a right nephroureterectomy. Histology revealed IgG4-positive cell (IgG4/PC) infiltration, obliterator phlebitis, and storiform fibrosis in the removed mass, leading to the diagnosis of IgG4-RKD. Notably, IgG4 PCs were suggestive of mature tertiary lymphoid tissue (TLT). IgG4+ PCs surrounded the TLT. Because renal function gradually worsened, the patient was admitted. Although neither extra-renal organ involvement nor an imaging abnormality of the left kidney was

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
noted, glucocorticoids were initiated and prevented renal deterioration, suggesting that IgG4-TIN was the cause of the left kidney.

**Discussion:** IgG4-TIN was incidentally detected with involvement of the UPJ, regardless of a lack of abnormalities in images of the kidney. IgG4-PC was distributed beneath the kidney capsule and around arteries and veins accompanying TLT. This case suggests that IgG4-TIN develops from common sites of TLT with TLT formation prior to the appearance of imaging abnormalities.

**FR-PO695**

**A Case of Concurrent Multiple Myeloma and LECT2 Amyloidosis**

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**Introduction:** Multiple myeloma is a cancer of plasma cells that can lead to kidney problems, and lysosome chemostatic factor 2 amyloidosis (ALCFT2) is one of the most recently described forms of amyloid with unknown etiology, strong ethnic predominance and manifests as slow progressive renal failure.

**Case Description:** 44-year-old Hispanic female with no prior past medical history, presented to the ER with headaches, nausea, fatigue and RLE pruritic rash x2 months and lab values concerning for acute kidney failure. Symptoms worsened 2 weeks prior to presentation with persistent headaches, emesis, hypoprosopnia and dyspnea on exertion. Physical exam with mild diffuse abdominal tenderness and dry RLE rash. Initial labs with BUN 58 mg/dl & Cr 5.40 mg/dl (1.1 mg/dl 5 months prior). Urine studies revealed UA with 1+ protein, protein-Cr ratio 4.52 g. CBC remarkable for anemia and thrombocytopenia. Abdominal ultrasound unremarkable except moderate hepatomegaly. Work-up remarkable for positive ANA, SPEP with kappa light chain monoclonal peak in gamma region and abnormal renal & urose K/L ratio. Renal biopsy showed amyloidosis with positive Congo red stain for amyloid deposits suspicious for LECT2 Amyloid and focal atypical kappa light chain dominant casts; 30% IFTA. Skeletal survey with multiple skull lytic lesions. Bone marrow biopsy and staining consistent with IgG Kappa multiple myeloma. Patient started Velcade/Dex for IgG kappa multiple myeloma. Discharged with outpatient follow up.

**Discussion:** Renal LECT2 amyloidosis is an uncommon form of amyloidosis of unknown etiology that causes slowly progressive renal failure with affinity to kidney and liver and more commonly in African Americans. No available treatment except renal transplantation once end stage kidney disease is established. There are different types of myeloma, classified by the type of immunoglobulin produced by the abnormal plasma cells. IgG kappa type is the most common abnormal M protein. There has been overlap between multiple myeloma and amyloidosis, we incidentally diagnosed with multiple myeloma and AL amyloidosis, which is not the case in our patient with multiple myeloma and LECT2 amyloid. Thus, thorough categorization of patients presenting with renal amyloidosis should be encouraged to broaden the understanding of these subtypes and afford appropriate therapy and accurate prognosis to avoid unnecessary treatment.

**FR-PO696**

**Cinacalcet-Induced Permanent Hypocalcemia in a Patient with Primary Hyperparathyroidism and Normal Kidney Function**

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**Introduction:** Cinacalcet (C) increases sensitivity of calcium (Ca) sensing receptor to extracellular Ca and suppresses parathyroid hormone (PTH) secretion. C is used in patients with primary hyperparathyroidism (PHPT) who are not surgical candidates. We report a case of irreversible hypocalcemia after 6 months of C administration in a patient with PHPT.

**Case Description:** A 58-year-old Caucasian male with PHPT, recurrent nephrolithiasis, osteoporosis in femoral neck and normal kidney function (eGFR-90ml/min/1.73m²) underwent surgical resection of 2 parathyroid glands. Postoperatively, PTH remained elevated (PTH 227 pg/ml, normal level [10-60]) in association with albumin-corrected Ca (aCa) 10.40 mg/dL [8.2-10.2], ionized Ca (iCa) 1.44 mmol/L [1.15-1.35] and hypercalciuria (24-hr urinary Ca 427mg). Due to persistent PTH and refusal of further surgery Ca 30 mg daily was initiated. C resulted in resolution of hypercalcemia, normalization of Pi and PTH in 139 days (19 weeks). However, 6 months later the patient presented to the hospital with newly developed widespread paresthesia and hypocalcemia (aCa 7.2mg/dL, iCa 0.96 mmol/L), hyperphosphatemia (4.65mg/dL) and suppressed PTH (7pg/dL). C was discontinued and Ca supplements were initiated leading to normalization of iCa (1.17 mmol/L) and PTH (33pg/ml). However, the patient continued to have hypercalcemia and required continuous oral Ca supplementation to avoid paresthesia and maintain eucalcemia even 12 months later. Repeat DXA showed improvement in bone mineral density.

**Discussion:** Reversible hypocalcemia due to C was mainly reported in patients with advanced CKD and it usually responds to a reduction or discontinuation of C. The present case has several novel features. Firstly, C-induced hypocalcemia developed in a patient with normal kidney function. Secondly, because PTH has normalized after temporal C exposure, we suggest that C can induce apoptosis of PTH-producing parathyroid cells. Lastly, we suspect the development of a defect resembling renal PTH resistance based on the presence of persistent hypercalcemia despite normal PTH levels with resultant hypocalcemia requiring continuous Ca supplementation. Further clinical investigations are needed to understand whether in some patients cinacalcet can cause or unmask renal PTH resistance.

**FR-PO697**

**Calcium Maldistribution: A Case of Calcium Nephrolithiasis, Aortic Calcification, and Osteopenia**

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**Introduction:** Epidemiologic studies show that patients with nephrolithiasis have a high prevalence of aortic calcification and bone demineralization compared to those without nephrolithiasis. We present a case of calcium nephrolithiasis with concomitant aortic calcification and osteopenia.

**Case Description:** A 62-year-old post-menopausal woman was seen for evaluation of new calcium stones. She was a chronic smoker and had a 10-pack/year smoking history. Work up revealed serum K 4.8 mg/mL, CO2 26 mg/dl, creatinine 0.8 mg/dL, calcium 9.6 mg/dL, phosphorous 3.9 mg/dL, intact parathyroid hormone 31 pg/mL, 25-hydroxy vitamin D 42 ng/mL and urinary pH ≥6.2 on all urinalyses (n=4), suggesting possible incomplete renal tubular acidosis. Stone analysis showed 100% calcium phosphate. Urine supersaturation showed marked hypocitraturia (235 mg/day) without hypercalcuria (153 mg/day). On computed tomography, she had numerous right kidney stones and significant abdominal aortic calcification [figure]. Dietary history revealed low calcium intake. Dual-energy x-ray absorptiometry (DEXA) was performed and showed osteopenia in the lumbar spine (T score -2.3, Z-score -0.7) and left femoral neck (T score -1.4, Z-score -0.2). As part of Fracture Risk Assessment Tool, her 10-year fracture risk for a major osteoporotic fracture was 8.4%. Given above findings, we recommended smoking cessation, increasing dietary intake of calcium, fruits and vegetables, and to continue monitoring bone density.

**Discussion:** This is a case of calcium maldistribution, in which there was excesses deposition of calcium in the kidney and aorta, and bone demineralization. The presence of nephrolithiasis and arterial calcification prompted us to perform a DEXA scan, which led to a more comprehensive treatment plan. More importantly, the case highlights an important need to better understand the pathophysiologic underlying the maldistribution and excessive deposition of calcium.

**FR-PO698**

**Case Study: A Report on the Efficacy of Hydroxychloroquine in Treating Hypercalcemia**

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**Introduction:** Sarcoidosis is a rare autoimmune disease resulting in the formation of non-cacating granulomas. Hypercalcemia occurs in 10 to 30 percent of sarcoidosis cases due to 1-alpha-hydroxylation over expression in granulomas. This enzyme increases 1,25-dihydroxy vitamin D levels, by conversion of 25-OH to 1,25-OH vitamin D. Hypercalcemia may be seen in any granulomatous disease. If hypercalcemia is uncontrolled it may lead to complications including necrobiocinosis, renal lithiasis, and irreversible renal failure. Glucocorticoids are the mainstay of treatment of sarcoidosis, including the complication of hypercalcemia. Antimalarial agents such as chloroquine and hydroxychloroquine are known to impair production of 1,25-OH Vitamin D by blocking 1-alpha-hydroxylation activity. We report a case of a 56-year old caucasian female with sarcoidosis complicated by hypercalcemia successfully treated with hydroxychloroquine.

**Case Description:** A 56-year-old caucasian female with history of diabetes mellitus, hypothyroidism, and hypertension was referred for management of recent onset of worsening hypercalcemia. Her electrolytes were notable for serum calcium of 12.4 mg/dL (baseline 9.1-9.7), ionized calcium 1.49 mmol/L (NR 1.11-1.30), and serum creatinine of 1.7 mg/dl (baseline 0.9-1.1). Her calcium level remained elevated in spite of stopping daily Vitamin D3 supplementation and treatment with Denosumab injections. Differential diagnosis; included lymphoma and sarcoidosis: sarcoidosis was confirmed by tracheobronchial lymph node biopsy. Since pulmonary function was normal, there was a desire to avoid systemic steroid treatment. The patient was started on 200 mg hydroxychloroquine twice a day to control her hypercalcemia without the use of steroids. Within 2 months after initiation of hydroxychloroquine, calcium normalized and renal function returned to baseline. Hydroxychloroquine was then decreased to once a day and calcium remained normal over a period of greater than 2 years.
Discussion: This case uses hydroxycloroquine as a steroid sparing alternative in the treatment of hypercalcemia. This case demonstrates the efficacy of hydroxycloroquine in the treatment of hypercalcemia, by directly inhibiting the 1-alpha-hydroxylase activity. Based on this mechanism of action it should be considered as a treatment strategy in any disease resulting in 1-alpha hydroxylase overproduction.

FR-PO699

Overcorrection of Severe Hyponatremia in a Chronic Alcoholism Patient: A Case Report of Osmotic Demyelination Syndrome
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Introduction: Patient with chronic alcoholism can have chronic hyponatremia from multiple mechanisms. Both chronic alcoholism and severe hyponatremia predispose patient to the osmotic demyelination syndrome. Rapid correction of serum sodium can lead to severe neurological damage.

Case Description: 45-year-old man with chronic alcoholism presented with confusion, generalized weakness, nausea, and vomiting for 3 days. He had history of heavy alcohol drinking for 3 years. Initial labs showed serum sodium level of 99 mmol/L. He was given intravenous 3% NaCl at 50 ml/hr to correct hyponatremia. Three hours later lab result showed a sodium level of 113 mmol/L. The patient was more lethargic and was found to have ataxia. CT head showed diffuse atrophy but no acute abnormality. FLAIR MRI showed hyperintensity of supratentorial white matter, likely due to mild chronic microangiopathy. He was given intravenous 5%Dextrose at 100 ml/hr for overcorrection of hyponatremia. Later in hospital course he was more alert. His sodium level later increased to 127 mmol/L over the next 4 days. Patient was discharged to the nursing facility. He presented to hospital again with dysphagia, generalized weakness and spastic quadraparesis. His sodium level is 134 mmol/L. MRI showed abnormal restricted diffusion in the pons and bilateral thalamus. There was subtle abnormal enhancement in the abnormal area in the pons which suggested osmotic demyelination syndrome.

Discussion: Patients who are high risk for osmotic demyelination syndrome should raise awareness when correcting hyponatremia. Rapid sodium correction in this group of patients may lead to deterioration of neurological status due to neuronal shrinkage. The rate of sodium correction should not exceed 6-8 mEq/L in 24 hours period. Clinical manifestations of osmotic demyelination syndrome includes lethargy, dysarthria, dysphagia and seizure. Patients usually presented 2-6 days after correction. Our patient developed symptoms during the next 8 days. Even though it was later than the average onset, the risk factors and his symptoms are typical. MRI may not become positive until four weeks after onset. If the initial MRI is negative, it does not exclude osmotic demyelination syndrome.

FR-PO700

Peculiar Case of Life Threatening Hypokalemia
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Introduction: Severe hypokalemia causes muscle weakness and cardiac arrhythmias. We present a case of life threatening hypokalemia due to RTA.

Case Description: 32-year-old woman presented with subacute weakness and muscle pain. She denied personal or family history of nephrolithiasis, autoimmune, malignancy, deafness, growth retardation, fracture, anorexia, diarrea, medication, illicit drug or heavy metal exposure. EKG showed QTC 756 ms and U waves. Labs revealed creatinine 0.75 mg/dL, K+ 1.7 mEq/L, Mg2+ 2.9 mg/dL, HCO3- 13 mEq/L, pH 7.28, urine pH 7.5, trace urine albumin, urine anion gap 7 mmol/L and urine osmolal gap 39 mOsm/kg. 24 hour urine showed K+ 133 mEq, calcium 836 mg, phosphate 1150 mg, protein 690 mg and citrate <60 mg. Her imaging was notable for nephrocalcinosis. Calciumid was 6.5 mg/ml and peak CPK was 5145 U/L. PTH decreased from 205.8 pg/mL (calcium 7.5 mg/dL) to 42.9 pg/mL (calcium 8.9 mg/dL). Chest imaging without hilar adenopathy. SS-A and SS-B antibodies were negative. Genetics screen was obtained and pending. After 880 mcg of K, her plasma K reached > 4. K citrate was started at 120 mcg daily and her acidosis resolved after 3 days. She was discharged with 80 mcg of K Citrate daily with stable chemistries.

Discussion: Distal RTA (dRTA) is characterized by inability to secrete H+ in the distal tubule. It is associated with hypokalemia if non-voltage mediated. It can lead to hypercalcuria, hyperphosphaturia, hypocitraturia and consequent nephrocalcinosis. dRTA yields alkaline urine but urinary pH is maintained >6.5 because bicarbonate is not significantly lost. However, this patient had urinary pH 7.5 and tubular proteinuria suggesting proximal tubule injury. The etiology of the patient’s proximal tubule injury is unclear, but the hypovitaminosis D is glaring. Overall, this case represents a peculiar presentation of RTA, with likely long-standing dRTA and sub-clinical nephrocalcinosis coupled with proximal injury resulting in life threatening hypokalemia. Clinicians should consider RTA as the cause of hypokalemia.

Nephrocalcinosis

FR-PO701

Hyponatremia due to Primary Adrenal Insufficiency Treated by Cortisol Replacement
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Introduction: Hyponatremia complicating malignancy is most commonly seen due to the syndrome of inappropriate antidiuretic hormone secretion. We present a unique case in which metastatic non-small cell lung cancer (NSCLC) led to primary adrenal insufficiency and hyponatremia.

Case Description: A 66-yr-old man was admitted for symptomatic hyponatremia. He was evaluated at an outside facility for a month history of blood-streaked sputum and weight loss. He was hypotensive with initial serum sodium (SNa) 125 mEq/L, potassium 5.3 mEq/L, bicarbonate 22 mEq/L, chloride 86 mEq/L and Creatinine 0.5 mg/dL. After receiving 1 L of normal saline, he became confused with an associated fall in SNa 116 mEq/L prompting transfer to our institution. On arrival, he was lethargic and disoriented. His vital signs were normal. Physical examination revealed a disoriented man with digital clubbing. Laboratory studies revealed a serum osmolality 235 mOsm/kg. urine osmolality (UOsm) 271 mOsm/kg and urine sodium 74 mmol/L. CT of head showed superior cerebellar mass with vasogenic edema. Further imaging revealed right upper lobe lung mass and bilateral adrenal nodules. He was treated with dexamethasone 6 mg every 6 hours for vasogenic edema and suspicion for adrenal insufficiency. Repeat laboratory studies showed improvement of SNa to 123 mEq/L and decrease in UOsm to 129 mOsm/kg. The SNa decreased to 120 mEq/L while the UOsm increased to 382 mOsm/kg after tapering of dex. A cosyntropin stimulation test was consistent with primary adrenal insufficiency. Hydrocortisone therapy at replacement doses resulted in normalization of SNa.

Discussion: Adrenal glands are commonly involved in metastatic cancer but primary adrenal insufficiency uncommonly ensues, unless majority of the adrenal cortex is destroyed. Although it has been reported with advanced breast cancer and colon carcinoma, to our knowledge only a handful of cases of adrenal insufficiency leading to hyponatremia due to NSCLC have been reported. The pathogenesis is related to loss of negative feedback of cortisol on vasopressin which acts as a secretagogue for ACTH. The rate of rise of sodium is ideally 6-8 mcg/Q2 hours, but needs cautious monitoring since erratic changes may be seen (observed in our case). Dex is the initial corticosteroid of choice as it doesn’t interfere with cortisol assay during cosyntropin stimulation test.

FR-PO702

Pseudohyperphosphatemia in Multiple Myeloma
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Introduction: Hyperphosphatemia commonly occurs in renal failure or hyperparathyroidism. If severe it can cause severe hypocalcemia leading to cardiac or neurologic symptoms. Pseudohyperphosphatemia is rarely seen and it is due to interference by other serum elements in the phosphorous assay.

Case Description: We present here a 58 year old woman with refractory IgG kappa myeloma. SCr was 0.6 mg/dL, eGFR ~90 ml/min, Pi 34 mg/dL, iCa 1.06 mmole/L, PTH 32 pg/mL, uric acid 6.2 mg/dL, LDH 212 U/L, IgG 7888 mg/dL, total protein 13.2 g/dL, serum globulin 10.3 g/dL. In the setting of normal renal function, normal PTH, no laboratory evidence of tumor lysis syndrome and discrepancy between serum phosphorus and calcium levels we suspected this was a case of pseudohyperphosphatemia.

Discussion: It has been stated that paraproteins interfere with spectrophotometric measurement of phosphomolybdate which is the actually measured adduct in the routine laboratory phosphorous (P) assay. The inherent flaw in the design of this test is its dependence on light penetration into the sample, thus any condition that increases the turbidity of the sample would falsely elevate the reading. Also, the abnormal serum proteins may themselves bind phosphate which may spuriously increase the total serum
phosphate, but not the biologically active form of phosphate. The level of serum phosphate returns to normal when it is measured after deproteinization with sulfosalicylic acid or trichloroacetic acid. Instead of precipitating the proteins we performed a mixing study using normal serum with a Pi of 2.3x10^{-7} mole2/L2. When the ionized calcium is 1 mmole/L the free serum Pi level has to be 0.23 mmol/L. Using an activity coefficient of Pi of 0.23, the patient’s activity was decreased by about 1 mmol/L or ~ 3mg/dL. It is interesting that a falsely elevated Pi level does not occur in every patient with paraproteinemia thus it is likely that the type of paraprotein produced by the clone may have specific chemical attributes that leads to the spurious measurement.

FR-PO703
A Case of Spurious Hyponatremia in Hyperleukocytosis
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Introduction: Hyponatremia is commonly seen in the oncology population. Here we report a case of discordance between serum sodium and whole blood sodium measurements in the setting of severe leukocytosis.

Case Description: A 72-year-old male with blastoid variant mantle cell lymphoma presented with fatigue and nausea. He appeared hypovolemic on exam. Laboratory evaluation revealed a WBC count of 476 K/uL. Serum sodium (SNa) was 117 mmol/L, potassium > 10 mmol/L, BUN 27 mg/dL and creatinine 1.36 mg/dL. Whole blood potassium was 3.73 mmol/L. Glucose was 96 mg/dL and total protein was 5.2 g/dL. Urine chemistry showed sodium < 10 mmol/L, chloride < 15 mmol/L, potassium 66.0 mmol/L, osmolality 722 mosm/kg. SNa initially improved with normal saline hydration to 121, but did not improve further over the next 24 hours. No alternative causes for hyponatremia were identified. SNa at our institution is measured by the direct ion-specific electrode method which makes pseudohyponatremia from lipids or proteins unlikely. Whole blood sodium (WBNa) checked on day two was 131.7 mmol/L while concurrent SNa remained did not improve further over the next 24 hours. No alternative causes for hyponatremia could be identified. SNa at our institution is measured by the direct ion-specific electrode method which makes pseudohyponatremia from lipids or proteins unlikely.

FR-PO705
Linezolid-Induced SIADH: A Rare Cause of Hyponatremia
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Introduction: Linezolid is a oxazolidinone antibiotic against gram-positive organisms that inhibits bacterial protein synthesis. Thrombocytopenia is common, but hyponatremia is rare after linezolid use.

Case Description: An 89-year old woman with MRSA wound infection after lumbar laminectomy required prolonged linezolid therapy. She was admitted to the hospital for seizures and was found to be profoundly hyponatremic with a hemoglobin level of 6.4 g/dL and a sodium level of 127meq/l on admission over a 3-week period. Patient was hypotensive with blood pressure of 90/50 mm Hg, but her sodium levels failed to improve with isotonic fluids. Labs showed serum sodium of 122meq/l, serum osmolality 235mOsm/kg, urine osmolality 389mOsm/kg, urine sodium 125mmol/l and serum uric acid level of 2.6 mg/dL. Rest of the work-up including serum cortisol and TSH were normal. All labs were suggestive of SIADH and as further investigations towards finding the underlying etiology did not reveal any other cause, linezolid was considered to be the culprit. Linezolid was stopped, and patient was started on fluid restriction and salt tablets, her sodium improved from 122meq/l to 130meq/l over 4 days. Anemia was attributed to myelosuppression caused by linezolid, which is one of its serious side-effects.

Discussion: This case was given 6 points using Naranjo adverse drug reaction (ADR) probability score indicating an association between hyponatremia and Linezolid use. Linezolid has previously been reported to cause hyponatremia with a frequency of 18% in a retrospective cohort study. Exact mechanism remains unknown but could be secondary to ADH release due to the medication or from underlying inflammation. There are 3 other cases published to date reporting hyponatremia from linezolid use. Interestingly, most of these reports have been on Asian population, possibly hinting towards a higher incidence in this group. However, more research is needed to explore this hypothesis. It is important to increase awareness of this side-effect as new drug-resistant bacteria emerge and Linezolid increase in use. Close monitoring of serum sodium is important in patients on prolonged treatment with Linezolid, since it also lowers the seizure threshold. The use of Linezolid can lead to neurologic side effects of hyponatremia, ranging from mild effects such as tremor, incoordination to severe such as seizures.

FR-PO706
Guess the “Glucose”
Nishanth Giria Kumar, David Sheikh-Hamad. Baylor College of Medicine, Houston, TX.

Introduction: Hyponatremia is the most common electrolyte abnormality encountered in clinical practice. Proper interpretation of the various laboratory tests helps differentiate the various types of hyponatremia. Treatment varies with the nature of causes - acute or chronic, severity and symptoms.

Case Description: 39 year old man who recently immigrated from Guatemala 1 week ago was admitted for seizures witnessed by his family. Review of systems was positive for urinary incontinence and tongue biting. Vital signs showed Temperature 97.3F, BP 126/97, HR 112, RR 16. Physical exam was normal for Tachycardia, dry mucous membranes and decreased skin turgor. Laboratory data was significant for Sodium of 102, Glucose > 4000, BUN 50 and Serum Osmolality 350. A diagnosis of Hypertonic Hyponatremia due to Hyperglycemia was made. Patient was treated in the ICU for 2 days with Insulin and potassium/magnesium/water. During hospitalization, patient was started on fluid restriction and salt tablets, her sodium improved from 122meq/l to 130meq/l over 4 days. Anemia was attributed to myelosuppression caused by linezolid, which is one of its serious side-effects.

Discussion: This case was given 6 points using Naranjo adverse drug reaction (ADR) probability score indicating an association between hyponatremia and Linezolid use. Linezolid has previously been reported to cause hyponatremia with a frequency of 18% in a retrospective cohort study. Exact mechanism remains unknown but could be secondary to ADH release due to the medication or from underlying inflammation. There are 3 other cases published to date reporting hyponatremia from linezolid use. Interestingly, most of these reports have been on Asian population, possibly hinting towards a higher incidence in this group. However, more research is needed to explore this hypothesis. It is important to increase awareness of this side-effect as new drug-resistant bacteria emerge and Linezolid increase in use. Close monitoring of serum sodium is important in patients on prolonged treatment with Linezolid, since it also lowers the seizure threshold. The use of Linezolid can lead to neurologic side effects of hyponatremia, ranging from mild effects such as tremor, incoordination to severe such as seizures.
Inheritance with additional gene variants may be required to trigger clinically significant disease, and screening will likely explain a significant number of mildly affected cases. Oligogenic inheritance with two known ciliopathy genes segregating with the mutation. ALG8 (PKD3) Spanish family, significantly affected individuals had splicing variants to one or both known genes. ALG8 mutations have been described to cause ADPLD in 5 families. Nine families were studied for PKD related genes and no mutation was found. ADPKD-GANAB affected mother had no liver cysts on CT scan. The father has been diagnosed with PKD related genes and no mutation was found.

**FR-PO708**

Expanding the Variability of the ADPKD-GANAB Clinical Phenotype: A New Family of Italian Ancestry

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**Introduction:** Causative GANAB mutations have been described reported in only 12 families, 9 diagnosed with late-onset mild ADPKD and 3 with ADPLD. We describe a new family with mild, late-onset ADPKD due to p. R839W GANAB mutation, previously reported in an ADPLD patient requiring liver transplantation.

**Case Description:** Diagnosis of ADPKD was made in a 45-year old man during pre-surgical screening for umbilical and inguinal hernia repair. Hematuria, hypertension and aortic root dilatation were documented. At age 52, he experienced acute flank pain. Abdomen CT scan showed bilateral renal cysts (TKV 565 cc), nephrolithiasis, normalized liver with multiple cysts, and colonic diverticula; renal function was normal. PKD1-PKD2 NGS and MLPA analyses were negative; analysis of additional PKD related genes showed a heterozygous p. R839W GANAB mutation. Familial study revealed p. R839W GANAB mutation in the mother. The elderly parents had normal renal function, normalized kidneys with multiple bilateral kidney cysts (mainly parapelvic in the father). The ADPKD-GANAB affected mother had no liver cysts on CT scan. The father has been studied for PKD related genes and no mutation was found.

**Discussion:** Since ADPKD-GANAB is a rare condition, we need further families to better characterize the phenotypic features of this new cystic disease. In our family, the p. R839W GANAB mutation, previously associated with severe ADPLD, was associated with a mild ADPKD, although showing several renal and extrarenal manifestations. The overlapping cystic phenotype and the plethora of renal and extrarenal manifestations are in agreement with the hypothesis that in GANAB disease, hepatic and renal cysto-genesis is the result of the common defective polycystin-1 pathway.

**FR-PO707**

Characterization of ADPKD-Like Patients Monoallelic for ALG8 Mutations

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**Background:** Among our single-center ADPKD cohort (186 patients), we selected monoallelic GANAB and DNAJB11 mutations in 137 gene panel of described ADPKD, ARPKD, ADPLD, ADPKD and ciliopathy genes, plus candidate loci. Identified families were characterized by segregation, imaging and analysis of the clinical phenotype.

**Methods:** Here we screened 723 ADPKD-like patients without mutations in the known ADPKD genes employing a 137 gene panel of described ADPKD, ARPKD, ADPLD, PPKD and ciliopathy genes, plus candidate loci. Identified families were characterized by segregation, imaging and analysis of the clinical phenotype.

**Results:** One gene, ALG8, stood out as the result of the common defective polycystin pathway. In agreement with the hypothesis that in GANAB disease, hepatic and renal cysto-genesis is the result of the common defective polycystin-1 pathway.

**Discussion:** Since ADPKD-GANAB is a rare condition, we need further families to better characterize the phenotypic features of this new cystic disease. In our family, the p. R839W GANAB mutation, previously associated with severe ADPLD, was associated with a mild ADPKD, although showing several renal and extrarenal manifestations. The overlapping cystic phenotype and the plethora of renal and extrarenal manifestations are in agreement with the hypothesis that in GANAB disease, hepatic and renal cysto-genesis is the result of the common defective polycystin-1 pathway.

**FR-PO709**

ADPKD: Rare PKD1 and PKD2 Complex Genotypes May Explain Intrafamilial Phenotypic Variability

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**Background:** Discordant affected relative-pairs are seen in nearly 10% of ADPKD families. Complex genotypes may result in renal disease variability beyond that predicted by the sole effect of a PKD mutant allele, leading to the discovery of biallelic or digenic disease. Here we illustrate such complexity in 6 ADPKD pedigrees showing a marked intrafamilial phenotypic variability.

**Methods:** Among our single-center ADPKD cohort (186 patients), we selected pedigrees (P) in which marked phenotypic variability was investigated by NGS analysis of PKD1 and PKD2 genes.

**Results:** In P1 and P2, the index cases (IC), presented with very early onset (vEO) disease. In P1, with neonatal onset, the ADPKD affected father transmitted a PKD1 truncating (T) mutation, whereas the mother, without cystic phenotype, transmitted a PKD1 hypomorphic mutation. In P2, the ADPKD-PKD2 mother’s pregnancy was complicated by Potter sequence. Parent’s PKD1 gene analysis was negative. Two non truncating (NT) mutations in PKD1/PKD2 genes were detected in the healthy father. Therefore, a complex PKD inheritance was suspected in the fetus. P3: early onset (EO) ADPKD in two monozygous twins was underpinned by a PKD1 NT mutation on their inherited paternal allele and by a de-novo PKD1 T mutation. In P4 a digenic ADPKD was diagnosed in the two most severely affected siblings: a PKD2 T mutation and a PKD1 NT mutation were detected. Elderly parents in P5 and P6 had few kidney cysts and preserved eGFR, whereas IC showed moderate/severe CKD due to ADPKD. In P5 the IC carried a homozygous PKD1 NT mutation; in P6 the IC harbored 2 PKD1 mutations (in trans). We screened for PKD related genes and no mutation was found.

**Discussion:** Our study illustrates the genetic complexity in an otherwise “simple” Mendelian disorder, providing insights into the genetic basis of ADPKD intrafamilial disease variability.

**Funding:** Government Support - Non-U.S.
FR-PO712
Clinical Whole-Genome Sequencing Enables Diagnostic Certainty in Autosomal Dominant Polycystic Kidney Disease
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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common inherited renal cystic disease. It is genetically heterogeneous: 72-75% of ADPKD cases are related to mutations in the PKD1, 15-18% to PKD2 and the remaining 7-10% affect�ally unresolved (GUR). Both genes are characterized by high level of allelic heterogeneity. It is rare to identify the same germ-line mutation in different families, since mutations are “private”. The age at disease onset, the severity, and the clinical outcome contribute to the intra and interfamily variability. Aim of the study was to evaluate the clinical characteristics of PKD2 gene-linked families with the same germ-line mutation.

Methods: Patients (pts) with PKD2 were enrolled and followed prospectively. Diagnosis of ADPKD was made upon the revised Ravine’s criteria. Complete clinical details were recorded, including family history and pedigree. We performed WES for sequencing analysis to identify mutations. The eGFR was calculated CKD-EPI equation. The progression of CKD was determined by the change in eGFR per year. Data were shown as mean ± sd or median (min-max).

Results: Twenty-five pts (14male) were included in the analysis, belonging to 10 PKD2 gene-linked families with the same germ-line nonsense mutation (c.2533C>T, p.Arg845Ter). 7/10 families had their origin from the same geographical area. The other three families originated from an area 100 km away. Four of them reached ESRD (50%) affecting different families. In 3/4 families at least one relative of ESRD pts did not required RRT at the same age. Moreover, in family 2 relatives were not even CKD. Nine patients (414 yrs) are still not affected by CKD; 6/9 pts have at least one ESRD relative. Eleven patients (61.9 yrs) have CKD stage 2-3 and a progression rate estimated of 2.3 ± 0.8/year (0.7-3.1). One of them is a fast grower and he is in treatment with Torvaptan.

Conclusions: We found the same PKD2 germline mutation in 10 families maybe due to a founder effect in our region. High intra-interfamily variability in ADPKD pedigrees was observed, despite the same germline mutation. This could be explained by other clinical or genetic factors (environmental, SNPs, modifiers genes, etc) that may affect disease severity.

FR-PO711
Diagnostic Utility of Whole-Exome Sequencing in Autosomal Dominant Polycystic Kidney Disease
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Background: Exome sequencing (WES) is increasingly being used to screen for certain genetic conditions, including some genetic forms of kidney disease. However, there are challenges in sequencing adult polycystic kidney disease (ADPKD) due to PKD1 having 6 pseudogenes. We examined the WES accuracy in individuals with clinical diagnosis of ADPKD, as well as in an unselected cohort.

Methods: We examined data from 31,391 subjects in the Geisinger-MyCode population as part of the Regenser-DiscovEHR collaboration. WES was performed using a modified version of the IDT xGen Exome Research Panel. Average depth of coverage for PKD1 and PKD2 were 27X and 33X, respectively. We identified subjects with PKD1 or PKD2 putative loss-of-function (pLoF) mutations (stop-gain, frameshift, canonical splice) as well as large deletions encompassing PKD1 or PKD2 detected in WES-based CNV analysis. ADPKD phenotyping was done by identification of individuals who had a diagnosis code for polycystic kidney disease, followed by confirmation by chart review.

Results: Out of the 31,391 subjects, we identified 22 (0.07%) patients with clinical diagnosis of ADPKD using a phenotype-first approach, and 26 (0.08%) pLoF mutation carriers using a genotype-first approach. With a phenotype-first approach, we found pLoF mutations in 21/22 (95.5%) patients with clinical diagnosis of ADPKD (13 PKD1 and 8 PKD2 carriers). Of the 26 pLoF carriers, there were 18 PKD1 carriers and 8 PKD2 carriers. All 8 PKD2 carriers had clinical diagnosis of ADPKD by chart review. Of the 18 PKD1 carriers, 12 had ESRD although the remaining 6 patients without evidence of ADPKD were in their 30s and lacked adequate abdominal imaging.

Conclusions: When conducted with a sequencing platform that achieves sufficient depth, WES provided 100% diagnostic accuracy in PKD2 pLoF carriers and showed high sensitivity but limited specificity for PKD1 pLoF carriers. WES may have diagnostic value in a genotype-first approach in identifying ADPKD patients, but additional confirmation of PKD1 mutations may be needed.

Funding: NIDDK Support

FR-PO713
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Background: While polycystic kidney disease (PKD) is considered a rare disease, it accounts for the 4th most common cause of ESRD in the United States (US). Estimates of PKD prevalence in Europe and the US are similar (30-50 per 100,000 persons) but whether differences exist across race/ethnicities is relatively unknown. We examined trends in the prevalence of diagnosed PKD in a large, diverse healthcare delivery system with over 4.6 million members in the US.

Methods: Diagnosed PKD was identified among members aged ≥15 years in each calendar year from 1998 through 2018. PKD was defined as ≥2 separate diagnostic codes for PKD (ICD9 codes 753.12, 753.13, 753.14, and ICD10 code Q61.2, Q61.19, Q61.3). Race/ethnicity was determined by self-report. Temporal trends in diagnosed PKD was examined overall and by race/ethnicity.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Pancreatic cysts and neonatal death. Pkd1TAG;Pkd1
cliniques de Montreal, Montreal, QC, Canada
Model: Insights into Pkd1 Regulation
Therapeutic Targeting Strategies in Pkd1 Loss-of Function Mouse
Tomokazu Chiga,1 Hiroaki Fujimaru,1 Takayasu Mandai,1 Motoko Okado,1 Tatemitsu Iimori,1 Naohiro Mandai,1 Tomokazu Okado,1 Tatemitsu Rai,1 Shinichi Uchida,1 Eisie Sohara,1 Tokyo Medical and Dental University, Tokyo, Japan;2 University of Tsukuba, Tsukuba, Japan.

Background: Unlike pediatric patients, nephronophthisis-related ciliopathies (NPHP-RCs) are often suspected only after renal biopsy in adult patients, because they usually do not have specific extra-renal complications of NPHP-RCs. However, histological findings of NPHP-RCs, such as microcyst and interstitial fibrosis, are also commonly seen in any chronic tubulointerstitial disorders in general. In addition, comprehensive genetic testing is not easily available. Therefore, identification of representative histopathologic pattern of NPHP-RCs is useful for precise diagnosis of adult patients.

Methods: We analyzed 16 adult patients who were suspected as NPHP-RCs by renal biopsy. All patients had no extrarenal findings (retinitis pigmentosa and liver function disorder). This information can help tailor strategies for identifying and managing this important population, based on the underlying population. Moreover, these data point to the potential to generate additional insights on the natural history/clinical course of this potentially modifiable genetic kidney disease.

Results: A total of 7,580,947 members were included in the study period. Between 1998 and 2018, 3,524 members were identified as PKD with an overall prevalence of 46.5 cases per 100,000 people. The mean age of the PKD population was 49 years and no pancreatic cysts and survive up to ~3 mo. Renal cysts develop likely from differential tubular and temporal regulatory response to Pkd1 either insufficient or over-expression. SBP;Pkd1 mice with 0.87-fold Pkd1 endogenous level exhibit very mild renal cyst formation at P0 and escape neonatal lethality. This targeting strategy required multiple SBP-Tg copies to produce Pkd1 therapeutic levels similar to the SBP/Pkd1 and provided evidence for regulatory region within the Pkd1 gene-body. Identification of cystic nephron segments will shed light on the mechanism.

Conclusions: Our results demonstrate that Tg foetal Pkd1 expression can substantially delay cystogenesis and extend mouse lifespan. This study shows that Pkd1 re-expression not only requires high spatiotemporal regulation by the Pkd1 upstream region but also by regulatory elements within the Pkd1 gene-body.

Funding: Government Support - Non-U.S.

FR-PO716
Betaine Supplementation Ameliorates Renal Disease Severity in Experimental ADPKD
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Background: We have recently shown that kidney tissue levels of the methyl donor betaine and betaine dependent remethylation are lower in ADPKD, and correlate with disease severity. However, the effects of betaine supplementation have not been explored in ADPKD. We hypothesized that chronic betaine supplementation would increase renal betaine concentration and ameliorate disease progression in murine ADPKD.

Methods: One month old Pkd1 RC/RC mice were divided into three groups and started treatment with regular water or regular water supplemented with 1 or 2% betaine for 5 months (n=16 per group). All mice were euthanized at 6 months of age, and kidneys were harvested. Cystic index was determined from histological sections. H-NMR-based metabolomics analysis was performed from kidney tissue, urine and plasma samples.

Results: One and 2% betaine supplementation increased plasma and tissue betaine concentrations (p<0.001), reduced kidney/body weight to 1.82 and 1.85 vs 2.25 (p<0.01), and cystic index to 11.1 and 9.4 vs 21.1 (p<0.01) (Fig. 1). Tissue betaine concentrations correlated inversely with kidney/body weight (R=0.386, p<0.01). Metabolomics analysis from tissue and plasma identified significant differences in mitochondrial fatty acid oxidation and TCA cycle pathways among the groups.

Conclusions: Chronic betaine supplementation ameliorates disease severity in murine ADPKD possibly through improving mitochondrial function. These observations may represent a promising intervention from early stages of the disease.

Funding: NIDDK Support, Other NIH Support - DK118391

FR-PO714
Tubular Basement Membrane Duplication and Cell Interposition Are Distinctive Histological Findings in the Adult Patients Genetically Diagnosed with Nephronophthisis-Related Ciliopathies
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Background: Because microscopic cysts are likely formed in ADPKD kidneys, we aimed to describe novel microscopic cysts in the tubular basement membranes (TBM) of 16 ADPKD patients, aged 5-83 yr, without extrarenal findings (retinitis pigmentosa and liver function disorder), no family history of NPHP-RCs. Comprehensive genetic testing was performed in each patient. All patients had no extrarenal findings, retinitis pigmentosa and liver function disorder. Three patients had mutations and three patients with NPHP1, NPHP4, CEP164 respectively. We hypothesized that disorders of TBM could be specific findings in the adult patients genetically diagnosed with NPHP-RCs. These findings are potentially beneficial for optimal diagnosis of adult NPHP-RCs and are suggestive of the pathogenesis of the diseases.

Funding: Government Support - Non-U.S.

FR-PO715
The Therapeutic Targeting Strategies in Pkd1 Loss-of Function Mouse Model: Insights into Pkd1 Regulation
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Background: Autosomal dominant polycystic kidney disease (ADPKD) causes renal and extrarenal phenotypes, mainly due to PKD1 mutations. As a therapeutic strategy, CRISPR-Cas is attractive but the high frequency of off-targets precludes clinical application. Because microscopic cysts are likely formed in ureter in ADPKD kidneys, we targeted at early renal stage wild type Pkd1/+/ mouse protein from 3 series of transgenic (Tg) lines in Pkd1+/- mice, to assess for long-term cure/improvement of severe renal and pancreatic cysts and neonatal death.

Methods: Re-expression of Pkc1 was generated via three Tg matings: a) a systemic Pkd1+/- mouse (16 Tg copy) b) 2 renal-specific SBP/Pkd1 mice (2 and 20 Tg copy) or c) a novel Tg line targeting Pkd1 (DNA with renal-specific elements, SBP (16 Tg copy)). Longitudinal molecular and histological analyses were performed on kidneys and pancreas.

Results: Pkd1+/- mice expressing 7-fold over the endogenous Pkd1 gene are totally rescued from renal or pancreatic phenotypes. From 8 mo onwards, Pkd1+/- mice, relative to parental Tg line, display later renal cysts consistent with gene-dosage increase pathogenic mechanism. SBP/Pkd1+/- mice with mild -0.64 or notable 7-fold renal Pkc1 overexpression are rescued from neonatal death. In the mild expressor with Tg copies comparable to endogenous, renal and pancreatic cysts are detected at P5 and deaths occurs at P10-P15 whereas the high expressor display renal cysts later at P15 but no pancreatic cysts and survive up to ~3 mo. Renal cysts develop likely from differential tubular and temporal regulatory response to Pkd1 either insufficient or over-expression. SBP/Pkd1 mice with 0.87-fold Pkd1 endogenous level exhibit very mild renal cyst formation at P0 and escape neonatal lethality. This targeting strategy required multiple SBP-Tg copies to produce Pkd1 therapeutic levels similar to the SBP/Pkd1 and provided evidence for regulatory region within the Pkd1 gene-body. Identification of cystic nephron segments will shed light on the mechanism.

Conclusions: Our results demonstrate that Tg foetal Pkd1 expression can substantially delay cystogenesis and extend mouse lifespan. This study shows that Pkd1 re-expression not only requires high spatiotemporal regulation by the Pkd1 upstream region but also by regulatory elements within the Pkd1 gene-body.

Funding: Government Support - Non-U.S.
Metformin Improves Relevant Disease Parameters in the Hypomorphic Pkd1<sup>RC/RC</sup> ADPKD Mouse Model

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**Background:** Autosomal dominant polycystic kidney disease (ADPKD), caused by mutations in PKD1 or PKD2, presents with progressive development of renal cysts and eventual end-stage kidney disease and has limited treatment options. Previous work showed that metformin treatment reduces cyst growth in two early, rapid ADPKD mouse models, potentially through inhibition of CFTR-mediated fluid secretion, mTOR signaling and AMPK activation. Here we tested whether metformin treatment ameliorated ADPKD manifestations in a relevant, slowly progressive ADPKD mouse model.

**Methods:** Using the slowly developing ADPKD mouse model with an R3277C knock-in point mutation in both alleles of the Pkd1 gene (Pkd1<sup>R3277C</sup> mice), male and female mice were treated with metformin (300 mg/kg/day in drinking water) from 3 months through 9-12 months of age. During this treatment period, we periodically measured tail cuff blood pressures, glomerular filtration rates (GFR) by the FITC-sinistrin technique, and blood studies by i-Stat. At euthanasia, we assessed kidney histology (e.g., cystic index), total kidney weight/body weight ratio (TKW/BW), and mRNA and protein expression by qPCR and immunoblotting of key cell signaling, injury and inflammatory markers.

**Results:** As previously reported, Pkd1<sup>R3277C</sup> females had a more severe disease phenotype as compared with males. Metformin treatment reduced TKW/BW relative to age- and sex-matched controls at both 9 and 12 months of age. Metformin treatment also improved systolic blood pressures and increased GFR relative to controls at 9 months in both sexes. Moreover, metformin improved anemia (increased hematocrit) at both 9 and 12 months of age and generally lowered blood urea nitrogen (BUN) levels relative to controls in both sexes. Finally, metformin treatment also reduced the gene expression of key injury markers, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), and the inflammation markers tumor necrosis factor-α and interleukin-6 in these mice, along with KIM-1 protein expression.

**Conclusions:** Metformin improves various key ADPKD disease parameters in a relevant, slowly progressive ADPKD model. Additional studies to examine effects of metformin in PKD clinical trials and the potential additivity of these metformin effects are ongoing.

**Funding:** Other U.S. Government Support

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2-Deoxy-D-Glucose Effectively Retards Kidney and Liver Cysts Growth in the Mouse at a Plasma Concentration That Is Safe in Humans: A Bridge Study to Design a First Safety Trial in ADPKD Patients

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**Background:** Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a genetic disorder characterized by renal and liver cysts. The first therapy, tolvaptan, was recently approved. However, the presence of side effects and low tolerability calls for development of alternative therapies. We previously showed that inhibition of glycolysis by 2-deoxy-glucose (2DG) significantly retards disease progression (Rowe et al Nat Med, 2013; Chiavarrili et al, JASN, 2016). To translate the results for application in humans, we studied long term oral administration of 2DG and precise pharmacokinetic (PK) parameters.

**Methods:** We used a slowly progressive murine model by inactivating Pkd1 at P45 (Pkd1<sup>fl/fl</sup>/TmCre). Cohorts of 13 mice were treated for 4.5 months with oral administration of 2DG (100mg/kg) daily, for 5 days a week followed by 2 days of washout. Total kidney volume (TKV) was monitored by MRI, renal function by blood urea nitrogen and creatinine. At sacrifice kidney/body weight and histological analysis were performed. Liver cysts were identified by Cytokeratin-19 staining. Body weight, food intake as well as serum levels of ALT, AST, ALB and CK were detected for safety analysis. For the PK study of 2DG blood was collected after gavage at different time points (15, 30, 45, 60, 120, 180 min, 12 h, 24 h) and determined with HPLC pre-column fluorescence derivatization.

**Results:** 100mg/kg of 2DG significantly reduces TKV and restores renal function in the Pkd1<sup>fl/fl</sup>/TmCre mice. Biliary cysts were significantly reduced in number, length and area after 2DG treatment (p<0.05). Importantly, no sign of toxicity can be detected, neither in Pkd1<sup>fl/fl</sup>/ TmCre-mice in wt mice. PK analysis revealed that 100mg/kg 2DG and area after 2DG treatment (n=8). Importantly, no sign of toxicity can be detected, neither in Pkd1<sup>fl/fl</sup>/ TmCre-mice in wt mice. PK analysis revealed that 100mg/kg 2DG reduced TKW/BW relative to controls in both sexes. Finally, metformin treatment also reduced the gene expression of key injury markers, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), and the inflammation markers tumor necrosis factor-α and interleukin-6 in these mice, along with KIM-1 protein expression.

**Funding:** Other U.S. Government Support

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Correcting the Trafficking of CFTR, NHE3, and ENaC in ADPKD Reduces Cysts and Improves Renal Function

**Murali K. Yanda, Liudmila Cebotaru, Johns Hopkins School of Medicine, Baltimore, MD.**

**Background:** Autosomal dominant polycystic kidney disease (ADPKD), caused by malfunction of either PCK1 or PCK2, is associated with progressive enlargement of cysts, leading to a decline in function and renal failure. We demonstrated previously that a CFTR corrector, used to rescue CFTR trafficking, reduces cyst growth in mouse models.

**Methods:** To address the mechanism of how this occurs, we used proximal tubule-derived, cultured Pkd1<sup>-/-</sup> nephrons and the Pkd1<sup>ΔΔN</sup>: Pcdh8<sup>Cre</sup>: TmOE-cre mouse model. Treating the mice with doxycycline (doxy), ablates PCK1 in renal tubular epithelial cells and causes the development of multiple large cysts which leads to a decline in renal function.

**Results:** We found that cysts are reduced when the mice are treated with VX-809 and renal function improved. VX-809 treatment of cultured Pkd1<sup>-/-</sup> nephrons increased the activity of NHE3. We assessed the location of NHE3 and ENaC in the cystic kidneys using confocal microscopy. In the mice treated with doxy, NHE3 and ENaC were present in large cysts, but not at the apical membrane. NHE3 and ENaC primarily colocalized with Rab11, a marker of recycling endosomes. In the mice treated with doxy and VX-809, NHE3 and ENaC colocalized with a plasma membrane marker consistent with an increase in NHE3 and ENaC activity and protein expression. In the mice were treated with doxy large cysts developed and the CFTR was colocalized with the ER marker, and to a small amount with apical membrane marker. When mice were treated with doxy and VX-809, most of the CFTR was rescued from the ER and colocalized with the basolateral membrane (Fig.1) and total protein levels increased. Interestingly, basolateral localization of CFTR occurs in the sweat duct, a normally CI absorbing epithelium.

**Conclusions:** The data suggest that VX-809 reduces cyst size in the PC1-null mice by promoting an absorptive phenotype. Given that administration of VX-809 is safe, this drug potentially offers a new way to treat patients with ADPKD.

**Funding:** Other U.S. Government Support
these mice with SRR923A0 leads to improved kidney-body weight ratios and Blood Urea Nitrogen levels versus controls.

Conclusions: Our in vitro data indicate that modulating the activity of β1-AR has a direct effect on cystogenesis. Our in vivo data further suggest that β1-ARs are potentially interesting therapeutic targets in the treatment of ADPKD in that antagonizing β1-AR activity may reduce cAMP accumulation and thus cyst growth in both vasopressin-sensitive and insensitive nephron segments.

Funding: NIDDK. Support

FR-PO721

Chronic Exercise Ameliorates the Progression of Renal Dysfunction in Polycystic Kidney Disease Model Rats

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most frequent hereditary renal disease, but the exact mechanisms of cystogenesis remain to be elucidated. PKD leads to renal dysfunction, and it is a major cause of ESRD. Several clinical studies have shown that chronic exercise (Ex) exerts beneficial effects in CKD patients. However, the beneficial effects of Ex on renal function have not been reported in PKD. The present study investigated the effects of Ex in polycystic kidney (PCK) rats with PKD.

Methods: Five-week-old male PCK rats were divided into the sedentary (Sed) group and Ex group. Ex underwent forced treadmill exercise (28min/min, 60 min/day, 5 days/week) for 12 weeks. Plasma and urinary parameters and renal histology were examined.

Results: Ex significantly decreased the body weight, kidney weight, urine volume, urinary protein excretion, plasma creatinine and ameliorated renal cystic formation and interstitial fibrosis. Ex significantly decreased the Ki67 and TGF-β expressions in tubulointerstitial cells and the desmin expression in glomeruli. Ex also increased the PGC-1α expression and stimulated the phosphorylation of AMPK in the kidney.

Conclusions: Chronic exercise ameliorates renal dysfunction with inhibition of cystic formation and podocyte injury via an AMPK-PGC-1α-mediated metabolic switch in PCK rats. Ex may be a novel therapeutic approach for the development of renal dysfunction in PKD patients.

Funding: Government Support - Non-U.S.

FR-PO722

Pioglitazone and Tolvaptan in a Mouse Model of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is characterized by fluid-filled cyst formation and mainly caused by mutations in the PKD1 gene. Currently, the only treatment option for ADPKD is the use of drugs that target cystic formation and growth. Pioglitazone (PIO) is a thiazolidinedione that activates peroxisome proliferator-activated receptor γ (PPARγ), which plays a role in the regulation of renal cystogenesis. Tolvaptan (TVP) is an osmotic diuretic that decreases extracellular fluid volume and urine output. This study aimed to investigate the effects of combining these two drugs in a mouse model of ADPKD.

Methods: We used an inducible adult onset PKD model (mMCDs-Pkd1−/−) to investigate the effects of combining PIO and TVP in the kidney. PPARγ agonists, such as PIO, have been shown to inhibit cystogenesis in vitro and in vivo. TVP is an osmotic diuretic that decreases extracellular fluid volume and urine output. This study aimed to investigate the effects of combining PIO and TVP in the kidney.

Results: PIO improved renal survival and reduced cyst growth, confirming our model's relevance to ADPKD. Despite in vitro efficacy and using a clinically relevant dose, PIO had no therapeutic benefit in vivo, possibly due to low expression of PPARγ in mouse kidneys. Further research on the expression levels of the PPARγ gene and the PPARγ protein in relevant rat models and patients are ongoing.

Funding: Private Foundation Support

FR-PO723

Dual Targeting of the G Protein-Coupled Receptors CaSR and V2R for Treating Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is the 4th leading cause of end stage renal disease in the US. It is caused by mutations in PKD1 or PKD2 genes, which lead to excessive cell proliferation and fluid secretion, and ultimately cyst formation and growth. Reduced resting cytosolic calcium (Ca2+) and increased cAMP levels, associated with the tonic action of vasopressin, are two central biochemical defects in ADPKD. Currently there is no cure for the disease. The vasopressin V2 receptor (V2R) antagonist tolvaptan is the only drug approved to delay the progression of ADPKD, however it causes serious idiosyncratic hepato-cellular toxicity. Simulations on a multiscale computational model of drug-induced liver injury indicate that the novel V2R antagonist lixivaptan has a safer liver profile. Here, we show that co-targeting two GPCRs, the Calcium Sensing Receptor (CaSR), which finely regulates extracellular calcium (Ca2+) homeostasis and V2R has a synergistic combination with lixivaptan, reduced cyst progression in two animal models of human PKD.

Methods: PKC rat and Phd1−/− mouse littersmates were fed with ground rodent chow without or with lixivaptan (0.5%) and R-568 (0.025% for rats and 0.04% for mice), alone or in combination, for 7 weeks.

Results: In PKC rats, lixivaptan induced a significant reduction in kidney weight, cyst and fibrosis volumes by 20%, 31% and 60%, respectively, compared to animals fed with standard diet. The combined treatment strongly decreased the same parameters by 24%, 46% and 73%, respectively. R-568 alone induced a significant reduction only in kidney weight by 9% and fibrosis volume by 52%. Similar results were obtained in Phd1−/− mice.

Conclusions: These data suggest an intriguing new application for two known drugs. The potential for synergy between these two compounds suggested in these animal studies warrants further investigation in clinical settings.

Funding: Commercial Support - Amgen Inc.; Palladio Biosciences, Inc.

FR-PO724

New Therapeutic Approach Based in Inhibition of Metalloproteases in Polycystic Kidney Disease

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Background: Polycystic Kidney Disease (PKD) is a group of genetic disorders characterized by the presence of multiple cysts in the renal parenchyma, as well as others extrarenal manifestations such as hepatic cysts (Polycystic Liver Disease or PLD). Mutations in genes PKD1 and PKD2 caused the dominant form called ADPKD, by other band mutation in PKHD1 caused the recessive form or ARPKD. To this day, it have been reported several altered molecular pathways in the PKD but the key mechanism of cystogenesis (process by which cysts are formed) remains unknown. In that studio, with the use of animal models we reported a study about metalloproteases or MMPs of Extracellular Matrix (ECM) in the renal and hepatic cystogenesis and its therapeutic potential.

Methods: We use the rodent model PKD1–/– (Emx2−ΔEx2/Ex2−ΔEx2) or Phd1–/–, models of ADPKD and ARPKD respectively, as well as for the study at molecular level of the role of the MMPs, as models for the testing of a new therapeutic approach, called MTT. Furthermore, the understanding of the disease has been addressed by histological (hematoxylin and eosin, immunohistochemical, pathophysiological (renal and/or hepatic function) and transcriptomic (RT-qPCR) techniques.

Results: We have realized a complete study of the MMPs present in kidney and liver of our animal models, as well as have studied different pro-fibrotic and inflammatory markers related to the enzymatic activity of MMPs. Our study indicates that in renal and hepatic cystogenesis the levels of these markers and genetic expression of MMPs are increased, and therefore that this molecular pathway may be a possibility of therapeutic approach. MTT is an inhibitor of the extracellular matrix metalloproteinases that our group wanted to test as a possible therapy for ADPKD and ARPKD. We have seen that MTT inhibits the gene expression of several MMPs, reduces renal and hepatic fibrosis, improves renal function and inhibits renal and hepatic cystogenesis.

Conclusions: In this work, we evaluate the role of matrix metalloproteases (MMPs) in the cystogenesis of PKD. In addition, the MMP inhibitor MTT was examined in two different rodent models reducing hepatic and renal cystogenesis, and offering a new possible approach.
**FR-PO725**

Development and Implementation of Novel Morphometric 3D Capsule Device to Constrain Structural Change of Polycystic Kidney: A Feasibility Study in a Rat Model

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Background: Polycystic kidney disease is characterized by progressive enlargement of kidneys as a consequence of uninhibited formation and expansion of numerous kidney cysts. Current therapeutic options for polycystic kidney disease are limited in their effectiveness at halting disease progression. The objectives of the study were to (1) develop and implant a computed tomography (CT) image-derived morphometric 3D capsule device to encase a kidney and (2) to demonstrate experimental outcome of the device to constrain structural change of polycystic kidney in a rodent model.

**Methods:** Kidney capsule devices were designed from CT images of wild-type and Cy/+ rats. Capsule devices were surgically implanted on kidneys in six surgical sessions over a period of 14 months in 7 wild-type rats 6.5-8 weeks of age (3 sham operation, 2 right, 2 left) and 6 Cy/+ rats 6.5 weeks of age (2 sham, 3 left, 1 bilateral). After operation, rats were followed for 5.4-12 weeks to grow and sacrificed to retrieve kidneys. During the follow-up, serum creatinine was measured. Retrieved kidneys were weighed. Histological analysis including cystic area measurement and immunohistochemistry was performed.

**Results:** Morphometric capsule devices were configured and developed by image processing technique and produced using 3D printing technique. Encapsulated Cy/+ kidneys (n=5; mean weight 3.64g) were consistently smaller in size (by 21-36% p<0.001) than unencapsulated Cy/+ kidneys (n=7; mean weight 5.52g). Encapsulated Cy/+ kidneys (mean 5% cyst area: 29.4%) showed smaller histologic cystic area (by 28-58% p<0.001) than unencapsulated Cy/+ kidneys (mean 5% cyst area: 48.6%). Cell proliferation and macrophages were also markedly reduced in encapsulated Cy/+ kidneys, compared to unencapsulated Cy/+ kidneys.

**Conclusions:** We developed a CT image-derived morphometric 3D capsule device to constrain and demonstrated that the device constrained structural change of polycystic kidney in a rodent model as a feasibility study toward a novel potential therapeutic avenue for halting progression of polycystic kidney disease.

**FR-PO726**

Anti-Polyamine Therapy Restrains Polycystic Kidney Disease in Orthologous Mice

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Background: Autosomal-dominant polycystic kidney disease (ADPKD) is caused by mutations in PKD1 or PKD2 and is characterized by cysts derived from renal tubules. Cysts slowly expand due to aberrant proliferation and secretion of cyst-lining epithelial cell products that destroy the kidney by compression and resulting fibrosis. Only one FDA-approved drug is available for ADPKD, so there is a critical need for new therapies for this disease. The polyamines are metabolites of the amino acid ornithine and are produced by all cells. These metabolites are involved in a large number of cellular processes, including proliferation, for which they are essential. Polyamine production is often elevated in proliferative diseases, and are produced by all cells. These metabolites are involved in a large number of cellular processes, including proliferation, for which they are essential. Polyamine production is often elevated in proliferative diseases, including multiple types of cancer, and inhibition of polyamine synthesis has been shown in some cases to restrain cancer progression. We hypothesized that polyamines promote cyst cell proliferation and disease progression in ADPKD. We tested this by treating an ADPKD-orthologous mouse model with DFMO in the drinking water (665 mg/l) to achieve a dose of 133 mg/kg starting at PN28.

**Methods:** Mice were sacrificed at 6 months of age and serum and kidneys were collected for assessment of 2 compounds on cell viability and proliferation in two ADPKD cell lines as compared to treated HK2 cells. Flutamide had the strongest impact on ADPKD cell viability (65.4% in WT9-7, 67.8% in WT9-12, 92.0% in HK2 cells). Flutamide on top significantly reduced cell proliferation in ADPKD cells (41.1% in WT9-7 and 41.9% in WT9-12) as compared to HK2 cells (92.8%).

**Conclusions:** Flutamide significantly hampers cell viability and cell proliferation of ADPKD cells and warrants follow-up studies to investigate its potential as novel treatment option for patients with ADPKD.

**Funding:** Government Support - Non-U.S.

**FR-PO727**

Computational Drug Screening Identifies the Androgen Receptor Antagonist Flutamide as a Potential Treatment Option for Polycystic Kidney Disease

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**Background:** Treatment options for patients with autosomal dominant polycystic kidney disease (ADPKD) are limited and novel therapies are needed. A key hallmark of ADPKD is enhanced tubuloglomerular epithelial cell proliferation. We computationally screened compound libraries with the ADPKD molecular model using data from the Connectivity Map and a constructed library of literature-based drug mechanism of action models.

**Results:** The computational drug screening identified flipping positive overlap with the ADPKD molecular model. Four compounds had a significant negative impact on cell viability in ADPKD cell lines as compared to treated HK2 cells. Flutamide had the strongest impact on ADPKD cell viability (65.4% in WT9-7, 67.8% in WT9-12, 92.0% in HK2 cells). Flutamide on top significantly reduced cell proliferation in ADPKD cells (41.1% in WT9-7 and 41.9% in WT9-12) as compared to HK2 cells (92.8%).

**Conclusions:** Flutamide significantly hampers cell viability and cell proliferation of ADPKD cells and warrants follow-up studies to investigate its potential as novel treatment option for patients with ADPKD.

**Funding:** Government Support - Non-U.S.

**FR-PO728**

Ciclopirox-olamine Alters Ferritin Trafficking and Plays a Protective Role in Polycystic Kidney Disease

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**Background:** The search for safer and better drugs for Polycystic kidney disease (PKD) continues despite successful launch of Telvaptan. We have recently shown that the Notch3 signaling pathway is activated in renal cyst epithelial cells. To determine in vivo role of Notch inhibition, we used Ciclopirox-olamine (CPX). CPX can inhibit Notch and other pathways by its property to chelate iron and thus inhibit the activity of iron dependent enzymes such as gamma secretase (involved in Notch pathway activation).

**Methods:** We used primary normal human kidney (NHK) cells of collecting duct origin and primary cells from cysts of ADPKD patients (ADPKD cells). The effect of CPX on cell viability, ability to form cAMP dependent 3D cysts in vitro and cellular ferritin status was evaluated by both Western blotting and immunochemistry. CPX was also injected into a mouse model of PKD (Pkd1+/−/−) for 27 consecutive days and disease was analyzed and compared to the vehicle injected controls for Notch signaling and ferritin (another target of CPX).

**Results:** CPX (0.2 micro mol) inhibited cyst formation in ADPKD cells and resulted in a 40% reduction in cyst area. In vivo use of CPX in an orthologous mouse model of PKD also resulted in amelioration of cyst progression. A significant reduction in cystic index and kidney to body weight ratio was observed. However, the disease rescue did not involve Notch3 inhibition. We then focused on iron metabolism, because CPX is an iron chelator. First, we found that ferritin levels were significantly elevated in the kidney lysates from PKD mice and CPX significantly down regulated that to the level of WT mice. Human ADPKD cells were highly enriched in ferritin and CPX reduced the ferritin
Targeting Axoneme Polyglutamylation as a Potential Therapeutic Approach for ADPKD Treatment
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Background: ADPKD is the most common inherited renal disorders mainly caused by mutations of PKD1 or PKD2, which encodes Polycystin 1 (PC1) and Polycystin 2 (PC2) respectively. PC1 and PC2 co-localize to the primary cilium of kidney epithelial cells and have been proposed to form a receptor/channel complex to sense environmental cues. Recently, the structural mapping of ADPKD pathological mutations indicates that the pathogenic mechanism of PKD mutations are mainly associated with the incorrect folding or trafficking of PC1/PC2 complex. Thus, theoretically, correcting the proper cilia localization of PC1/PC2 complex could restore its functional dosage and holds strong potential for being developed as a therapeutic strategy to delay or even prevent the renal cystogenesis. However, pursuing this strategy is impeded by the lack of understanding of how the ciliary motility of polycystin is controlled. Polyglutamylation is one of the most abundant PTMs that occurs during the development and disease states. We recently discovered a novel paradigm that axoneme polyglutamylation is essential for the ciliary anchoring of polycystins, indicative of its potential for being used as a drug target.

Methods: 1. Imaging-based drug screen. 2. Immunofluorescent. 3. 3D culture. 4. Embryonic kidney culture.

Results: Here, by implementing axoneme polyglutamylation as readout, we performed an imaging-based small molecule screen and discovered several hits that can increase PC2 dosage and restore the correct cilia localization of PC2 in PKD cell model by promoting axoneme hyperglutamylation. Mechanistically, these drugs strongly promote the ciliary trafficking of TTLL5 and TTLL6, the key tubulin polyglutamylases that localize to primary cilia. We also have pinpointed the real molecular target of identified hits for inducing axoneme hyperglutamylation. We characterized 1928 cells from a wildtype littermate and 3702 cells with specific genetic pathology (PKD1 +/-). Using similar analyses for analyses of CD206+ cells in urine samples of PKD1 +/- mice. We showed that tissue-resident macrophages promote renal cystic disease severity in mice; however, the relevance of this observation to ADPKD patients was unknown. While key markers that define resident macrophages in mice cannot be used in humans (e.g., macrophage marker F4/80 is encoded by gene Emr1), it is expressed exclusively by human eosinophils, we recently identified CD206 as a candidate marker of renal fibrosis.

Results: In vivo targeting of miR-210-3p with an anti-miR reduces both fibrosis and proliferation in PLM areas and significantly improved renal function at PN42. M0 phenotype assessment of anti-miR-210-3p treated kidneys demonstrates a significant reduction in M2 (from 1900 cells to 1000, p < 0.05). Data from co-culture experiments demonstrate CEC, M-MØs show an increased change to M2-like phenotype, assessed by flow cytometry and expressed increased levels of Arg1, Mcrv, Fcm, Retna and decreased levels of Tnf transcripts when co-cultured with CEC in comparison to WTEC.

Conclusion: We demonstrated that in vivo miRNA inhibition of miR-210-3p significantly reduced fibrosis by reducing M0 phenotypic change to M2-like. In agreement with published studies miRNAs regulated transcription factors associated with M0 phenotype change to M2. Induction of M0 phenotypic change to M2-like by the CEC via miRNA changes within the M0has not been studied in depth and requires further investigation. miRNAs are an attractive target as these molecules are small in size and exogenously administered anti-miRs concentrations in the kidney.

Funding: Private Foundation Support
FR-PO732
Urinary CD206+ Cells Correlate with Rate of Renal Function Loss in Autosomal Dominant Polycystic Kidney Disease
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Background: We showed that tissue-resident macrophages promote renal cystic disease severity in mice; however, the relevance of this observation to ADPKD patients was unknown. While key markers that define resident macrophages in mice cannot be used in humans (e.g., macrophage marker F4/80 is encoded by gene Emr1), it is expressed exclusively by human eosinophils, we recently identified CD206 as a candidate marker of renal fibrosis.

Methods: We evaluated CD206+ immune cell populations in kidneys from ADPKD patients (vs non-ADPKD controls) using flow cytometry and confocal immunofluorescence microscopy approaches. We used similar analyses for analyses of CD206+ cells in urine samples from ADPKD patients.

Results: We found that CD206+ cells accumulated in regions adjacent to renal cysts. While the average number of intrarenal CD206+ cells was higher in ADPKD kidneys (vs controls), the variability was high and this difference did not reach statistical significance (0.0252 vs. 0.006 percent of total renal cells; p = 0.170). Also, we found that the urinary CD206+ cell-based index (e.g., after adjustment for urine creatinine concentration) correlated moderately with a rate of GFR decline (over 5 years) in a small cohort of ADPKD patients (n=30). This effect was independent of kidney length (KL), recently described CKD stage 3B predictor in ADPKD with similar AUC 0.88 as height-adjusted total kidney volume. The correlation between average GFR decline rates and KL was comparably strong (r=0.406; p=0.029), the correlation between the eGFR decline rates and urine albumin to creatinine ratio was weaker (ACR; r=0.192) in this cohort.

Conclusions: Together with studies on resident macrophages in animal models, these data suggest that resident macrophages participate in the disease pathogenesis in ADPKD patients. They also point to urinary CD206+ cells as a novel candidate marker of the disease activity in ADPKD.

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FR-PO733

Global MicroRNA Profiling in Human Urinary Exosomes Reveals Novel Disease Biomarkers and Cellular Pathways for ADPKD

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Background: ADPKD is the most common genetic kidney disease and the fourth most common cause of end-stage renal disease (ESRD) world-wide. Although PKD1 and PKD2 patients present different phenotypes, a high intra-familial variability in disease progression has been observed, suggesting that other genetic or environmental factors may have major influences on progression of ADPKD.

Methods: Spot urine specimens were collected from patients with ADPKD and healthy controls. Global miRNA-sequencing was conducted in urine exosome-derived miRNAs from healthy volunteers, ADPKD patients with early (eGFR > 60 mL/min) or late (eGFR < 60 mL/min) disease in a discovery cohort (n=22). TagMan qPCR was carried out in a clinically phenotyped validation cohort (n=60) and in a Phdl mouse model. In silico bioinformatic analyses identified altered miRNA target genes and disease pathways.

Results: Discovery phase RNA-seq identified a number of dysregulated miRNAs in ADPKD derived exosomes. Two candidate miRNA families identified (mir-192/mir-194-2 and mir-30) were selected for testing by qPCR in a validation cohort (n=60) and in an established mouse Pkd1 model. We confirmed that mir-192-5p, mir-194-5p, mir-30a-5p, mir-30d-5p and mir-30e-5p were significantly downregulated in human urinary exosomes and in Phdl cystic kidneys. Expression levels of all five miRNAs showed significant correlations with baseline eGFR-EPI and ultrasound-mean kidney length (MKL) and improved the diagnostic performance (AUC) of MKL for the rate of disease progression. Finally, by analysing inverse correlations of these two miRNA families with the increased expression of their predicted target genes, we identified several dysregulated pathways and transcriptional networks. These included novel miR-194-5p interactions with the 3' UTR of ANO1 and PIK3R1. Inhibition of these two candidate genes in human PKD1 cystic cells significantly reduced cyst growth in vitro, confirming their functional significance.

Conclusions: Our results demonstrate that urine exosome global miRNA profiling can be a powerful tool to identify ADPKD patients with rapid disease progression who could benefit from disease modifying treatment. We have identified a subset of urinary exosomal miRNAs that could serve as novel biomarkers of disease progression and also suggest potential new therapeutic targets in ADPKD.

Funding: Government Support - Non-U.S.

FR-PO734

Exosomes Generated from Cystic Renal Epithelial Cells Regulate Cellular Communication and Cystogenesis in ADPKD

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Background: The exosomes have recently drawn considerable interest as they are implicated in many pathophysiological processes of human diseases, including ADPKD. Cells can use these vesicles to communicate with both adjacent cells via the molecules present on the surface of these vesicles and distant cells via the circulation. Urinary exosomes have been proposed as a potential diagnostic tool in ADPKD. However, the basic cellular biological understanding of the exosomes in cellular communication and the role of circulating exosomes in ADPKD is lacking.

Methods: To investigate if exosomes regulate cell-to-cell communication and cystogenesis, we isolated exosomes from urine of ADPKD patients and normal individuals (control) as well as from culture media of Pkd1-/- and null renal epithelial cells. The isolated exosomes were used to treat Pkd1-/- renal epithelial cells for a cell proliferation assay and cystogenesis in 3D cultures. Circulating exosomes was isolated from blood to evaluate if exosomal PD-L1 is associated with disease progression of ADPKD and with response to treatment in Pkd1 animals.

Results: We found that treatment with exosomes isolated from ADPKD patient urine, and from media of cystic renal epithelial cells increased cell proliferation of NRK-52E cells and mMCCD cells compared to those cells treated with exosomes isolated from normal individuals and wild type renal cells in an exosome concentration dependent manner. In addition, we found that NRK-52E cells treated with ADPKD urinary exosomes developed cyst-like structures in collagen gels within 2 days, which continued to grow progressively up to day 8, whereas NRK-52E cells treated with normal urinary exosomes only developed tubule-like structures in collagen gel up to day 8. We further found that urinary ADPKD exosomes induced the activation of ERK and mTOR signaling in treated cells. The expression of PD-L1 was increased in cystic renal epithelial cells and we are now evaluating if the increase of PD-L1 in exosomes isolated from blood of Pkd1 animals and ADPKD patients can be used as a biomarker for ADPKD.

Conclusions: Urinary ADPKD exosomes and exosomes from cystic renal epithelial cells regulate renal epithelial cells proliferation and cystogenesis. The levels of PD-L1 in circulating exosomes may be a potential biomarker for ADPKD.

Funding: NIDDK, Support

FR-PO735

Diverse Receptor Tyrosine Kinase Phosphorylation in Urine-Derived Immortalized Tubular Epithelial Cells of ADPKD Patients

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Background: Clinical features of autosomal dominant polycystic kidney disease (ADPKD), including responses to drugs, differ among patients even if they have the same gene mutation in PKD1 or PKD2. This suggests that there is diversity in the expression of other modifier genes or in the underlying molecular mechanisms of ADPKD, but these are not well understood. In this study, we analyzed the diversity in receptor tyrosine kinase (RTK) phosphorylation in tubular epithelial cells of ADPKD patients.

Methods: Urine-derived epithelial cells were primarily cultured, and immortalized cell lines were established by SV40 large T gene transfection. SLC12A3-positive colonies, which is a specific marker of distal tubules, were used for experiments. RTK phosphorylation and its downstream signaling were analyzed in established cell lines. Three-dimensional culture of MDCK cells was used as a cyst formation model of ADPKD.

Results: Comprehensive analysis of RTK phosphorylation in immortalized tubular epithelial cells from 8 ADPKD patients and 4 healthy controls revealed diversity in the activation of several molecules, such as Axl (Gn6 receptor) and Met (HGF receptor), and there were differences even among patients from the same family. Golvatinib, a selective Met inhibitor, or transduction of siRNA for Met suppressed cell proliferation as well as downstream signaling, such as phosphorylation of Akt, only in the cell lines in which phosphorylation of Met was observed. In three-dimensional culture of MDCK cells, HGF activated Met and its downstream signaling, such as Akt or Erk, resulting in an increased total cyst number and total cyst volume. Golvatinib treatment inhibited these phenotypes in MDCK cells.

Conclusions: The analysis of urine-derived tubular epithelial cells demonstrated diverse RTK phosphorylation in ADPKD, and Met phosphorylation was noted in some patients. Given the difference in the effects of golvatinib on immortalized tubular epithelial cells among patients, this analysis may aid in determining suitable drugs for individual ADPKD patients as “precision medicine”.

Funding: NIDDK Support, Other NIH Support - NIH Office of Research Infrastructure Programs, Commercial Support - DiscoveryBioMed, Inc.

FR-PO736

3D In Vitro Cystogenesis Assays Utilizing Human Patient-Derived ADPKD Kidney Cells for Drug Screening


Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a slowly progressive genetic renal disorder that is caused by mutations in either the PKD1 gene (polycystin 1) or the PKD2 gene (polycystin 2). ADPKD is characterized by the formation of fluid filled cysts in both kidneys leading eventually to end-stage renal disease. Several in vivo and in vitro models of ADPKD exist, although many of them fall short of fully recapitulating the human disease phenotype, driving the failure of most therapeutic candidates in human clinical trials.

Methods: We have developed a unique 3D Biogel-based platform in 384-well tissue culture format utilizing cells isolated from individual cysts on human ADPKD donor kidneys. Cysts from each individual cyst are genotyped to determine the PKD1 or PKD2 mutation. Interestingly, from 9 human ADPKD donor tissues to date (8 with PKD1 mutations, 1 with a PKD2 mutation), we have discovered that only a subset of donors are prone to second somatic hits in single cyst-derived cultures, in addition to the germline mutation. These cells form cysts over 3-4 weeks in culture that can be tracked by high-content imaging with cyst size and number being quantified through algorithm-based image analysis. This platform can be used for screening or validation of candidate drugs and provides significant advancement in throughput and pathophysiological relevancy.

Results: Here, we show the effects of proprietary small molecules derived from a pre-clinical Cystic Fibrosis (CF) drug discovery program. In human bronchial epithelial cells, these compounds confer a dual effect of CFTR correction and ENaC inhibition. In our system, they are capable of reducing both the size and total number of cysts present after more than a week in culture.

Conclusions: The exact mechanism of action remains to be elucidated, but our data suggests two key findings. First, primary cultures of human cyst cells can be derived from individual cysts of ADPKD kidney tissues and can form cysts in 3D Biogel in a medium- throughput cystogenesis system to profile candidate PKD therapeutic. Second, treatments once reserved for CF and other genetic diseases might open new avenues for treatments of PKD. DBM acknowledges the Mayo Clinic PKD Center Genotyping Core for genotyping services.

Funding: NIDDK Support, Other NIH Support - NIH Office of Research Infrastructure Programs, Commercial Support - DiscoveryBioMed, Inc.
FR-PO737

Vascular Disease in PKD: A Novel Role for MLL1 in the Hedgehog-GLI1 Regulated Pro-Angiogenic Genes in Endothelial Cells

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Background: We have previously reported that activation of the Hedgehog (Hh) pathway is severely impaired in Polycystic Kidney Disease Endothelial Cells (PKD-ECs), leading to endothelial dysfunction and development of vascular defects. Furthermore, the severity of vascular dysfunction cannot be completely accounted for by the genetic defects, suggesting that other factors play a role. Here, we hypothesized that epigenetic changes modulating PKD-ECs transcriptome are responsible for the abnormal endothelial phenotype.

Methods: We studied the expression and regulation of pro-angiogenic molecules, such as vascular endothelial growth factor A (VEGFA), Angiopoietin 1 (ANG1) and Angiopoietin 2 (ANG2) using Chromatin Immunoprecipitation (ChIP) and gene expression assays in ECs stimulated with SMOOTHENED agonist (SAG, 100 nM for 24 hrs).

Results: ChIP studies demonstrated that VEGFA, ANG1 and ANG2 are direct targets of the transcription factor GLI1, after activation of the Hh pathway. Furthermore, PKD-ECs displayed lower binding of GLI1 (Fig. 1A) and histone mtyhyltransferase MLL1 (Fig. 1B) to the promoter region of those pro-angiogenic genes, compared to WT-ECs. Importantly, analysis of Histone 3 Lysine 4 methylation revealed a lower enrichment of methyl groups in PKD-ECs compared to WT (Fig. 1C).

Conclusions: Our data suggest that there is a specific epigenetic pathway affected in PKD controlling the ECs phenotype. These studies provide the base for the development of novel therapeutic strategies that, through modulation of epigenetic mechanisms, focus on the vascular aspects of PKD.

Funding: NIDDK Support, Other NIH Support - R01 CA136526, R01 HL119795

FR-PO738

Serum Global Metabolic Profiling Identifies Key Metabolic Networks Dysregulated in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a monogenic disorder, caused by mutations in either the PKD1 or PKD2 gene, that eventually leads to end-stage renal disease. Despite this prognosis, treatment options for ADPKD are limited. Kidney volume has been qualified by both FDA and EMA as a prognostic enrichment biomarker for selecting patients at high risk for progressive decline in renal function for inclusion in interventional clinical trials for ADPKD. However, an ADPKD-specific, easily-accessible and reliable biofluid biomarker for identification, stratification and monitoring of disease progression is lacking.

Methods: As several signaling and metabolic pathways are known to be dysregulated during ADPKD progression, we examined the global metabolic profiles of serum samples from a Pkd2−/− mouse model of ADPKD (n=6) and WT normal (n=6) mice; as well as ADPKD patients (n=22) and healthy volunteers (n=15) to investigate whether a metabolic profile could be established to aid in assessing disease progression. Dysregulated metabolites were identified and interrogated for their correlation to BUN, eGFR or HtBV.

Results: Global metabolic profiling carried out in mouse and human serum samples detected a total of 841 and 1156 metabolites, respectively. In human serum samples, principal component analysis showed a clear separation of serum global metabolic profiles between ADPKD and healthy populations. Sex and age were also contributing factors, accounting for 20% and 25% of the metabolite differences observed between the respective human populations. As anticipated, serum creatinine and urea were among the dysregulated metabolites increased in ADPKD samples and were highly correlated to eGFR (r=0.949) and BUN (r=0.078), respectively. Importantly, we have identified a targeted list of serum metabolites (including those involved in lipid metabolism) that showed differential abundance in both human and mouse ADPKD compared to their respective healthy cohorts.

Conclusions: Our comprehensive evaluation of the global metabolic profiles of serum samples from a mouse model of ADPKD as well as ADPKD patients have identified significant dysregulation in several key metabolic networks. Our results point to the potential use of serum metabolites as translational biomarkers for ADPKD.

Funding: Commercial Support - Regulus Therapeutics Inc.

FR-PO739

Global DNA Hypomethylation in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) affects an estimated 600,000 individuals in the United States. We have previously demonstrated that the serum level of s-adenosyl methionine (SAM): s-adenosyl homocysteine (SAH), an indicator of cellular methylation potential, is decreased in ADPKD patients with normal to mildly decreased kidney function. As the alteration in the methylation potential may influence DNA methylation, we hypothesized that global DNA hypomethylation may occur in ADPKD.

Methods: Global DNA methylation status was assessed in DNA extracted from whole blood and from kidney tissue by measurement of 5-methylcytosine content by ELISA (Epigentek, Farmingdale, NY). Blood samples were obtained from 17 subjects with ADPKD and normal or near normal kidney function and 12 age- and sex-matched healthy control subjects. Kidney tissue was available from 2 ADPKD patients and 2 control subjects.

Results: Global DNA methylation was significantly lower in the ADPKD subjects compared to healthy subjects (Table 1). Similarly, global DNA methylation was lower in the ADPKD kidney tissue (2.54% vs 5.80%). Renal blood flow decreases early in the course of disease and we show that SAM:SAH (methylation potential) is significantly correlated with renal blood flow (r = 0.45, p = 0.02). These findings suggest that decrease in methylation potential may be an early event in ADPKD.

Conclusions: Global DNA hypomethylation is present in ADPKD both in peripheral blood cells and in kidney tissue. As DNA hypomethylation might play a role in disease progression, agents that increase global DNA methylation might have therapeutic potential in ADPKD.

Funding: Private Foundation Support

Global DNA methylation in ADPKD and healthy subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ADPKD (N=15)</th>
<th>Healthy Controls (N=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>41 ± 11</td>
<td>45 ± 11</td>
</tr>
<tr>
<td>Male/Female</td>
<td>9/6</td>
<td>2/0</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td>73 ± 12</td>
<td>106 ± 70</td>
</tr>
<tr>
<td>HgA1c (total/albumin kidney volume ml)</td>
<td>6.0 ± 1.86</td>
<td>0.5 ± 0.18</td>
</tr>
<tr>
<td>% methyalted DNA (blood cells)</td>
<td>1.1 ± 0.35</td>
<td>1.5 ± 0.20</td>
</tr>
</tbody>
</table>

data presented as mean and standard deviation

FR-PO740

Identification of Cystogenic Signaling Pathways in a Newly Developed, Inducible-Kidney Epithelial Cell Model of Pkd2-Mediated Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder. Loss-of-function mutations of Pkd1 and Pkd2 genes cause the disease. However, initiating signaling events, most proximal to the polycystins, have not been precisely identified. Here, we developed in vitro inducible Pkd2 gene knockout (KO) model to explore the immediate consequences of Pkd2 KO and to identify the initiating factors that drive cystogenesis.

Methods: A doxycycline (Dox)-inducible Pkd2 KO renal medulla epithelial cell line was established from Pkd2/−/−/Pax8×rtTA/LC1 KO mice crossed with the SV-40 LTA “immorto mouse”. For RNA-Seq, Dox treated cells were compared to isogenetic controls. 4 replicates from two different passages were analyzed. Libraries were constructed from mRNA and sequenced (2×75 bp, paired-end). Sequence reads were aligned on the mouse genome GRCm38/pf, and downstream analyses were performed with R packages and multiple bioinformatics tools.

Results: The inner medullary epithelial cell line forms a polarized, electrically-tight, monolayer on filter supports, and as assessed by Western blot analysis, allows complete regulation of Pkd2 expression. For RNA-Seq, Dox treated cells were compared to isogenetic controls. 4 replicates from two different passages were analyzed. Libraries were constructed from mRNA and sequenced (2×75 bp, paired-end). Sequence reads were aligned on the mouse genome GRCm38/pf, and downstream analyses were performed with R packages and multiple bioinformatics tools.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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suppression of SHH and alter cilia as cytogenetic drivers. In addition to G63 of SHH, 108 other transcription factor genes were significantly changed, including TF associated with cilia (G63 and Pan3), Wnt signaling and ER stress.

**Conclusions:** RNA-Seq analysis of our newly established inducible Plkd2 KO kidney epithelial cell line identified gene networks that are rapidly changed in response to PKD2 repression, providing clues about the proximal cytogenetic signaling events in PKD.

**Funding:** NIDDK Support, National Institutes of Health, Bethesda, MD.

**Background:** Mutations in *Pkd1* are identified in the majority of cases of autosomal dominant polycystic kidney disease (ADPKD). This gene encodes a large trans-membrane protein, Polycystin 1 (PC1), which undergoes complex processing that results in multiple cleavage products. The complexity and low abundance of PC1 makes investigation into the functions of endogenous protein extremely challenging, and most of our knowledge of PC1 comes from study of recombinant protein over-expressed in heterologous systems. In order to investigate PC1 function under physiological conditions, we generated a knock-in mouse model that expresses a chimeric PC1-eGFP-3HA fusion protein under the control of its native promoter using the CRISPR/Cas9 method.

**Methods:** We characterized the expression of PC1-eGFP-3HA by immunoblot (IB), immunoprecipitation (IP), and immunofluorescence (IF) in mouse tissues and in Human Embryonic Fibroblasts (HEFs) and Renal Epithelial Cells (REC) derived from the mouse line. The*Pkd1-eGFP-3HA/Pkd1 and Pkd1/KO mouse lines were intercrossed to test if the fusion protein was functional.

**Results:** Genomic PCR and sequencing performed confirmed the successful insertion of eGFP and 3HA tag sequences into the *Pkd1* locus. Offspring of *Pkd1-eGFP-3HA/Pkd1 X Pkd1/KO* crosses were obtained at mendelian ratios. Neither the kidneys nor livers of *Pkd1-eGFP-3HA homozygotes* were cystic at 1 year, and they remain healthy at >1.5 years without other apparent abnormality. The PC1-eGFP-3HA fusion protein can be reliably detected by IB and IP in various tissues and cell lines. Multiple previously reported PC1 cleavage products were detected in a variety of tissues. However, we have not yet been successful in detecting PC1-specific signal above background by IF in any tissues. Live cell imaging and IF in MEF cells using various antibody, fixation and microscopy methods failed to detect PC1. So far, we can only visualize the fusion protein unambiguously by IF in primary cilia of REC.

**Conclusions:** The PC1 fusion protein function appears to be as functional as untagged protein and could be detected more easily and reliably. Using GFP-nanobodies magnetic bead isolation from rat kidney tissue prepared for immunoprecipitation by suspension flow cytometry. In conclusion, the PC1 fusion protein is also more efficient. This model will be a helpful resource for studying endogenous PC1 trafficking in live cells and how it interacts with other proteins.

**Funding:** NIDDK Support

**FR-PO744**

**Primary Patient Material as Model for a High Content 3D In Vitro Screening Assay to Study ADPKD**

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**Background:** Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by the formation of fluid-filled cysts in the kidney. Currently only one drug is on the market for ADPKD, a vasopressin receptor 2 inhibitor Tolvaptan. However, Tolvaptan does not prevent cysts from forming but slows down cyst swelling. Identifying the mechanisms involved in cystogenesis and identification of treatments is hampered by the lack of pathophysiological models relevant in vitro models. Here, we report the development of an ex vivo 3D cyst screening assay that uses primary cells from resected kidneys from ADPKD patients to facilitate in vitro studies for ADPKD.

**Methods:** Patient tissue was harvested directly from resected kidneys and cultured in 3D in an optimized hydrogel and culture medium until cryopreservation. Short expansion culture was performed in similar culture conditions. Compound testing was done in 384 well plates. After 24h pre-culture, compounds were added for 48h. Plates were fixed and stained for nuclei and F-actin. Plates were imaged and using Omier™ high throughput image analysis software the entire z-stack of each well was recapitulated for 3D quantification and morphometric analysis.

**Results:** Cultures propagated from cryopreserved tissue developed a cystic phenotype that was stably maintained in 3D culture. Swelling of these cysts could be induced using forskolin, which activates adenylycllase and using desmorepressin, which activates the vasopressin 2 receptor. Effect of Merformin, Rapamycin, Roscovitine and Tolvaptan was examined in combination with desmorepressin or forskolin. Compound effects were visualized with high content imaging. Using Omier™ images were analyzed. Measurement of phenotypic characteristics such as nucleus morphology and thickness of the cyst wall enabled discrimination of compounds that reduced cyst swelling and compounds that were cytotoxic. All reference compounds showed the expected decrease in cyst swelling.

**Conclusions:** We have developed a 3D screening assay that uses low-passage patient primary cell model of renal cysts. With this assay, we have successfully tested a panel of reference compounds. Using our image-based approach we are able to discriminate between efficacy or toxicity inducing compounds. This assay offers a powerful tool for future drug and target discovery as well as mechanistic studies for ADPKD.

**Funding:** Commercial Support - Ocelio

**FR-PO743**

**A Novel CIRSPR/Cas9 eGFP Knockin Mouse for Characterizing Endogenous Polycystin 1**


**Background:** Mutations in *Pkd1* are identified in the majority of cases of autosomal dominant polycystic kidney disease (ADPKD). This gene encodes a large trans-membrane protein, Polycystin 1 (PC1), which undergoes complex processing that results in multiple cleavage products. The complexity and low abundance of PC1 makes investigation into the functions of endogenous protein extremely challenging, and most of our knowledge of PC1 comes from study of recombinant protein over-expressed in heterologous systems. In order to investigate PC1 function under physiological conditions, we generated a knock-in mouse model that expresses a chimeric PC1-eGFP-3HA fusion protein under the control of its native promoter using the CRISPR/Cas9 method.

**Methods:** We characterized the expression of PC1-eGFP-3HA by immunoblot (IB), immunoprecipitation (IP), and immunofluorescence (IF) in mouse tissues and in Human Embryonic Fibroblasts (HEFs) and Renal Epithelial Cells (REC) derived from the mouse line. The*Pkd1-eGFP-3HA/Pkd1 and Pkd1/KO mouse lines were intercrossed to test if the fusion protein was functional.

**Results:** Genomic PCR and sequencing performed confirmed the successful insertion of eGFP and 3HA tag sequences into the *Pkd1* locus. Offspring of *Pkd1-eGFP-3HA/Pkd1 X Pkd1/KO* crosses were obtained at mendelian ratios. Neither the kidneys nor livers of *Pkd1-eGFP-3HA homozygotes* were cystic at 1 year, and they remain healthy at >1.5 years without other apparent abnormality. The PC1-eGFP-3HA fusion protein can be reliably detected by IB and IP in various tissues and cell lines. Multiple previously reported PC1 cleavage products were detected in a variety of tissues. However, we have not yet been successful in detecting PC1-specific signal above background by IF in any tissues. Live cell imaging and IF in MEF cells using various antibody, fixation and microscopy methods failed to detect PC1. So far, we can only visualize the fusion protein unambiguously by IF in primary cilia of REC.

**Conclusions:** The PC1 fusion protein function appears to be as functional as untagged protein and could be detected more easily and reliably. Using GFP-nanobodies magnetic bead isolation from rat kidney tissue prepared for immunoprecipitation by suspension flow cytometry. In conclusion, the PC1 fusion protein is also more efficient. This model will be a helpful resource for studying endogenous PC1 trafficking in live cells and how it interacts with other proteins.

**Funding:** NIDDK Support

**FR-PO742**

**Microinjection-Based Analyses in a 3D Cyst Model**

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**Background:** ADPKD is characterized by continuous cyst growth. Hereby fluid secretion into the cyst lumen plays a major role. We could show that in addition to cAMP-mediated chloride secretion also ATP- and Ca2+-dependent chloride secretion contributes to cyst enlargement. Hereby the binding of luminal ATP to P2Y2-receptors leads to activation of the apical chloride channel Anoctamin 1. Functional studies in our established in vitro cyst model are partly restricted, since applied pharmaceuticals and substances only reach the basolateral side of the cysts. In addition, the quantification of the apical secretion rate of various molecules such as ATP is not possible. Our goal was to establish a micro puncture technique for in vitro cysts, which would allow us to inject or withdraw substances into or out of the cyst lumen.

**Methods:** In our in vitro 3D-cyst model, principal-like MDCK collecting duct cells (pMDCK) form cysts within a collagen matrix. Those cysts get punctured and substances injected utilizing a microinjector in combination with a micromanipulator and a high-resolution macroscope. Successful injection can be monitored by co-injection of a dye into the cyst’s lumen. Injected cysts can then be tracked over time in a live cell imaging chamber.

**Results:** With this new technique we are able to puncture cysts and inject substances into in vitro cysts starting at a size of >10μm. Correct application can be visualized by applying a coloured dye in addition and visualizing the cyst thereafter in a live cell imaging chamber. Therefore, we are able to apply various substances of interest at the apical side of the cysts and analysing their direct effect on cyst growth. In addition, small amounts of fluid can be extracted from the cysts and further analysed. This technique will be used to test for luminal ATP concentrations under different culture conditions.

**Conclusions:** We have established a new method, allowing us to puncture in vitro cysts and apply substances luminally or measuring concentrating at different locations in the cyst lumen such as ATP by extracting cyst’s fluid. In addition, the punctured cysts can be imaged over time in our live cell imaging setup.
FR-P0745

Heterozygous Inactivation of PKD1 in Miniature Pigs Induces Embryonic Cyst Formation and Progressive Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Murine models do not faithfully recapitulate important features of human ADPKD or its dominant inheritance. Gene editing and somatic cell nuclear transfer in large animals have provided superior models for human genetic disorders that have improved our understanding of disease mechanisms and the translational value of preclinical studies for novel therapies. Porcine anatomy, development, physiology, genetics and body size are like those of humans. We generated a new ADPKD model in the Yucatan miniature pig to monitor renal cyst formation in utero and postnatal PKD progression.

Methods: Gene targeting methods were used to insert a blasticidin cassette into intron 30 of PKD1, which resulted in a null allele, and somatic cell nuclear transfer to generate PKDI−/− cloned pigs. Breeding colonies were established to generate PKDI−/− and wildtype littermates. Kidneys were collected at embryonic days 30, 60, 90, newborn (~120 embryonic days) and 3, 6, 9 and 12 months postnatal to evaluate cyst development. Embryonic kidneys were imaged by micro-CT and larger kidneys were sectioned using a tissue slicer for measurement of cystic index. Thin tissue sections were stained with antibodies to AQP-2 to identify collecting ducts and PCNA, a marker of cell proliferation.

Results: Embryonic PKDI−/− pigs had sporadic cysts and cystic dilations that appeared to form in clusters, consistent with the proposed mechanism of early cyst development in human ADPKD. The number of cysts and total cystic area progressively increased after birth; however, changes in kidney weight relative to body weight were not similar genetics, disease presentation and progression, and the large kidney size suggest that PKD1 inactivation in the miniature pig may be a suitable model for adult human ADPKD.

Conclusions: Our results demonstrate that inactivation of one PKD1 allele induces renal cyst formation in utero and progressive ADPKD in a new porcine model ADPKD.

Funding: NIDDK Support, Commercial Support - Exemplar Genetics

FR-P0746

Kidney and Cystic Volume Imaging for Disease Presentation and Progression in the Cat ADPKD Large Animal Model

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Background: Persian cats have a variant in polycystin-1 (PKD1) causing autosomal dominant polycystic kidney disease (ADPKD). The variant (c.10063C>A) causes a protein truncation (p.C3243X) and is the only known variant in cats. As in humans, the variant is lethal in utero when in the homozygous state. Affected cats have a total range of progression and severity of disease. However, cats are an overlooked biomedical model and have not been used to test therapeutics and diets that may support human clinical trials. To reinvigorate the cat as a large animal model for ADPKD, the efficacy of imaging modalities in cats was demonstrated and supported robust estimates of kidney and fractional cystic volumes.

Methods: Three imaging modalities, ultrasound, computed tomography (CT), and magnetic resonance imaging, were used to examine variation in disease presentation and disease progression in 11 felines with ADPKD. Imaging was compared with previously published biomarkers for chronic kidney disease and glomerular filtration rate. Total kidney volume, total cystic volume, and fractional cystic volume (FCV) were determined for the first time in ADPKD cats. A few cats had follow-up examinations to evaluate progression.

Results: The size of the cat’s kidney supported the determination of FCV measurements. CT was a rapid and efficient modality for evaluating therapeutic effects that cause alterations in kidney volume and/or FCV. Biomarkers, including glomerular filtration rate and creatinine, were not good indicators of kidney function. The wide variation in cystic presentation suggested genetic modifiers likely influence disease progression in cats. Disease modalities had clear cut resolution to those acquired for humans, and software used for kidney and cystic volume estimates in humans can be used in cats.

Conclusions: Veterinary-based imaging protocols are robust and efficient for evaluating ADPKD in cats as in humans. Cats can be identified as fast and slow progressors, thus, could assist with modifier discovery. Software to measure kidney and cystic volume in human ADPKD kidney studies is applicable and efficient in cats. The longer life span, similar genetics, disease presentation and progression, and the large kidney size suggest cats an efficient biomedical model for evaluation of ADPKD therapeutics.

Funding: NIDDK Support

FR-P0747

Angiominin Knockout Causing Glomerulotubular Nephropathy May Be via an Activated Hippo Signalling Pathway

Yaohua Zhang,1 Nural Jannah Binti Ahmad,1 Qingsong Lin,1 Jerrold M. Ward,2 Ji Jin Sun,1 Hui Kim Yap,3 Kar Hui Ng,1 pae/imm National University of Singapore, Singapore, Singapore; 2National University Hospital, Singapore, Singapore; 3Global VetPathology, Montgomery Village, MD.

Background: Angiomin (Amot) is an angiostatin binding protein involved in endocytosis of Angiomin. Using CRISPR/Cas9, we created Amot knockout (KO) rats that developed cysts from 1 month and proteinuria by 6 months. Histology revealed dilated tubules, podocyte hypertrophy, foot process effacement, thick glomerular and tubular basement membranes. We aimed to elucidate the pathomechanism of Amot KO with iTRAQ (isobaric tags for relative and absolute quantitation) based quantitative proteomics.

Methods: Kidney cortex from 1-mth rats were homogenized and labelled with iTRAQ. Quantitative proteomic analysis was performed using 2D-nLC-MS/MS. Peptide identification and quantification was carried out on ProteinPilot 5.0 software using Paragon database search algorithm (5.0.0.0.4767) and integrated false discovery rate (FDR) analysis Data. Search were matched against UniProtKB protein sequence databases. Statistically significant differences were based on fold change ≥1.5 and p-value <0.05. Rat glomeruli were isolated for ex vivo podocyte culture or total RNA extraction. Immunofluorescence (IFM) and western blot (WB) were performed on podocytes for Yap (Yes-associated protein) nucleus translocation analysis. Real-time PCR were performed for Yap target genes.

Results: 5030 proteins were quantified with confidence corresponding to peptide FDR <0.01 and with ≥2 unique peptides per protein. We identified 101 upregulated proteins and 299 downregulated proteins in KO compared to WT rats. Expression of TEAD1, a major Yap target transcription factor, was significantly decreased. IFM and WB showed increased Yap nucleus deposition. Transcriptional expression of Yap target genes (Ank1, Cyr61, Diaph3, Apln and Cgfl) were increased.

Conclusions: In vivo Amot KO caused Yap nucleus translocation and activated the Hippo/Yap pathway.

Funding: Government Support - Non-U.S.

FR-P0748

Notch Overexpression in a Mouse Model of Polycystic Kidney Disease

Brian C. Belyea, Maria Luisa S. Sequeira Lopez, Roberto Ariel Gomez. University of Virginia, Charlottesville, VA.

Background: Polycystic kidney disease (PKD) is a major cause of end stage renal disease and characterized by enlarged kidneys containing numerous fluid-filled cysts, hypertension, anemia, and progressive loss of kidney function. PKD is autosomal dominant (ADPKD), caused by mutations in the PKD1 or PKD2 genes, or autosomal recessive (ARPKD), caused by mutations in the PKHD1 gene. While the genetic basis of PKD is known, the downstream molecular mechanisms which lead to deregulation of proliferation, apoptosis, and differentiation remain poorly understood. Previous work has demonstrated Notch activation in mouse models of ADPKD and ARPKD. In addition, we have shown that aberrant Notch signaling during kidney development leads to an alteration in cell fate. Thus, we hypothesize that Notch overexpression during kidney development may play an important role in PKD pathogenesis.

Methods: We generated mice with overexpression of Notch1 in renal lineage cells using the Cre-lox system. Specifically, we crossed mice which express Cre recombinase under the control of the renin locus (Ren1Cre+) with transgenic mice containing a sequence encoding an intracellular portion of the mouse Notch1 gene inserted into the ubiquitously expressed Rosa26 locus (Rosa26m Notch1). Control mice (Ren1Cre−;Rosa26m) and mutant mice (Ren1Cre+;Rosa26m) were studied at 3, 6, and 9 months of age.

Results: Mutant mice developed large kidneys with numerous cysts by 3 months of age and this phenotype worsened with advancing age. Histologic examination confirmed the presence of numerous cysts throughout the kidney cortex of mutant mice. Mutant animals had decreased Renin expression shown by PCR and decreased RENIN protein levels in the kidney and plasma as shown by immunohistochemistry and ELISA respectively. In addition, mutant animals developed anemia and worsening renal function with age. Finally, mutant animals did not live beyond 9 months of life, likely dying secondary to renal failure and/or anemia.

Conclusions: Mice with overexpression of Notch1 in renal lineage cells develop numerous renal cysts, enlarged kidneys, anemia, progressive renal insufficiency and early death – recapitulating many features of human PKD. To our knowledge, this is the first model of PKD resulting from overexpression of Notch signaling, and this work highlights the importance of aberrant Notch signaling in PKD.

Funding: NIDDK Support

FR-P0749

Sprouty1 Regulates FGF Signaling-Mediated Nephrin Progenitor Maintenance

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Background: Nephrin progenitors maintain and differentiate with various signaling cascades. FGFR and FGFR2 play pivotal roles in generating and maintaining nephrin progenitors during kidney development. However, molecules regulating FGF signaling during nephron progenitor development are not known. Sprouty (Spry) is an antagonist of FGF signaling and Sprouty1 (Spry1) is expressed in the developing kidney and podocyte during early stages of kidney development. FGF signaling is required for podocyte differentiation and proliferation, while Sprouty1 expression is observed in the developing kidney and podocyte during early stages of kidney development. In this study, we showed that Sprouty1 regulates FGF signaling and podocyte differentiation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author. 634
and regulates Ret-GDNF-dependent renal branch morphogenesis. Although Spry1 also expression of Spry1 progenitors, function of Spry1 in this population is still elusive.

Methods: To understand whether Spry1 antagonize function of FGF9/20 induced nephron progenitors, we generated Spry1, Fgf9, Fgf20 triple mutant animals and evaluated kidney phenotypes.

Results: Deletion of Spry1 rescues bilateral renal agenesis caused by deletion of both Fgfr9 and Fgfr20. In addition, deletion of Spry1 normalizes number of nephron progenitors in Fgfr9 and Fgfr20 hypomorphic kidneys. Nephron progenitor specific deletion of Spry1 also rescues loss of Fgf9 and Fgf20 induced bilateral renal agenesis. Further genetic analyses identified Fgf9 compensates loss of Fgf9 and Fgf20 at the background of Spry1 mutant.

Conclusions: This data demonstrate that Spry1 expressed in nephron progenitors antagonize FGF signaling to balance nephron progenitor maintenance.

Funding: NIDDK Support

FR-PO750

Fibroblast Growth Factor Signaling Mediates Progenitor Cell Aggregation and Nephron Regeneration in the Adult Zebrafish Kidney

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Background: The zebrafish kidney regenerates after injury by development of new nephrons from resident adult kidney stem cells. Although adult kidney progenitor cells have been characterized by transplantation and single cell RNA seq, signals that stimulate new nephron formation are not known.

Methods: Adult wild type and Tg(lhx1a:EGFP) and Tg(bsp70-ds-red) transgenic zebrafish embryos were injected with lentiviral vectors encoding dominant negative receptor constructs (i.e., renal vesicle, comma- and S-shaped body structures) in DM_.

Results: We demonstrate that fibroblast growth factors and FGF signaling is rapidly induced after kidney injury and that FGF signaling is required for recruitment of progenitor cells to sites of new nephron formation. Chemical or dominant negative blockade of Fgf1 prevented formation of nephron progenitor cell aggregates after injury and during kidney development. Implantation of FGF soaked beads induced local aggregation of lhx1a:EGFP+ cells in normal kidneys.

Conclusions: Our results reveal a previously unexplored role for FGF signaling in recruitment of renal progenitors to sites of new nephron formation and suggest a role for FGF signaling in maintaining cell adhesion and cell polarity in newly forming kidney epithelia.

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FR-PO751

Six2+;Cited1+ Cells: The Culprit of Wilms Tumor Development?

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Background: Wilms tumors (WT) account for 95% of renal pediatric malignancies and is characterized by uncontrolled proliferation of nephron progenitors (NP) without generation of functional nephrons. Due to the inability of isolating these human NP, little is known about WT initiation and growth. In this study, we isolated NP expressing Six2 and CITED1 (the master genes regulating nephrogenesis) from WT samples and from human fetal kidneys (hFK) and performed in vivo and in vitro experiments to study the regulation of self-renewal vs differentiation of NP.

Methods: WT and hFK samples were histologically analyzed, digested to single cell suspension, incubated with SmartFlare-probe and SIX2-CITED1+ cells immediately sorted and processed for RNA-seq, single-cell RNA-seq and for other analysis. Xenografts of WT-NP and FK-NP were generated and tumor formation was assessed. Using a nephrogenic specific media, we established conditions for long-term culture of NPCs and studied mechanisms that regulate self-renewal vs differentiation were performed.

Results: Histology confirmed a different pattern of expression for SIX2 and CITED1 across WT with a different prognosis and stages compared to IFK. Our RNA-seq analysis confirmed of mechanisms overexpression of tumorigenic genes in WT-NP compared to WT- NP. When transplanted in vivo WT-NP demonstrated marked capacity of tumorigenesis, which in some instances induced metastasis, while Fk-NP did not. Single-cell RNA-seq after xenotransplantation of WT-NP defined precise cancer-associated cellular identities compared to WT-NP. In vivo experiments confirmed that modulation of integrin signaling leads to blockade of self-renewal in NP by decreasing CITED1 expression, activating b-catenin and inducing specification by stimulating the activation of LEF1.

Conclusions: This work evidenced that SIX2+CITED+ cells in WT represent a population of cancer stem cells with tumorigenic ability. Our characterization also highlighted important differences in self-renewal potential in favorable and unfavorable WT samples, with b-catenin playing a key role in regulating this biological process. These studies can help increase our knowledge of human nephrogenesis and the development of new strategies aimed at halting tumor progression.

Funding: Private Foundation Support

FR-PO752

In Utero Exposure to Maternal Diabetes Impairs Nephron Progenitor Differentiation

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Background: The incidence of diabetes mellitus has significantly increased among women of childbearing age worldwide and infants exposed to maternal diabetes in utero are at increased risk of congenital renal anomalies. In this study, we utilized a genetic model of maternal type 1 diabetes, the Akita (In2–C96Y) mice, to evaluate its effect on kidney development.

Methods: Diabetic In2–C96Y females were bred with wildtype C57BL/6 males and, wildtype offspring exposed to maternal diabetes in utero (DM_Exp) were assessed. Wildtype offspring from C57BL/6 dams were used as controls. Kidneys were collected at different stages (E11.5, E15.5, P2 and P34). Nephron numbers were estimated using the gold-standard physical dissector/fracturator method. The expression of nephron progenitor and developing nephron markers was analyzed by qPCR, immunohistochemistry and/or Western blot.

Results: Adult DM_Exp mice (P34) exhibited a nephron deficit of approximately 25% (n=3) compared to wildtype siblings. Our results also suggest an association with impaired renal progenitor-specific self-renewal. Additionally, we speculated that the impaired self-renewal of nephron progenitors in DM_ mice was due to a reduction in the number of self-renewing progenitor cells and/or an increase in the rate of differentiation. Further investigations into these possibilities are currently underway.

Conclusions: Together, these data suggest that the diabetic intrauterine environment impairs the differentiation of nephron progenitors into nephrons, which may be mediated by diminished Wnt/b-catenin and Notch signaling pathways.

FR-PO753

Development of a New Nephron Progenitor Cell Replacement System for Application in Human Induced Pluripotent Stem (iPS) Cell-Derived Nephron Progenitor Cells (NPCs)

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Background: Previously, we generated a transgenic mouse model that enabled diphtheria toxin (DT)-induced ablation of Six2-positive NPC’s (Six2-iDTR mouse). After eliminating host NPCs, we transplanted allogeneic or autologous NPCs into the metanephric mesenchyme. Donor NPCs were differentiated into neo-nephrons, which have the ability to filter and produce urine, and were connected to the host mouse ureteric bud. In the future, we aim to use this system in kidney regeneration using human iPS cells. However, human cells permanently express diphtheria toxin receptors and in vivo, can undergo apoptosis when treated with DT. Therefore, a new NPC elimination system is warranted. In this study, we developed a new transgenic mouse model to ablate NPCs without affecting human cells using tamoxifen instead of DT (Six2 CreERT2-DTA mouse) for application in human cell-based therapy.

Methods: Six2-CreERT2 mice were crossed with Rosa26-foxed stop DTA mice to obtain Six2CreERT2-DTA mouse offspring, which were used as hosts. We attempted regeneration from dissociated cells derived from E13.5 mice and E15.5 rat nephrons, and NPCs differentiated from human iPS cells. We injected these dissociated cells below the renal capsule of the E13 transgenic mice metanephros. The injected metanephros were isolated, and the organs were cultured for 7 days with 4OH-tamoxifen. After culturing, the metanephros were analyzed using immunofluorescent staining. To verify the blood-inducing ability of the regenerated nephrons in vivo, we additionally transplanted Six2CreERT2-DTA mice metanephros injected with dissociated cells derived from E13 mice into immunodeficient mice under tamoxifen administration and evaluated the results.

Results: We successfully eliminated Six2-positive NPCs from the cap mesenchyme by the Six2CreERT2-DTA mouse strategy. Moreover, we successfully regenerated chimera kidneys that have blood-inducing ability from mouse metanephros. Human iPS cell-derived NPCs were engrafted in the Six2CreERT2-DTA mouse metanephric cap mesenchyme.

Conclusions: We developed a new nephron progenitor cell elimination and replacement system that can be utilized in human cells.

FR-PO754

ZEB2 Controls Ureteral Smooth Muscle Cell Fate

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Background: ZEB2 is a SMAD-interacting transcriptional factor and loss-of-function ZEB2 mutations are associated with Mowat-Wilson Syndrome (MWS), a genetic disease with multiple congenital defects including hydroreter and hydronephrosis. Ureteral smooth muscle cells (SMCs) derive from Tbx18 mesenchymal progenitors and abnormal
development of ureteral SMCs can lead to hydroureter and hydronephrosis. However, the molecular role of ZEB2 in ureteral SMCs development from TBX18+ mesenchymal progenitors is not known. 

**Methods:** We analyzed Zeb2 ureteral mesenchyme-specific conditional knockout mice Zeb2cre;Tbx18cre (Zeb2 cKO) and their wild-type littermates for controls during early ureter development. At E14.5-E15.5, there was an increase in SOX9 expression in ureteral mesenchymal cells but a decrease in TBX18 expression in Zeb2 cKO mice, suggesting an early abnormal development of ureteral SMCs. We also found that both apoptosis and proliferation were increased in ureteral mesenchyme cells, and the SMAD signaling was disturbed in Zeb2 cKO mice.

**Results:** We found that at P0 and E16.5, Zeb2 cKO mice developed hydroureter and hydronephrosis with dilated ureter devoid of ureteral smooth muscle cells as compared to wild-type littermate controls. Cell marker study showed that TAGLN1 ACTA2 ureteral SMCs did not appear but there was an expanded layer of FOXD1 POSTN ureteral tunica adventitia in Zeb2 cKO mice during early ureter development. At E14.5-E15.5, there was an increase of growth arrest specific protein 6 expression in ureteral mesenchymal cells but a decrease in TBX18 expression in Zeb2 cKO mice, suggesting an early abnormal development of ureteral SMCs. We also found that both apoptosis and proliferation were increased in ureteral mesenchyme cells, and the SMAD signaling was disturbed in Zeb2 cKO mice.

**Conclusions:** ZEB2 is expressed in ureteral mesenchymal cells. In the absence of ZEB2, ureteral inner mesenchymal cells differentiate into FDX1 POS+ ureteral tunica adventitia rather than ureteral SMCs. These data suggest that ZEB2 controls ureteral smooth muscle cell fate in ureteral mesenchymal cells. Loss of ZEB2 leads to depletion in the ureteral smooth muscle layer formation, which eventually causes hydroureter and hydronephrosis phenotype in Zeb2 cKO mice.

**Funding:** NIDDK, Support

**FR-PO755**

A Hedgehog (Hh)-TGFβ Signaling Axis Controls Murine Stromal Cell Development and Ureteropelvic Junction Patency

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**Background:** Signaling mechanisms that control stromal differentiation from Oct4+ progenitors during normal and malformed renal development are largely undefined. Hh proteins bind cell surface PTCH1, thereby disabling PTCH1-mediated inhibition of SMO and increasing Hh-mediated transcriptional activity. We showed that Cre-mediated Pchd1 deletion in Oct4+ progenitor cells at mouse E9.5 increased Hh signaling and induced formation of an ectopic population of Foxd1+Raldh2+ cells that block the ureteropelvic junction (UPJ) and are present in obstructing tissue in human UPJO (Shehani-Deloui et al., 2018). Here, we investigated molecular mechanisms that function downstream of Hh in this developmental disease context.

**Methods:** Hh and TGFβ signaling was investigated in mice with Tamoxifen (TM)-induced deficient either Pchd1, Tgfbr2, or both. EGFP+Oct4+ cells were isolated by flow sorting and analyzed by RNASeq. Kidney tissue was analyzed by histology, immunostaining, and light sheet fluorescence imaging. TGFBR2 deficiency was induced with ITD-1, which causes proteosomal degradation of TGFβRII (Willems et al, 2012), at different timepoints (E12.5, E15.5, E17.5, P1, P3, P5, P7, P14, P21, P28, and P40) and localized by RNASeq. Kidney tissue was analyzed by histology, immunostaining, and light sheet fluorescence imaging. TGFBR2 deficiency was induced with ITD-1, which causes proteosomal degradation of TGFβRII (Willems et al, 2012).

**Results:** RNASeq of Oct4+ cells isolated from ureteral ridges of Oct4-EGFP-Cre-;Pchd1floxP/foxg1afoxg1a mice at E13.5, 2 days post TM, demonstrated increased Tgfbr2 expression compared to controls (P=0.02). Yet, TM-dependent Cre-mediated sorting and analyzed by RNASeq. Kidney tissue was analyzed by histology, immunostaining, and light sheet fluorescence imaging. TGFBR2 deficiency was induced with ITD-1, which causes proteosomal degradation of TGFβRII (Willems et al, 2012), at different timepoints (E12.5, E15.5, E17.5, P1, P3, P5, P7, P14, P21, P28, and P40) and localized by RNASeq. Kidney tissue was analyzed by histology, immunostaining, and light sheet fluorescence imaging. TGFBR2 deficiency was induced with ITD-1, which causes proteosomal degradation of TGFβRII (Willems et al, 2012).

**Conclusions:** Increased Hh signaling in Oct4+ cells increases TGFβ signaling that controls formation of ectopic Raldh2+ stromal cells and obstruction of the UPJ.

**Funding:** Government Support - Non-U.S.

**FR-PO756**

Loss of Dicer in the Peri-Wolffian Duct Stroma Leads to aberrant Ureteric Budding and Increased Rates of Vescoureteral Reflex

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**Background:** Vescoureteral reflex (VUR) is associated with urinary tract infections, hypertension, and reflux nephropathy, a leading cause of pediatric end-stage renal disease. Formation of the vescoureteral junction is determined largely by the induction site of the ureteric bud from the Wolffian duct, which depends on signals from the surrounding stroma. VUR is heritable, but no single genetic mutation causes most known cases of VUR. We hypothesized that peri-Wolffian duct stroma (mutant=Tbx18cre; DicerloxP/loxP) mice would demonstrate gene expression changes post-transcriptionally. We hypothesize that miRNAs are necessary for vescoureteral junction development and prevention of VUR.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: 1. Draining the early development, PDGFRβ and α-SMA were expressed in the structures that were pericyte-like cell clusters, which were perilobular bundles of tubules, and urticaric buds, while desmin was mainly expressed in cap-mesenchyme in early stage. 2. As more and more tubules extended into medulla, their expressions were decreased and confined to interstitial cells in the mature kidney, while perilobular vessels expressed CD34 instead. PDGFRβ was expressed at both fibroblast and pericyte, while α-SMA and desmin were respectively expressed at fibroblast and pericyte. 3. Through the kidney development, both PDGFRβ and α-SMA were expressed in the structure, closely associated with the artery and arteriole, with former in the outer layer (adventitia) while latter in the inner layer of peripheral vessel cells, next to CD34 positive endothelial cells. No co-localization was observed. 4. All of the were expressed in young glomeruli while α-SMA vanished in the mature glomeruli.

Conclusions: Although the expressions of PDGFRβ and α-SMA are associated with renal vasculosperonecrosis and angiogenesis, their expressions are related with different vascular structures of endodermally derived mesenchymal and pericyte smooth muscle cell, while desmin is related to the differentiation of renal progenitor interstitial cells, including pericytes.

Funding: Government Support - Non-U.S.

FR-PO759

Optimal Generation of Mesangial Cells and the Stromal Progenitor Cell Lineage from a Platelet-Derived Growth Factor Receptor Alpha Fraction of Fetal Enzymatically Treated Kidneys

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Background: We previously transplanted a cell population comprising several heterogenic types of renal progenitor cells (RPCs) from mouse metanephrines into the nephrogenic zone of other mouse metanephrines and generated nephrons derived from the transplanted RPCs. However, mesangial cells of the regenerated glomeruli comprised cells derived from the host. We could not confirm the regeneration of mesangial cells by the transplanted cells. Therefore, we optimized the RPC cell composition via cell sorting and examined the possibility of regenerating the mesangial cells.

Methods: Metanephros was harvested from GFP mice, and an enzymatic treatment extracted the dissociated single cells (DSCs) from the metanephrines. Stromal progenitor cell components were extracted via cell sorting by targeting the platelet-derived growth factor receptor alpha (PDGFRα) fraction from the DSCs. Three groups of cells, i.e., the PDGFRα-sorted cells, non-sorted cells, and fibroblasts as controls, were transplanted into the nephrogenic zone of metanephrines. Then, these groups were transplanted under the retropitoneum of the para-aortic region of adult B6 mice and harvested after 2 weeks. Specimens were assessed via immunofluorescence staining. Furthermore, the regenerative cells were counted to the extent to which the transplanted cells reached.

Results: In the fibroblast group, the cells transplanted to the nephrogenic zone did not colonized in the metanephrines. In the non-sorted group, although some cells colonized, there was negligibly regeneration of the mesangial cells. However, in the PDGFRα-fraction sorted group, we confirmed regeneration of the mesangial cells from the eozogenic cells in 92% of glomeruli (n=13). Furthermore, the proportion of the eozogenic mesangial cells with a single glomerulus unit was 67.5%. We also confirmed regeneration of other stromal progenitor cell lineages, such as interstitial fibroblasts, vascular pericytes, and juxtaglomerular cells.

Conclusions: When we increased the ratio of the stromal progenitor cells via cell sorting targeting the PDGFRα fraction from DSCs, we succeeded in efficiently regenerating the mesangial cells and other stromal progenitor cell lineages, such as interstitial fibroblasts, pericytes, and juxtaglomerular cells, in the kidney of the mouse embryos.

FR-PO760

Endothelial-Specific Phosphatase VEPTP/PTPRB Is Essential for the Development of the Renal Mesangium

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Background: The angiopoietin-Tie2 signaling pathway plays an essential role in vascular development and homoeostasis while its dysregulation is associated with a number of diseases including pathologiacal neoangiocarization, glaucoma, diabetic nephotrophy, and acute kidney injury. The endothelial-specific phosphatase VEPTP/PTPRB plays a major role in the negative regulation of Tie2 receptor phosphorylation. We genetically inactivated the Ptprb gene in mice in order to elucidate its significance in renal vascular development.

Methods: Global genetic inactivation of a conditional floxed allele of Ptprb was accomplished using a tetracycline-inducible Cre-based recombination system. Mouse kidney sections were processed for histology and immunostaining while glomerular ultrastruicture was analyzed by transmission electron microscopy.

Results: PTPRB-deficiency results in notable simplification of the glomerular tuft and glomerular aneurysms in neonatal (P0) kidneys due to the impaired establishment of the mesangium reminiscent of genetic loss of components of the PDGFR signaling system (PDGfβ, Pdgfrb, and Nrp1). Immunochemistry for mesangial markers and ultrastructure analysis revealed the absence of mesangial structures, which were pericyte-like to scanty bundles of tubules, and urticaric buds, while desmin was mainly expressed in cap-mesenchyme in early stage. As more and more tubules extended into medulla, their expressions were decreased and confined to interstitial cells in the mature kidney, while perilobular vessels expressed CD34 instead. PDGFRβ was expressed at both fibroblast and pericyte, while α-SMA and desmin were respectively expressed at fibroblast and pericyte. Through the kidney development, both PDGFRβ and α-SMA were expressed in the structure, closely associated with the artery and arteriole, with former in the outer layer (adventitia) while latter in the inner layer of peripheral vessel cells, next to CD34 positive endothelial cells. No co-localization was observed. All of the were expressed in young glomeruli while α-SMA vanished in the mature glomeruli.

Conclusions: Although the expressions of PDGFRβ and α-SMA are associated with renal vasculosperonecrosis and angiogenesis, their expressions are related with different vascular structures of endodermally derived mesenchymal and pericyte smooth muscle cell, while desmin is related to the differentiation of renal progenitor interstitial cells, including pericytes.

Funding: Government Support - Non-U.S.

FR-PO761

Defining the Role of Vascular Endothelial Growth Factor 3 (VEGFR3) in the Fenestrated Microvasculature Beds of the Kidney

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Background: The vasculature of the mammalian kidney is heterogeneous due to the need to carry out highly specialized functions such as glomerular filtration, urinary concentration and electrolyte homeostasis. The vascular endothelial growth factor tyrosine kinase receptor 3 (VEGFR3) is best known for its essential role in lymphatic endothelial cell proliferation however it is also highly expressed in fenestrated microvascular beds in the kidney. We hypothesize that VEGFR3 is required for proper maturation of renal microvascular beds and that loss of VEGFR3 will alter the recruitment of progenitor cells into the kidney vasculature.

Methods: We generated a new conditional mouse model to study Vegfr3 function in the kidney vasculature (Vegfr3flox/flox). This model allows for endothelial-specific excision of the floxed Vegfr3 allele using the vascular-specific Cre driver strain Cdh5/CreERT2. We evaluated a Vegfr3flox/CreERT2 reporter mouse to analyze expression of Vegfr3 within the microvascular beds of the kidney. Mouse kidney sections were processed for histology and immunofluorescence.

Results: Analysis of Vegfr3flox/CreERT2 reporter mouse demonstrates that Vegfr3 is expressed in multiple fenestrated microvascular beds of the kidney including the glomeruluses, and various mesangial structures. Twenty percent of mice heterozygous for the intact neo-cassette-containing floxed Vegfr3 allele (Vegfr3flox/+ ) exhibit chylosis ascites suggesting disruption of the neo-cassette containing Vegfr3 allele. These mice demonstrate reduced viability and exhibit several vascular pathologies including blood filled lymphatic capillaries and hemorrhage of intestinal Peyers patches.

Conclusions: VEGFR3 is expressed in many specialized microvascular beds within the kidney and may play an important role in their development and maintenance. We have generated a novel conditional mouse model to comprehensively study the role of VEGFR3 in renal vasculature. Using this model and genetic knockout of Vegfr3 through development will provide valuable insights into specialized functions of fenestrated microvascular beds in the kidney.

Funding: NIDDK Support

FR-PO762

Modeling Vascular Diseases Using Organ-Specific Endothelial Cells

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Background: The establishment of vascular network initiates with the specification of endothelial cells and the formation of primitive vascular network. While primitive vascular network supplies nutrients to the developing embryo, postnatal vascular system mainly originates from aorta-gonad-mesonephros (AGM) that eventually gives rise to both endothelial and hematopoietic lineages. During development, homogenous endothelial cells further differentiate to acquire organ-specific identities to accomplish diverse functions of different organs. Endothelial cells may also be derived from multipotent progenitor cells within certain mesodermal organs. Recent study has shown that renal progenitors could at least partially contribute to renal vasculature. We established a kidney organoid differentiation platform that can generate renal-specific endothelial cells from human pluripotent stem cells. This differentiation platform enables us to study vascular development and diseases in an organ-specific manner.

Methods: Kidney Organoid Differentiation Single Cell RNA Sequencing Disease Models.

Results: We established a kidney organoid differentiation platform that can generate renal-specific endothelial cells from human pluripotent stem cells. This differentiation platform enables us to study vascular development and diseases in an organ-specific manner.

Funding: Government Support - Non-U.S.
FR-PO763

Vascularized Kidney Organoids for Modeling PKD
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Background: Various models of 3D culture have been developed to model PKD cystogenesis. Recent studies demonstrated the utility of hPSC-derived kidney organoids for modeling ADPKD, even control organoids exhibited cyst formation when forskolin was administered. Moreover, those organoid models displayed cyst formation in both proximal and distal nephrons, which may not fully recapitulate cyst pathogenesis of PKD patients. We postulate that vascularized kidney organoids developed in vitro under flow may provide a better model for in vivo cystogenesis via alteration of ciliary signals without the need for forskolin.

Methods: PKHD1-mutant hPSCs were generated by CRISPR-Cas9 genome editing. Heterozygous and homozygous mutants with frameshift mutations were selected with deep-seq. Kidney organoids were generated following our reported protocol and cultured in vitro under static or flow conditions. Forskolin was tested for cyst formation. cAMP activation was evaluated by ELISA. Control and cystic organoids were characterized by immunostaining and transcriptome analyses. To evaluate differential gene expression profiles, microarray (3D-Gene®) and Metacore® were used.

Results: CRISPR-mutant kidney organoids (static culture) with homozygous mutations in PKHD1 exhibited cyst formation in both proximal and distal nephrons when treated with forskolin, while a heterozygous mutant did not form cysts. Forskolin significantly increased cell proliferation marked by Ki67 in both tubular cells and interstitial cells in homzygous mutant organoids. Further, microarray analysis revealed differential gene expression induced by forskolin and/or PKHD1 homzygous mutations, which was associated with >50 signal pathways. Some signal pathways have been implicated in PKD cystogenesis, yet others, apparently altered by forskolin, appeared to be non-specific to PKD cystogenesis. By contrast, CRISPR-mutant, vascularized kidney organoids cultured under flow exhibited cyst formation and Na-K-ATPase mislocalization solely in distal nephrons without addition of forskolin, which are consistent with clinical findings.

Conclusions: The fluidic chip model of PKD organoids demonstrated clinically relevant phenotypes of PKD patients, which would complement current PKD models to better understand PKD pathomechanisms for new therapeutic development.

Funding: NIDDK Support, Commercial Support - Ajinomoto, Private Foundation Support

FR-PO764

Uremic Vasculopathy Modeling with Induced Pluripotent Stem Cells and Uremic Toxin Mixtures
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Background: Cardiovascular complications remain as major causes of morbidity and mortality in end-stage renal disease (ESRD) patients. Although uremic vasculopathy substantially contributes to the development of cardiovascular complications in ESRD, it is largely unknown how uremic vasculopathy with current research methods like animal models or cell culture experiment. In this study, we aimed to develop a simplified uremic vasculopathy model using uremic toxin mixtures on endothelial cells differentiated from induced pluripotent stem cells (iPSC-ECs).

Methods: Human umbilical vein endothelial cells from a normal control and an ESRD patient were reprogrammed to iPSCs using Sendai virus, then iPSC-ECs were differentiated from iPSCs. Uremic toxin mixtures comprised of diverse combination of urea, creatinine, uric acid, indoxyl sulfate, and advanced glycation end-product were tested in a cell culture model of iPSC-ECs. Reactive oxygen species (ROS), apoptosis, and tube formation or scratch migration assay were measured to evaluate dysfunction of iPSC-ECs. Media alone was used as a negative control and 15% serum from ESRD patients receiving hemodialysis was used as a positive control.

Results: Urea, uric acid, and indoxyl sulfate significantly suppressed the tube formation of iPSC-ECs, while creatinine alone did not affect ROS levels or the tube formation of iPSC-ECs. Uremic toxin mixtures comprised of high concentration of urea, creatinine, uric acid, and indoxyl sulfate increased ROS production and apoptosis, whereas decreased tube formation of iPSC-ECs similarly with ESRD patients’ serum. ESRD patient-specific iPSC-ECs showed impaired wound healing potential which was decreased tube formation of iPSC-ECs similarly with ESRD patients’ uremic serum. Uremic toxin mixtures comprised of diverse combination of urea, creatinine, uric acid, and indoxyl sulfate, while creatinine alone did not affect ROS levels or the tube formation of iPSC-ECs. Uremic toxin mixtures were used as a positive control.

Conclusions: The results demonstrated the utility of iPSC-derived kidney organoids for modeling ADPKD, even control organoids exhibited cyst formation when forskolin was administered. Moreover, those organoid models displayed cyst formation in both proximal and distal nephrons, which may not fully recapitulate cyst pathogenesis of PKD patients. We postulate that vascularized kidney organoids developed in vitro under flow may provide a better model for in vivo cystogenesis via alteration of ciliary signals without the need for forskolin. In addition, our uremic toxin mixtures neurotoxicity in iPSC-ECs, while creatinine alone did not affect ROS levels or the tube formation of iPSC-ECs. Uremic toxin mixtures comprised of diverse combination of urea, creatinine, uric acid, and indoxyl sulfate, while creatinine alone did not affect ROS levels or the tube formation of iPSC-ECs. Uremic toxin mixtures were used as a positive control.

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FR-PO767
Development of Novel Real-Time Biosensor Kidney Organoids to Study AKI
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Background: Kidney disease is on the rise worldwide. Persistent acute kidney injury and chronic kidney disease inevitably both lead to tubular atrophy, kidney fibrosis and eventually end-stage renal disease. The exact mechanisms are poorly understood and there are currently no treatments. Recent advances in generating human kidney organoids in vitro, have provided an invaluable tool to study kidney disease and injury, and a new tool for small molecule screening. We utilize a recently developed human kidney organoid protocol from induced pluripotent stem cells (iPSCs) to generate a new biosensor to deepen our understanding of acute kidney injury and fibrotic tissue development in this model.

Methods: As a real-time readout of acute injury and to test the efficacy of new compounds we developed an early apoptosis reporter, Cytochrome C-GFP. Healthy cells in the organoids express green GFP in the mitochondria, upon injury the GFP signal loses mitochondrial localization and becomes cytoplasmic after activating the apoptotic Caspase 3/7 apoptotic pathway. We establish optimal dosage with known nephrotoxins and a real-time response using Cytochrome C-GFP organoids to validate our biosensor.

Results: Using the Cytochrome-C-GFP biosensor iPS line we show that the healthy iPSCs and organoids exhibit mitochondrial Cytochrome-C-GFP expression as shown by co-labelling with MitoTracker Red CMXRos. Upon injury with nephrotoxins the GFP signal relocates from the mitochondria towards the cytoplasm and becomes cytoplasmic. Co-labelling with apoptotic Caspase 3/7 stains showed that it co-localizes with the injured cells (cytoplasmic Cytochrome-C-GFP expression) in the tubules.

Conclusions: Using the Cytochrome-C-GFP biosensor iPS line we show that the healthy iPSCs and organoids exhibit mitochondrial Cytochrome-C-GFP expression. Using this model, we are able to observe the injury response in a real-time manner with the use of Cytochrome-C-GFP organoids for early apoptotic response. In addition, this system is an excellent model for investigating mitochondrial injury and early apoptosis in acute kidney injury.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

FR-PO768
Optimizing Human Kidney Organoids for Modeling Nephrotoxicity, Kidney Injury, and Kidney Diseases and for Screening to Identify Therapeutic Options
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Background: To optimize their potential in modeling nephrotoxicity and kidney disease, pluripotent stem cell-derived kidney organoids are being optimized for enhancing reproducibility, differentiation, scalability and reducing costs.

Methods: Organoids were generated by modification of our laboratory’s prior published techniques. Importantly, organoids were generated without use of undefined factors. We used common differentiation protocols for forming renal structures including NPCs, renal tubules, stromal cells, and endothelial cells in anatomically juxtaposed contexts. Avoidance of undefined factors facilitates potential use of these organoids for more clinically relevant applications. Variation on the simplified and cost-effective protocols results in variation in composition of cell types and structures along with varying connectivity among cell types. Immunostaining for markers including KIM-1, TSC2+/−, αSMA, cPLA2, and γH2AX showed that kidney organoids containing multiple distinct structures present together were more sensitive to nephrotoxins compared to organoids generated to have predominant amount of proximal tubules lacking other cell types.

Conclusions: Protocols have been developed to generate human kidney organoids without undefined matrices in a more streamlined cost effective manner with programmed relative amounts of distinct kidney component structures. Proximal tubule susceptibility to toxicity is altered by adjustments in the organoid generation that change the surrounding contextual environment of other kidney structures.

Funding: NIDDK Support, Other NIH Support - NCATS

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FR-PO769
Modeling Renal Manifestations of Tuberous Sclerosis Complex with iPSC-Derived Kidney Organoids
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Background: Renal manifestations are the second most common clinical finding in patients with TSC. Here we tested the ability of human induced pluripotent stem cell (iPSC) lines carrying heterozygous or homozygous mutations in the TSC2 locus, to differentiate into human kidney cells and to model the cellular pathophysiology of TSC kidney lesions.

Methods: An iPSC cell line derived from a patient carrying a heterozygous microdeletion in the TSC2 locus (TSC2−/−), and a TALEN-engineered isogenic line carrying the microdeletion in both TSC2 alleles (TSC2−/−), were incubated with CHIR99021 (CHIR), Activin and FGFR, presented in a sequential fashion. The same concentration and stimulation duration for each growth factor were used for both iPSC lines.

Results: After modifications to the original chemically defined differentiation protocol developed by Morizane et al., both iPSC lines successfully generated SIX2+, PAX2+ nephron progenitor cells with high efficiency by day 9 of differentiation. By day 14, self-organized renal vesicles had formed in the cultures of both cell lines, albeit visible cyst-like structures were observable in TSC2−/− vesicles but not in TSC2−/− vesicles. In low attachment 3D culture conditions, TSC2−/− organoids but not TSC2−/− organoids, presented expanding spheroidal cysts. Histological analysis of TSC2−/− and TSC2−/− organoids on day 21 of differentiation showed the presence of major kidney cell types including glomerular PDX1-expressing podocytes, ECadherin-expressing distal tubules, and proximal tubules with brush borders. Cyst-like, dilated proximal and distal tubules with increased phosphorylation of p70-S6-kinase were observed in TSC2−/− organoids but not in heterozygous ones.

Conclusions: We have established a protocol for directed differentiation of TSC iPSCs into 3D organoids containing multi-segmented nephron structures that recapitulate TSC-specific cystic phenotypes. This novel biosensor tool will provide valuable insight into the cellular and molecular mechanisms of renal abnormalities and set the basis for patient-specific phenotypic drug screens.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

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FR-PO770
Kidney Organoid Model of Selective Podocyte Injury
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Background: Podocyte injury triggers progressive loss of kidney function. Determining the mechanisms involved in the progression of podocyte damage is critical to developing renoprotective therapies. We previously generated a transgenic mouse line, NEF5P, which expresses human (h) CD25 on podocytes. Selective podocyte injury can be induced by the IC525-targeted immunotoxin, LMB2. In addition, we analyzed podocyte-specific gene expression profiles utilizing Ribotag mice, which selectively express hemagglutinin (HA)-tagged ribosomal protein in podocytes. In the present study, to efficiently investigate the function of altered genes during podocyte injury, we aimed to generate NEF5P/Ribotag kidney organoids and establish an in vitro model of podocyte injury.

Methods: Neprin progenitor cells (NPCs) were established by culture-dependent purification (CDP) method from 12.5-dpc NEF5P/Ribotag mouse kidneys (Cell Stem Cell 2016, 19, 516-29). Kidney organoids were generated by transient stimulation with FGF2 and CHIR99021 of NPC aggregates and subsequent 6–8 day culture. Podocyte-specific polyzymes were obtained via immunoprecipitation using an anti-HA antibody.

Results: We confirmed that the organoids show glomerulus-like and tubule-like structures. Immunostaining revealed that the former expressed nephrin, WT1, podocalyxin, and synaptopodin and the latter expressed LTL and megalin. Neprin-positive podocytes also expressed ICDC25 and HA. Q-PCR confirmed that Nphs1 (33.3), Nphs2 (21.2), Wt1 (24.9), and Dach1 (6.2) were concentrated in HA-immunoprecipitated LTL and megalin expressed lysates. Using the ICDC25-targeted immunotoxin, LMB2 (20 nM) for 4 days, podocalyxin and WT1 staining disappeared. Nphs1 and Nphs2 mRNAs became undetectable, Wt1 (0.05 fold) and Dach1 (0.37) decreased, and Ccl11 (4.2) and EphA8 (55.6) increased, thus reproducing vivo injured podocytes.

Conclusions: We established kidney organoids in which podocytes can be selectively injured and podocyte mRNA can be selectively obtained. This organoid system will be a powerful tool for investigating mechanisms underlying podocyte injury.

Funding: Government Support - Non-U.S.
A Drug-Specific Nephrotoxicity Prediction System Using Kidney Organoids

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Background: Drug-induced nephrotoxicity is increasingly recognized as a serious clinical problem, leading to acute kidney injury (AKI) and chronic kidney disease. Lack of reliable models with physiological function of human kidneys results in the difficulty to predict nephrotoxicity of new drugs in preclinical trials. Here, we demonstrate kidney organoids containing multi-segmented nephron epithelial cells generated from human pluripotent stem cells (hPSCs) as a new technology for pre-clinical nephrotoxicity assessment.

Methods: We generated kidney organoids from hPSCs by a directed differentiation protocol and validated the maturation of organoids using immunostaining and transcriptome analyses. Organoids were treated with various nephrotoxins which cause injury in a segment-specific manner via specific drug transporters. Injury responses were analyzed by immunostaining, qPCR, and biomarker assays. We also generated reporter organoids to evaluate the toxicity with a real-time biosensor of ATP/ADP ratio in 384-well culture plates.

Results: We confirmed increased expression of drug transporters including OAT1, OCT1, OCT2, and PMAT with matured gene expression profiles in kidney organoids during 5 to 7 weeks of differentiation. Organoids simulated various drug-induced injury such as biomarker upregulation, DNA damages, and morphological changes specifically in the tubules or in the glomeruli by low concentration of nephrotoxics mediated by these transporters (OATs: tenofvir and aristolochic acid [AA], OCT: cispatin, PMAT: penicillin). The injury induced by tenofvir and AA, or cisplatin were alleviated by OAT1 inhibitor probenecid or OCT2 inhibitor cicetemide, respectively. On the other hand, high concentration of these nephrotoxins resulted in widespread injury to all nephron compartments and interstitial cells. In addition, nephrotoxins significantly reduced the ATP/ADP ratio within 24 hours of treatment.

Conclusions: Kidney organoids faithfully recapitulate drug-induced AKI by reflecting the toxicity characteristics of the drugs, allowing to distinguish between drug-specific and generalized toxicity responses. The reporter organoids may realize high-throughput and real-time nephrotoxicity screening, providing a new platform to evaluate nephrotoxicity as preclinical trials.

Funding: NIDDK Support, Commercial Support - Ajinomoto, TORAY, Private Foundation Support, Government Support - Non-U.S.

Modeling a Recurring Wilms Tumor-Associated Mutation in Kidney Organoids

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Background: Wilms tumor (WT) is the most common pediatric kidney cancer and blastemal-predominant tumors represent a more lethal, chemotherapy-resistant form of WT. Poorer outcomes have been associated with the nephrogenic niche of the fetal kidney, suggesting it arises from a malignant transformation of these cells. We previously demonstrated the unique ability of the SIX1-Q177R mutation to drive kidney organoid differentiation in vitro, resulting in the formation of complex nephron-like structures. Building upon established protocols, we have developed a modified, minimal 3D protocol and validated the maturation of organoids using immunostaining and transcriptome analyses. Organoids were treated with various nephrotoxins which cause injury in a segment-specific manner via specific drug transporters. Injury responses were analyzed by immunostaining, qPCR, and biomarker assays. We also generated reporter organoids to evaluate the toxicity with a real-time biosensor of ATP/ADP ratio in 384-well culture plates.

Results: We confirmed increased expression of drug transporters including OAT1, OCT1, OCT2, and PMAT with matured gene expression profiles in kidney organoids during 5 to 7 weeks of differentiation. Organoids simulated various drug-induced injury such as biomarker upregulation, DNA damages, and morphological changes specifically in the tubules or in the glomeruli by low concentration of nephrotoxics mediated by these transporters (OATs: tenofvir and aristolochic acid [AA], OCT: cispatin, PMAT: penicillin). The injury induced by tenofvir and AA, or cisplatin were alleviated by OAT1 inhibitor probenecid or OCT2 inhibitor cicetemide, respectively. On the other hand, high concentration of these nephrotoxins resulted in widespread injury to all nephron compartments and interstitial cells. In addition, nephrotoxins significantly reduced the ATP/ADP ratio within 24 hours of treatment.

Conclusions: Kidney organoids faithfully recapitulate drug-induced AKI by reflecting the toxicity characteristics of the drugs, allowing to distinguish between drug-specific and generalized toxicity responses. The reporter organoids may realize high-throughput and real-time nephrotoxicity screening, providing a new platform to evaluate nephrotoxicity as preclinical trials.

Methods: We generated kidney organoids from hPSCs by a directed differentiation protocol and validated the maturation of organoids using immunostaining and transcriptome analyses. Organoids were treated with various nephrotoxins which cause injury in a segment-specific manner via specific drug transporters. Injury responses were analyzed by immunostaining, qPCR, and biomarker assays. We also generated reporter organoids to evaluate the toxicity with a real-time biosensor of ATP/ADP ratio in 384-well culture plates.

Results: We confirmed increased expression of drug transporters including OAT1, OCT1, OCT2, and PMAT with matured gene expression profiles in kidney organoids during 5 to 7 weeks of differentiation. Organoids simulated various drug-induced injury such as biomarker upregulation, DNA damages, and morphological changes specifically in the tubules or in the glomeruli by low concentration of nephrotoxics mediated by these transporters (OATs: tenofvir and aristolochic acid [AA], OCT: cispatin, PMAT: penicillin). The injury induced by tenofvir and AA, or cisplatin were alleviated by OAT1 inhibitor probenecid or OCT2 inhibitor cicetemide, respectively. On the other hand, high concentration of these nephrotoxins resulted in widespread injury to all nephron compartments and interstitial cells. In addition, nephrotoxins significantly reduced the ATP/ADP ratio within 24 hours of treatment.

Conclusions: Kidney organoids faithfully recapitulate drug-induced AKI by reflecting the toxicity characteristics of the drugs, allowing to distinguish between drug-specific and generalized toxicity responses. The reporter organoids may realize high-throughput and real-time nephrotoxicity screening, providing a new platform to evaluate nephrotoxicity as preclinical trials.

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FR-PO775
Low Nephron Number Resulting from SIRT3 Deficiency Increases Susceptibility to Renal Dysfunction Later in Life
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Background: Low nephron endowment is a risk factor for chronic kidney diseases (CKD) in adulthood but no causal correlation has been formally proved. We have demonstrated that mice lacking the mitochondrial protein Sirtuin 3 (SIRT3) are more susceptible to acute kidney injury than wild type (WT) mice. Here, we explored whether Sirt3−/− mice can be used as a low nephron number model and are more susceptible to CKD.

Methods: Metanephroi were isolated from WT and Sirt3−/− mice to study nephrogenesis. The susceptibility of Sirt3−/− mice to CKD was studied in adriamycin (ADR) or bovine serum albumin (BSA)-induced progressive nephropathies.

Results: We demonstrated that, at the embryonic day 12.5, Sirt3−/− mice had less ureteric bud branching and fewer metanephric SIX2+ progenitor cells. Impaired nephrogenesis in Sirt3−/− mice resulted in a nephron deficit compared to WT mice (40% reduction at postnatal day 7, P<0.001), due to altered mitochondrial dynamics, biogenesis, mitophagy and energetic metabolism. Notably, low nephron endowment at birth is not enough to cause renal disease in adulthood, but enhances the susceptibility of Sirt3−/− mice to renal damage. Specifically, when Sirt3−/− mice were exposed to ADR or BSA overload, they experienced more severe proteinuria (35% loss (% reduction in WT−1 cell density: Sirt3−/−, 68% vs WT, 30%, P<0.01) and vascular rarefaction than WT mice (% reduction in MECA-32+ cell density: Sirt3−/−, 57% and WT, 43%, P=0.05). We also proved that nephron deficit can be corrected through prenatal SIRT3 boosting. Indeed, in a model of low nephron number and reduced renal SIRT3 levels – WT mice born to mothers fed a low protein diet – nephron number was restored through NAD+ precursor nicotinamide riboside (NR) treatment.

Conclusions: Our results provide evidence that low nephron endowment is a critical determinant of susceptibility to CKD when the kidney is challenged by additional hits, and support the use of SIRT3 boosting during nephrogenesis as a therapeutic option for increasing nephron number.

Funding: Private Foundation Support

FR-PO776
Loss of Hypoxia-Regulated MicroRNA-210 Results in Decreased Nephron Number
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Background: Low nephron number increases an individual’s risk for developing hypertension and chronic kidney disease, which affect approximately 30% and 15% of American adults, respectively. Intrauterine growth restriction and fetal hypoxia are significant causes of low nephron number; however, the underlying molecular mechanisms that drive this are unknown. Nephron number, in turn, is determined prior to birth in humans. microRNA-210 (miR-210) is the most consistently induced microRNA in hypoxia and regulates various processes including metabolism, cell cycle progression, and apoptosis. We hypothesize that loss of miR-210 results in abnormal kidney development.

Methods: To test this hypothesis, we obtained a global miR-210 knockout (KO) mouse. We used the “gold standard” physical dissector/fractionator combination method to estimate nephron number at postnatal day 30 (P30). We collected wildtype (WT) and KO littermates right before the burst in nephrogenesis at P0 and right before the end of nephrogenesis at P2. To measure changes in gene expression in nephron progenitors and their derivatives, we performed qPCR, immunofluorescent staining, and Western blot assays.

Results: We found an approximately 35% reduction in nephron number in miR-210 KO male kidneys and a 28% reduction in both WT and KO female kidneys, compared to WT males. Analysis of nephron progenitor proliferation, apoptosis and differentiation markers showed no discernable difference in kidney development at P0. However, we observed decreased expression of the differentiation marker Jag1 by Western blot at P2, as well as fewer total Lef1, Jag1, and Ncad1-positive differentiating nephron structures. We observed no difference in nephron progenitor proliferation nor apoptosis at P2. However, there was an approximately 35% increase in the total number of cleaved-Casp3-positive cells and its immunofluorescent staining suggests that there is an increase in apoptosis in differentiating nephron structures. Furthermore, we found increased mRNA expression of several pro-apoptotic miR-210 target genes (Casp3, Casp6/FLASh, Pmp2, and Bmp3).

Conclusions: miR-210 KO kidneys have a nephron deficit, which is associated with decreased differentiating nephron structures and increased apoptosis within those structures.

Funding: NIDDK Support

FR-PO777
Caloric Restriction During Pregnancy Reduces Nephron Endowment and Impairs Adult Kidney Function by Inactivating mTOR and the Methionine Salvage Pathway
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Background: Maternal malnutrition during pregnancy correlates with lower nephron numbers and higher risk of chronic kidney disease (CKD) in adulthood, but the underlying molecular mechanisms are still unknown. The nephron progenitor pool exhausts abruptly in the third postpartum day in mice with no nephrogenesis at later stages. We used a mouse model to study the effects of maternal caloric restriction on kidney development and nephron progenitor cells (NPCs).

Methods: Pregnant CD1 mice were monitored in metabolic cages and their daily caloric intake was reduced by 30% compared to the average consumption of the control group at the same gestational age. The effect on kidney morphology and function was measured by immunostaining, kidney biomarkers analysis and nephron count. Six2+ GFP NPCs were extracted from Six2 CreRor E18.5 embryos of calorically restricted pregnant dams or controls and isolated by FACS. mRNA expression and metabolic activity in sorted NPCs were evaluated by bulk RNAseq and mass spectrometry, respectively. Key findings were validated using western blots.

Results: Animals exposed to caloric restriction in utero had 50% fewer nephrons after birth and throughout adulthood as well as lower kidney function, as demonstrated by higher serum urea levels. Nephrogenesis was shorter by at least 24 hours. Calorically restricted E18.5 Six2+ NPCs had decreased expression of mTOR pathway genes, and lower overall mTOR activity, reflected in lower levels of phosphorylated ribosomal protein S6. Mass spectrometry of metabolites from isolated NPCs identified a strong reduction in the methionine salvage pathway.

Conclusions: Reduced mTOR signalling and methionine salvage activity in NPCs from fetuses carried by malnourished mothers led to a premature end of nephrogenesis, reduced nephron numbers, and the associated increased risk for CKD in adulthood.

Funding: Government Support - Non-U.S.

FR-PO778
Ontogeny and Phylogeny: Our Evolutionary History and Bioenergetics Explain High Variation in Nephron Number (NN) at Birth
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Background: Low NN at birth is recognized as a major lifetime risk factor for chronic kidney disease (CKD), but its origin is poorly understood. Recent studies based on the Barker hypothesis suggest that epigenetic downregulation of nephrogenesis modulated by maternal-fetal stressors (e.g. hypoxia, undernutrition) contributes to CKD in adulthood. Application of evolutionary biology to medicine has led to new approaches in cancer and infectious diseases research, and shows promise in nephrology (Chevalier, Kidney Int Rep 2:302, 2017; J Am Soc Nephrol 29:705, 2018).

Methods: Data abstraction: Medline searches including the terms “kidney, evolution, physiology, genetics, bioenergetics, and development” 1970 to the present.

Results: The rapid evolution of hominids was a product of increased nutrient quality and availability – 2 million years ago, resulting from transition of the east African environment from forest to savannah. Natural selection favored doubling brain size from Homo habilis to Homo sapiens over a period of 1 million years. Our brain consumes 90% of basal metabolic rate (BMR) at birth, 50% at 1 year of age, and 20% in adulthood. Maternal energy consumption in pregnancy and during breastfeeding increases BMR by 20%, which must be balanced by high kidney oxygen consumption tied to BMR. Maternal protein restriction during pregnancy in mice resulted in 75% reduction in NN; offspring of mice lacking DNA methyltransferase 1 (Dnmt1) in nephron precursor cells developed 50% reduction in NN. Nutrients and oxygen signal energy metabolism to mitochondria through the hypoxia-inducible factor (HIF) pathway to regulate nephron morphogenesis. This epigenetic response is driven by metabolic reprogramming of nephron precursor cells from glycolysis (maintenance of self-renewal) to differentiation (cessation of neprogenesis) mediated by the Hif pathway.

Conclusions: Energy, the currency of evolution, is constrained by the environment. Selection pressure favors allocation of available energy from kidney to brain growth in early development. Through genetic evolution of metabolism, reduced allocation of nutrients available during pregnancy proportionately restricts nephrogenesis. Since only 18% of children with congenital kidney anomalies develop end-stage CKD before 15 years of age, this evolutionary strategy favors reproductive fitness in the majority of cases.

Funding: Support
FR-PO779

Cell Turner Dynamics in the Human Kidney Using Radiocarbon Dating
Christina Jones,1 Keng-Yeh Fu,1 Endre Kiss,1 Kanar Aklass,1 Anders Kjellman,1 Jaakko Parnak,1 Samuel Bernard,1 Henrik Drudi,1 Kirsty Spalding,1 Karolinska Institutet, Huddinge, Sweden; 2CNRS, Villeurbanne, France.

Background: Kidney cell turnover is fundamental to maintain organ homeostasis and to replace lost cells in response to injury. This study aims to define regeneration in the human kidney and explore turnover kinetics in health and disease. Proximal tubular epithelial cells are known to turnover, however questions remain about the dynamics and source of replacement cells. Podocytes were traditionally considered irreplaceable, however reports of putative progenitors have sparked interest in podocyte regeneration. The novel method of radiocarbon dating DNA to determine human cell age (Spalding et al. 2005) has been used to answer fundamental questions about human regeneration in the brain, heart, and adipose tissue. This study adapts the method to address these important questions in the kidney.

Methods: Human kidney nuclei sorting was developed for this study. The method is effective for whole kidney tissue and isolated glomerular fraction analyses, from either fresh or frozen tissue from both nephrectomy and postmortem sources. Podocyte, endothelial and proximal tubule nuclei were isolated, antibody-labeled and sorted by flow cytometry. This method yields over 10 million cell-type specific nuclei per sample with over 95% sort purity required for radiocarbon dating. DNA was extracted using carbon-clean methods and sent for carbon isotope analysis using accelerator mass spectrometry.

Results: Preliminary results from a cohort of 10 kidneys, collected from nephrectomy, indicates human proximal tubule cells have an average age of 13.3 years (±2.6), turning over at a rate of 7.7% per year. This was not impacted by patient age. Endothelial and podocyte nuclei dating is ongoing. DNA content analysis, via flow cytometric analysis of DAPI-labeled nuclei, indicates limited endoreduplication.

Conclusions: Radiocarbon dating has the potential to definitively answer questions regarding kidney regeneration in humans. Nuclei-based sorting provides an unbiased method to efficiently sort large numbers of cell-specific nuclei for a range of downstream analyses. Preliminary results of proximal tubules and ongoing successful sorts of podocytes and endothelial cells provides proof-of-principle that human kidney cell age can be determined. From physiological turnover, this study forms the basis for ongoing examination of kidney regeneration in pathology.

Funding: Commercial Support - AstraZeneca, Government Support - Non-U.S.

FR-PO780

Using Next-Generation Imaging Technologies to Construct 3-D Multi-modal Molecular Atlases of the Human Kidney
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Background: Little is known about the integration, interactions, and molecular cross-talk between the different cell types and cellular compartments in normal kidneys. As part of the Human BioMolecular Atlas Program (HuMIAP), we are developing an ultra-high content imaging mass spectrometry (IMS)-based 3-D imaging pipeline to characterize the molecular signatures of different cell types at high resolution in normal, intact human kidneys.

Methods: Fresh discarded human kidneys obtained from surgical nephrectomy specimens were frozen on dry ice/isopentane slurry. Sequential sections were obtained through tissue blocks, scanned for autofluorescence (AF), and alternate sections prepared for IMS and multiplexed immunofluorescence (MxIF). IMS data was collected using a prototype MALDI timsTOF Pro Mass Spectrometer. Two cycles of MxIF were performed using a panel of validated, fluorophore-conjugated antibodies, and image fusion used to integrate information from IMS-generated molecular maps with autofluorescence and MxIF images. DNA, IMS/AF/MxIF images were then registered and mapped to the 3-D coordinate system using data from sequential sections with in house tools.

Results: A preliminary lipidomics study of human kidney tissue has been performed using our custom 3-D multimodal molecular imaging platform. The data set consists of 32 serial sections collected from the cortex of the kidney. Each 2-D tissue section is ~48 μm thick and they were imaged using IMS at 20 μm spatial resolution, resulting in ~150,000 pixels per section. AF/IMS and MxIF image registration pipelines enabled the construction of high-spatial resolution ion volumes. The entire 3-D volume was ~4x8x32 mm and contains ~4.8 million voxels (20x20x10 μm). The fully constructed 3-D molecular atlas enabled the visualization of various lipids to specific substructures in the kidney, including the proximal and distal tubules and glomeruli. For example, C24 Sulfatide and PI-Cer(42:0) (putative identifications) were found to track with distal tubules throughout the 3-D volume.

Conclusions: We have developed a novel pipeline for 3-D biomolecular multimodal tissue imaging that will enable the construction of high-resolution molecular atlases of the human kidney.

Funding: Other NIH Support - Hubbard Metropolitan Authority

FR-PO781

Phenotype Expansion of Heterozygous FOXC1 Mutations Towards Involvement of CAKUT
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Background: Heterozygous FOXC1 mutations have been identified as the cause of Axenfeld-Rieger syndrome type 3 and anterior segment dysgenesis 3. Patients present with variable eye malformations. Syndromic cases may present with abnormalities in brain, heart, blood vessels, and hearing loss. Congenital anomalies of the kidney and urinary tract (CAKUT) have not been associated with mutations in FOXC1.

Methods: In order to identify novel monogenic causes of CAKUT we performed whole exome sequencing (WES) in 514 families with CAKUT.

Results: By WES analyses, we discovered 7 FOXC1 heterozygous mutations in 8 CAKUT families. Five of the families have isolated CAKUT, while the other 3 families have syndromic CAKUT with anomalies in eyes, blood vessels, brain, bones, or facial dysmorphologies. CAKUT phenotypes include renal agenesis, renal dysplasia, multicystic dysplastic kidney, ureteropelvic junction obstruction, hydropsphrosis, vesicoureteral reflux, and posterior urethral valve. None of the 7 mutations were reported in patients with Axenfeld-Rieger syndrome or anterior segment dysgenesis before. Two of the mutations are novel and the others are present in <5 individuals as heterozygote of 125,000 healthy controls in the gnomAD database. We thereby discovered CAKUT as a new phenotype of heterozygous FOXC1 mutation. Interestingly, mouse models for FOXC1 (Green, 1970; Kume et al., 1998; Kume et al., 2000; Motojima et al., 2016) show severe CAKUT and CAKUT phenotype in males with FOXC1 mutations. We propose the presence of CAKUT in heterozygous FOXC1 mutation is due to allelism, we conducted genotype-phenotype correlations. There are 40 truncating and 34 missense mutations known in Axenfeld-Rieger syndrome or anterior segment dysgenesis. All 34 missense mutations are in the forkhead domain. In contrast, in the 8 CAKUT families, we did not find any truncating mutations and only 1 out of 4 missense mutation is in the forkhead domain.

Conclusions: We propose a phenotype expansion of FOXC1 to include CAKUT, potentially explained by allelism.

Funding: NIDDK Support, Other NIH Support - T32-GM007748

FR-PO782

PLXNB2 Mutations Are a Likely Cause of Congenital Anomalies of the Kidneys and Urinary Tract in Humans and Mice
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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) constitute the most common cause of end-stage renal disease in children, but the genetic basis of CAKUT remains poorly understood. Gene mutations are the underlying cause of CAKUT. Current molecular analyses of CAKUT cases in humans are primarily based on whole exome sequencing. In our CAKUT WES data to discover novel candidate CAKUT genes. Functional studies were carried out to verify the pathogenesis of variants in these candidate genes. To identify novel monogenic causes of CAKUT in humans, we performed whole exome sequencing (WES) in a worldwide cohort of 703 individuals with CAKUT. Based on the mode of inheritance in mice and pl1 scores (Loss of function intolerant) in the ExAC database for the 185 murine CAKUT genes, we screened for variants in these genes in our CAKUT WES data to discover novel human candidate CAKUT genes. Functional studies were carried out to verify the pathogenesis of variants in these candidate genes.

Results: We identified 6 different heterozygous mutations in PLXNB2 in 7 individuals from unrelated families, one heterozygous mutation occurred de novo. Affected individuals exhibited a broad spectrum of CAKUT phenotypes, while 7% of individuals exhibited syndromic features. With functional studies, we found mutations in PLXNB2 destabilized the PLXNB2 protein, damaged the synthetic PLXNB2 protein transport, weakened the binding ability of the PLXNB2 protein to its receptor, Semaphorin 4, and influenced the cells migration and the activity of CDC42 and Rac in models are important research tools for human CAKUT, to date, 185 genes that if mutated cause murine CAKUT phenotypes is in the MGI database (http://www.informatics.jax.org). Most of them could also be a potential cause of CAKUT in humans.

Conclusions: We identified novel monogenic causes of CAKUT in humans, whole performed whole exome sequencing (WES) in a worldwide cohort of 703 individuals with CAKUT.

Methods: In order to identify novel monogenic causes of CAKUT in humans, we performed whole exome sequencing (WES) in a worldwide cohort of 703 individuals with CAKUT. Based on the mode of inheritance in mice and pl1 scores (Loss of function intolerant) in the ExAC database for the 185 murine CAKUT genes, we screened for variants in these genes in our CAKUT WES data to discover novel human candidate CAKUT genes. Functional studies were carried out to verify the pathogenesis of variants in these candidate genes.
Mutations in UMOD Are Associated with FSGS and Can Be Mistaken for a Glomerular Disease

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Background: Steroid-resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. We previously identified causative recessive mutations in NOS1AP in two SRNS families and demonstrated that NOS1AP mutations impaired CDC42 activation, podocyte migration rate (PMR) and focal adhesion formation (Majmundar et al, JASN, 29:682, 2018). To further delineate the pathogenesis of SRNS due to NOS1AP loss-of-function, we generated a mouse model and performed additional cell culture studies.

Methods: We show that the human SRNS phenotype due to recessive mutations in NOS1AP is characterized by dysregulated focal adhesion structures leading to podocyte foot process effacement. We show that the human SRNS phenotype due to recessive mutations in NOS1AP is characterized by dysregulated focal adhesion structures leading to podocyte foot process effacement.

Results: We developed a mouse model for SRNS due to NOS1AP mutations and showed that NOS1AP-deficient mice developed proteinuria starting at the age of 5 months when compared to wild-type and monoallelic littermates. These mice were also characterized by significant foot process effacement and dysregulated focal adhesion structures.

Conclusions: We show that the human SRNS phenotype due to recessive mutations in NOS1AP is characterized by dysregulated focal adhesion structures leading to podocyte foot process effacement. These findings provide new insights into the pathogenesis of SRNS due to recessive mutations in NOS1AP and implicate dysregulated focal adhesion structures as a key feature of the SRNS phenotype.

Funding: NIDDK Support

FR-PO784

Whole-Exome Sequencing Identifies Mutations in ARHGEF6 as a Potential Novel Monogenic Cause of Congenital Anomalies of the Kidney and Urinary Tract

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Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease in the first 3 decades of life. Although over 40 monogenic genes have been implicated in human CAKUT so far, many causes remain elusive.

Methods: In order to identify novel monogenic causes of CAKUT we performed whole exome sequencing (WES) in 514 families with CAKUT. Results: By WES, we discovered a missense mutation (p.1444N) in the X-linked gene ARHGEF6 in 3 affected male subjects of family A5124 with CAKUT. Evaluation of our WES data of 514 unsolved CAKUT families revealed 3 further hemizygous ARHGEF6 mutations in 3 families (family GM1: p.R191L; B115S: p.L378A*58; GM2: c.2135A>G). All affected males in these families were previously reported in association with uromodulin associated kidney disease (UAKD). Consistent with the features for UAKD, most patients in our study presented with autosomal dominant inheritance, subnephrotic range proteinuria, minimal hematuria, and renal impairment. These patients with UMOD associated kidney disease did not have the classic clinical characteristics of goiter, hyperuricemia, or presence of renal cysts on renal ultrasound. Kidney biopsies showed histologic features of glomerular injury consistent with secondary FSGS including focal sclerosis and podocyte foot process effacement.

Conclusions: Our study demonstrates that using our standard clinical testing using a kidney biopsy, patients with UAKD can be mistaken for FSGS since there are no specific histopathological features for UAKD. Genetic testing can clarify the diagnosis of UAKD with secondary FSGS. Genetic testing should be considered for families diagnosed as familial FSGS or hereditary glomerulonephritis of unclear etiology.

Funding: NIDDK Support

FR-PO785

Recessive Mutations in TNL1, PAX, or ARHGEF17 Are Potential Novel Causes of Nephrotic Syndrome in Humans

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Background: Steroid-resistant nephrotic syndrome (SRNS) almost invariably progresses to end-stage kidney disease. Although more than 60 single-gene causes of SRNS are known, a large proportion remains unexplained. Recently, we identified pathogenic variants in UMOD, a gene encoding the tubular protein uromodulin, in seven families with suspected or biopsy proven FSGS.

Methods: We reviewed the clinical and pathology reports of seven families identified to have pathogenic variants of UMOD. Sanger sequencing of affected and unaffected to have pathogenic variants of UMOD. Sanger sequencing of affected and unaffected

Conclusions: Our findings confirm that Rho-like small GTPase signaling is part of CAKUT pathogenesis.

Funding: NIDDK Support

FR-PO786

Nos1ap-/- Mice Replicate the Human Nephrotic Syndrome Phenotype Potentially via a CDC42-Diaphanous-Related Mechanism

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. We previously identified causative recessive mutations in NOS1AP in two SRNS families and demonstrated that NOS1AP mutations impaired CDC42 activation, podocyte migration rate (PMR) and focal adhesion formation (Majmundar et al, JASN, 29:682, 2018). To further delineate the pathogenesis of SRNS due to NOS1AP loss-of-function, we generated a mouse model and performed additional cell culture studies.

Methods: Mouse model for SRNS due to NOS1AP mutations was generated by crossing Nos1ap knockout mice with C57Bl/6 mice. Mice lacking Nos1ap exon 3 (Nos1ap exon 3 knockout mice) were screened monthly for proteinuria, and urine albumin, creatinine-ratios, BUN and serum creatinine levels were measured. The conducted live cell imaging in a human podocyte cell line under shRNA-mediated downregulation of Nos1ap and cDNA over-expression of Nos1ap, CDC42 or Diaph3 as well as pharmacologic inhibition of DIAPH proteins (by SMIFH2).

Results: We examined Nos1ap-/- mice carrying biallelic Nos1ap Exon 3 deletion alleles for albuminuria. Mice developed albuminuria starting at the age of 5 months when compared to wild-type and monoallelic littermates but had not developed renal failure by the age of 12 months. In a podocyte cell culture system we further studied the role of Nos1ap within the signaling pathway of CDC42 and its downstream effectors, the diaphanous proteins. Filopodia formation upon Nos1ap cDNA overexpression was assessed in the presence of the DIAPH protein inhibitor SMIFH2 and reduced in a dose-dependent manner similarly to prior CDC42 inhibition by CASIN. Reversely, defective PMR, an established intermediate phenotype of SRNS, in Nos1ap shRNA-mediated knock-down podocytes was rescued by overexpression of DIAPH3 cDNA and constitutively active CDC42.

Conclusions: We show that the human SRNS phenotype due to recessive Nos1ap mutations is replicated in Nos1ap-/- mice. We demonstrate that DIAPH function is part of the CDC42 mediated pathogenesis of SRNS due to Nos1ap loss-of-function.

Funding: NIDDK Support, Government Support - Non-U.S.

FR-PO787

Mutations in the Diaphanous Related Formin DAAM2 as a Novel Cause of Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second most frequent cause of end-stage renal disease in the first 3 decades of life. Identification of ~55 monogenic causes of NS has rendered insights into disease mechanisms of NS (Nat Rev Nephrol. 12:133, 2016). Diaphanous related formins (DRF) regulate actin polymerization, filopodia and lamellipodia formation. The basal state interaction of the C-terminal DID domain with the C-terminal DID domain is autoinhibitory and is relieved by monomeric changes induced by GTPases. Accordingly, mutations in the DID domain of the formin gene, IN2, cause NS (Nat Gen 42:72, 2010).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: To identify novel monogenic causes of NS we performed whole-exome sequencing (WES) in a worldwide cohort of ~1,200 NS patients. We discovered 60 genes linked to autosomal dominant focal segmental glomerulosclerosis (FSGS). We here discovered recessive mutations linked to autosomal dominant focal segmental glomerulosclerosis (FSGS). We identified likely disease-causing mutations in \textit{BSN} in four unrelated families with NS, revealing a novel monogenic cause of human glomerular disease.

Funding: NIDDK Support

FR-PO790

Recessive Mutations in \textit{SYNO2} May Cause Nephrotic Syndrome via Mesangial Cell Dysfunction

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Background: Steroid-resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in children and young adults. Major insights into its pathogenesis came from discovery of ~60 monogenic causes, contributing to ~12-30% of SRNS with onset <25 years of age. However, a significant proportion remains without a genetic diagnosis.

Methods: To identify novel pathogenic genetic variants, we performed whole-exome sequencing (WES) in a worldwide cohort of ~800 individuals from different families with SRNS. We evaluated potential pathogenicity of genetic variants by in-silico prediction scores, evolutionary conservation and allele frequency in public genome sequencing databases.

Results: We identified 6 individuals from different families with recessive deleterious mutations in the \textit{BSN} gene (bassoon). Two individuals harbored different homozygous mutations (p.S1048T and p.S988LeL), while 4 had compound heterozygous mutations (p.R519W / p.R268K, p.R566Q / p.R1193H, p.N262L /p.K2697E; and p.R503A / p.I15; p.H3716N). Age of SRNS onset was 7 months to >21 years old. Of 4 patients who underwent renal biopsies, 3 had focal segmental glomerulosclerosis, and 1 had minimal change disease. Four patients had extra-renal manifestations (microcephaly, atrial septal defect, short stature, seizures, and intellectual disability). Bassoon is a scaffolding protein found in the neuronal active zones and localization of voltage-gated calcium channels (\textit{Front Synaptic Neurosci} 7:19, 2015). Podocytes have been shown to contain structures resembling synaptic vesicles. Four patients had extra-renal manifestations (microcephaly, atrial septal defect, short stature, seizures, and intellectual disability). Bassoon is a scaffolding protein found in the neuronal active zones and localization of voltage-gated calcium channels (\textit{Front Synaptic Neurosci} 7:19, 2015). Podocytes have been shown to contain structures resembling synaptic vesicles.

Conclusions: We have discovered recessive \textit{BSN} mutations as a novel monogenic cause of nephrotic syndrome, leading to mesangial cell dysfunction through Rac1-GTPase dysregulation.

Funding: Other NIH Support - DK07683, Friedhelm Hildebrandt

FR-PO791

First Identification of a Rare \textit{PODXL} Splice Site Mutation in a Case of Focal Segmental Glomerulosclerosis

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Introduction: Podocalyxin plays an important role in the regulation of podocyte morphogenesis and function. We recently identified heterozygous \textit{PODXL} nonsense mutations linked to autosomal dominant focal segmental glomerulosclerosis (FSGS). Here, we reported the first heterozygous \textit{PODXL} splice site mutation identified in FSGS.

Methods: Identification: A 35 year old Chinese female was admitted to the ward in December 2018 for persistent proteinuria (maximum 2500mg/24hr) and hypertension (140/90mmHg) for three months. Serum creatinine and albumin were within normal range and ultrasound revealed normal sized and echogenic kidneys. Renal biopsy suggested FSGS (Figure 1A-B). Father of the patient was died of renal failure and no history of renal disease found in other close relatives. Whole exome sequencing performed on the patient revealed a \textit{PODXL} donor splice site variant (c.712+1G>A, rs137907090, allele frequency 0.0002) (Figure 2A), leading to the 58bp deletion identified in \textit{PODXL}. The 58bp deletion in the 3’ UTR of \textit{PODXL} is a rare splice site variant in the \textit{PODXL} gene and it is predicted to cause a frameshift mutation.

Results: We confirmed c.712+1G>A in the patient. cDNA sequencing (WES) in the unaffected father revealed no variant. cDNA sequencing (WES) in all family members revealed that the patient is the only one with c.712+1G>A variant.

Conclusions: We identified a novel \textit{PODXL} splice site mutation in a patient with FSGS.
Discussion: This case expands the genetic spectrum of PODXL-associated FSGS and further supported that down-regulation of podocy tin expression linked to FSGS.

Representative microscopic images of the patient.

Mutation and its consequences.

FR-P0792

Nephrin Mutation in Childhood-Adult Onset Nephrotic Syndrome (NS)
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Background: Nephrin, a slit diaphragm protein, is essential to integrity of podocyte structure. Mutations in the nephrin gene, NPHS1, typically result in congenital NS. Variants causing similar disease in later childhood and adults are rare. We believe our family is the first case report in which all members of the family have this mutation. A 18-year-old Caucasian female was referred for steroid and calcineurin inhibitor resistant NS. Her first renal biopsy was at age 7 due to proteinuria with normal renal function and blood pressure. All 18 sampled glomeruli and interstitium appeared normal by light microscopy (LM), but electron microscopy (EM) showed partial foot process effacement. Repeat biopsy at age 18 when eGFR < 30 ml/min/1.73m² showed focal segmental glomerulosclerosis, not otherwise specified (FSGS-NOS). She received Rituximab as attempted salvage therapy. With consent, both patients and their parents were genotyped.

Methods: Genomic DNA was extracted from peripheral blood cells and genotyped in 3 different groups of known or candidate VACTERL genes: i) mutations in the 4 known VATERL genes FOXF1, HOXD13, PTEN, and ZIC3, ii) in 108 VACTERL candidate genes of the 8th or 9th chromosome, and iii) in 58 syndromic human CAKUT genes. In addition, we evaluated WES data for potential novel VACTERL genes under 5 different monogenic hypotheses: (i) recessive, (ii) dominant, (vi) deleterious and (vii) digenic recessive mutations. We detected no mutation in any of the 4 known VACTERL genes (above group i). In group ii we detected potential mutations in 11 different genes. In group iii we detected potential mutations in 13 genes. When evaluating for potential novel VACTERL genes, we identified recessive (group iv, n=4), B9D1, CORO7, TTT1LI, NKX2.5, dominant (group v, n=5), de novo (group vi, n=1), digenic dominant (group vii, n=11) and digenic recessive mutations (group viii, n=3). Overall, we detected mutations in 25/33 families in 44 genes (17 had more than one potential gene). Interestingly, in 7 individuals at least one mutation in a known gene for syndromic CAKUT together with a second mutation in another syndromic CAKUT or VACTERL candidate gene could be found.

Results: We performed unbiased whole exome sequencing (WES) to identify monogenic or digenic causes in 33 families with VACTERL or VACTERL-like phenotype.

Conclusions: This study establishes that WES can identify mutations in potential candidate genes in 76% of families with VACTERL or VACTERL-like phenotype. Furthermore, WES shows a potential digenic mode of inheritance in 51% of our cohort.

FR-P0794

Variable Penetration of the Therapy-Resistant Phenotype Among Children with the Genetic Form of Nephrotic Syndrome
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Background: Currently, genetic forms of nephrotic can be classified as highly penetrant, pathogenic variants in single genes (“monogenic”) or common risk alleles contributing to the diseases pathogenesis such as APOL1 high-risk (HR) genotypes. Monogenic NS is thought to be therapy-resistant, with an inability to achieve complete remission (CR). However, APOL1 NS has a lower odd of achieving CR. There have been reports that some patients with monogenic diseases may achieve CR. Factors associated with remission among genetic NS is still unclear. Therefore, this study used a large North American cohort of children with NS to (1) describe the prevalence of CR as a function of genetic profile and (2) identify factors potentially modifying the CR phenotype.

Methods: 70 genes implicated in monogenic forms of NS and the two APOL1 risk alleles were analyzed in 215 children from the Nephrotic Syndrome Study Network (NEPTUNE) who had undergone whole genome sequencing. A variant penetrance pipeline was applied to identify patients with putative monogenic NS and APOL1 HR genotypes. General characteristics and CR were compared among patients classified with putative monogenic NS, APOL1-attributed NS, and no known genetic form of NS.

Results: Monogenic NS was found in 15 patients (7%) and APOL1 attributed NS was found in 4 patients (2%). Compared to no known genetic NS, monogenic and APOL1 attributed NS had lower rate of ever achieving CR (83% vs 43% and 59%, p=0.002 and 0.01, respectively) and lower likelihood to achieve remission (Hazard ratio 4.0 for both, p = 0.02 and 0.009, respectively, at 6 months of follow up). Loss of function Mendelian variants and those co-existing with other Mendelian variants or APOL1 HR genotype, tended to result in lack of CR.

Conclusions: Children with monogenic or APOL1 attributed NS were significantly less likely to achieve CR. Despite this, a substantial proportion of children with genetic NS still are able to achieve CR. Mendelian variants and APOL1 HR alleles in this North American, population-based NS cohort appear to increase risk of not achieving CR, rather than being fully penetrant for this phenotype. Further functional analysis is essential in increasing the accuracy of classifying patients with monogenic NS and making subsequent clinical correlations.

Funding: Other NIH Support - NRSA institutional Postdoctoral Training Grants (T32, grant number: 5T32DK007378)
Genotype-Phenotype Correlation for the COL4A3 2881+1 G>A Founder Mutation in the Croatian Population

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Background: Alport syndrome (AS) and thin glomerular basement membrane nephropathy (TBMN) are genetically heterogeneous disorders caused by mutations in COL4A3, COL4A4 and COL4A5 genes. Genetic heterogeneity with various types and number of mutations with no mutational “hot spots” can make diagnostic process challenging. Some type of mutations increase the likelihood of a severe phenotype but recent studies also showed that same mutations can result in different clinical presentation.

Methods: Total of 26 patients from 10 unrelated families with heterozygous for COL4A3 splice donor 2881+1 G>A mutation detected by next generation sequencing (Illumina MiSeq platform) for COL4A3, COL4A4 and COL4A5 genes mutations was tested as part of a project “Genotype-Phenotype correlation in Alport’s syndrome and Thin Glomerular Basement Membrane Nephropathy” founded by the Croatian Science Foundation. There were 11 females and 15 male patients, age range 5-72 years (median 44 years).

Results: According to available clinical data majority of patients (88.5%) presented with haematuria and 73.7% with proteinuria. Decline in kidney function was present in 65% of patients; 40% being mild, 15% severe and 10% suffered from end stage renal disease (2 transplanted patients). Three patients had sensorineural hearing impairment. Kidney biopsy was performed in 50% of cases. On light microscopy focal segmental sclerosis was present in 30% of specimens, whereas, electron microscopy showed TBMN in 40%, TBMN with focal lamellation in 20% and changes suggestive of AS (Figure 1) in 40% of patients.

Conclusions: Here we present genotype-phenotype correlation for COL4A3 2881+1 G>A founder mutation in Croatian population showing clinical and pathohistological heterogeneity. Therefore, identification of modifiers causing such heterogeneity is of grave importance for better understanding of collagen IV nephropathies.

Funding: Government Support - Non-U.S.

A Case of Autosomal Dominant Alport Syndrome with a Gene Variant of ESPN, a Hearing Loss-Causative Gene, That Was Diagnosed by Whole-Exome Analysis

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Introduction: Alport syndrome (AS) is a rare hereditary disease that presents with chronic kidney disease and sensorineural hearing loss and is diagnosed by its clinical features, pathological features on renal tissue, and mode of inheritance. AS has three genetic modes of heterozygosis: X-linked, autosomal recessive, and autosomal dominant. Because the clinical and pathological features of autosomal dominant AS are much milder than those of the other two modes of heredity, definitive diagnosis is difficult.

Case Description: We report a woman in her 20s who exhibited persistent haematuria and haematuria and sensorineural hearing impairment. Her family members exhibited the same clinical findings among three generations and were suspected of having autosomal dominant AS (ADAS). Renal biopsy showed minimal glomerular abnormalities on light microscopy and extensive thinning of the glomerular basement membrane on electron microscopy. Whole-exome analysis revealed a missense variant on c. 2510 G>C (p. Gly837Ala) in COL4A4 (type IV collagen α4). Two cases with the same variant have been reported previously, one as ADS and the other as autosomal recessive AS. However, these two cases exhibited no sensorineural hearing loss. The analysis in the present case revealed another missense variant in ESPN (Espin), an actin-bundling protein, which is a causative gene for sensorineural hearing loss. Although the pathophysiological significance of such missense variant need to be clarified, computational analysis predicted that the variant creates a new phosphorylation site for protein kinase C.

Discussion: By applying whole-exome analysis, we confirmed the diagnosis of ADAS for the present case. Our case suggests a possible association of hereditary sensorineural hearing loss with ADAS. When a suspicious hereditary disease exists, direct sequencing of the gene is usually performed. Although direct sequencing of the specific gene is crucial for diagnosis, other possible mutations may be missed. Whole-exome analysis should be considered as a method to diagnose hereditary and multiple-organ disorders.
Antenatal Membranous Nephropathy and Axonal Charcot-Marie-Tooth Type 2 with c.466delC Mutation in the Metallo-Membrane Endopeptidase Gene: A Warning Signal About Long-Term Use of Neprilysin Inhibitors

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Background: First cases of truncating mutations in the neprilysin/metallo-membrane endopeptidase (MME) gene were identified in 2002 as the cause of alloimmunization during pregnancy, resulting in moderate to severe forms of antenatal membranous nephropathy (MN). Ten years later, two sisters and one brother of the originally reported Moroccan family, found homozygous for the c.466delC mutation in the MME gene, developed rapid motor and sensory neurological disorders, leading to the diagnosis of axonal Charcot-Marie-Tooth (CMT2). We report here the description of clinical and electrophysiologic investigations.

Methods: Clinical features and ancillary test results were collected from laboratory database and patient charts. Electrodiagnostic tests were carried out by standard techniques with surface electrode recording.

Results: Patient 1 had experienced antenatal MN during her second pregnancy at the age of 23 years. She presented with vasomotor transient episodes and progressive muscle weakness of the lower limbs at the age of 35 years. Two years later, she developed progressive foot drop disturbances, distal lower limb weakness with foot drop, and occasional knee falls. This was improved by foot orthotics. Neurological examination revealed moderate muscle weakness of the lower limbs at the age of 33 years. Two years later, she developed falls. This was improved by foot orthotics. Neurological examination revealed moderate muscle weakness of the lower limbs at the age of 44 years and subsequently broke her foot needing osteosynthesis. First neurologic manifestations of Patient 3, their brother, were painful nocturnal cramps at the age of 30 years. All these patients had normal kidney function parameters and exhibited a typical CMT2 phenotype being demonstrated by the clinical picture and electrodiagnostic test results.

Conclusions: This is the first family associating renal and neurological abnormalities linked to MME gene mutation. This observation confirms that neprilysin/MME is involved in peripheral nerve functioning. Neurological surveillance is recommended in prolonged treatment with neprilysin inhibitors.

FR-PO801

Features of Glomerulopathy with Fibronectin Deposits

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Background: Glomerulopathy with fibronectin deposits (GFND; OMM: 601894) is a rare inherited kidney disorder characterized by massive fibronectin deposits, leading to end-stage renal disease (ESRD). Differential diagnosis of GFND from other immunotactoid glomerulopathy is important in treatment. We systematically reviewed and analyzed clinical features and genotypes of patients with GFND.

Methods: Electronic databases were searched using related terms (till May 30th, 2019). This report adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Results: From 1663 articles searched, there were 23 eligible studies with 86 patients with GFND from 44 families. Female patients were 40% (34/86) and most (70/83, 84%) patients had family history. 33 patients (38%) had hematuria and 38(47%) had nephrotic proteinuria. Median age at onset was 14.5 years for hematuria and 24 for proteinuria. Half of the patients had hypertension (18/35, 51%). ESRD was reported in 22 out of 68 patients (26%) at 34 median years. Of the 50 patients available for pathology reports, most patients showed negative immunofluorescence stains and fibrillary deposit in the electron-microscopy with the fibrils sized 9-14 nm in diameter. 42 patients underwent genetic tests for FNI and 3(8%) had no mutation. Of the 39 with FNI mutation, and 35 (35/39, 89%) had a missense mutation, 3 (8%) had deletion, and 1 had an intrinsic mutation. Mostly affected was the heparin-binding site where 92% (32/39) of the mutations occurred. c.2918A->G was the most commonly reported mutation. There was no genotype-phenotype correlation in this study.

Conclusion: The GFND may proceed to ESRD at third decade of life. Hypertension and nephrotic syndrome are often accompanied. Some patients with GFND may present without family history and may be negative for FNI mutation.

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FR-PO802
Prednisone Reduced Proteinuria and Stabilized Serum Creatinine in a Patient with Familial Fibronectin Glomerulopathy

Introduction: Fibronectin Glomerulopathy (FNG) is a rare, autosomal dominant disease characterized by proteinuria, hematuria and progressive renal failure associated with glomerular deposition of fibronectin, typically leading to ESRD in the 2nd to 6th decade. There is no established treatment for this condition beyond conservative measures such as blood pressure control and use of ACE inhibitors. We present a case of FNG associated with progressive CKD and nephrotic range proteinuria showing a sustained response to prednisone treatment.

Case Description: A 57 year old G2P female presented with 3 g of proteinuria, serum creatinine 0.7 mg/dl, inactive urinary sediment and normotension without medication. She was part of a large family with glomerular disease, including 3 members who died of cerebral hemorrhage or stroke in their thirties. The patient’s kidney biopsy showed mesangial deposition of fibronectin consistent with FNG. No interstitial fibrosis was seen. Genotyping revealed the Y973C fibronectin gene mutation. Despite maximal tolerable ACE inhibition, proteinuria increased to 4-6 g/g creat and serum creatinine increased to 1.0 mg/dl. Based on its use in IgA nephropathy, she was treated with prednisone 60 mg (~1 mg/Kg) for 2 mos, tapering by 20 mg every 2 mos. Proteinuria decreased to ~1 g/g creat for > 5 yrs and creatinine stabilized in the 1.2 mg/dl range with treatment. No significant side effects were encountered.

Discussion: Prednisone induced a sustained response in this patient. This is one of the first reports of effective treatment of FNG with immunosuppressive therapy. In conclusion, this protocol should be considered in FNG patients with nephrotic range proteinuria despite maximal ACE/ARB inhibition who have relatively preserved renal function.

FR-PO803
Mechanism of Mutation of AarF Domain-Containing-Kinase 4 (ADCK4) Glomerulopathy
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Introduction: AarF domain-containing-kinase 4 (ADCK4) is a mitochondrial resident protein kinase belonging to the Ubip protein kinase-like family. ADCK4 is thought to facilitate the ATP dependent biosynthesis of coenzyme Q10 (CoQ10). Mutations in ADCK4 cause early-onset proteinuria, focal segmental glomerulosclerosis/nephrotic syndrome, followed by end-stage renal disease (ESRD). The regulation of ADCK4 in CoQ10 biosynthesis is not well understood.

Case Description: We report a patient who was discovered with proteinuria on routine screening at age of five-year-old. Renal biopsy showed FSGS. Renal functions and proteinuria continued to worsen over the years. Whole exome sequence revealed a novel compound heterozygous for two mutations in the aarf domain-containing-kinase 4 (ADCK4) gene. Her father has proteinuria related to fibrillary GN and bilateral duplicated collecting system, brother with right ureteropelvic junction obstruction and sister with unilateral duplicated collecting system. Genetic analysis using whole exome sequencing for this family with proteinuria and structural anomalies of the kidney and urinary tract revealed a novel compound heterozygous mutation in the ADCK4.

Discussion: We generated a computational model to understand the mechanism of action of 2 novel identified mutations: I346S in the C-lobe of the ADCK4 kinase domain, and a termination at W520 that leads to the truncation of the C-terminal a5 helix. The alterations of ADCK4 c.1560G>A and c.1037T>G are novel mutations. The model suggests potential mechanisms for alterations in protein function through either destabilization of important allosteric interactions necessary for kinase activation and/or conformational changes that facilitate enzyme activity (Figure 1).

FR-PO804
Sanger Sequencing Pitfall Exists in Hereditary Thrombotic Microangiopathy with Homozygous Mutation Identified in Only One Biological Parent
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Background: The aim of this study was to elucidate the underlying etiology of a mutation appeared to be homozygous which was identified in only one of parents in one boy with hereditary thrombotic microangiopathy.

Methods: One boy was diagnosed as steroid-resistant nephrotic syndrome at 2.4 years old. Urinary protein recurrence occurred 1.5 years later, while serum creatinine (Scr) increased to 83 umol/L and platelet (PLT) decreased to 40×10^9/L. One point eight years later, hemoglobin (Hb) was 72 g/L, PLT 29×10^9/L, Scr 120 umol/L. Five point nine years later, his renal function was normal. Light microscopy, electron microscopy and immunofluorescence of renal biopsy indicated thrombotic microangiopathy. Genetic analysis revealed he had homozygous DGKE (NM_003647) missense variant c.1420G>A (p. Asp474Asn) which was identified in only his father. Six short tandem repeats (STR) were selected to confirm biological relationships between the boy and his parents. Quantitative PCR was performed to detect the deletion by Bio-Rad CFX real time PCR system using SYBR Green I PCR SuperMix (TransGen Biotech, China, AQ131).

Results: Six loci alleles in different chromosomes demonstrated typical Mendelian inheritance with paternal and maternal alleles being detected in the patient, which indicated that biological relationship of the boy and his parents. Further analysis showed the breakpoints in DGKE exon 11 of the boy was half of the normal control while normal in his parents. Further analysis showed the breakpoints in DGKE were exon 1 and exon 12. It may be a de novo heterozygous deletion.

Conclusions: Cases were demonstrated to be homozygous due to a large deletion encompassing a missense/small deletion in DGKE gene.

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FR-PO805
Clinical and Genetic Characteristics of Pregnancy-Associated aHUS in Japan
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Background: Complement dysregulations mostly by the genetic alterations of the complement related factors are involved in the pathogenesis of atypical hemolytic uremic syndrome (aHUS). Pregnancy can impact on the onset of aHUS. Clinical courses and pathogenesis of pregnancy-associated aHUS is not yet fully clarified.

Methods: Blood samples of aHUS patients were analyzed by hemolytic assay, anti-CFH antibody test and whole exome sequences. Pregnancy-associated aHUS was defined as aHUS that occurs during pregnancy or pernatorial period. TMA cases with active underlying diseases were excluded.

Results: Out of 264 cases consulted to our division, 6 cases were associated to the pregnancy. All the cases developed TMA immediately after delivery within 12 hours, and no TMA events during pregnancy were observed. The ages of the patients ranged from 25 to 33 years old, and all the cases were primipara. 2 cases underwent Caesarean sections. 5 cases showed both liver and kidney dysfunctions, leading to the diagnoses of aHUS and HELLP syndrome. Hemolytic assays were negative to weak positive, and anti-CFH antibody tests were all negative. Whole exome sequencing detected diverse mutations in complement related factors (C3 V535I, C3 S562L, CHF R1215G, CFI R201S, CFB K533R, MCP S137F). Each mutation corresponds to each case, and there are no common mutations to them. 4 mutations are found in the idiopathic aHUS patients in our cohort, one (CFB K533R) is previously described as an aHUS causing mutation and one (C3 V535I) is novel. One case (CFI R201S) required temporary hemodialysis for severe acute kidney injury. 5 cases recovered the kidney function, while one case (CFB K533R) reached to the end stage kidney disease 1.5 years after the onset of the disease.

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One case (CFH R1215G) continued eculizumab therapy every two weeks until now. All the cases were followed up for up to 5 years and one case had the second pregnancy with successful delivery. No recurrence of TMA was observed during follow-up period.

**Conclusions:** The clinical and genetic characteristics of pregnancy-associated aHUS in our cohort are: 1) postpartum TMA with HELLP syndrome is typical, 2) the recurrence rate of aHUS is low, 3) the recovery of kidney and liver functions is generally good, 4) diverse mutations in complement related factors were detected, but they might not be the sole factors responsible for the onset of the disease.

**Funding:** Government Support - Non-U.S.

**FR-PO806**

**Genotype and Phenotype Correlation in a Chinese Cohort with Autosomal Dominant Tubulointerstitial Kidney Disease**

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**Background:** Autosomal dominant tubulointerstitial kidney disease (ADTKD) characterized by tubulointerstitial damage and progressive chronic kidney disease might be an important cause of chronic kidney disease for patients with family aggregation of ESRD. UMOD, HNF1B, MUC1, REN, and SEC61A1 were reported to be the disease causing genes. In this study, we screened genetic variations and did a follow-up study in a Chinese suspected ADTKD cohort.

**Methods:** 80 individuals from 53 families suspected with ADTKD were enrolled. Demographic data, clinical data and family history of the 53 probands were obtained from clinical record. Genetic testing for UMOD, HNF1B, REN, MUC1 and SEC61A1 were performed with suitable method of direct sequence, multiple ligation-dependent probe amplification (MLPA) or next generation sequencing (NGS). We performed a 1.5 years follow-up study for the 53 probands.

**Results:** According to the genetic variants identified in the cohort, 11 persons were diagnosed as ADTKD-UMOD, 1 as ADTKD-REN and 1 as ADTKD-HNF1B. Pathogenic variant in MUC1 and SEC61A1 genes were not confirmed. The mean age of diagnosis was 30±11years, and numbers of males and females were almost equal. Hyperuricemia and decreased kidney function were the common features. But clinical features were similar between patients with genetic variants and without variants (ADTKD-NOS). Follow-up study from the 18 probands was available while 18 probands lost. According to the follow-up study, ADTKD-NOS patients had better outcome than those patients identified genetic variants (p=0.011). Among the 11 variants in UMOD, 5 affected cysteine and 6 affected other amino acid. 80%ADTKD-UMOD patients with pathogenic variants lead to cysteine substitution did not develop to ESRD while 83.3%ADTKD-UMOD patients with other amino acid substitution developed ESRD.

**Conclusions:** 24.5% patients diagnosed ADTKD in a Chinese suspected ADTKD and UMOD was the mainly disease causing gene. Clinical features are not specific in patients carried pathogenic mutations compared to those without mutations. Renal survival of ADTKD-UMOD is better than patients identified genetic variants. ADTKD-UMOD patients with pathogenic variants lead to cysteine substitution tend to have better outcome.

**Funding:** Government Support - Non-U.S.

**FR-PO808**

**Predictors of Age of ESRD in Autosomal Dominant Tubulointerstitial Kidney Disease due to UMOD Mutations**

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**Background:** The aim of this work was to identify parameters that may explain the significant intra- and interfamilial variation in the age of onset of ESRD in patients with ADTKD-UMOD. The minor rs4293393 variant residing in the UMOD promoter has an allele frequency of 19% and decreases uromodulin synthesis by approximately 50%. It was postulated that if the minor variant was in cis with the disease-causing mutation of UMOD (mUMOD), it would result in decreased mUMOD production and improved survival. A Mendelian randomization experiment was therefore attempted.

**Methods:** The study included 983 individuals with 127 different UMOD mutations, with 722 undergoing genetic testing and 261 being historically affected. An in vitro score was created for 29 prevalent mutations based on transit time through the endoplasmic reticulum. Other parameters included in the evaluation were parental age of ESRD, median age of ESRD for the patient’s family, BMI, history of gout, age of gout.

**Results:** The rs4293393 minor allele variant frequency was 16.4% when trans to mUMOD and 5.4% when cis to mUMOD, resulting in Hardy Weinberg equilibrium being present (p=0.03) and precluding a Mendelian randomization study. The following factors were found to be significantly associated with age of ESRD: age of gout (p<0.001), parental age of ESRD (p<0.001), body mass index (p=0.033), and median age of ESRD for the family (p=0.007). The in vitro score was also significant (p=0.03).

**Conclusions:** The minor variant was significantly less commonly linked to the mUMOD. The minor variant may lead to decreased mUMOD production and milder disease that was less frequently identified. An in vitro score was an excellent predictor of age of ESRD according to mutation. Parental age and age of gout were highly predictive of age of ESRD.

**Funding:** NIDDK Support
FR-PO809

Prevalence and Clinical Features of ADTDK-UMOD in Hemodialysis Patients in a Geo-Referenced Population in Southeastern Brazil: The REGENT Study

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Background: Autosomal dominant tubulointerstitial kidney disease due to UMOD mutations (ADTDK-UMOD) is a rare genetic kidney disease whose prevalence is not well known. We studied the prevalence and clinical aspects of ADTDK-UMOD in hemodialysis (HD) patients in a metropolitan health region of Southeastern Brazil (Metro-II).

Methods: The REGENT study (Familial Renal Disease, Epidemiology and Genetics in Niteroi) was designed to study familial renal diseases in Metro-II (2 million inhabitants). Between 2017/2018, we evaluated HD patients geo-referenced in Metro-II. Each patient was asked whether any other family members had developed ESRD. If affirmative, after clinical exclusion of causes such as nephrotoxic drugs, diabetes, ESRD in 1st-degree relatives, polycystic kidney disease, DSM, polyarthritis, etc., blood was collected for UMOD genetic analysis.

Results: 209 of 1308 patients (15.4%) indicated a family history of kidney disease. Of these, 70 remained as index cases of an unknown familial kidney disease (5.4% of the total). These patients reached ESRD at a younger age (p < 0.05), did outpatient treatment before dialysis (p = 0.001), and were on dialysis for more years (p < 0.01). Family pedigrees showed a dominant pattern in 35%. Three of the index cases were found to have unique UMOD variants, consisting of 3 heterozygous missense mutations (c.163 G>A; p.Gly55Ser) (c.667 T>G; p.C222Gly) and (c.263 G>A; p.Gly88Asp). The first family consisted of 3 HD, 1 CAPD, 1 transplant and 2 outpatients. Genotyping in the 3 families revealed a total of 18 UMOD affected individuals, regardless of HD, age or symptoms. Metro-II calculated prevalence was 10 ppm. Juvenile gout was not present, and no patients had symptoms of pili torti or hearing problems.

Conclusions: Familial renal disease without diagnosis constitutes a significant proportion of ESRD patients in Brazil. ADTDK is rare, but frequently underdiagnosed.

Funding: Government Support - Non-U.S.

FR-PO810

Molecular Genetic Investigations Identify New Clinical Phenotypes Associated with BCS1L-Related Mitochondrial Disease

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Introduction: The human BCS1L gene encodes a homolog of the Saccharomyces cerevisiae bcs1 protein, which has a known role in the assembly of Complex III of the mitochondrial respiratory chain. Several human disease phenotypes have been reported with mutations in BCS1L, including respiratory chain enzyme deficiencies, pili torti, and hearing problems.

Methods: We describe a case of BCS1L-related mitochondrial disease, including respiratory chain enzyme activities in the muscle but a decrease in Complex III assembly.

Case Description: A 49-year-old woman presented with progressive chronic kidney disease and is approaching end stage renal disease. The diagnosis was not obvious. Whole genome sequencing revealed a protein-truncating heterozygous variant together with a novel pathogenic heterozygous variant c.205C>T, p.Arg66*.

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FR-PO815
Clinical and Genetic Feature of Membranous Nephropathy in Patients with Primary Sjögren Syndrome
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Background: In our previous study, membranous nephropathy (MN) was the most common pathological patterns of glomerular involvement in patients with primary Sjögren’s Syndrome. In this pilot study, we try to observe the clinical features and genetic background of MN patients with primary Sjögren’s syndrome (pSS-MN).

Results: During the study period, totally 60 patients were diagnosed with membranous nephropathy. 58 patients received blood test for plasma anti-PLA2R, and 55 patients’ pathological slide were successfully proceeded to IF staining of podocyte PLA2R. Within patients receiving both evaluation (n=53), there are 24 patients with double positive results (45.3%), and 19 patients with double negative results (35.8%). 3 patients have plasma anti-PLA2R assay but not positive results of podocyte PLA2R enhanced expression (5.7%). 7 patients have no plasma anti-PLA2R antibody but got positive results of podocyte PLA2R enhanced expression (13.2%). Discrepancy of serum anti-PLA2R and podocyte PLA2R expression account for totally 18.9% of enrolled patients.

Conclusions: The reason of discrepancy of serum anti-PLA2R and podocyte PLA2R expression is still not known yet. Further studies are still needed. Currently, serum anti-PLA2R antibody (ELISA) and microarray (Atlas®) were tested to be useful tools for diagnosis of PLA2R-associated membranous nephropathy.

FR-PO816
Can Multidrug Resistance-Associated Protein-1 and P-Glycoprotein Expression on Peripheral Blood Lymphocytes Be Used as Biomarkers to Predict Steroid Resistance in Idiopathic Nephrotic Syndrome?
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Background: Steroid remains mainstay therapy for Idiopathic Nephrotic Syndrome (INS). Other pharmacogenomic factors may also affect steroid response. Overexpression of P-glycoprotein (P-gp) and Multidrug resistance-associated proteins 1 (MRP-1) modulate the pharmacokinetics of steroids and may contribute to steroid resistance.

Methods: P-gp, and MRP-1 expression were evaluated on whole blood and functional activity on PHMCs in steroid-sensitive nephrotic syndrome (SSNS) (n=170, M=103, age=8.54±4.3 yrs); steroid-resistant nephrotic syndrome (SRNS) (n=81, M=43, age=7.43±4.6 yrs) patients. The genetic variants G2677T/A of MDR-1 gene were genotyped by PCR-RLFP technique.

Results: Biochemical difference were found in 24hrs urinary protein/Creatinine ratio (SSNS=0.13±0.06, SRNS=3.67±0.91, p<0.001), total cholesterol (SSNS=144.21±34.6, SRNS=460.52±201.09, p<0.001). Percentage expression of P-gp (9.80±3.44 and 4.36±2.05, p<0.001); and MRP-1 (13.46±8.10 and 7.75±3.32, p<0.001) was significantly higher in SSNS than SRNS. P-gp expression on CD4+ (6.08±1.95 and 4.34±1.97, p=0.008) and CD8+ cells (6.65±1.92 v/s 3.96±1.77, p=0.001) was significantly higher in the patients of homozygous mutant alleles (p<0.001) as compared with the patients of wild type allele.

Conclusions: P-gp, and MRP-1 expression are different in whole blood and functional activity on PHMCs in steroid-sensitive nephrotic syndrome (SSNS) as compared with steroid-resistant nephrotic syndrome (SRNS). Genetic variants G2677T/A of MDR-1 gene may be useful biomarkers in steroid-resistant nephrotic syndrome.
therapeutic potential of the sialic acid precursor N-acetylmannosamine (ManNAc) in three different nephrotic mouse models.

Methods: We created neuraminidase-induced and adriamycin-induced nephrotic mice and a nephrotic knock-in mouse model deficient in Gne, a central enzyme in sialic acid biosynthesis. ManNAc was administered in drinking water (~1 g/kg/d) to all three mouse models and clinical/biochemical parameters were assessed at different timepoints. Human glomerular sialylation was assessed by lectin histochemistry and confocal imaging in kidney biopsies of 123 well-phenotyped subjects with focal segmental glomerulosclerosis (FSGS; 69 subjects), minimal change disease (MCD; 29 subjects), or membranous nephropathy (MN; 25 subjects) supplied by the Nephrotic Syndrome Study Network (NEPTUNE).

Results: In all three mouse models, ManNAc administration increased glomerular sialylation and markedly reduced proteinuria and podocyte injury within a week of treatment. Hyposialylation was detected in an unexpectedly high percentage (>60%) of human kidney biopsies across all three disease entities, indicating that this condition may occur frequently, remains greatly unexplored and, importantly, may be treatable. Analysis of the association of sialylation status to clinical, pathological or other documented subject data showed a trend of correlation of severe glomerular hyposialylation with decreased eGFR, increased intertstitial fibrosis and increased tubular atrophy, in particular in FSGS subjects.

Conclusions: These encouraging preclinical data, together with minimal toxicity of oral ManNAc therapy in humans (demonstrated in Phase 1 and 2 clinical trials for the rare hyposialylation disorder GNE myopathy) led to obtaining an Investigational New Drug approval to start a Phase 1 clinical trial to evaluate the safety, tolerability and pharmacokinetics of ManNAc in subjects with primary podocyte diseases (ClinicalTrials.gov NCT02639260). Preliminary results of this ongoing study are promising regarding safety and tolerability with glomerular disease.

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FR-PO819

Tar Sequence (Double-Stranded-RNA)-PKR Activation Mediated Podocyte Injury with HIV-1 Infection

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Background: Podocyte damage by Human Immunodeficiency Virus (HIV-1) is critical to the pathogenesis of HIV-1 associated nephropathy (HIVAN). There is an evidence that viral RNA and proteins detected in podocytes, but there is no productive infection. While APO1 risk genotypes for FSGS is also the risk for HIVAN. We reported that activated PKR (interferon-induced double-stranded RNA-activated protein kinase) by double-stranded RNA (dsRNA) of APO1 mediates APO1 nephrpathy (Figure). HIV-1 also has dsRNA structures called tar sequence. Our hypothesis is that activated PKR by tar sequence could be cause of podocyte injury in HIVAN.

Methods: We prepared virus stocks were prepared by transfecting 293T cells with lymphocyte tropic PN4.3 and Macrophage-Tropic PN4 (AD8) titrated by p24 ELISA assay. Differentiated conditionally immortalized human podocytes were cultured a 6 well plate and infected with virus (p24 100 ng/ml/6-well).

Results: After 6 hours incubation, activated PKR signal was observed and prominent in podocyte cell line from APO1 risk genotype with pNL (AD8). WT-1 signal was decreased in Podocyte cell line after 96 hours incubation. Virus RNA (rev, vpu, env, and nef) was detected in podocytes by RNA sequence analysis, however, there is no productive infection. Next we generate tar sequence mutated virus (Figure). Activated PKR signal was not observed with mutated tar sequence. Specific PKR inhibitor demonstrated that PKR inhibitor reduced activated PKR and antagonist WT-1 decline.

Conclusions: HIV-1 direct infection on podocyte cell line providing mechanism by which tar sequence of HIV-1 contributes to cell injury via PKR. Targeting tar sequence - PKR opens novel therapeutic approaches to treating HIVAN.

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FR-PO820

Akt Downregulation Induces Tubular Apoptosis via FoxO-1-Induced BIM Activation in Proteinuric States

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Background: Proteinaemia induces tubular apoptosis preceeding tubular atrophy but the underlying molecular mechanism remains undetermined. We demonstrated that cell survival protein, protein kinase B(Akt) is downregulated in proximal tubule epithelial cells in response to albumin overload. We hypothesize that inhibition of Akt expression decreases phosphorylation and activation of its downstream targets Forkhead box (FoxO) transcriptional factors leading to mitochondrial apoptosis in proteinuric states.

Methods: In-vitro albumin overload: Human kidney proximal tubule epithelial cells (HKC-8) were incubated with 10mg/ml endotoxin free human albumin for 6, 16 and 24 hours. Chromatin immunoprecipitation (CHIP) assay was used to probe protein-DNA interactions. In-vivo albumin overload: Wild type and Akt1/2 cko SGLT2 cko mice underwent daily intraperitoneal albumin injections (10mg/g) for 6 weeks. Human kidney biopsies with minimal change disease and focal segmental glomerulosclerosis (FSGS) were investigated for Akt activation.

Results: Exposure of phosphorylated Akt-Ser 473 and Akt-Thr 308 was downregulated in association with increased caspase-3 activity and BIM expression in HKC-8 cells with albumin overload. Treatment of HKC-8 cells with pan Akt inhibitor MK-2206 and constitutively active(CA-Akt) Akt resulted in down regulation and upregulation of apoptosis respectively with albumin overload. In-vivo albumin overload decreased active p-Akt expression in association with tubular apoptosis. Akt1/2 cko SGLT2 cko mice displayed increased BIM expression in mitochondria and isolates in association with tubular apoptosis in response to albumin overload indicating a close causal link between inhibition of Akt and mitochondrial apoptosis in proximal tubule epithelial cells. Furthermore, patient kidney biopsies (n=5) with FSGS displayed decreased proximal tubule Akt expression. Albumin overload caused decreased Akt phosphorylation of FoxO-1 and 3 and nuclear translocation of FoxO-1. CHIP assay revealed transcriptional activation of BIM by FoxO-1.

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FR-PO818

Nuclear Magnetic Resonance Metabolomic Profiling in Distinguishing Primary from Secondary FSGS

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Background: FSGS is a renal histologic lesion with diverse etiologies that cause podocyte injury and depletion. Subclasses of FSGS include primary, genetic, and secondary forms. These subclasses differ noticeably in management and prognosis. Without an accepted biomarker that discriminates among these FSGS types, classification of patients is often challenging. NMR-based urine metabolomics has shown potential in biomarker discovery. We hypothesized that urine metabolites can distinguish such patients.

Methods: We used high resolution NMR spectroscopy to study urines of 12 participants with primary FSGS and 14 patients with secondary or genetic FSGS. NMR spectra were binned and normalized by total spectrum area. Using non-specific feature selection, we analyzed the top 50% ranked bins in the dataset by partial least squares discriminant analysis (PLS-DA). Cross-validation was used to choose tuning parameters and to estimate predictive performance. The 95% confidence interval was estimated using the score test.

Results: PLS-DA score plot demonstrated considerable overlap within the secondary/genetic group relative to the primary group (Figure). When comparing these two groups, the top 5 spectra bins corresponding to highest variable importance included the following metabolites: choline, acetyl-carnitine, histidine, betaine, taurine N-phenylacetylglutamine and two unknown metabolites. Estimated predictive accuracy was 65.4% (95% CI 46.2-80.1%). Sensitivity was 58.3% (95% CI: 32.0-80.7%) and specificity was 71.4% (95% CI: 45.4-88.3%).

Conclusions: This study found that a panel of urine metabolites could potentially discriminate primary from secondary FSGS. Further studies are needed to identify the unknown compounds. Understanding the differential expression of these metabolites could shed new insights into the biology of FSGS.

Funding: Private Foundation Support

Figure. PLS-DA score plot of NMR spectra showing separation between patients with Primary and Secondary/Genetic FSGS.
FR-PO821
Network-Based Assessment of Minimal Change Disease Identities Glomerular IL7 Pathway Activation as Potential Mechanism for Biomarker Discovery and Drug Testing
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Background: Minimal change disease (MCD) is a major cause of the nephrotic syndrome. With a substantial number of patients requiring long-term immunosuppression leading to significant morbidity, our study aim was to determine the glomerular transcriptome of MCD to serve as base for biomarker discovery and drug target identification. Respective animal work showed podocyte injury induced by IL7/IL7R signaling (Zhai S, BBRC, 2018).

Methods: Renal biopsies from adult patients representing the following groups were selected from the Norwegian Kidney Biopsy Registry: MCD (n=14), as well as normal tissue (n=8) and primary membranous nephropathy (MN; n=12) as two reference groups. Glomerular RNA for 75 base-pair, paired-end RNA-seq was obtained via laser capture microdissection from archival FFPE cross-sections. Systematic delineation of condition-specific alteration in transcriptional landscapes was achieved by combining pathway-centered analyses with methodologies derived from network science and integrating multiple bioinformatics resources.

Results: Compared to normal glomeruli, glomeruli from MCD displayed an inflammatory signature that appeared to be predominantly governed by the IL1 and IL7 systems. While enrichment of IL1 production and secretion was a shared feature of MCD and MN compared to normal tissue, responses involving IL7 pathway activation were unique to MCD. Indeed, IL7R expressed by glomeruli was the most up-regulated gene of the interleukin-family in MCD vs normal controls. IL7 pathway activation was paralleled by significant enrichment in adaptive immune system processes and transcriptional regulation, and by depletion in pathways related to energy metabolism and transcription. Downregulation of these organ function-related themes again occurred predominantly in MDC and were significantly less pronounced in MN.

Conclusions: Our results demonstrate that archival renal biopsies can be used to generate condition-specific expression profiles suitable for systemic delineation of kidney diseases. We provide a data-driven rationale to experimentally address the MCD-specific features as biomarkers and as novel drug targets. In this context, inhibiting the activation of IL7 pathway is particularly promising.

FR-PO822
Expression of Beta-3 Adrenergic Receptor (β3-AR) in Normal and Pathological Renal Tissue
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Background: The β3-adrenoreceptor (β3-AR) is a G-protein coupled receptor whose expression has been reported in multiple nephron segments of the murine kidney, including thick ascending limb (aTAL), thick ascending limb (TAL), distal convoluted tubule (DCT) and cortical collecting duct (CCD). However, no information is available regarding β3-AR presence in human kidney. The aim of our study was to investigate the presence of β3-AR at the glomerular and tubular level in normal and pathological human renal tissue.

Methods: We used β3-AR antibodies detected by polyclonal antibodies was present at the glomerular and tubular level in all renal samples with more intense staining in tubules from GD patients. β3-AR staining was also present in normal tubules from ADPKD samples but it was reduced in cystic tubules. Immunofluorescence studies performed using monoclonal antibodies confirmed β3-AR presence in tubular markers in TAL, DCT and CCD.

Conclusions: This is the first report on β3-AR localization in human kidney. Our data demonstrate that β3-AR is present in glomeruli and in nephron segments involved in water and solute reabsorption. The presence of this receptor in tissue from normal and diseased kidney suggests that β3-AR expression could be correlated to their pro-inflammatory and prothrombotic properties. Neutrophils carry complement proteins, and when activated, release these complement proteins and contribute to their activation via NETs. By improving our understanding of the interaction of the complement system and neutrophils and their respective response to produce these NETs, we will be able to better understand how neutrophils and NETs play a role in complement-mediated diseases such as C3 glomerulopathy (C3G), in which both neutrophils and complement are expected to contribute to disease pathogenesis.

Methods: Neutrophils freshly isolated from healthy controls (HC) were used (male, ages 18-24 years old). Experiments were done at least threefold (N=3). We either applied our established protocol of complement activation via the use of a sensitizing antibody (monoclonal anti-human CD59 antibody) in combination with 50% NHS using healthy control (HC) neutrophils or investigated patient-derived neutrophils incubated in autologous serum or serum-free media. Complement deposition (C3b; C5b-9) on neutrophils was detected via IF and flow cytometry. NETosis was detected using SYTOXGreen assay and immunofluorescence (IF).

Results: We found that complement activation of neutrophils resulted in (i) surface deposition of C3b and C5b-9, (ii) formation of circulating Histone 3 (ci-H3) and myeloperoxidase (MPO) release; (iii) the stepwise completion of NETosis after the transfer of neutrophils into serum-free media (SFM). In addition, we found that CSG patient-derived neutrophils (i) were positive for surface complement deposition; (ii) were positive for ci-H3; and (iii) completed NETosis after transfer from autologous serum into SFM. Finally, HC neutrophils (i) when incubated with C3G patient-derived serum showed ci-H3 formation, and (ii) NETosis when transferred into SFM.

Conclusions: Complement activation of neutrophils induces NETosis in a step-wise fashion with ci-H3 formation in serum (“priming”) and full NETosis in SFM. These findings can be interpreted as resemblance of an intra- vs. an extra-vascular environment, suggesting that neutrophils are primed intra-vascularly and committed to full NETosis only extra-vascularly.

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FR-PO824
Minimal Residual Autoimmunity After Rituximab in ANCA-Associated Vasculitis Patients
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Background: B-cell depletion with rituximab (RTX) is an effective treatment for ANCA-associated vasculitis (AAV) patients. Repeated RTX upon B-cell repopulation or return of ANCAcs improved therapeutic efficacy, which indicates the presence of minimal residual autoimmunity (MRA) after RTX. Therefore, this study aimed to perform in-depth phenotypic and functional analyses of B and plasma cells after RTX in AAV patients.

Methods: EuroFlow-based highly sensitive flow cytometry (HSFC) was used during longitudinal follow-up of RTX-treated AAV patients (n=12). To investigate MRA in the memory B-cell compartment after RTX, peripheral blood mononuclear cells (PBMCs) were stimulated with CpG, IL-2 and IL-21 in vitro to induce plasma cells (PCs) and ANCA-IgG and -IgM were measured in these supernatants and in paired serum samples by ELISA.

Results: By employing HSFC we demonstrated that 12 weeks after RTX, low but significant numbers of circulating CD19+ B cells (0.21±10^5 cells/L) could still be detected (reduction of -99.7%). While naïve B-cells, memory B-cells and CD20+ plasmablasts (PB) were rapidly depleted, CD20+ PCs were reduced slower and depleted incompletely. Residual CD20+ PCs were 0.05±10^5 cells/L (-95.8% from baseline), whereas 57% were mature CD138+ PCs. Early repopulation at 12 weeks was dominated by CD20+ CD138+ PCs, followed by CD20+ PBs at 24 weeks while memory and naïve B cells remained suppressed. Simultaneously, serum ANCA IgG, IgM and IgA, produced by autoreactive PCs, decreased but did not disappear after RTX. Interestingly, 24 weeks after RTX, serum anti-MPO-IgG and -IgM decreased in 34 patients, which associated with repopulating CD20+ PBs. This suggested remaining autoreactive B cells despite RTX treatment, which was further studied by in vitro PBMC cultures. In these supernatants both anti-MPO-IgG and -IgM were measured in these supernatants and in paired serum samples by ELISA.

Conclusions: RTX results in a strong but not complete B cell depletion. In-depth analysis demonstrated that both ANCA-producing PCs and ANCA-memory B cells can be detected after RTX, indicating residual B-cell autoimmunity in AAV patients. Further investigation of MRA could be worthwhile for guiding personalized treatment in AAV patients.
FR-PO825
Non-specific Inflammatory Markers Can Be Predictors of Disease Activity in ANCA-Associated Vasculitis

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Background: The purpose of the study was to compare non-specific inflammatory markers such as high sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR) and procalcitonin level (PCT) in clinically active ANCA associated vasculitis (AAV) before and after the induction therapy.

Methods: 28 patients with AAV diagnosed in the Nephrology Clinic between 2014 and 2017 were included. hsCRP was measured using nephelometry assay (BNII Siemens) with a cutoff point 0.8 mg/dl and procalcitonin level using electrochemiluminescence method (Elecsys BRAHMS PCT Cobas, Roche) with the upper reference range of 0.046 ng/ml. Statistical analysis was performed using Mann-Whitney, Wilcoxon signed-rank and Kruskal-Wallis tests (SPSSv18).

Results: 28 patients with a median age 58 years (67.9% female) were included. Granulomatosis with polyangiitis (GPA) was diagnosed in 16 (57%) patients, microscopic polyangiitis (MPA) in 13 (43%). The most frequently affected organs were: lungs (83%), joints (83%) and kidneys (75%). Before the treatment the median BVAS/WS score was 7 points, the median hsCRP was 2 mg/dl, median ESR 56 mm and the median PCT was 0.17 mg/ml. Severe, systemic disease (EULAR) was diagnosed in 12 patients (42.8%). The these cases median hsCRP (10.3 mg/dl), ESR (81.6 mm) and PCT (3.4 mg/ml) were significantly higher in comparison to the rest of the study group (p=0.006,0.007, <0.001 respectively). The mean serum creatinine concentration (SCr) was 3.4 ±2.2 mg/dl, eGFR 33.2 ±30.4 ml/min/1.73 m², 12 patients were treated with hemodialysis. The median ANCA level was 51 IU/ml. In all patients concomitant infections were excluded. After 6 months of treatment the whole group reached clinical remission. Median hsCRP was 0.2 mg/dl, ESR 17 mm, PCT 0.05 mg/ml and were significantly lower (p<0.001) in comparison to the levels before the treatment. The mean ANCA level was 4.5 IU/ml and were significantly lower after the induction treatment (p<0.001).

Conclusions: Non-specific inflammatory markers such as CRP, ESR, procalcitonin levels are associated with AAV activity and decreases after immunosuppressive, induction therapy.

FR-PO826
Difference Between Urinary Vesicle Fibroblast Specific Protein 1 and Urinary-Soluble CD163 as a Marker of Crescent Formation


Background: Extracellular vesicles (EVs) are present in urine. We previously reported that fibroblast-specific protein 1 (FSP1) levels in urinary EVs (U-EVs) reflect active and ongoing glomerular injury, such as cellular crescent formation. However, it is unknown whether FSP1 in U-EVs is superior to urinary soluble CD163 (U-SCD163) which was established as a biomarker of crescentic glomerulonephritis.

Methods: To address this issue, we collected urine samples from 37 patients with various types of glomerular disease (6 with ANCA-associated nephritis, 11 with IgA nephropathy, 11 with membranous nephropathy, 6 with minimal-change disease and 3 with lupus nephritis), and purified U-EVs using total exosome isolation regent. We also reported that fibroblast-specific protein 1 (FSP1) levels in urinary EVs (U-EVs) reflect active and ongoing glomerular injury, such as cellular crescent formation. However, it is unknown whether FSP1 in U-EVs is superior to urinary soluble CD163 (U-SCD163) which was established as a biomarker of crescentic glomerulonephritis.

Results: FSP1 levels in U-EVs correlated positively with U-SCD163 levels (r=0.367, P<0.05). FSP1 levels in U-EVs also correlated positively with rates of biopsy-proven cellular crescent formation (r=0.562, P<0.001). Meanwhile, U-SCD163 levels correlated positively with rates of biopsy-proven cellular (r=0.595, P<0.001), fibrocellular (r=0.511, P<0.001), and fibrous (r=0.501, P<0.001) crescent formation. FSP1 levels in U-EVs and U-SCD163 levels for predicting cellular crescent formation affecting more than 20% of total glomeruli was 2.4 ±0.95 mg/Cr and 14.5 ±mg/Cr, respectively, with an area under the ROC curve of 0.88 (95%CI, 0.693 to 1.070) and 0.82 (95%CI, 0.673 to 0.961) (P=0.58). Both U-SCD163 levels and FSP1 levels in U-EVs were significantly reduced after treatment (median: 4.90 ±0.35 mg/Cr; mean: 2.72 to 0.14 mg/Cr).

Conclusions: These data suggest that both FSP1 in U-EVs and U-SCD163 are available biomarkers of active and ongoing glomerular injury, such as crescent formation. However, it was FSP1 level in U-EVs that specifically reflected cellular crescent formation requiring urgent treatment.

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FR-PO827
Patients with ANCA-Associated Vasculitis (AAV) Display Major Phenotypic Significance of T-Cell Dysfunction

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Background: In chronic infection and tumors, persistent T cell stimulation results in functional T cell exhaustion and anergy but limited data are available on the association between chronic inflammation in AAV and T cell dysfunction.

Methods: We performed a comprehensive flow-cytometric analyses of major T cell markers (Th1, Th2, Th17 cells dysfunction; CD25+ regulatory T cells) and intracellular IFN-g, IL-4, IL-17 production in the same study groups.

Results: We found a remarkable and statistically significant increase in CD4+ and CD8+ T cells with exhausted and anergic phenotype in AAV patients compared to HC (Fig. IA-D). AAV patients also displayed significantly higher levels of circulating Treg (Fig. IE). Despite Treg increase, we did not record a significant difference in intracellular cytokine production.

Conclusions: Patients with AAV display a unique immune phenotype characterized by extensive T cell dysfunction, associated with increased Treg, suggesting the existence of chronic inflammation before clinical onset of the disease.

FR-PO828
Antibodies to Plasminogen and a Pathogenic Myeloperoxidase (MPO) Epitope Precede MPO- and Proteinase 3-ANCA in Patients with ANCA Vasculitis

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Background: The preclinical immunopathogenesis of anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis has not been elucidated. Antibodies to plasminogen (anti-PLG) and a specific epitope of myeloperoxidase (MPO<sup>147-153</sup> anti-KIV) are associated with active disease. The presence of these antibodies has not been examined prior to diagnosis. We hypothesized that anti-PLG and anti-KIV precede detectable MPO-ANCA and proteinase 3 (PR3)-ANCA.

Methods: Up to 4 serum samples collected before clinical diagnosis were available from 64 patients with ANCA vasculitis (50 PR3, 12 MPO, 2 unknown) and 63 healthy controls (HC) matched for age, gender, ethnicity, and timing of sample through the Department of Defense Biorepository. Anti-PLG, anti-MPO, and PR3-ANCA were measured by ELISA. Analyses accounted for matched pairs using McNemar tests and odds ratios and 95% confidence intervals from stratified exact conditional logistic regression.

Results: Anti-PLG was detected in 17/64 (27%) of cases prior to diagnosis (median t = -8.8 years [IQR -13.1, -2.0]). Anti-PLG was positive before ANCA in 76% (13/17) of cases. Anti-KIV was detected in 21/64 (33%) of cases. Prior to diagnosis (-6.6 years [-15.0, -4.1]), it was elevated before ANCA in 71% (15/21) cases, and elevated when MPO-ANCA was negative in 33% (4/12) of MPO-ANCA patients. ANCA patients were more likely to have elevated anti-PLG and anti-KIV than matched controls (sensitivity testing anti-PLG at 10% of ANCA patients, the odds ratio for anti-PLG remained statistically significant; the odds ratio for anti-KIV was the same albeit not statistically significant.

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Underline represents presenting author.
FR-PO829
CD4+ T Cell Abnormalities in the Myeloperoxidase-ANCA-Associated Vasculitis
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Background: In ANCA-associated vasculitis, MPO-specific CD4+ T cells have been reported to involve in renal injury. Although in Granulomatosis with Polyangiitis (GPA), it has been found that lymphopenia is a common clinical feature, and the effect of lymphopenia was excluded. However the pathogenesis of T cell involvement is not fully elucidated. Thus, we dissect whether the microscopic polyangiitis patients have the similar symptoms and the underlying pathogenesis.

Methods: Clinical data from 143 newly diagnosed microscopic polyangiitis patients (Collection time prior to use of Glucocorticoid and immunosuppressants) and 176 healthy controls was collected and analyzed. The phenotypic characterization of peripheral blood lymphocytes in 33 of MPA patients was measured by Flow cytometry. Meanwhile, disease activity of these patients according to the Birmingham Vasculitis Activity Score was marked. The cytokine produced by relevant CD4+ T cells was detected. Chemokine and chemokine receptors axis concerning T cell recruitment was observed by immunohistochemistry in formaldehyde-fixed kidney nephritidal tissue.

Conclusions: T cell abnormalities of MPA patients are characterized by lymphopenia and abnormal blood was significantly decreased compared with healthy control. Besides, abnormal CD4+ T cell subsets was detected. Chemokine and chemokine receptors axis concerning T cell recruitment was observed by immunohistochemistry in formaldehyde-fixed kidney nephritidal tissue.

FR-PO830
Single-Cell RNA Sequencing Uncovers Distinct Clusters of T Helper 17 Cells in Renal Autoimmune Disease
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Background: T cells play a pivotal role in the pathogenesis in various autoimmune diseases by their ability to differentiate into pathogenic effector Th1 and Th17 cells, which includes human and experimental glomerulonephritis. CD4+ T cells and Th17 cells in particular can have a high degree of plasticity in the brain and intestine but show limited plasticity within this population. We discovered 10 clusters based on transcriptional similarities. The degree of heterogeneity and expression profiles of the different clusters could build the basis for the analysis of potential cell-cellar interactions that include resident kidney cells.

FR-PO831
Novel Assays to Distinguish Between Properdin-Dependent and Properdin-Independent C3 Necrotic Factors Provide Insight for Properdin-Inhibiting Therapy
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Background: C3 glomerulopathy (C3G) is a severe renal disorder caused by dysregulation of the alternative complement pathway and is characterized by depositions of C3 fragments in the glomeruli. C3 necrotic factors (C3NeFs) are found in the blood of more than half of C3G patients. These autoantibodies recognize the alternative pathway C3 convertase and prolong its activity. C3NeFs can be dependent or independent of the complement regulator properdin for their convertase-stabilizing function. However, studies to determine the properdin-dependency of C3NeFs are rare and not part of routine patient investigations. Until recently, only supportive treatments for C3G were available. Complement-directed therapies are now being investigated. We hypothesized that patients with properdin-dependent C3NeFs may benefit from properdin-inhibiting therapy to normalize convertase activity.

Methods: Therefore, we have validated two hemolytic assays to distinguish between properdin-dependent and properdin-independent C3NeFs by assessing the convertase activity and convertase stability in alternative pathway. The hemolytic complement activity and duration of C3 convertase stabilization by patient immunoglobulins in properdin-depleted serum. The second measures convertase stabilization directly in patient serum supplement with the Salp20, a properdin-blocking agent.

Results: Blood samples from 13 pediatric C3G patients positive for C3NeF were tested for convertase stabilization in absence of properdin. Three patients presented with properdin-dependent C3NeFs as no C3NeF activity was observed in absence of properdin, whereas the C3NeF activity of the other 10 patients was independent of properdin. In conclusion, the results of the patients with properdin-dependent C3NeF will be presented. The properdin-blocking agent Salp20 normalized the convertase activity profile.

Conclusions: These results indicate that inhibition of properdin in patients with properdin-dependent C3NeFs can normalize alternative pathway convertase activity and could be used as a novel therapy. Our assays provide a tool for identifying C3G patients who may benefit from properdin-inhibiting therapy and should be incorporated into standard C3G laboratory investigations.

FR-PO832
High Levels of Intestinal-Activated IgA B Lymphocytes Support the Pathogenic Role of Intestinal Mucosal Hyper-Responsiveness in IgA Nephropathy (IgAN) Patients
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Background: In the last years, the role of mucosal immunity in IgAN, together with that of the gut microbiota in the activation of innate and adaptive immune cells, has gained importance. Particularly interesting is the role of the microbiota and intestinal immunity in IgAN, due to the activity of secretory IgA in the intestinal mucosa. Here we studied the intestinal-renal axis connections analyzing levels of BAFF, APRIL and intestinal-activated B cells in patients and healthy subjects (HS).

Methods: Serum and fecal samples were collected from 44 IgAN patients and 23 HS. BAFF and APRIL serum levels were measured by ELISA assay. Metabolomic analysis of gut microbiome was performed by mass spectrometry. B cell subsets were identified by FACS. We used anti-IgA, anti-Integrin J7 and anti-CCR9 antibodies to identify B cell subsets producing IgA and B cells from intestinal mucosa.

Results: IgAN patients had increased levels of BAFF correlating to higher amounts of 5 specific microbiota metabolites (p=0.012). We found also high April levels in IgAN patients. BAFF and APRIL can be produced by the intestinal epithelium, in response to signals triggered by TLRs activated by the commensal bacteria in the intestinal lumen. In addition, we found that IgAN patients have a higher proportion of circulating Breg activated at the intestinal level (CCR9 INTB7) compared to HS (p=0.02). Moreover, IgAN patients also had high levels of CCR9 INTB7 memory B cells (p=0.006) and of intestinal IgA-producing memory B cells (CCR9 INTB7/IgA p=0.03). Interestingly, they were significantly increased in IgAN patients but not in non-IgA glomerulonephritis. Finally, we found that IgAN patients had high levels both of total plasmablasts (p=0.001) and of intestinal-activated plasmablasts (p=0.01).

Conclusions: The results of our study showed for the first time an important difference in the amount of intestinal-activated B lymphocytes among patients with IgAN and HS, confirming the hypothesis of the pathogenic role of intestinal mucosal hyperresponsiveness in IgAN patients. Therefore, our findings provide new targets for research for new targeted therapies aiming to stop the evolution towards end stage renal disease.

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Underline represents presenting author.
FR-PO833

B Cell and Monocyte Phenotyping in IGA Nephropathy: A Quick Asset to Investigate the Immune Status in Patients with IGA Nephropathy

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Background: IGA nephropathy (IGAN) is the most common glomerulonephritis. Naive and adaptive immune cells play a major role in the development and progression of disease, therefore unraveling a correlation between changes in the immune status of the patient and clinical outcomes is of great value. We aimed to investigate B cell and monocyte phenotype, comparing the IGAN patients with disease controls (patients with polycystic kidney disease) and healthy individuals.

Methods: IGAN patients (n = 13) were recruited from Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden. Patients (men 46%) with median age of 45 years (IQR 38-60), median eGFR of 57 ml/min x1.73m2 (IQR 42-84) and median urine albumin-to-creatinine ratio of 74 mg/mmol (IQR 18-116). Disease controls with polycystic kidney disease (n = 13) were matched for eGFR, gender- and age (±10 years). Healthy controls (n = 13) were gender- and age-matched (±5 years) with patients. CD3+ cells were isolated from freshly separated peripheral blood mononuclear cells by positive selection using a magnetic cell sorting system. CD3+ and CD3- cells were then divided and stained for different subsets of B cells and analyzed by flowcytometry. Cytokines were analyzed by ELISA.

Results: We report an increase in the proportion of CD14+CD16++ cells (non-classical monocytes) in patient with IGAN compared to healthy individuals and disease controls. Decrease in the proportion of CD19+CD27+ IgG+ cells (pre-switched B), CD19+CD27+CD38+ cells (plasmablasts) in the peripheral circulation of IGAN patients. IGAN and disease control showed an increase in CD19-CD27hi CD38 hi (transitioned plasma cells). We report a higher proportion naive/pre switched in IGAN patients compared to healthy- and disease controls. We report significantly higher IL-6 in IGAN compared to healthy controls.

Conclusions: The decrease in the number of circulating pre-switched B cells and plasmablasts, but an increase of transitioned plasma cells in our study suggests trafficking of subsets of B cells in IGAN patients between peripheral blood and extravascular lymphoid tissues. The increase in the proportion of inflammatory monocytes in IGAN patients may play a role in the high inflammatory state and possible crosstalk between different sectors of the immune system through the IL-6 axis.

FR-PO834

Transglutaminase 2 (TGM2) and Lysozyme Significantly Upregulated in Staphylococcus Infection-Associated Glomerulonephritis (SAGN): A Mass Spectrometry Study

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Background: SAGN and primary IgA nephropathy (IGAN) are considered separate disease entities with different treatment approaches. However, overlapping histologic features and mesangial IgA deposits in both lead to diagnostic dilemma. A proteomic study on kidney biopsies was performed to identify potential distinguishing biomarkers.

Methods: Formalin fixed paraffin embedded (FFPE) tissue was used - SAGN (4), primary IgAN (8), baseline transplant biopsies (7), and acute tubular necrosis (ATN) (8) for laser capture and HPLC-MS/MS using the Oribtrap Elite instrument. Spectral counts were modeled as negative binomial distribution and compared. Immunohistochemistry (IHC) was performed on 20+ slides (5 SAGN, 10 IgAN). Significantly higher number of lysozyme positive cells, coupled with severe ATN and diffuse tubulointerstitial staining for TGM2 may favor SAGN over primary IgAN, in the appropriate clinical context.

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FR-PO835

Genome-Wide Association Study for Serum Galactose-Deficient IgA1 in IgA Nephropathy

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Background: Galactose-deficient IgA1 (Gd-IgA1) is the most common primary glomerulonephritis worldwide. Galactose-deficient IgA1 (Gd-IgA1) plays a key role in the pathogenesis of IgAN. Although the heritability of serum Gd-IgA1 levels is high (ranging from 54% to 80%), the genetic association between Gd-IgA1 and IgAN has not yet been clearly determined. To further identify novel susceptibility loci, we carried out a genome-wide association study (GWAS) for serum Gd-IgA1 levels in IgAN patients.

Methods: We performed a quantitative trait GWAS for serum Gd-IgA1 levels, with discovery and follow-up in 1,127 IgAN patients in a Chinese population. Gd-IgA1 levels were measured using a Helix aspersa lectin-based ELISA method. The mRNA levels of susceptibility genes in peripheral blood mononuclear cells (PBMCs) were evaluated by mRNA microarrays (Affymetrix PrimeView Human Gene Expression Array and Illumina HT-12 v4 Expression BeadChip).

Results: We identified two loci passing genome-wide significance, including GALNT12 (P = 1.67 × 10^-10, Beta = 0.68) and C1GALT1 (P = 3.10 × 10^-10, Beta = 0.24). Additionally, we confirmed reported association of C1GALT1 with serum Gd-IgA1 levels, including rs1008897 (P = 9.75 × 10^-10) and rs13226913 (P = 3.89 × 10^-10), which are common variants in Europeans but rare in East Asians (MAF 34% vs. 5% and 58% vs. 7%). C1GALT1 variant associated in our study is in partial linkage disequilibrium with rs1008897 (D' = 0.92, r^2 = 0.07) and rs13226913 (D' = 0.44, r^2 = 0.02). Compared with healthy controls (n = 61), GALNT12 and C1GALT1 showed lower mRNA expression in PBMCs from IgAN patients (n = 94) (0.86-fold change, P = 1.00 × 10^-6 and 0.90-fold change, P = 1.92 × 10^-10, respectively). Sub-phenotype analysis showed that the risk allele of GALNT12 variant was associated with decreased serum C3 levels (P = 0.02, Beta = -0.05).

Conclusions: Our study identifies two loci, which encode two enzymes (GALNT12 and C1GALT1) involved in O-linked glycosylation, are associated with serum levels of Gd-IgA1 in IgAN. Down-regulation of these two enzymes may contribute to the generation of aberrantly glycosylated IgA1 in IgAN.

FR-PO836

RNA Sequencing Identifies Novel Genes Implicated in the Pathogenesis of IgA Nephropathy

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Background: IgA nephropathy (IGAN) is one of the most common form of glomerulonephritis throughout the world and also the leading cause of kidney failure among Asian populations. Previous genetic studies have identified several genetic factors predisposing to IGAN, however, the transcriptome changes of kidney tissue of IGAN are not thoroughly investigated yet, which was crucial for the exploration of the molecular pathogenesis of this disease.

Methods: We used RNA-sequencing to study the whole transcriptome of kidney biopsies of 8 IGAN patients and 5 control samples. Differentially expressed genes (DEG) were identified using DESeq2. GO and pathway enrichment analysis were applied to explore the biology relevance of these DEGs to IGAN.

Results: We identified 54 genes with differential expression between the IGAN patients and the healthy controls, with 41 genes were up-regulation and 13 were down-regulation in the IgAN patients (fold change >1.5 and FDR<0.1). Pathway enrichment analysis revealed that these DEGs were involved in cotranslational protein targeting to membrane, humoral and innate immune response and endothelium development. Among these, the top of six susceptible genes (P<1x10^-6) were MMP7, SERPINA3, SLPI, RPS27A, FLT1 and NES, which were related to renal fibrosis, innate mucosal defense,

Mean Lysozyme positive cells/glomerulus.
Urinary Biomarkers for Kidney Injury in IgA Nephropathy

FR-PO837

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Background: IgA nephropathy is the most common primary glomerular disease leading to chronic kidney disease. Clinical management and prognosis rely heavily on renal pathology; reliable biomarkers are needed for non-invasive evaluation of the kidney. The aim of this study was to investigate potential urinary biomarkers of kidney injury severity in IgAN.

Methods: Spot urines were collected from 45 IgAN patients at the time of diagnostic kidney biopsy and 29 healthy volunteers (control). Biopsies were classified by the Oxford system and the degree of activity and chronic damage was recorded blindly as none, mild, moderate or severe by the renal pathologist. The candidate biomarkers of kidney injury we assessed were adiponectin, CD163, EGF, NGAL, ICAM1, VCAM1 and complement component C5a. These were measured in urine using R&D DuoSet ELISAs. ANOVA, nonparametric Wilcoxon test and multiple linear regression were done using JMP14 pro for data analysis.

Results: Urine adiponectin, CD163, C5a and VCAM-1 were significantly different than healthy controls with fold-increases of 7, 399, 28 and 7 respectively (all p<0.0001). While EGF decreased by 1.4-fold compared to control (p=0.0015). Urine EGF was inversely correlated with interstitial fibrosis and tubular atrophy (IFTA, R²=0.35, p<0.001) and overall chronicity (R²=0.49, p<0.0001), while C5a positively correlated with IFTA (R²=0.21, p=0.0018). Adiponectin and C5a were both positively correlated with overall activity (based on biopsy MEST score) (R²=0.51, p=0.0008 and R²=0.38, p<0.008, respectively). Using receiver operating characteristic analysis, the area under the curve for the panel was 0.80 (p<0.001).

Conclusions: Urinary EGF could serve as a biomarker for chronic kidney lesions in IgAN while adiponectin and complement 5a may be biomarkers for active kidney lesions. These biomarkers could be helpful in non-invasively evaluating the efficacy of therapies for IgAN.

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FR-PO838

Aberrant Immune Response to Periodontopathic Microbiota in Patients with IgA Nephropathy

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Background: Aberrant mucosal immune response is implicated in terms of the multi-hit theory of IgA nephropathy (IgAN) development, however, microbiota responsible for pathogenic IgA production in IgAN remained obscure. We have focused until now on roles of microbiota in tonsillar crypts and its relationship with galactose-deficient IgA1 (Gd-IgA1).

Methods: We assessed Gd-IgA1 levels in each fraction of serum of IgAN patients and healthy controls using flow cytometry.

Results: The serum levels of Gd-IgA1 in IgAN patients were significantly higher (1.53±1.06 mg/dl) than controls (0.90±0.65 mg/dl, p<0.002) and patients with non-IgAN (0.89±0.70 mg/dl, p<0.001). HRMS analyses confirmed that less O-glycosylated glycoforms were predominantly presented in IgAN patients with high values of Gd-IgA1. A significant reduction of Gd-IgA1 serum levels was found during the follow-up compared to baseline values (p=0.01). This decline was more prominent in patients who received corticosteroids (n=8, p=0.008). The values of Gd-IgA1 did not influence the progression of renal damage (50% reduction of baseline eGFR).

Conclusions: High Gd-IgA1 serum levels characterize patients with IgAN at the time of kidney biopsy. During the clinical course of the disease Gd-IgA1 levels decline but this reduction is more prominent in patients receiving CS. This biomarker may be used for monitoring the effects of CS therapy.

Funding: Clinical Revenue Support

FR-PO839

Validation Study of KM55 ELISA Kit in IgA Nephropathy (IgAN)

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Background: Serum levels of Gd-IgA1 may be considered the first biomarker of IgAN. In the past, Gd-IgA1 was detected by sophisticated methods such as mass spectrometry (MS) and lectin based assay. Recently, a monoclonal antibody KM55 that specifically binds Gd-IgA1 has become commercially available. Aim of our study has been i) to validate this tool, ii) to analyze relationships between serum Gd-IgA1 levels and the outcome of the disease and iii) to study the effect of corticosteroids (CS) on this non-invasive biomarker.

Methods: Serum levels of Gd-IgA1 were measured using ELISA Kit (Immuno-Biological Lab. Co. LTD, Japan) in a cohort of 63 IgAN patients, 31 healthy blood donors (BD) and 31 primary non-IgAN (enrolled at the time of kidney biopsy in the Dept of Nephrology, Aristotle Univ of Thessaloniki, Greece). Fourteen IgAN patients were followed-up for a median time of 8.6±1.1 years. High resolution mass spectrometric (HRMS) analysis was used to study 2 IgAN patients with high level serum of Gd-IgA1, 2 IgAN patients with low serum Gd-IgA1 levels and 2 BD, to confirm the profile of Gd-IgA1 O-glycoforms.

Results: Patients with IgAN had higher values of Gd-IgA1 (1.53±1.06 mg/dl) than controls (0.90±0.65 mg/dl, p<0.002) and patients with non-IgAN (0.89±0.70 mg/dl, p<0.001). HRMS analyses confirmed that less O-glycosylated glycoforms were predominantly presented in IgAN patients with high values of Gd-IgA1. A significant reduction of Gd-IgA1 serum levels was found during the follow-up compared to baseline values (p=0.01). This decline was more prominent in patients who received corticosteroids (n=8, p=0.008). The values of Gd-IgA1 did not influence the progression of renal damage (50% reduction of baseline eGFR).

Conclusions: High Gd-IgA1 serum levels characterize patients with IgAN at the time of kidney biopsy. During the clinical course of the disease Gd-IgA1 levels decline but this reduction is more prominent in patients receiving CS. This biomarker may be used for monitoring the effects of CS therapy.

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FR-PO840

Quantitative Determination of Human IgA Subclasses in Plasma and Their Fc-Glycosylation Patterns by Using Peptide Analogue Internal Standard and an UHPLC-Triple Quadrupole Mass Spectrometry

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Background: Glycosylation on the Fab and Fc regions of immunoglobulins is important for immune function. In this study, we developed and validated a method for the quantification of immunoglobulin A by using affinity purification and UHPLC (ultra-high-performance liquid chromatography)-MS/MS. Twenty-seven IgA-related Fc N-glycopeptides were also detected.

Methods: Peptide M was used to purify IgA, and a peptide analog was added as an internal standard. After on-bead digestion, samples were analyzed by UHPLC/MS/MS. After validation, the method was applied to plasma samples from 24 patients and 6 healthy controls, and the results were compared to those from ELISA assays.

Results: Correlation coefficients were greater than 0.999 for the IgA1 and IgA2 calibration curves and greater than 0.982 for glycopeptide regression curves. Intraday and interday precisions for IgA1 and IgA2 were <1.6% and <5.1% RSD, respectively. Intraday and interday accuracies ranged from 102.6-114.9% and 103.5-113.5% for IgA1 and IgA2, respectively. Recoveries for IgA1 and IgA2 in long-term and short-term stability ranged from 96.0-109.4%. Recoveries after three freeze-thaw cycles ranged from 93.2-113.2% for IgA1 and IgA2. The Pearson’s correlation was 0.84 when comparing the quantification of the 30 clinical samples by ELISAs and the developed UHPLC-MS/MS method.

Conclusions: IgA1 and IgA2 were isolated by peptide M purification. An efficient on-bead digestion process was used prior to UHPLC-MS/MS analysis. The validated method was successfully applied to clinical samples which showed high correlation to the total IgA quantification ELISA results. This method has potential for investigating IgA profiles from human plasma.
FR-PO841

Prevalence of Periodontal Disease Bacteria in Tonsils of IgA Nephropathy Patients

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Background: IgA nephropathy (IgAN) is one of the most common primary glomerulonephropathies, whose pathogenesis has remained unclear. We had reported that C. rectus and T. denti. tica, kinds of major periodontal disease bacteria, in tonsils with IgA nephropathy patients were specific to IgAN patients compared with chronic tonsillitis. (Nomura et al., Plos One, 2014). We also reported C. rectus and S. mutans increased in tonsils of IgAN patients, although P. gingivalis had not been evaluated in IgAN patients, although P. gingivalis was well known as one of most common periodontal disease bacteria. In this study, we evaluated the periodontal disease bacteria including P. gingivalis in tonsils of IgAN patients, and the relationship between these periodontal bacteria clinical features in IgAN patients.

Methods: Tonsils were obtained from 23 IgAN patients and 63 chronic tonsillitis patients when the tonsillectomy was operated. MRNs were extracted from tonsils and the prevalences of C. rectus and T. denti. tica, and P. gingivalis were evaluated by RT-PCR using bacteria specific primers. All patients gave the written informed consent which was approved by Hyogo College of medicine.

Results: Average age was 33.1±14.8 in IgAN patients, and the age in control patients was 27.7±7.3. The average proteinuria in IgAN patients was 0.9±1.1 g/cre, and average hematuria was (2±1). The prevalence of C. rectus in IgA patients was 76%, while the prevalence in control patients was 62%. The prevalence of T. denti. tica was very low in both groups (0%, 1.6%). The prevalence of P. gingivalis in IgA patients was significantly higher than that in control patients (33% vs 3.2%, respectively, P<0.001), which had not been reported. IgAN patients with C. rectus had greater proteinuria than those without C. rectus (1.2±0.4 vs 0.5±0.3, respectively). IgAN patients with or without P. gingivalis had same levels of proteinuria (1.1±0.4 vs 1.1±0.3, respectively). The types of cilia of P. gingivalis (fim A types) were also evaluated. Obviously untypeable of fim A, which is usually minor type, was dominant in IgAN patients.

Conclusions: Periodontal disease bacteria including P. gingivalis in tonsils were related with IgAN. The type of cilia of P. gingivalis might have some relationship with pathogenesis of IgAN.

FR-PO842

TLR7-GalNAcT2 Axis Modulated IgA O-Glycosylation in Patients with IgA Nephropathy

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Background: IgA nephropathy (IgAN) was featured with galactose deficient-IgA1 (Gd-IgA1) complex deposit in kidney of patients. O-glycosyltransferases were responsible for O-glycan synthesis, which made them crucial for the production of Gd-IgA1. Toll-like receptors (TLRs) were shown to be related with pathogenesis of IgAN. The underlying mechanism between TLRs and the production of Gd-IgA1 was not known yet.

Methods: Biopsy proven IgAN patients with clinical features of primary IgAN, MCD, MN, LN were enrolled in this study. Paraflin-embedded sections of kidney biopsies were subjected to immunofluorescence staining for analysis of TLR7 expression. Peripheral blood mononuclear cells (PBMCs) were prepared and used for real-time PCR analysis or cell-culture experiments.

Results: Here we found that TLR7 proteins were abundantly presented in infiltrated leukocyte infiltrate of kidney of IgAN patients (n=90), as compared with healthy donors and patients with MCD or MN. The mean fluorescence intensity of TLR7 was associated with renal function deterioration. Renal expression of TLR7 protein was evidently present in CD19+ B cells. Moreover, mRNA levels of TLR7 were significantly correlated with those of GalNAcT2 in PBMCs and they were both increased in B cells of IgAN patients. After activation with TLR7 ligand-RS48, PBMCs from IgAN patients secret more Gd-IgA1 molecules than controls and expression GalNAcT2 was increased in sorted B cells from IgAN patients. Over-expression of TLR7 led to up-regulated expression of GalNAcT2, whereas knockdown-expression of TLR7 led to down-regulated expression of GalNAcT2. Over-expression of GalNAcT2 in B cells resulted in augmented synthesis of Gd-IgA1 molecules, but not total IgA1 molecules.

Conclusions: Taken together, the abundant presence of TLR7 play important roles in pathogenesis of IgAN nephropathy, by promoting GalNAcT2 expression in B cells and later the synthesis of Gd-IgA1 molecules.

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FR-PO843

Novel Urine Metabolite in Human as a New Differential Diagnosis Biomarker for Lupus Nephritis

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Background: Lupus nephritis (LN) is one of the major causes of mortality and disability in patients with systemic lupus erythematosus (SLE). LN shows many phenotypes so diagnosis is not easy and takes time and labor. Non-invasive biomarkers are required to accelerate diagnosis. The present study aimed to identify urine metabolites as new biomarkers for screening for LN from another nephritis.

Methods: Using capillary electrophoresis and mass spectrometry (MS), we analyzed low molecular weight metabolites in a total of 394 urine samples obtained from Japanese patients with biopsy-proven LN (n=27, n=13), membranous nephropathy (n=78, n=43), diabetic nephropathy (n=29, n=14), MCNS (n=74, n=22), FSGS (n=29, n=10), IgA nephropathy (n=18, n=10), and rheumatoid arthritis (n=19, n=8), in discovery (n=274) and validation (n=120) cohorts, respectively. All urine samples were collected at the time of diagnosis. Multivariate analyses were used for the identification of marker candidates and development of discriminative models. Identification of chemical structure was made on the basis of NMR and liquid chromatography and MS/MS.

Results: We found that an initially unknown metabolite (peak ID: CU040) was present in the urine of LN patients and that measurement of its concentration could distinguish LN from another nephritis. Logistic regression models facilitated the discrimination between LN and other nephritis, and CNK showed high area under receiver-operating characteristic areas. The area under the curve values, sensitivity, and specificity were 0.8218, 0.7037 and 0.9717 in the discovery cohort, and 0.8698, 0.8462 and 0.9346 in the validation cohort, respectively. Based on the result of chemical structure analysis, the CU040 was identified as 3',4'-didehydro-3'-deoxyuridine (CH31H11N3O4, MW 225.07). To the authors’ knowledge, this metabolite has not been detected in humans, but it has been reported in 2013 as a novel biomarker for infection of Plasmodium berghei in the urine of malaria model mice (PMID: 24047624).

Conclusions: The 3',4'-didehydro-3'-deoxyuridine in urine was a novel and excellent differential diagnosis biomarker for LN. Our results may suggest the existence of a common molecular mechanism between malaria and SLE, and it is also very interesting from the viewpoint of understanding the pharmacological effect of Hydroxychloroquine.

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FR-PO844

CTLA4-ICOS Intergenic Variants Associated with Lupus Nephritis in Chinese Populations

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Background: Lupus nephritis (LN) is one of the most prevalent and serious complications of systemic lupus erythematosus (SLE). CTLA4 (cytotoxic T lymphocyte-associated protein 4) and ICOS (inducible T cell co-stimulator) are good candidate genes for SLE because of their role in regulating T cell activation. And the combination of CTLA-4Ig and cyclophosphamide therapy very effectively arrested the progression of murine lupus nephritis. Therefore, the aim of the present study was to identify susceptibility variants in CTLA4-ICOS intergenic region along with its functional significance.

Methods: In genetic association analysis, the discovery Beijing cohort (500 LN patients and 500 healthy controls) was adopted from previous reported GWAS data with the use of Immunochip arrays. The replication cohort was recruited from Henan population (508 LN patients and 912 healthy controls) and the genotyping was conducted by Sequenom Massarray. To identify functional significance, we analyzed publicly available Encyclopedia of DNA Elements data on transcription factor binding sites, blood expression quantitative trait loci data. The effect of SNP on expression was referred to GTEx2015 v6 and Westra2013 eQTL studies.

Results: In the discovery stage, a total of 136 single-nucleotide polymorphisms in a region spanning 113 kb encompassing CTLA4-ICOS was analyzed in 1000 individuals from Beijing cohort. Twenty four of them were significantly associated the susceptibility to LN (p<0.05). rs17268364 and rs13029135 were the top signals (p = 1.41 x 10^-7, OR = 0.77, 95% CI 0.62 - 0.95) and were in high linkage disequilibrium (r2 = 0.99, D’ = 1). This genetic association of rs17268364 was successfully replicated in an independent cohort with 508 LN patients and 912 healthy controls in Henan cohort (p = 3.08 x 10^-6, OR 0.71, 95% CI 0.58 - 0.85). After combined analysis of Beijing cohort and Henan cohort, the association was further reinforced (p = 1.31 x 10^-9, OR 0.73, 95% CI 0.64 - 0.84). Functional analysis predicted conservative and regulatory features of rs17268364. In eQTL analysis, rs17268364 was associated with the expression of CTLA4 (r = 0.26, p<10^-3) and ICOS (r = 3.6 x 10^-3).

Conclusions: Our results suggested genetic association between variants in the intergenic region of CTLA4-ICOS and LN risk in Chinese population.

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FR-PO845

Angiotensin II Type 1 Receptor Agonist Antibodies Are Prevalent in Lupus Nephritis Patients and May Be Associated with Vascular Damage

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Background: Angiotensin type II receptor antibodies (AT1R-Ab) have been linked to hypertension, vascular inflammation and atherosclerosis in human diseases. The aim of this study was to determine the association between AT1R-Ab and intima-media thickness (IMT), microvascular damage and lupus nephritis (LN) activity.

Methods: Plasma AT1R-Ab were evaluated in 107 patients with biopsy proven LN. Then 80 patients were prospectively followed for one-year. Plasma AT1R-Ab, double-strand DNA antibodies (dsDNA-Ab), complement C3 and C4 were assayed in plasma samples obtained at 3, 6 and 12-months from the start of treatment. Morphometric analysis of the kidney biopsy vessels was performed to determine intimal fibrosis and medial layer thickness. Carotid IMT was evaluated by USG at the time of biopsy and then at one-year in 22 AT1R-Ab patients. The comparisons between AT1R-Ab+ and AT1R-Ab- patients were performed by Chi-square and Mann-Whitney’s U. Association between the AT1R-Ab course and other parameters was evaluated by linear mixed models.

Results: AT1R-Ab positivity in 58 (54%) patients than higher than in inactive LN patients and kidney donors. AT1R-Ab+ patients had higher dsDNA-Ab (287 U/ml [97-814] Vs. 26 U/ml [26-182], p = 0.001), lower complement C3 (62mg/dl [43-80] Vs. 74mg/dl [50-101], p = 0.016), higher histologic activity index (5 [3-11] Vs. 2.1 [1-7], p = 0.003), higher segmental lesions (67% Vs. 43%, p = 0.013) and more class III LN (43% Vs. 20%, p = 0.019) than AT1R-Ab- patients. The prevalence of subintimal fibrosis >10% was 47% and the percentage of subintimal fibrosis was higher in AT1R-Ab+ patients (12% [6-20] Vs. 7% [3-16%], p = 0.025). The area of medial layer hyperplasia was greater in AT1R-Ab+ patients (72um2 [16-162] Vs. 54um2 [5-142], p = 0.014). Their histologic features were independently associated with the degree of medial hyperplasia. The course of AT1R-Ab in follow-up was associated with the course of dsDNA-Ab (r = 0.45, p = 0.001), complement C3 (r = -0.185, p = 0.049) and C4 (r = -0.281, p = 0.013). There were no significant changes in IMT after 12 months of follow-up between AT1R-Ab+ and AT1R-Ab- patients.

Conclusions: AT1R-Ab are associated with vascular medial hyperplasia and segmental glomerular damage in LN patients and are associated with serological biomarkers.

FR-PO846

Increased CaMK4 Expression in Podocytes from Renal Biopsies of Patients with Lupus Nephritis Is Mirrored by Its Levels in Cultured Podocytes

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Background: Lupus nephritis (LN) is a devastating and potentially fatal disease that mainly affects women of child-bearing age. We previously demonstrated that Calmodulin Kinase IV (CaMK4) inhibition in podocytes by cell targeted therapy prevents LN in mice. Here we explore the association of renal CaMK4 expression with the presence of LN in patients with SLE and describe novel noninvasive methods to identify patients prone to develop LN.

Methods: Expression of CaMK4 in frozen renal biopsy specimens from thirty individuals referred to rule out LN was evaluated by immunofluorescence. Logistic regression models were used to analyze the predictive value of CaMK4 in the development of LN. Immortalized human podocytes were examined for CaMK4 expression before and after exposure to IgG from ten SLE patients with and without LN and 5 healthy controls. We further devised a novel method to rapidly isolate urinary podocytes by using magnetic beads and successfully extract RNA.

Results: CaMK4 expression in podocytes is a strong predictor of active LN (p<0.01, β 2.36). Culture of podocytes in the presence of IgG from patients with active LN led to increased CaMK4 expression along with reduction in expression of nephrin while no changes were demonstrated in the presence of IgG from normal subjects or from individuals with SLE without nephritis. CaMK4 deficiency or pharmacologic inhibition preserved nephrin expression. CaMK4 inhibited GSK3β by phosphorylating it at threonine 9 which led to stabilization of transcription factor SNAIL and subsequent repression of nephrin transcription. Urinary podocytes from fresh urine were successfully and rapidly isolated by a novel magnetic bead method. Urinary podocytes from patients with active LN, but not from those without kidney disease, displayed increased expression of CaMK4 and CD80.

Conclusions: We conclude that CaMK4 expression in podocytes is a feature of patients with LN and more importantly, we present two novel assays to replace the need for kidney biopsy. We have shown that rapidly isolated urinary podocytes from patients with LN, using a new protocol, and cultured podocytes exposed to IgG from patients with LN express CaMK4 which reflects the levels detected in the kidney biopsy material of patients with active LN.

Funding: NIDDK Support

FR-PO847

Self-Clustering of Tissue Gene Expression to Classify Patients with Lupus Nephritis

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Background: Histologic classification of kidney biopsy in lupus nephritis (LN), while used for treatment decisions, is not sufficiently robust to account LN’s molecular heterogeneity that affects treatment response and outcomes. We tested whether unsupervised clustering of LN biopsies based on tissue gene expression was feasible to classify LN. We postulated that such a classification of LN would reflect disease pathobiology and would be more relevant to managing LN with drugs targeting specific pathogenic pathways.

Methods: Transcript levels of ~500 genes involved in autoimmunity were measured using NanoString in microdissected glomeruli from 57 LN patient biopsies, and then used for unsupervised hierarchical clustering. For each gene, mRNA abundance was compared between each cluster group (CG) and the mean abundance of the other groups to determine genes that were differentially expressed. Differentially-expressed genes from each CG were used for pathway analysis. Demographic, clinical and histopathologic data were also compared between CGs using ANOVA and Fisher’s exact test as appropriate.

Results: Clustering resulted in 4 CGs. There were no significant differences in baseline creatinine, proteinuria, NIH activity or chronicity indices, or ISN/RPS class between CGs. Canonical pathway and upstream regulator analysis differentiated CGs (Table).

Conclusions: Transcript expression in the glomerular compartment of LN kidney biopsies identifies 4 subsets of patients. Immuno-pathways expression appears to have highest G2 followed by G4, and relatively suppressed in G1 & 3. We suggest it may be feasible to tailor treatment to patients based on their CG classification of injury pathways that are differentially expressed.
Peripheral Blood RNA Signatures for Active Kidney Injury in Lupus Nephritis

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Background: Because lupus nephritis (LN) is a manifestation of a systemic process it is reasonable to ask whether circulating leukocytes can serve as a source of biomarkers of active kidney disease. To begin to examine this question we characterized the immune transcriptome of peripheral blood cells at the time of kidney biopsy and looked for associations with renal histology.

Methods: We studied 44 patients with SLE and kidney biopsies consistent with LN, 9 patients with IgAN as immune complex disease controls, and 5 healthy controls. Total RNA was extracted from buffy coats collected at the time of kidney biopsy and tested on a customized gene expression nCounter GX CodeSet. The Nano-String raw data were analyzed with nSolver™ 4.0 software and JMP 14 pro statistical program. Differential expression of significant transcripts was further confirmed by TaqMan gene expression real-time RT-PCR. The NIH activity (AI) and chronicity (CI) indices of the patients’ kidney biopsies were scored by a renal pathologist.

Results: Compared to healthy and disease controls 57 out of 199 transcripts were overexpressed in LN patients. Of these, 25 genes were significantly increased 2-fold or more in active LN (P<0.0001). Over half of these 25 genes are involved in type I interferon signaling. Other differentially-activated pathways included cytokine-mediated responses, B-cell activation and apolipoprotein metabolism. The top overexpressed transcripts in LN were IL27, CD169, LAMPA and DNAPTP6 which were 49, 21, 18 and 12-fold higher than healthy and disease controls. PCR confirmed these RNA signatures with IFI192 (243-fold and CD169 24-fold higher than disease controls). AI correlated positively with APOEBC3A and IL-1A (both R^2=0.19) and negatively with TRADD (R^2=0.31), while MIP-1a (R^2=0.2368) positively correlated with CI (all, P<0.01).

Conclusions: Interferon-I signaling, cytokine response, B-cell activation and lipoprotein metabolism are the major differentially-activated in peripheral blood cells during LN flares. AI and CI correlates are mainly cytokines, mediators of innate immunity, and apoptosis.

Funding: Clinical Revenue Support

FR-PO849

Development of Novel Algorithms to Characterize Lupus Nephritis (LN) Renal Activity and Chronicity Using Urine Proteomics

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Background: We assessed the utilization of the widely available, high throughput platform for multiplex analysis of urine proteomics to define limited sets of baseline markers correlating with LN histopathology results assessed by the NIH Activity (NIH-AI) and Chronicity (NIH-CI) Indices. Novel algorithms were developed to characterize patients into high and low subgroups. Longitudinal urine sample were used as surrogates to monitor the disease indices over time.

Methods: Baseline urine samples were collected from 42 LN patients. Baseline LN biopsies were interpreted by an expert pathologist. Additional LN samples were collected over a year. Urine samples were tested on a large Luminex multiplex platform. Stepwise regression and single variable regression results were combined to limit the possible candidate urine biomarkers. A multivariate logistic regression model (MLRM) was applied to the remaining markers. Selection criteria for biomarkers were p values < 0.05, high area under the curve, and a low misclassification rate. Receiver operating characteristic curves based on cross-validations evaluated the predictiveness of selected biomarkers.

Results: Data from 288 markers were reduced to 177 by assessing assay robustness. Four markers (CD163, ferritin, KIM-1, and antileukoproteinase) were identified (P<0.05) in the MLRM, which predicted 93% of the NIH-AI high patients with a false positive rate (FPR) of 11%. The predicted probability of high activity patients decreased over time relative to baseline as serum albumin increased and proteinuria decreased, reflecting decreased activity. The markers identified for NIH-CI were hepatocyte growth factor, Eotaxin-2, IL-6Rβ, and ITAC. The model predicted 81% of patients with high NIH-CI with a FPR near 0%.

Conclusions: This study supports the continued evaluation of urine biomarkers with a multiplex immunoassay platform validated to clinical laboratory standards and could support wide distribution as a Luminex-based test. Novel combinations of markers were associated with renal histopathologic activity and chronicity (high and low categories) in LN. Treatment led to alterations in activity and chronicity longitudinally.

Funding: Commercial Support - Astra Zeneca

FR-PO850

Study of T-Regulatory Cells and B-Regulatory Cells in Lupus Nephritis: A Prospective Observational Study

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Background: Studies in lupus nephritis (LN) have shown impairment in both T regulatory (Treg) number and function. The data on B regulatory (Breg) is limited in LN. We conducted a prospective observational study of Treg and Breg populations in LN and their trend after initiation of immunosuppression.

Methods: Study included 20 patients of treatment-naïve LN of ISN/RPS Class III/IV (Va, VI (Va), V and 10 healthy controls (HC)). Immunophenotyping was performed for peripheral blood mononuclear cell samples using fluorochrome labelled monoclonal antibodies for identification of Tregs (CD3+CD4+CD25+CD127−FoxP3+), Bregs (CD19+CD5+CD14+IL-10+), immature cells (CD19+CD24+CD25−) and B10 cells (CD19+CD24+CD27−), each expressed as percentage of T and B cells. Each lymphocyte population was analysed at baseline, 2 and 6 months after initiation of immunosuppression. Regulatory cells between groups was analysed by Mann Whitney U test and within groups by Wilcoxon signed rank test and Friedman’s test, as applicable.

Results: Bregs were significantly decreased compared to HC at baseline (p=0.002). With immunosuppression, Bregs showed significant increase at 2 and 6 months (p<0.03). Bregs in responders showed an increasing trend at 2 and 6 months (p=0.05), while they did not in non-responders (p=0.247). The increase in Bregs did not significantly differ between different immunosuppressive regimes given. At baseline, Bregs in responders and non-responders were not significantly different. Immature cells and B10 cells were significantly higher compared to HC (p<0.001). Tregs did not differ significantly from HC and did not show significant increase at 2 and 6 months, in both responders and non-responders.

Conclusions: We observed that Breg populations in treatment-naïve LN were significantly reduced compared to HC and increased significantly with immunosuppression. Responders had a trend toward increase in Bregs over time, whereas non-responders did not.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: The results suggest that Xe may shed light of therapeutic value in treating such cases of LN although it might warrant further study.

Funding: Government Support - Non-U.S.

FR-PO853

Kidney Biopsy Proteome Reveals Novel Molecules and Pathways in Lupus Nephritis

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Background: Lupus nephritis (LN) is a major cause of morbidity and mortality. Pathogenesis of LN is largely unclear. Identification of molecules that are differentially expressed between LN classes and normal control kidneys may help in elucidating mechanisms of LN and to help to identify potential new targets of treatment. Our objective in this study was to identify differences in specific proteins and molecular pathways between LN classes and normal kidneys. We hypothesized that morphologic changes that define the pathology of each class of lupus nephritis are characterized by specific protein expression.

Methods: Forty-eight formalin-fixed, paraffin embedded kidney biopsy specimens were obtained from UCLA Pathology repository. Kidney specimens included 10 histologically normal kidneys and 38 biopsy-proven LN by the 2003 International Society of Nephrology/Renal Pathology Society classification. These tissues were subjected to proteomics analysis using nano-scale liquid chromatography tandem mass spectrometry (nLCMSMS) and tandem mass tag method for protein labeling. Quantitative relative expression data is extracted using Proteome Discoverer 2.2 Software. Ingenuity software was used for pathway analysis. Clinical and histological data were collected.

Results: A total of 2190 peptides were identified in all 48 kidney specimens. Of the 2,190 peptides, 655 were differentially expressed between LN and normal control kidneys (FDR <0.05). Some of the top upregulated proteins included alpha-1-antichymotrypsin, keratins, collagen type IV proteins, alpha-1-antitrypsin, vimentin, and complement components. The top downregulated proteins included apoptosis-inducing factor 1, glutathione S-transferase, V-type proton ATPase catalytic subunit A, transforming acidic coiled-coil-containing protein 3, and dipeptidase 1. Pathway analysis of differentially expressed peptides revealed a set of upregulated molecular pathways including immune cell communication, acute phase response signaling, glucocorticoid receptor signaling, and complement system, while pathways linked to oxidative phosphorylation, fatty acid oxidation, and amino acid degradation were reduced in LN compared to controls.

Conclusions: Using a relatively large cohort of LN kidney biopsies, we report a novel antibody using mass spectrometry for defining molecular pathogenesis of LN and for identifying novel target pathways.

FR-PO854

Serum Biomarkers of Histologic Activity in Lupus Nephritis Kidney Biopsies

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Background: The kidney biopsy is the gold standard for diagnosing and managing lupus nephritis (LN) but it is not practical to repeat biopsies frequently to follow disease status. Because LN is part of a systemic disease we interrogated the serum of LN patients for biomarkers that could non-invasively reflect biopsy findings.

Methods: Serum was collected at the time of biopsy from 50 LN patients and from 9 healthy controls. Fifty pro-inflammatory cytokines and immune mediators were measured using the Luminex multiplexing platform. Data were analyzed by Milliplex Analyst Version 5.1. NIH activity (AI) and chronicity (CJ) indices of the LN biopsies were scored by a renal pathologist. Mild, moderate and severe acute injury were defined as AI scores of 1-4, 5-9, and >10, respectively.

Results: IL-2R, CXCL16, M-CSF, TNFR1 and VCAM-1 were increased 2.7, 1.9, 2.6, 3.4 and 2.1-fold respectively in LN compared to healthy controls (all p < 0.01). Adiponectin, NGAL and M-CSF were significantly elevated in Class IV LN compared to healthy controls (all p < 0.01). IL-2R correlated with moderate-severe crescents and necrosis, while NGAL and M-CSF correlated with moderate-severe necrosis.

Conclusions: Serum M-CSF and PTX appear to reflect severe intra-renal injury in LN. These biomarkers may be useful in managing LN if they can be shown to decrease as crescents and necrosis resolve.

Funding: Other NIH Support - NIAMS
FR-PO855
Pediatric Patients with Membranous Glomerulopathy: A Single-Center Retrospective Study
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**Background:** Membranous nephropathy is a rare cause of pediatric nephrotic syndrome. The purpose of this study is to characterize the clinical presentation, treatment and outcomes of pediatric patients with membranous glomerulopathy in a single center over a 15 year period.

**Methods:** Patients with membranous nephropathy, age 18 years or less, were identified through an existing database of renal biopsy specimens at Indiana University and through billing records. Their charts were reviewed for clinical presentation, treatment and outcomes data.

**Results:** From 2002 to 2019, there were a total of 777 renal biopsy specimens interpreted at Indiana University with a diagnosis of membranous nephropathy. Of these, there were 14 patients, age 18 years or less, identified with primary membranous nephropathy and met inclusion criteria. An additional 4 patients were identified from billing data. Our cohort was primarily female (12/18) with a median age at presentation of 13 years (IQR 10.5–15.5). At presentation, nephrotic range proteinuria was present in 72%, hypoalbuminemia in 70%, edema in 62%, hematuria in 29%, and hypertension in 43% of patients. Renal function was normal in 17/18 patients at presentation. 3 patients had PLAB-R staining on biopsy and 2 were positive. 15 patients had treatment and/or outcomes data available. Median time to most recent follow-up was 20 months (IQR 7–35). 10/15 patients were treated with steroids; 12/15 had documented partial or complete remission at some point during their clinical course. Of the available data, 80%, 36%, and 15% had nephrotic range proteinuria at 3, 6, and 12 months, respectively. 27% and 38.5% of patients had entered complete remission at 6 and 12 months, respectively. One patient was steroid-dependent and relapsed when steroids were stopped. 14/15 patients were treated with an ACEi and/or ARB. One patient was treated with a steroid-sparing agent, mycophenolic acid, and did not enter remission. 14/15 patients had a creatinine less than 1.0 mg/dL at last follow-up. There were no documented complications of nephrotic syndrome such as thrombosis.

**Conclusions:** In our cohort, pediatric patients with membranous nephropathy presented with similar clinical characteristics as adult patients. Our patients had a good clinical response to steroids and/or ACEi/ARB with few documented adverse effects.

FR-PO856
Long-Term Exposure to Air Pollution and Increased Risk of Membranous Nephropathy in China
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**Background:** We have previously shown that long-term exposure to PM2.5 was associated with an increased risk of membranous nephropathy(MN) in a large renal biopsy series in China, which partly accounted for the doubling of MN in patients with renal biopsy during the last decade. Due to limitation of the data, we were not able to assess the effect of the components of air pollution and to distinguish MN by presence and absence of PLA2R antigen in the tissue.

**Methods:** In the current study, we analyzed 94,388 renal biopsies conducted at 1,205 hospitals spanning 262 cities in China from 2015 to 2018, of which 31,481 (33.35%) were of primary MN, thought the relationship appeared to be non-linear for PM2.5 and linear for CO, NO2, O3, and SO2 (Figure 1). Among the cases with primary MN, 7,947 had PLAB-R staining on biopsy and the city-specific rate varied greatly, ranging from 73.68% to 88.26%. The overall PLA2R positive rate was 80.29%. Similarly, higher exposure to each component was associated with increased risk of PLAB-R-related MN. The overall PLA2R positive rate was 80.29%.

**Results:** From 2002 to 2019, there were a total of 777 renal biopsy specimens...
FR-PO858

Clinical Predictors of Acute Tubular Necrosis in Membranous Nephropathy
Joshua Leisring, Shaili S. Kothari, Udayan Y. Bhatt, Anjali A. Satoskar, Brad H. Revin, Samir V. Parikh. Ohio State University Medical Center; Columbus, OH.

Background: Acute tubular necrosis (ATN) is a common and important complication associated with membranous nephropathy (MN). Proteinuria magnitude is suggested as a cause for ATN in MN however clinical contributors to ATN in MN have not been previously evaluated. We queried the OSUWMC kidney biopsy repository to investigate predictors associated with ATN, and specifically explored the relationship between proteinuria magnitude and ATN in MN.

Methods: Ninety-five patients who underwent kidney biopsy from 2004 to 2017 were found to have MN. Pathology reports were reviewed for histologic findings including ATN. Patient demographics and clinical metrics collected at the time of biopsy were analyzed to determine their ability to predict ATN using univariate and multivariate testing. Metrics considered included age, gender, race, serum albumin, cholesterol, and proteinuria magnitude at diagnosis.

Results: A histologic diagnosis of ATN was identified in forty-three patients (45%) with MN. Serum creatinine at time of biopsy was higher in patients with ATN (1.39 mg/dL, IQR 1.06-2.3) compared to those without ATN (1.18 mg/dL, IQR 0.89-1.63), p=0.04. Proteinuria magnitude was the only clinical variable associated with ATN on multivariate testing (p=0.05). Proteinuria magnitude was then stratified into quartiles and analyzed to determine their ability to predict ATN using univariate and multivariate testing. Metrics considered included age, gender, race, serum albumin, cholesterol, and proteinuria magnitude at diagnosis.

Conclusions: ATN commonly accompanies MN and is associated with a higher degree of renal impairment. Patients with MN and > 4 g/d proteinuria are at higher risk for ATN which may have both therapeutic and prognostic implications. Interestingly higher degrees of proteinuria did not further increase ATN rate suggesting additional factors may be involved and requires further study.

ATN Frequency According to Proteinuria Level

<table>
<thead>
<tr>
<th>Magnitude of Proteinuria</th>
<th>Frequency of ATN</th>
</tr>
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<tbody>
<tr>
<td>0-4 g/d</td>
<td>22.7%</td>
</tr>
<tr>
<td>4-11 g/d</td>
<td>93.5%</td>
</tr>
<tr>
<td>11+ g/d</td>
<td>93.17%</td>
</tr>
</tbody>
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FR-PO859

Substitution of Oral for Intravenous Cyclophosphamide in Membranous Nephropathy
Leonnella Luzardo, Gabriela Ottati, Jimena Cabrera, Mariela Garau, Maria C. Gonzalez-Bedat, Ruben J. Coititho rosa, Lucia A. Auchayna, José Santiago, Ricardo Silvarino, Alejandro Ferreiro, Liliana Gadola, Hena M. Caorsi, Oscar A. Noboa.

Background: Optimal treatment for idiopathic membranous nephropathy (MN) is still a matter of controversy. Current guidelines recommend oral cyclophosphamide combined with steroids, but concerns about the cumulative toxicity of oral cyclophosphamide persist. During the last 30 years, MN has been treated with steroids plus a low-dose intravenous (IV) cyclophosphamide-based regimen in Uruguay. The aim of the study was to assess the efficacy of this regimen to induce remission in MN.

Methods: We performed a retrospective analysis of patients with membranous nephropathy, treated with a 6-month course of alternating monthly steroids (months 1, 3 and 5) plus IV cyclophosphamide (a single dose of 15 mg/kg IV the first day of months 2, 4, and 6).

Results: 55 patients treated between 1990 and 2017 were included; the median age was 53 years (IQR=38–64) and 69% of the patients were men. The follow-up was 7.1 years (3.2–13.9). Forty two (76.4%) patients achieved remission, 24 (43.6%) complete and 18 (32.7%) partial, respectively. Thirteen patients (23.6%) remained nephrotic. Time to achieve partial remission after treatment was 5.9 (4.6–16.0) and 11.5 (5.9–15.0) months to achieve complete remission (Table 1). During the follow up, six (10.9%) patients (one with partial and five with no remission) required chronic renal replacement treatment (Figure 1). The latency between diagnosis and end stage renal disease was 3.5 years (2.3–10.1).

Conclusions: Monthly IV cyclophosphamide plus steroids is an effective and safe treatment for membranous nephropathy and is worthwhile to be considered in prospective clinical trials.
FR-PO860

The Significance of Glomerular C1q Deposits in Primary Membranous Nephropathy
Kazuo Torikoshi, Nishi-Kobe Medical Center, Kobe, Japan.

Background: Unlike a previous report of no C1q deposition in idiopathic membranous nephropathy (IMN), recent studies have shown trace C1q deposition even in IMN due to improvements in the sensitivity of detection methods. The aim of study was to examine the clinical and pathological significance of glomerular C1q deposits in IMN.

Methods: 1) This single center retrospective study included 54 patients with MN who underwent renal biopsy from January 2005 to December 2017 (mean follow-up of 3.62±4.4 years). We evaluated remission of proteinuria (<1 g/gCr) and other clinical examinations. 2) Next, after excluding patients with secondary MN (including hepatitis C virus infection, systemic lupus erythematosus, MCTD, malignancy and medication) (n=16), and those without immunofluorescence study (n=3), we selected 35 patients for further study. A variety of clinical parameters, outcomes and other serum and urine factors was compared in patients with and without significant glomerular capillary C1q deposits.

Results: 1) In 54 patients, 16 patients (29.6%) were diagnosed with secondary MN due to the detection of secondary causes including drugs, malignant tumors, autoimmune diseases and infectious diseases. A total of 40 patients (74.1%) achieved remission of proteinuria: 26 (48.2%) complete and 14 (25.9%) partial remission. 2) Glomerular C1q deposition was detected on capillary walls by immunofluorescence in 21/35 (60.0%) patients with IMN. In the group with glomerular C1q deposits, the remission of urinary protein was significantly delayed using a log rank test (log rank =0.019). In IMN, glomerular C1q deposition was an unfavorable predictor for remission of proteinuria (hazard ratio (HR) 2.41, 95%CI=1.13-5.14, P=0.022) in Cox proportional hazards analysis.

Conclusions: These results suggest that glomerular capillary C1q deposition was associated with poor renal outcome.

FR-PO861

Estimation of Nephron Number and Related Single Nephron Parameters in Patients with Idiopathic Membranous Nephropathy
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Background: Studies using animal models suggested that glomerular hyperfiltration as well as impaired hydraulic permeability play a crucial role in the progression of membranous nephropathy. To date, total nephron number and the related single nephron parameters have not been evaluated in patients with idiopathic membranous nephropathy (IMN) due to technical difficulties in counting nephrons in a clinical setting.

Methods: The total nephron number was calculated using a simplified method based on combined use of unenhanced computed tomography and stereology-based estimation of non-sclerotic glomerular density in biopsy specimens (Sasakid T et al. 2018, ASN). Single-nephron glomerular filtration rate (SNGFR) and single-nephron urinary protein excretion (SNUPE) were calculated by dividing GFR or UPE by total nephron number, respectively.

Results: A total 49 IMN patients was included (age, 60±14 years; 49% male; UPE 4.1±3.1 g/day). The total nephron number ranged from 197,561 to 1,824,272 per kidney. Compared to patients with CKD stage 1 or 2, the SNGFR showed a tendency to be low in patients with CKD stage 3 or higher. Patients with CKD stage 3 or higher were characterized by elevated SNUPE level (Figure). Nephron number and the related single nephron parameters were not associated with Ehrenreich-Churg stage of the glomerular basement membrane (GBM) lesions.

Conclusions: This study for the first time estimated total nephron number and the related single nephron parameters in IMN patients. Impaired single nephron functions may be involved in IMN patients with advanced-stage CKD regardless of severity of GBM lesions.

FR-PO862

Levels of Anti-Phospholipase A2 Receptor Antibodies (PLAR2) in Patients with Membranous Nephropathy in Argentina
Antonio R. Vilchez, Biaian Maria Elena, Gustavo Laham, Carlos H. Diaz, CEMIC, Buenos Aires, Argentina.

Background: Primary membranous glomerulopathy (NM) is the most common histological and immunohistochemical phenotype in adult non-diabetic nephrotic patients. 70% of untreated patients are positive for anti-PLAR2 and this proportion is fairly constant throughout the entire experience of single center of the levels of antiPLAR2 in patients with NM or with a nephrotic syndrome without a renal biopsy and correlated with the histological and immunohistochemical phenotype and the clinical status at the time of the assay.

Methods: We identified 169 adult patients who had anti-PLAR2 antibody levels determined using ELISA between July 2015 and November 2018 in Argentina. We obtained relevant data on 101 patients

Results: The median time between the dosing and the biopsy was 12.1 (2.8-45) months. Levels were positive in 30.6%, doubtful in 4.7% and negative in 64.7%, with no significant differences between positive or negative groups in terms of age, sex, initial presentation, albuminuria, proteinuria and renal function. In patients whose first dosage was performed within 6 months of the biopsy (some had already started immunosuppressive treatment), the assay was positive in 45.5% and negative in 54.3%. In the primary forms it was positive in 25, negative in 45 and doubtful in 4 patients. In secondary cases it was positive in only 1 patient and negative in 10 All patients with lupus MN were negative as were patients with other Glomerulopathies. Of four patients with a transplant who had a recurrence of MN in the graft 1 was positive, 1 had a doubtful result and 2 were negative All three pregnant women with a nephrotic syndrome were negative. In 12 patients the anti-PLAR2 antibody titre decreased in response to immunosuppressive treatment (11) or spontaneous remission (1). Two patients who were negative in the course of a complete remission turned positive during a relapse.

Conclusions: Our data show less positivity for anti-PLAR2 than that reported in the literature in untreated patients with MN This is likely due to the fact that many patients were in complete or partial remission, and that treatments mostly consisted of Ponticelli regimen which induce a quicker reduction of antibody levels than other therapeutic options Our results are probably indicative of the wide spectrum of our sample in terms of clinical status and previous treatments.

FR-PO863

Determination of Serum Anti-PLAR2 and Anti-ThSD7A Antibodies and Tissue Anti-PLAR2 in Brazilian Patients with Primary and Lupus Membranous Nephropathy
Ligia C. Battaini, HCFMUSP, São Paulo, Brazil.

Background: Membranous Nephropathy (MN) is a common cause of nephrotic syndrome in adults. In Brazil, it is the second most frequent cause of glomerulopathies in biopsies registries. Incidence variations among the various studies may reflect patterns of biopsy indication in different countries, but it may also be related to socioeconomic, ethnic and environmental characteristics. In the past years, the role of anti-phospholipase A2 (anti-PLAR2) receptor autoantibodies and the antibody against THSD7A (thrombospondin type 1 domain-containing protein 7A) in the pathogenesis of idiopathic MN were described. The determination of these serum antibodies and renal tissue anti-PLAR2 antibodies have not yet been performed in the Brazilian population.

Methods: Blood samples were collected from 28 patients diagnosed with MN, 17 patients with Lupus Membranous Nephropathy (LMN) and 8 patients with Focal and Segmental Glomerulosclerosis (FGS), confirmed by renal tissue biopsy (OM and IF). The serum anti-PLAR2 antibody was measured by the ELISA and IIFT techniques and antibodies against THSD7A by IIFT. In addition, immunohistochemistry was performed in paraffin blocks to identify the anti-PLAR2 antibody in these patients.

Results: All 17 patients with LMN and the 8 patients with FSGS were negative for anti-PLAR2 and anti-THSD7. A total of 28 patients with MN tested negative for anti-THSD7A. Among the patients with MN at admission, there was a positivity of 54% by IIFT and 39% by ELISA, considering VR of 20 RU/ml. When we reduced the ELISA reference value to 14 RU/ml the sensitivity of the test equals the IIFT test. The specificity of both methods was 100% in this sample. Immunohistochemistry was performed in 24 of the 28 patients with MN, 15 (63%) presented positive labeling for the antibody in renal tissue. Of the 15 patients with tissue positivity, 13 tested positive for the antibody in the serum.

Conclusions: In this Brazilian population of MN patients, there was 54% positivity for anti-PLAR2 and 63% for anti-THSD7. The sensitivity of the IIFT test is similar to that of the ELISA. The specificity of the IIFT test is similar to that of the ELISA. The sensitivity of the IIFT test is similar to that of the ELISA. The specificity of the IIFT test is similar to that of the ELISA.

Funding: Government Support - Non-U.S.

FR-PO864

Circulating Antibodies to Recombinant Exostosin 1 Are Detected in Patients with Primary and Secondary Membranous Nephropathy
Daven J. Case,1 Shiweta Tandon,2 Kenneth R. McLeish,2 David W. Powell,2 1University of Louisville, Louisville, KY; 2University of Louisville, Louisville, KY.

Background: Antibodies to phospholipase A2 receptor (PLAR2), a transmembrane protein, are found in 70% of cases of primary membranous nephropathy (MN). Antibodies to thrombospondin type-1 domain-containing 7A (THSD7A) account for approximately 10% of anti-PLAR2 negative patients. Anti-PLAR2

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO865

Anti PL-2R Antibody Tilters and Disease Course in Primary Membranous Nephropathy

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Background: The natural course of primary membranous nephropathy (pMN) is highly variable. Up to half of the patients presenting with nephrotic syndrome will show progressive kidney function decrease. The remaining patients will show a spontaneous remission of proteinuria. Early prediction of progression is needed to personalize treatment.

Methods: We included 216 pMN patients referred to our hospital for urine analysis and followed these patients until renal progression, defined as an increase in serum creatinine of >50% from baseline, >25% to a level >1.5 mg/dl, or start of therapy due to severe nephrotic syndrome, or spontaneous partial remission, defined as a reduction in proteinuria of >50% from baseline to a level >3.5 g/g creatinine with a stable serum creatinine. Anti-PLA2R antibody tilters were determined using a Euroimmun ELISA assay. We created a multivariate prognostic model using cause-specific Cox regression that includes baseline- and serial serum creatinine, anti-PLA2R antibodies, anti-PLA2R antibody tilter, α-1-microglobulin excretion rate.

Results: The table shows baseline characteristics for the study population. The prediction model showed good prognostic performance with a C-statistic of 0.78 (95%CI 0.71 to 0.84) for progression, and 0.78 (0.70 to 0.85) for spontaneous remission at 24 months. The table shows baseline characteristics for the study population.

In total 155 patients were included in the analysis. Baseline information and outcomes are presented in Table 1. Alkalizing agents were mainly used, cyclophosphamide in NL (81%) and chlorambucil in CZ (60%). Overall remission rates (partial- and complete remission) calculated from start of therapy, were not different. Most importantly, no delayed therapy complete remissions were observed frequently (Table 1).

Conclusions: The MN registry allows comparison of treatment protocols between centers. Our data support the safety of a delayed treatment strategy.

Funding: Government Support - Non-U.S.

Baseline characteristics and outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>NL (n=86)</th>
<th>CZ (n=69)</th>
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<tbody>
<tr>
<td>Mean age (y)</td>
<td>38 (31-46)</td>
<td>36 (30-46)</td>
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<tr>
<td>Gender (% males)</td>
<td>69 (78%)</td>
<td>58 (77%)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.5 (1.0-2.1)</td>
<td>1.9 (1.5-3.0)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>3.9 (2.5-7.5)</td>
<td>4.2 (3.0-7.0)</td>
</tr>
<tr>
<td>Partial remission (%)</td>
<td>66 (78%)</td>
<td>58 (74%)</td>
</tr>
<tr>
<td>Complete remission (%)</td>
<td>0 (0%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>31 (18-57)</td>
<td>54 (17-105)</td>
</tr>
</tbody>
</table>

Means, Median [IQR]

FR-PO866

Waiting for Spontaneous Remission in Primary Membranous Nephropathy: Is It Safe?

Coralien Vink- van Setten, Anne-Els van de Logt, Jack F. Wetzels. Radboud University Medical Center, Nijmegen, Netherlands.

Background: We advocate a restrictive treatment strategy in patients with primary membranous nephropathy (pMN): immunosuppressive therapy (IST) is started late, while awaiting spontaneous remission. Many patients thus have persistent nephrotic syndrome for >12 months. Since proteinuria is associated with podocyte loss, delaying treatment might increase the risk of podocyte depletion and secondary FSGS. We evaluated the outcome in patients with persistent proteinuria not receiving IS within 12 months after onset of disease.

Methods: We included patients with pMN, normal eGFR and nephrotic range proteinuria (urinary protein/creatinine ratio(uPCR) >3.0 g/10mmol) at presentation and followed for >2 years. We assume that in patients with podocyte loss and secondary FSGS, a complete remission(CR) will not occur. Therefore we selected patients with early and late spontaneous partial remission(SRem) and compared CR rate as outcome parameter.

Conclusions: Waiting for SRem in pMN is safe. Most patients with persisting proteinuria for more than 12 months develop a remission, even if immunosuppressive therapy is needed.

Comparison of early vs. late spontaneous remission in pMN

<table>
<thead>
<tr>
<th>Group</th>
<th>Early SRem (n=11)</th>
<th>Late SRem (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (%)</td>
<td>0 (0%)</td>
<td>17 (32%)</td>
</tr>
<tr>
<td>Median uPCR (g/dl)</td>
<td>4.7 (3.0-6.0)</td>
<td>3.9 (2.5-6.0)</td>
</tr>
</tbody>
</table>

*Median[IQR]

Funding: Private Foundation Support

FR-PO867

Early vs. Late Start of Immunosuppressive Therapy in Membranous Nephropathy

Anne-Els van de Logt1, Moniek W. Van de luitgaarden2, Coralien Vink- van Setten3, Barbora Svobodova3, Vladimir Tesar3, Jack F. Wetzels.2 General University Hospital, Prague, Czechia; 3Radboud University Medical Center, Nijmegen, Netherlands.

Background: Alkylating agents improve outcome in membranous nephropathy (MN). Guidelines advise restrictive treatment. Some centers wait beyond 6-12 months before start of immunosuppressive therapy. The risk of persisting proteinuria is podocyte loss, which may cause secondary focal glomerulosclerosis. This should reduce the likelihood of complete remissions. We evaluated the safety of delayed therapy.

Methods: We used data of two centers that participated in the MN registry (mnregistry.eu). In one center (Czech Republic (CZ)) treatment is started early after kidney biopsy, whereas in the Netherlands (NL) a restrictive treatment strategy is used. For the current analysis we included incident patients, with proteinurie of > 2 grams/24 hours, treated with immunosuppressive therapy (ISRs) and available follow-up. To allow evaluation of late treatment, we included only patients from NL with an interval of more than six months from kidney biopsy. Partial and complete remissions were defined according to KDIGO criteria.

Results: In total 155 patients were included in the analysis. Baseline information and outcomes are presented in Table 1. Alkylating agents were mainly used, cyclophosphamide in NL (81%) and chlorambucil in CZ (60%). Overall remission rates (partial- and complete remission) calculated from start of therapy, were not different. Most importantly, no delayed therapy complete remissions were observed frequently (Table 1).

Conclusions: The MN registry allows comparison of treatment protocols between centers. Our data support the safety of a delayed treatment strategy.

Funding: Government Support - Non-U.S.

Baseline characteristics and outcome

<table>
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<th>Variable</th>
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<th>CZ (n=50)</th>
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<td>Mean age (y)</td>
<td>41 (34-48)</td>
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<tr>
<td>Gender (% males)</td>
<td>62 (78%)</td>
<td>55 (70%)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.5 (1.0-2.1)</td>
<td>1.9 (1.5-3.0)</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>3.9 (2.5-7.5)</td>
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<td>10 (14%)</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>31 (18-57)</td>
<td>54 (17-105)</td>
</tr>
</tbody>
</table>

Means, Median [IQR]
Clinical Analysis of Short-Term Therapeutic Response Factors in Membranous Nephropathy

Takatuya Iwashita,1 Kari Takayangi,1 Maiko Yamasaki,1 Takayuki Hamada,1 Koki Ogawa,2 Ryo Yamamoto,2 Saek0 Sato,1 Toru Hida,2 Hiroko Hara,2 Taisuke Shimizu,1 Hajime Hasegawa,1 1Saitama Medical Center, Saitama Medical University, Saitama, Japan; 2Saitama Medical University School of Medicine, Kawagoe, Japan.

Background: Membranous nephropathy (MN) is known to affect frequently in elderly patients. Since the duration of MN treatment is likely to be prolonged, it is desirable that the treatment duration would be shortened by the concomitant use of immunosuppressant and prednisolone (PSL). Here, we examined clinical and histological parameters related to the rapid response to the therapy by the retrospective analysis.

Methods: Biopsy-proven 82 cases with MN, hospitalized between April 2009 and December 2017, were enrolled in this study. All cases were divided into three groups, 1st (high responder), 2nd (middle responder) and 3rd (low responder) quantiles, based on the proteinuria-reduction ratio at a month after the beginning of therapy including sole administration of PSL and concomitant use of immunosuppressants such as Cyclosporin or Mizoribine. Cases in 1st and 3rd quantile were comparatively studied. All biopsy specimens were stained by anti-phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain containing 7A (THSD7A) antibodies by standard protocol.

Results: Age of 1st (n=23) and 3rd (n=24) quantile groups were 66.7±2.16 vs 66.6±3.11, showing no difference. Estimated glomerular filtration rate (eGFR) and baseline urine protein-to-Cr ratio (PCR) in 1st quantile group were significantly higher than those in 3rd quantile group, eGFR: 72.7±27.8 vs 59.7±14.6 ml/min (p=0.018), baseline PCR: 8.39±3.7 vs 5.09±1.11 (p=0.039). There was no difference in intensity of immunofluorescent staining of IgG, A, M, C3 between 1st and 3rd quantile groups. We also studied the difference in immunofluorescent intensity of PLA2R, THSD7A and IgG subclass, however, we could not find significant difference in the both groups.

Conclusions: Obtaining higher eGFR and baseline PCR might be related to the rapid therapeutic response. Contrary to our expectation, staining intensity of PLA2R, THSD7A and IgG subclass might not be related the rapid response to the therapy.

Calcineurin Inhibitors Treatment and Renal Function Decline in Patients with Idiopathic Membranous Nephropathy

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Background: Calcineurin inhibitors (CNIs), including cyclosporine A(CSA) and tacrolimus, is an established therapeutic option suggested for treatment in IMN patients. The major concern with CNIs remains its propensity to induce renal function impairment. This study was designed to assess the influence of CNIs on renal function compared with cyclophosphamide(CTX), and seek factors that can predict renal function impairment in patients receiving CSA.

Methods: In this study, we included 555 IMN patients treated with CTX or CNIs, with or without glucocorticoids and other immunosuppressant. Data on age, sex, body mass index, presence of hypertension and diabetes, laboratory tests, and therapeutic regimens were retrospectively retrieved from medical record. Cox regression was employed to analyze risk factors indicating a 30% decline in estimate glomerular filtration rate(eGFR) or end-stage renal disease (ESRD) in total patients or those treated with CSA.

Results: During a median follow up of 2.9(1.0-4.6) years, 59(10.6%) patients developed a 30% eGFR decline or ESRD, of whom over 90% had been treated with CNIs. CNIs treatment was an independent risk factors associated with developing 30% decline in eGFR or ESRD (HR=5.7, 95%Ci 2.2-14.8, P=0.001), independently of age, sex, hypertension, baseline serum albumin, urine protein, and eGFR, and the dose of glucocorticoids. Further analysis restricted in patients receiving CSA age 50 years over 50 years old (HR=3.7, 95%Ci 1.8-7.3, P=0.001) and mean CSA dose over 2.2mg/kg/d (HR=1.8, 95%Ci 1.0-3.1, P=0.035) might indicate 30% decline in eGFR or ESRD.

Conclusions: CNIs treatment may associate with renal function decline independently in IMN patients, especially in patients over 50 years old or receiving CSA over 2.2mg/kg/d.

Efficacy of Cyclophosphamide in Association with Low-Dose Cyclosporine for the Treatment of High-Risk Primary Membranous Nephropathy

Bohdan Obrics, Roxana A. Jurubita, Bogdan M. Sorohan, Andreaga G. Andronescu. 1Gherla Clinical Institute, Bucharest, Romania.

Background: Ponticelli regimen is associated with the highest remission rate in the treatment of primary membranous nephropathy (pMN), but corticosteroids are associated important side effects. As such, we tested the efficacy of the combination of cyclophosphamide and low-dose cyclosporine in the management of high-risk pMN.

Methods: We prospectively followed 8 patients with high-risk pMN, treated with cyclophosphamide (15 mg/kg/month, for 6 consecutive months) and cyclosporine 100 mg/d (for proteinuria control) (CF/Cyc regimen). We compared this cohort to 8 consecutive, prospectively followed patients with pMN treated with the Ponticelli regimen, with a similar risk. Clinical and laboratory data were collected at baseline and at 1, 3, 6, 12- and 15-months thereafter.

Results: The two cohorts had similar baseline characteristics, except for higher antibody titer and proteinuria for patients treated with CF/Cyc regimen. The Ponticelli cohort had patients who had a mean age, serum albumin and eGFR of 50 ± 10 years, 4.9 g/dl and 69 ± 17.3 ml/min/1.73m², respectively (p=0.9, 0.4 and 0.3), while the median 24-hour proteinuria and anti-PLA2R-ab titer were 6.25 (5.25-11) g/day and 122.5 (71.25-211) UI/ml, respectively. By contrast, the CF/Cyc cohort had a mean age, serum albumin and eGFR of 50 ± 9 years, 4.9 g/dl and 72 ± 17.3 ml/min/1.73m², respectively (p=0.9, 0.4 and 0.3), while the median 24-hour proteinuria and anti-PLA2R-ab titer were 9.85 (7.15-13.15) g/day and 291.5 (100-571.75) UI/ml, respectively (p=0.1 and 0.06). CF/Cyc regimen was associated with a 79% and 90% decrease from baseline in mean proteinuria and anti-PLA2R-ab titer, respectively, to a 58% and 97% decrease from baseline following Ponticelli regimen (p=0.7 and 0.8, respectively). There was a 41% and 31% increase from baseline in mean serum albumin following CF/Cyc and Ponticelli regimen, respectively (p<0.9). Overall, the remission rate (CR and PR) was 62% and 50% in the CF/Cyc and Ponticelli cohort, respectively, while 50% of patients in both cohorts showed complete immunological remission by 6 months.

Conclusions: In our cohort of patients with high-risk pMN, treatment with cyclophosphamide and low-dose cyclosporine was as effective as the Ponticelli regimen in inducing disease remission and could represent an alternative to steroid-based regimens.
Results: Over a median follow-up of 36 (IQR 24 - 56) months, 100% of patients achieved PR and 82% of patients achieved CR at a median time of 3.4 and 13.1 months, respectively. After 1 year of treatment, median (IQR) UPCR declined from 8.2 (5.2 - 10.7) to 0.3 (0.2 - 0.7) g/g (P < 0.001). Fourteen SAEs occurred over 166 patient-years. One patient (2%) progressed to ESKD, and no patients died. Of those patients followed after B cell return (n = 25), only 1 patient relapsed over a median follow-up of 18 (IQR 6.2 - 37) months.

Conclusions: Treatment of primary membranous nephropathy with RCP resulted in high rates of complete remission and relapse-free survival.

Funding: NIDDK Support

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Baseline characteristics

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FR-PO874

Long-Term Outcome of Treatment of Relapsing Primary Membranous Nephropathy with Rituximab

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Background: Primary membranous nephropathy is often susceptible to relapse after treatment with usual immunosuppressive therapy consisting of cyclophosphamide and glucocorticoids, or a calcineurin-inhibitor or cyclophosphamide-based treatment. Patients with relapse may be treated with rituximab. However, its dose, frequency of administration and effect on long-term outcome have been incompletely evaluated.

Methods: Fourteen patients from our hospital were included in this study. The data were retrospectively extracted. Primary membranous nephropathy was diagnosed after exclusion of secondary causes, with finding of subepithelial deposits on electron-microscopy a anti-PLA2R antibodies. The inclusion criterion was relapse of a primary membranous nephropathy following a calcineurin-inhibitor- or cyclophosphamide-based treatment. Patients received a single dose of intravenous rituximab (500 or 1000 mg), with target B-cell count < 5 x 10^9/L. Subsequent courses of rituximab were administered following a repeat relapse.

Results: Ten patients were male and 4 female. The median age at time of diagnosis was 49 years (IQR 39-57 months). Median time from diagnosis to rituximab treatment was 17 months (IQR 10-41). During the median follow-up period of 47 months (IQR 32-68) months patients received one course of rituximab, 4 patients two courses and 2 patients three courses. Median time between two courses of rituximab was 16 months (IQR 6-26). Relapses following rituximab treatment responded to a repeat course of rituximab. There was a significant reduction in proteinuria from date of first rituximab treatment to date last seen (4±2.2 vs 1±1.1 g/m², P<0.001), while there was no significant difference in serum creatinine (12±4±5 vs 10±2±1 µmol/L). Two patients had severe infective complications after rituximab treatment.

Conclusions: Rituximab is a safe and effective option in long-term treatment of relapsing primary membranous nephropathy.

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FR-PO875

Low-Dose Rituximab Monotherapy Alone or in Combination with Tacrolimus Is Effective in Primary Membranous Nephropathy

Vivek Pathak, Nephrology, Kovai Medical Center and Hospital, Coimbatore, India.

Background: Previous therapies though effective had more adverse events. Rituximab has been used to induce remission in doses of 2gms. It was therefore used in our patients with lower doses alone or in combination with Tacrolimus to achieve remission. This is a retrospective study to evaluate the role of this treatment.

Methods: 15 patients aged 28 -72 years underwent treatment between since 2014 till 2018. Patients whose GFR was <40ml/min/1.73m² were excluded from the study. Rituximab was given as a fixed dose of 500mg each. It was repeated if there was no response at 3 months. Rituximab was given as a monotherapy for 9 patients. Tacrolimus was added in 4/9 patients at the end of 3 months because of poor response.

Conclusions: Rituximab is a safe and effective option in long-term treatment of relapsing primary membranous nephropathy.
Results: Rituximab caused complete remission in 4/9 patients and 1 patient attained partial remission in the first month. In the remaining 8 patients who were taking renin-angiotensin-aldosterone inhibitors (RAAIs), a single dose of 500mg while another 2 required 2 doses of 500mg each. There was one relapse in this group who responded to one more dose of 500mg. Tacrolimus was added in 4 remaining patients at the end of 3 months.2 went into complete remission after 3 months. The study was started along with first dose of Rituximab in 6 patients.2 patients received a single dose of 500mg, 2 received 500mg doses and 1 received 3 doses of 500mg and 1 received 4 doses of 500mg. All went into complete remission by mean time of 9 months.2 patients treated with rituximab and both were successfully treated with 500mg of Rituximab. There was no fatal event in any group. There was only 1 patient who failed to respond to Rituximab and Tacrolimus combined therapy and subsequently responded to steroid and cyclophosphamide therapy.

Conclusions: Complete remission was attained with a single dose of 500mg Rituximab monotherapy in 2 patients. This study showed complete or partial remission in 14/15 patients with this novel regimen with reduced side effects and cost by avoiding higher doses of Rituximab used in previous studies.

FR-PO878

Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus with or Without Lupus Nephritis

Yuko Oishi,1 Hidekazu Ikeuchi,2 Hiroko Hamatani,1 Masao Nakasatomi,1 Toru Sakairi,1 Yoriaki Kanozawa,2 Akito Maeshima,3 Keiju Hiromura,2 Gunma University, Maebashi, Japan; 2Gunma University Graduate School of Medicine, Maebashi, Japan; 3Jichi Medical University, Shimotsuke, Japan.

Background: Systemic lupus erythematosus (SLE) affects the pregnancy. Previous paper showed an increased risk of premature birth in patients who had a history of lupus nephritis. In the present study, we examined the outcomes of pregnancy in SLE patients with lupus nephritis (renal SLE) or without lupus nephritis (non-renal SLE).

Methods: We retrospectively examined 94 pregnancies in 53 SLE patients who treated in our department from January 1996 to March 2018.

Results: Mean patient age and serum creatinine at the beginning of pregnancy were not significantly different between renal and non-renal SLE patients: 29.4±5.8 vs 30.4±3.2 years (p=0.453) and 0.49±0.67 vs 0.48±0.11 mg/dl (p=0.738). Outcomes of pregnancy were shown in Table 1. Percentage of premature birth and low birth weight were more frequent in SLE patients in total, compared to the reported data of general population in Japan (19% vs 6% and 36% vs 10%, respectively). However, there were no significant differences between renal and non-renal SLE. SLE patients had higher rate of premature birth and low weight birth, compared to general population.

Conclusions: In our study, frequencies of premature birth and fetal loss were not different between renal and non-renal SLE patients. However, both renal and non-renal SLE patients had higher rate of premature birth and low weight birth, compared to general population.

Table 1. Outcomes of pregnancy in SLE patients with or without lupus nephritis

FR-PO879

Venous Thromboembolism in Lupus Nephritis by ISN/RPS Biopsy Classification

Ian D. Cooley,1 Keisha L. Gibson,2 Vimal K. Derebel,1 Carolina Alvarez,2 Caroline J. Poulton,2 Lauren N. Blakez,2 Andrew Love,2 Susan L. Hogan,3 J. Charles Jennette,3 Ronald J. Feld,2 Saira Z. Sheikh,1 University of North Carolina at Chapel Hill, Chapel Hill, NC; 2UNC Kidney Center, Chapel Hill, NC.

Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that can be associated with venous thromboembolism (VTE). Lupus nephritis (LN) has not been shown to be an independent risk factor for VTE. To our knowledge the risk of VTE has not been studied by International Society of Nephrology/Renal Pathology Society (ISN/RPS) LN classification.

Methods: A cross-sectional analysis was performed using data from the Glomerular Disease Collaborative Network (GDCN). Patients with class V LN were compared to those with class III or IV (but not associated class V) LN. Classes I, II and VI were excluded from analysis due to their low prevalence. The outcome of interest was image-confirmed VTE. Logistic regression was used to calculate odds ratios and 95% confidence intervals (OR, 95% CI), adjusted for age, sex, race, hormonal contraception use, serum albumin and use of hydroxychloroquine. Effect modification was assessed between the main effect and other covariates and considered if p<0.05.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Our cohort consisted of 533 patients; mean±SD age of 30.9±15.0 years (range 6-79 years), with an overall incidence of image-confirmed VTE of 54/533 (10.1%). In adjusted analyses, the odds of VTE were not significantly different for those with class III/IV compared to class V LN (OR, 95% CI: 1.00, 0.54-1.84). There was evidence of effect modification of LN class on VTE by age at biopsy. Among patients with an average age at biopsy of 15 (<1SD), class III/IV was associated with higher odds of VTE (OR, 3.38, 1.42-20.34) while among patients with an average age at biopsy of 45 (+1SD), class III/IV was associated with lower odds of VTE (0.26, 0.09-0.78).

Conclusions: VTE was common in LN patients in the GDCN, occurring in ~10%, and was similar among patients with class III/IV LN and those with class V LN. These findings suggest that the association between LN and VTE is not limited to class V-related nephrotic syndrome. Interestingly, however, age-specific analysis demonstrated increased odds of VTE with class III/IV LN diagnosed at a younger age and decreased odds of VTE with class III/IV LN diagnosed at an older age. This may suggest the presence of an age-sensitive modulation of LN class-specific VTE risk.

FR-PO880
Wide Fluctuation in Serum Creatinine Is Observed in Patient with Lupus Nephritis in Remission

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Background: Clinical trials in lupus nephritis (LN) typically base remission on proteinuria and the relative change in serum creatinine (sCr) to baseline. These sCr cutoffs have been arbitrary, however we observe considerable fluctuation of sCr levels in clinical practice. This study was undertaken to assess the variability of sCr in stable, non-flaring LN patients.

Methods: Patient-level clinical data from patients enrolled in the ALMS, MAINTAIN, and ELNT trials who had ≥3 consecutive sCr measurements while in MAINTAIN, and ELNT trials who had non-flaring LN patients. In clinical practice. This study was undertaken to assess the variability of sCr in stable, non-flaring LN patients.

Results: Changes in sCr over time are depicted in the figure. Group characteristics are described in the table. In the fluctuator group, 33%, 20%, and 12% of each patient’s creatinine measurements were >115% of baseline (fluctuators) and a group with no sCr measurements >115% of baseline (non-fluctuators). Disease characteristics and demographics were compared using ANOVA and logistic regression as appropriate. There was no significance difference between the two groups according to sex, race, C3 levels, hematuria, or ISN/RPS class. Univariate analysis revealed that older age and lower sCr levels were associated with fluctuation (p=0.007 and <0.001 respectively). In a multivariable model only sCr remained significant (p<0.001).

Conclusions: Wide fluctuation in sCr is observed in non-flaring patients with LN. The typically used 115% cutoff is too restrictive, and a 125% cutoff might be more reasonable. The fluctuation trend occurs more in patients with low sCr, where small absolute changes in sCr represent large percentage point changes.

FR-PO881
Lupus Patients with Low-Level Proteinuria: Time to Revisit the Guidelines

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Background: Kidney biopsy is an important diagnostic tool in lupus nephritis. ACR guidelines recommend biopsy for proteinuria (>1000 mg), or proteinuria (≥500 mg) with hematuria, cellular casts or high creatinine. The presence of low-level proteinuria (~1000 mg) alone doesn’t qualify for a kidney biopsy.

Methods: We evaluated 150 SLE patients with low level proteinuria who underwent kidney biopsies between June 2003 to September 2018. 84 patients had only low level proteinuria, 18 patients had low level proteinuria & hematuria, 48 patients had low level proteinuria & AKI.

Results: Patients only with low level proteinuria: 67 of 84 patients (79.7%) had LN on kidney biopsy: 21 (25%) had proliferative LN; 16 (19%) had class III and 5 (6%) had class IV. 11 (13.2%) had mixed classes (III or IV & V) and 17 (20.2%) had LN class V. The remaining 17 (20.3%) had non-lupus diagnosis. When hematuria was present, 17 of 18 (94.4%) had LN: 9 (50%) had proliferative LN; 5 (27.8%) had class III & 4 (22.2%) had class IV. 3 (16.6%) had mixed classes. 4 (22.2%) had LN class V. Only one patient (5.6%) had non-lupus diagnosis. Adding AKI to low level proteinuria: 37 of 48 (77.1%) had LN on kidney biopsy. 11 (22.8%) had proliferative LN, 6 (12.5%) had LN class III and 5 (10.4%) had LN class IV. 7 (14.6%) had mixed classes. 8 (16.7%) had LN class V. The remaining 11 (22.9%) had non-lupus diagnoses. Patients with AKI & low level proteinuria had a higher chronicity index (p-value 0.002) compared to patients with low level proteinuria alone.

Conclusions: SLE patients with low level proteinuria frequently have significant renal involvement on kidney biopsy including class III, IV, and mixed class. This study, contrary to ACR guidelines, supports performance of kidney biopsy in those with isolated low level proteinuria.

FR-PO882
Proteinuric Lupus-Related Kidney Disease: A Comparative Study of Pure Class V Lupus Nephritis vs. Lupus Podocytopathy

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Background: Lupus-related kidney disease research has focused on proliferative forms of lupus nephritis, and membranous (MLN) lupus nephritis is less studied. A newer clinical entity associated primarily with proteinuria is lupus podocytopathy (LP) which is...
minimal change disease (MCD) or focal segmental glomerulosclerosis (FGS) in patients with LN. Majority of patients (n=225) were confirmed with MCD, followed by FGS (n=24) and membranous nephropathy (n=15). The mean age of the patients was 38.7 ± 13.2 years (range 10-79 years), and 126 (36.0%) were men. Results of initial renal function tests showed normal serum creatinine (scr) and serum albumin (sAlb) in 68 (19.4%) patients. A strength of this study is length of follow-up with 3.3-5 years in our population. At initial presentation in final sAlb, sCr, or UPC despite lupus podocytopathy having a more severe glomerular sclerosis (r=-0.539, p<0.001), at 1 year of follow-up (50.7 vs. 86.4 ml/min/1.73m², p=0.001), and at the end of follow-up (47.7 vs. 50.5 ml/min/1.73m², p<0.001). Significantly more patients in the rTMA group reached the composite end-point of hemodialysis, death or GFR < 15 (79.5% vs.31.8%, p < 0.001). Patients with histological findings of microangiopathy had a lower mean of Hb, platelets and haptoglobin (10.3± 1.6 vs.11.1± 1.5 p=0.0018, 194± 88 vs. 253± 92 p=0.0001 and 119± 86 vs 180±104 p=0.02 respectively) and a higher LDL (391± 209 vs 303±147 p=0.008). However, if the classical diagnostic criteria for microangiopathic anemia (Hb <120, hapt <10 high DHL and platelet <150) were applied, no patient fulfilled the entire criterion. As expected, TMA group showed higher blood pressure (SBP 131±10.5 vs 124±17.3 p =0.01). There was no difference between groups concerning C3, C4, ANA, anti-Ro, and anti-La. Concerning histopathological features, rTMA group had significantly higher activity (9.0±4.8 vs. 6.0±4.5, p <0.001) and chronicity (4.4±2.9 vs. 2.7±2.2, p<0.001) scores. On the other hand, there was no difference in immunofluorescence.

Conclusions: The classical criteria of microangiopathic hemolytic anemia was not able to predict rTMA. For NL patients, these criteria could be more flexible. Serological data were also not predictors. Renal biopsy remains the critical method for diagnosis and rTMA was a frequent and serious finding. RTMA was an important risk factor for renal outcome, as demonstrated by lower GFR and higher hemodialysis rates in this group.
The Value of Repeated Kidney Biopsies in Patients with Lupus Nephritis
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Background: The indication to repeat renal biopsy in lupus nephritis (LN) flare is controversial. Studies with protocol biopsies had shown a mismatch between clinical and pathological remission, giving even more importance to repeated biopsies. The aim of our study was to evaluate the pathological changes in patients with LN with a repeated biopsy.

Methods: We analyzed 107 patients with LN biopsied between 1990-2018, we selected 26 patients who had 2 renal biopsies.

Results: Mean age at the diagnosis of LN was 29.6±3.4 years, 73.1% female and 73.1% Caucasian. At 1 biopsy 30.7% of the patients were class II, 7.7% class III, 38.5% class IV, 11.5% class V and 11.5% mixed class. Cyclophosphamide was the induction therapy in 53.8% of patients and mycophenolate in 23.1%. Time between biopsies was 71.5±20.7 years. Proteinuria was the most common reason to repeat biopsy (73.1%). At 2 biopsy, patients had lower SLEDIAI (12 vs 16, p=0.00) and less number of patients had anti-dsDNA antibodies (46.2 vs 73.1%, p=0.03). There were no differences in creatinine (SCR), proteinuria or complement.

Conclusion: Our study suggests the utility of repeated renal biopsies as 38.4% of patients changed to a higher class without relevant clinical expression. The percentage of CR at 12 month, %GE and CI were the main prognosis factors for LN.

A Fingerprint of Response to Treatment in Lupus Nephritis: Identification of a Panel of Eight Proteins from Baseline Renal Biopsies That Predict Response
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Background: Lupus nephritis (LN) carries significant morbidity & mortality risk. Only ~50% of patients respond satisfactorily to current standard of care. Likelihood of response & long term prognosis are unclear at the outset with no reliable predictors identified. We set out to establish a panel of baseline kidney biopsy proteins which by relative quantification SWATH mass spectrometry (MS) could reveal biomarkers associated with subsequent response to treatment or mechanisms of disease in non-responders.

Methods: 32 FFPE renal biopsy tissue blocks were identified for analysis: LN class IV: 4 complete responders (CR) & 8 non responders (NR); class V: 5 CR & 4 NR; Controls: 7 CR & 4 NR.

Results: Of the 5139 proteins identified, 57 were significantly up-regulated in CR compared to NR and included Th17 cell differentiation, metabolic & RNA degradation pathways. Downregulation in CR compared to NR was noted in 106 proteins which included IL-1β & MAPK signalling & melanogenesis. Further analysis revealed that a panel of 8 proteins separated CR from NR including moesin, a key protein in immunity, & eukaryotic translation elongation factor 1 epsilon-1, a negative regulator of cell proliferation, each downregulated in CR compared to NR. A validation study in a separate set of biopsies is underway.

Conclusion: Whilst the protein yields from FFPE blocks are extremely small (4-8µg protein), we demonstrate these can be successfully analysed by SWATH MS. Importantly, this approach allows us to use baseline biopsies to identify CR from NR using a panel of just 8 proteins and provides novel insights into the intra-cellular mechanisms of response to treatment in LN, biomarkers of response to therapy as well as potential targets for new therapeutics.

 Funding: Private Foundation Support
Results: The clinical characteristics were similar in both groups, except activity index (AI) at 13/25 (52%) at baseline to 9/25 (36%) at the time of re-biopsy. On the other hand, the number of patients with class V lesions increased from 6/19 (31.6%) at baseline to 14/21 (66.7%) at re-biopsy in the non-CNI group. We investigated risk factors for relapse of LN with class V lesions by performing multiple logistic regression analysis, and found that CNI was a negative risk factor with an odds ratio (95% confidence interval) of 0.211 (0.0351-0.839).

Conclusions: CNI may prevent the relapse of LN with class V lesions.

FR-PO892 Calcineurin Inhibitors May Prevent Diffuse Membranous Lesions In Lupus Nephritis Daiusuke Ikuma, Hiroki Mizuno, Masayuki Yamanouchi, Junichi Hoshino, Kenji Ikematsu, Yoshifumi Ubara. Nephrology center, Toranomon Hospital Kapiga, Kawasaki, Japan.

Background: Lupus nephritis (LN) is a relapsing disease. The pathologic features of LN may change with relapse, and such changes cannot definitely be predicted clinically. Current guidelines recommend selecting treatment for LN according to the 2003 ISN/RPS classification, which states that glucocorticoids (GC) are the key drugs. Little is known about whether or not other immunosuppressants are effective for LN, including cyclophosphamide, mycophenolate mofetil, azathioprine, and calcineurin inhibitors (CNI). In class V LN, accumulation of subepithelial immune complexes leads to glomerular inflammation. CNI have been reported to show a podocyte-protecting effect that is independent of their immunosuppressive activity. Accordingly, we examined the effect of CNI on class V lesions in patients with relapsing LN.

Methods: Forty-six Japanese patients with LN, who underwent one or more repeat renal biopsies at our hospital between May 1995 and May 2017, were analyzed retrospectively. Patients who received continuous administration of CNI were assigned to the CNI group and other patients were assigned to the non-CNI group.

Results: There were 25 patients in the CNI group and 21 patients in the non-CNI group. No significant differences of baseline characteristics were noted between the two groups. In the CNI group, the number of patients with class V lesions decreased from 13/25 (52%) at baseline to 9/25 (36%) at the time of re-biopsy. On the other hand, the number of patients with class V lesions increased from 6/19 (31.6%) at baseline to 14/21 (66.7%) at re-biopsy in the non-CNI group. We investigated risk factors for relapse of LN with class V lesions by performing multiple logistic regression analysis, and found that CNI was a negative risk factor with an odds ratio (95% confidence interval) of 0.211 (0.0351-0.839).

Conclusions: CNI may prevent the relapse of LN with class V lesions.

FR-PO893 Tacrolimus Combined with Short-term Corticosteroids for Inducing Remission in Membranous Lupus Nephritis: A Retrospective Study Yaoming Wang, Fei Han. First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China.

Background: We retrospectively analyzed the efficacy of Tacrolimus combined with short-term corticosteroids for inducing remission in membranous lupus nephritis.

Methods: We retrospectively reviewed purely class V LN patients that were followed up in our center between January 2012 and December 2017. They were divided into 2 groups: IVC group received intravenous cyclophosphamide (0.75g/m2 once monthly) combining with prednisone (0.6-0.8mg/kg/d) and the dose of prednisone was gradually tapered after 8 weeks. Tacrolimus group received tacrolimus (trough serum concentration 6-8ng/ml) combining with methylprednisolone (8-10mg/kg/d, maximum 300mg/d, for 3 days), with or without following methylprednisolone 40mg/d; the total duration of corticosteroids was less than 2 weeks.

Results: Totally 65 patients with class V LN were analyzed, including 26 patients in IVC group and 39 patients in tacrolimus group. There were no significant differences on serum albumin, proteinuria, blood cells and immunological index at baseline between IVC and Tacrolimus group. Also, there were no significant differences on the severity of pathologic changes such as glomerular sclerosis, crescent formation, mesangial proliferation, segmental necrosis and interstitial infiltration between two groups. In the maintenance period, there were no significant differences on the remission rates between IVC group and tacrolimus group (80.8% vs 64.1%). The median follow-up time was 15.0 (10.5, 36.0) months in IVC group and 12.0 (6.0, 24.0) months in tacrolimus group (P=0.119). At the end of follow up, the remission rate (CR and PR) was significantly higher in IVC group than in Tacrolimus group (86.7% vs 66.7%). There were 10 relapses including 3 (11.5%) relapses in IVC group and 7 (17.9%) relapses in tacrolimus group.
Type 2 diabetes mellitus: a review of the pathogenesis and treatment of the disease. The prevalence of type 2 diabetes mellitus has increased dramatically in recent years, with a corresponding increase in the prevalence of complications. This review will focus on the pathogenesis and treatment of type 2 diabetes mellitus.

Pathogenesis:
Type 2 diabetes mellitus is characterized by insulin resistance and pancreatic β-cell dysfunction. Insulin resistance is the result of a number of factors, including obesity, inflammation, and genetic factors. Pancreatic β-cell dysfunction is characterized by a decrease in insulin secretion and an increase in insulin sensitivity.

Treatment:
Treatment of type 2 diabetes mellitus involves lifestyle modifications, pharmacotherapy, and, in some cases, insulin therapy. Lifestyle modifications, such as weight loss and increased physical activity, can improve insulin sensitivity and decrease insulin resistance. Pharmacotherapy options include oral antidiabetic drugs, such as metformin, and insulin therapy.

Conclusion:
The pathogenesis of type 2 diabetes mellitus is complex and involves a number of factors. Treatment aims to improve insulin sensitivity, decrease insulin resistance, and improve β-cell function. Further research is needed to better understand the pathogenesis of type 2 diabetes mellitus and to develop more effective treatment options.
FR-PO989

Clinical Value of Complement Biomarkers in Autoimmune Glomerulonephritis

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Background: Complement activation plays a central role in the mechanisms of injury of autoimmune glomerular diseases. Urinary excretion of different complement biomarkers could indicate relevant activated pathogenic pathways (classical, lectin, alternate), parallel disease activity and add clinical value beyond proteinuria.

Methods: We performed a prospective observational cohort study of 81 patients included in local glomerulonephritis (GN) clinic. Serum and urinary biomarkers were assessed at presentation and at each follow-up visit. Urinary sC5b-9, C3dg, C3Dg, C4d, C3, C4, IgG and IgA were assessed. Results were compared between remission and non-remission status.

Results: Baseline urinary sC5b-9 was present in 39/81 (48%). Median sC5b-9 was higher in non-remission status (19.9 ng/mmol creatinine) compared to remission status (1.4 ng/mmol creatinine; p<0.001). Median sC5b-9 was significantly lower in complete remission status compared to non-remission (2.3 ng/mmol creatinine vs. 19.8 ng/mmol creatinine; p<0.001). 46% of patients had urinary C3dg at presentation, with a median value of 1.9 ng/mmol creatinine. Urinary sC5b-9 was associated with a lower proportional reduction of proteinuria at 6 months follow-up (p=0.039). Median sC5b-9 was lower in patients with complete remission at 6 months compared to patients without remission (1.8 vs. 19.9 ng/mmol creatinine; p<0.001). Median sC5b-9 was lower in C3dg compared to non-remission status (1.1 ng/mmol creatinine vs. 2.4 ng/mmol creatinine; p=0.003).

Conclusions: Complement biomarkers could indicate relevant activated pathogenic pathways (classical, lectin, alternate), parallel disease activity and add clinical value beyond proteinuria.

FR-PO909

Outcome of Membranoproliferative Glomerulonephritis and Postinfectious Glomerulonephritis Stratified by New Classification

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Background: The new classification of membranoproliferative glomerulonephritis (MPGN) has been based on the immunofluorescence (IF) staining: Immune complex (IC)-MPGN and C3 glomerulopathy. In addition, the possibility of overlap between C3 glomerulopathy and postinfectious glomerulonephritis (PIGN) has been raised because of high proportion of C3 dominance and poor renal outcome in PIGN. However, little is known about clinical features and outcomes of C3 glomerulopathy compared to IC-mediated GN.

Methods: Among patients with MPGN and PIGN, 39 (14%) and 36 (52%) were classified as C3DG. C3DG had higher proportion of women, lower C3, nephrotic range proteinuria and serum cholesterol, and higher serum albumin although renal function was not different at the time of biopsy (P>0.05). In addition, C3DG had almost no association with viral hepatitis B (31.3 vs. 29.2%, P=0.001), and lower tendency of ANA (P=0.085). After 6 months of biopsy, C3DG had significantly lower proteinuria and high rate for remission of proteinuria (P<0.05). The incidence of 40% decline in eGFR was significantly lower in C3DG compared to IC-mediated GN (16.3% vs. 31.5%, P=0.031). The incidence of stage renal disease (ESRD) was the highest in IC-MPGN and the lowest in C3-PIGN during 107 [28-247] months of median follow up (IC-MPGN, 37.4%; C3-MPGN; 26.3%; IC-PIGN; 22.2%; C3-PIGN, 9.1%; P=0.036). Together with MPGN and PIGN, C3DG was associated with better renal survival (P=0.016). Multivariate analysis showed the risk of eGFR decreased 0.396-fold increase of ESRD (95% CI; 0.192-0.814) compared than IC-GN.

Conclusions: C3DG had lower rate of moderate proteinuria and less likely to be associated with chronic infection and autoimmune disease at presentation. The 13.7% of C3DG progressed to ESRD in although it showed favorable renal survival compared to IC-MPGN.

FR-PO901

DNAJB9 Protein Accumulation in Fibrillar GN Is Not due to Local RNA Upregulation

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Background: Fibrillar glomerulonephritis (FGN) is characterized by glomerular accumulations of haphazardly arranged fibrils and deposition of IgG with DNAJB9, a protein in the ER stress/unfolded protein response pathway (UPR). In this study, we sought to determine the prevalence of fibrillar glomerular disease (FGR) in DNAB9.

Methods: We evaluated formalin-fixed paraffin embedded kidney biopsies from patients with FGN (n=6), non-fibrillary glomerular disease (n=2 amyloidosis, n=3 cryoglobulinemic gn, n=3 diabetic nephropathy) and normal controls (n=2). Confocal microscopy was performed on slides stained with a DNAJB9 RNA in situ hybridization probe and DAPI. Automated image analysis was performed and corroborated with DNAJB9 immunohistochemistry.

Results: By immunohistochemistry, FGN cases were DNAJB9-positive and non-FGR cases were DNAJB9-negative. DNAJB9 RNA signals were present in FGN, non-FGR glomerular disease, and normal controls; signals were identified in podocytes and mesangial regions as well as tubular, interstitial, and vascular tissue. There were no significant differences in glomerular DNAJB9 RNA signals (313 vs. 379, p=0.3), DNAJB9/DAPI ratios (2.23 vs. 3.3, p=0.3), or DNAJB9 signal intensity between FGN and non-FGR cases.

Conclusions: DNAJB9 RNA expression does not predict protein accumulation in FGN, suggesting that the pathogenesis of FGN is not dependent on local activation of the UPR. Our findings corroborate prior proteomic studies in which other components of the UPR pathway were not locally upregulated (PMID: 29097624), and provide contextual data to studies which identified increased levels of DNAJB9 protein in serum from patients with FGN (PMID: 31010480). This supports an alternate mechanism or circulating source for DNAJB9 accumulation in fibrillar GN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only.
FR-PO902
Proliferative Glomerulonephritis with Non-Organised Monoclonal Immunoglobulin Deposits (PGNMID): A Single-Centre Retrospective Study
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Background: PGNMID is a rare glomerular disease, most often seen in the context of MGSR. At present, optimal treatment is not established.

Methods: All native renal biopsies performed at the Hammersmith Hospital between 2006 and 2017 were analysed. 15 cases of PGNMID were identified. Baseline characteristics and clinical outcomes during follow-up to January 2019 are summarised in the Table.

Results: Mean age was 61, 31% were men, mean eGFR was 49 mL/min/1.73m2 and mean uPCR 384 mmol/mol. A circulating paraprotein was detectable in 5 (33%) of 15 patients. Most (73%) underwent bone marrow aspiration and trephine (BMAT), with a clone identified in two. One had a plasma cell clone and was not immunosuppressed, having presented at end stage with an eGFR of 7 mL/min/1.73m2 and 50% IFTA. The second patient had a B cell clone, with an eGFR of 83 mL/min/1.73m2 and 0% IFTA, and achieved remission of proteinuria and stabilisation of eGFR with prednisolone and rituximab. Three (20%) patients had a detectable paraprotein but no clone on BMAT, and all received treatment. Two progressed to ESRD despite steroids, rituximab and cyclophosphamide. One patient initially responded to steroids, MMF, rituximab and bortezomib, but relapsed following cessation of bortezomib due to peripheral neuropathy. 10 of 15 (67%) patients had no detectable paraprotein at diagnosis. Of these, 95% had partial or complete renal remission. Treatment of this group was variable; none had clone-directed therapy.

Conclusions: Our cohort of PGNMID patients corroborates the previously-described low rate of detection of circulating paraprotein and pathogenic clones in PGNMID. Further collaborative studies are required to establish the safety and efficacy of clone-directed therapy, and to guide optimal management in patients with PGNMID.

FR-PO903
Study of Anti-Complement Factor H Mediated Disease at a Tertiary Care Centre
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Background: Complement dysregulation is an important aetiology for glomerular diseases. Antibodies against complement factor H which regulates the alternate complement pathway can cause atypical HUS and C3 glomerulopathy. Aim of the study: To study the clinical profile and outcome of patients with anti complement factor H mediated disease at our centre.

Methods: Materials and methods: We studied the clinical profile and outcome of patients with anti complement factor H mediated disease at a tertiary care centre over 24 months (August 2016 to July 2018). We had a total of 18 cases during the study period. All patients were followed up to assess their response to therapy.

Results: A total of 28 cases of atypical HUS were seen during the study period of which anti factor H antibody was elevated in 18 (64.2%). Mean age of the patients was 26.6 +/- 3.2 years with 10 patients in the paediatric age group. There were 13 males (72.2%). 10 patients had a febrile prodrum (55.5%). All patients presented with hypertension with active urinary sediments and rapidly progressive renal failure. Mean serum creatinine at presentation was 6.8 +/- 1.2 mg/dl and mean proteinuria at presentation was 3+ by microscopic testing. Mean eGFR at presentation was 60 mL/min/1.73m2. Serum C3 was low in all patients with a mean of 68 +/- 12.2 mg/dl with normal C4 levels. LDH was elevated in all patients with a mean of 2878 +/- 211.4 IU/ml. All patients had schistocytes in peripheral smear. Anti complement factor H antibody was elevated in all patients with a mean of 549 +/- 90 AU/ml (normal - 0 to 100 AU/ml). Renal biopsy showed thrombotic microangiopathy in 12 patients (66.6%) while features were suggestive of C3 glomerulopathy in 6 patients (33.3%).

Conclusions: Our study shows that anti complement factor H mediated disease shows good response to plasmapheresis followed by immunosuppression with B cell targeted therapy. Anti CFH mediated disease should be ruled out in all patients with atypical HUS. It is more common in the paediatric age group with excellent response to plasmapheresis and immunosuppression in the form of oral steroids and cyclophosphamide. Also patients presenting with TMA have better prognosis compared to C3 glomerulopathy. Identification of the pathological clone of cells producing the anti factor H antibody would provide more insight into the nature of the disease. We also hypothesise that the clones producing antibody to the N and C terminals might be different.

FR-PO904
Outcome of First Relapse After Eculizumab Withdrawal in Atypical Hemolytic Uremic Syndrome: The CUREIHUS Study
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Background: Eculizumab was introduced as life prolonging therapy for patients with aHUS. However, the costs of therapy and potential side effects have stirred excitement about early drug withdrawal. The safety of an early withdrawal strategy is debated, since relapses may cause chronic kidney injury. In the Netherlands eculizumab is used according a restrictive treatment regime, with a preference to withdraw or taper the drug three months after start of therapy. Here, we present an interim analysis of the outcome of patients with a first relapse.

Methods: We evaluated outcome in all aHUS patients in whom eculizumab was tapered or withdrawn, and developed a (suspected) relapse necessitating renewed eculizumab therapy. Serum creatinine, eGFR (CKD-epi) and protein-creatinine ratio at 6 and 9 months after relapse and last follow-up were compared with baseline.

Results: We evaluated 34 patients (20 F, 14 M; median age 35 years, IQR 34) with aHUS, in whom eculizumab was tapered or withdrawn. Fourteen patients (41%), including 3 children, had a relapse. Of these, 93% were known with a genetic variant in complement genes. Eight patients had a kidney transplant. Restart of eculizumab was effective in most patients, with no significant difference between eGFR at baseline (median 42.6 mL/min/1.73m2, IQR 40) at 6 months (40.5 mL/min/1.73m2, IQR 48), 9 months (36.6 mL/min/1.73m2, IQR 42) after relapse, and at the end of follow-up (35.6 mL/min/1.73m2, IQR 53). At the end of follow-up (18 months, range 2-31), one patient with multiple relapses had developed ESRD, with notable and unexplained cystic malformation in both kidneys. In four other patients eGFR had decreased ≥20% compared to baseline. All
Mechanistic and Potency Evaluation of Complement Factor D and Factor B Inhibitors

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Background: Complement factor D (CFD) and factor B (FB) are serine proteases essential for complement alternative pathway (AP) activity. CFD activity and FB are present in normal human serum (NHS) at approximately 0.07 μM and 2 μM, respectively. Small molecule inhibitors of FB and FB have been discovered and a few, including ACH-4471 (FD inhibitor) and LPN023 (FB inhibitor), are in clinical development for multiple indications of AP dysregulation including the rare renal disease C3 glomerulopathy (C3G).

In this study, we evaluated FD and FB inhibitors for potency and mechanism of action. We also examined their effect on ex vivo C3 consumption in serum from C3G patients.

Methods: FB and FB inhibitor profiles were profiled by AP hemolysis with rabbit erythrocytes and NHS. Mechanism of action (MOA) and potency of inhibitors were assessed in soluble and bound C3 convertase studies with purified components, including FB titrations and order-of-addition tests; convertase activity was assessed from protease generation measured by ELISA. Compound inhibition in C3G patient sera mixed equally with NHS was assessed in fluid phase, with convertase activity assessed by monitoring C3 cleavage products.

Results: ACH-4471 and next generation FD inhibitors were more potent than LPN023 in AP hemolysis with 4.0-fold to 32-fold lower IC50 values. A reference FD inhibitor (Schubar et al, PNAS 2019) was less potent, with a 1.2-fold lower IC50 than LPN023. LPN023 potency was comparable to input serum FB concentration, suggesting a stoichiometric limit for FB inhibition and a relative advantage for FB inhibitors. MOA studies with C3 convertase revealed that LPN023 binds free intact FB, and that it inhibits AP convertase activity but not proconvertase assembly or its activation to convertase.

Conclusion: ACH-4471 and next generation FB inhibitors demonstrated greater achievable potencies than the FB inhibitor LPN023 in serum from healthy donors and C3G patients, likely due to the lower difference in systemic FD and FB concentrations.

Funding: Clinical Revenue Support - Achillion Pharmaceuticals

FR-P0906
C3 Inhibition with APL-2 Targets the Underlying Disease Process of C3G Complement Hyperactivity and Improves Proteinuria
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Background: C3G is a rare disease of complement dysregulation in which inappropriate C3 activation leads to excessive production of C3 breakdown products. The prognosis is poor with 30–50% of patients reaching end-stage renal disease within 10 years of diagnosis. APL-2, a cyclic peptide that inhibits C3 activation, has the potential to inhibit C3 activation, and improves proteinuria, in patients with C3G.

Methods: Adult and adolescent patients with primary C3G, proteinuria > 0.75 mg protein/μg creatinine and an eGFR > 30 mL/min/1.73 m2 were eligible for this Phase 2 open-label study (NCT04267669). C3G patients were randomized 2:1 to receive APL-2 300 mg subcutaneous injection (SCI) weekly or placebo SCI at baseline, week 8, then every 2 weeks for up to 104 weeks.

Results: A total of 91 patients (73% non-compliant to APL-2 dosing) were enrolled, and data from this patient population were included. Aplastin A (≥ 90 mg/dL) and CKD (GFR < 30 mL/min) were assessed as time-to-event outcomes. The primary endpoint was the percentage of patients achieving target C3G levels at 12 months. APL-2 improved C3G levels compared to placebo (p = 0.0265). APL-2 also reduced proteinuria compared to placebo at 12 months (p = 0.028).

Conclusion: APL-2 is effective in reducing proteinuria in patients with C3G. Further clinical studies are warranted to determine the optimal treatment duration.

Funding: Commercial Support - Apellis Pharmaceuticals, Inc.

FR-P0907
Accelerated suPAR-Mediated Kidney Disease in the Solitary Functioning Kidney
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Background: Kidney mass and number of functioning nephrons are determinants of renal long-term health. Single functioning kidney (SKF) is a rare disease (1:1,500 at birth) resulting in early onset chronic kidney disease (CKD) in over 50% of those affected. Similarly, kidney donors may have an increased risk for future CKD. The underlying mechanisms are not clear. The soluble urokinase receptor (suPAR) is an immune-derived circulating factor implicated in pathogenesis and prediction of CKD incidence and progression. We hypothesized that SKF condition could be more sensitive to increased suPAR levels and examined 3 different rodent models of SKF.

Methods: Uninephrectomy and sham surgeries were performed on C57B/6 mice, suPAR transgenic/knockout models or littermate controls. The minipumps with different concentrations of LPS were implanted subcutaneously. Proteinuria and suPAR were followed for 4 weeks. In congenital SKF rat model (HSRA), the recombinant human suPAR protein was injected intravenously into HSRA single kidney rats (HSRA-S) and two-kidney controls (HSRA-C). Proteinuria and beta3 integrin activity were assessed.

Conclusions: Increased circulating suPAR levels are induced by LPS, or from suPAR transgenic models or extrinsically injected, induce proteinuria in uninephrectomized mice or congenital SKF rats, when compared to their two-kidney controls. These findings suggest the importance of suPAR in SKF, possibly in kidney donors and support findings that suPAR cause declined renal function. Monitoring circulating suPAR levels might be useful in understanding risk and risk-control for patients who are born with or remain having only one functional kidney.

Funding: Clinical Revenue Support
found that the ablation of Syncp in Col4a5- or Col4a3Δ mice led to shortened life span and acceleration of disease progression, such as more severe proteinuria and glomerulosclerosis. We obtained the same results except for decreased life span in Col4a5- females; surprisingly, most Col4a3Δ mice could live 5 months regardless of the presence or absence of Syncp. Immunostaining showed that the expression of COL4A345 was upregulated in these mosaics female mice in the absence of Syncp.

Conclusions: We conclude that Syncp deletion exacerbates the Alport syndrome disease phenotype in Alport mice, revealing the podocyte actin cytoskeleton as a target for therapy.

Funding: NIDDK Support

FR-PO911
β2-Adrenergic (β2-AR) Agonist Protects Mice from Glomerular Injury Through the Activation of β2-AR Receptor in Podocytes
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Background: Podocytes have a remarkable ability to recover from injury, however, little is known about the recovery mechanisms involved in this process. In this report, we demonstrate that pharmacological activation of β2-AR-dependent MB (mitochondrial biogenesis) is involved in the recovery of podocytes from injury in a PGC-1α-dependent manner. We further demonstrate that the drug-induced podocyte recovery was significantly attenuated in podocyte-specific β2-AR knockout mice.

Methods: The β2-AR knockout human podocytes were generated using specific shRNA, and the podocyte specific β2-AR knockout mice were generated by crossing β2-AR flox mice with podocin cre (B6.Cg-Tg(PL2c295LmJ)1 mouse to remove β2-AR protein specifically in podocytes. The effect of a potent, specific, and long-acting β2-AR agonist formotol on MB was analyzed in control and β2-AR knockout podocytes by evaluating mtDNA (mitochondrial-DNA) copy number. Formotol-induced (1mg/kg body weight/day) recovery of renal function was analyzed in wild-type and β2-AR knockout mice by analyzing ACR, histological, ultrastructural and immunostaining analyses.

Results: β2-AR knockdown in cultured human podocytes reduced mtDNA copy number indicating β2-AR role in MB. While the podocyte-specific β2-AR knockout mice developed normally, interestingly, when these mice were injured by treatment with dihydroxy or nephrotoxic serum unlike their WT (wild type) littermates, they failed to recover in response to treatment with formotol and showed diseases glomerular morphology with consistent albuminuria.

Conclusions: Overall, these results confirmed that β2-AR plays a critical role in podocyte recovery from injury and genetic deletion of β2-AR affects the ability of mice to recover from injury. Overall these results suggest β2-AR as a novel therapeutic target for treating podocytodystrophy.

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FR-PO912
Melanocortin 5 Receptor (MC5R) Signaling Protects Against Podocyte Injury and Proteinuria
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Background: Melanocortin therapeutics represented by ACTH has a demonstrable steroidogenic-independent antiproteinuric and glomerular protective effect. It remains unclear whether MC5R receptors (MC5R) mediate this renal protective effect. MC5R was the last MC receptor to be characterized and has been involved in both biology and pathology. However, the role of MC5R in glomerular disease is unknown and was examined here.

Methods: Adriamycin (ADR) nephropathy was induced in MC5R knockout (KO) and wild-type (WT) mice. Proteinuria and glomerular injury were evaluated. In vitro, ADR- insulted murine podocytes were treated with a highly selective MC5R agonist and cellular injury assessed.

Results: Under physiological condition, KO were no different from WT mice and had normal kidney physiology and histology. Upon ADR injury, KO mice demonstrated an exacerbated glomerular injury, featured by heavier albuminuria and worsened glomerular pathology, including glomerulosclerosis, podocyte apoptosis, loss of podocyte markers and ultrastructural lesions in podocytes like foot process effacement and microvillous transformation. Mechanistically, GSK3β activation and the consequent phosphorylation of β-catenin and key regulator of podocyte injury, was more active in glomeruli of KO mice after ADR injury. This was concomitant with a potentiated activation of NFkβ RelA/p65, a cognate substrate of GSK3β, in glomeruli in KO mice, and reinforced de novo expression of proinflammatory cytokines in KO mice. In vivo, ADR-induced podocytes, treatment with a MC5R agonist rectified GSK3β overactivity, suppressed NFκβ activation and the consequent de novo expression of B7-1, cathepsin L and MCP-1, in podocytes. Moreover, paxillin, a focal adhesion-associate adaptor protein and GSK3β substrate, was more activated in glomeruli of KO mice after ADR injury, associated with more disruption of podocyte cytoskeleton, shown by filamentous actin staining. In contrast, in control mice, in vitro ADR insulted podocytes, treatment with a MC5R agonist rectified GSK3β overactivity, suppressed NFκβ activation and the consequent de novo expression of B7-1, cathepsin L and MCP-1, and inhibited paxillin phosphorylation, resulting in a protection against podocyte injury, marked by cell shrinkage, hypermotility, cytoskeleton disorganization and apoptosis.

Conclusions: MC5R-mediated melanocortinergic signaling protects against podocyte injury and proteinuria.

Funding: NIDDK Support
FR-PO913
Proteasomal Dysfunction Enhances the Glomerular Accumulation of the Membranous Nephropathy Antigen THSD7A Following Autoantibody Binding
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Background: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adult patients. In MN, podocyte membrane antigens such as the thrombospondin domain-like containing 7A (THSD7A) serve as targets to immunity. Diagnostic for MN is an enhanced antigen reactivity and antigen/antibody deposition in the subepithelial podocyte space and podocyte cytoplasm, for which the underlying mechanisms are unknown. The aim of this project is to investigate the modulation of THSD7A degradation under homeostatic conditions and upon autoantibody binding, and whether alterations of THSD7A degradation relate to the pathological glomerular THSD7A accumulation in MN.

Methods: THSD7A half-life and homeostatic THSD7A degradation pathways were investigated in kidney slice cultures, cultured podocytes, and naïve Balb/C mice treated with either vehicle, proteasomal or lysosomal inhibitors. Furthermore, mice with genetic lysosomal dysfunction were used. To assess the involvement of protein turnover for the subepithelial accumulation of THSD7A following autoantibody binding, cultured podocytes were treated with rabbit anti-THSD7A IgG, and the model of rabbit anti-THSD7A MN was induced in Balb/C mice in the absence or presence of proteasomal or lysosomal inhibitors. Cells and mice were analyzed by Western blot, qPCR and high-resolution confocal microscopy.

Results: In normal conditions THSD7A has a long half-life in vitro and in vivo, and its protein content is regulated by the lysosomal system in naïve cultured podocytes and mice. Upon autoantibody binding, THSD7A is cross-linked at the plasma membrane and internalized through the endosomal system into multivesicular bodies. Internalized autoantibody-THSD7A complexes are degraded by both the lysosomal and proteasomal system. Impairment of the proteasomal system results in the (for MN typical) glomerular deposition of THSD7A in the subepithelial space and podocyte cytoplasm.

Conclusions: Homeostatic THSD7A levels are regulated by lysosomal degradation. Upon autoantibody binding, pathological glomerular THSD7A accumulation additionally strongly depends on the proteasomal system.

FR-PO914
Apol1-DNA Cross-Talk with Cytosolic DNA Sensing Pathways in Podocytes
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Background: Viruses such as HIV are known to release double stranded DNA in cytoplasm and also known to induce activation of inflammasome Nod-like receptor (NL R) protein (P) 3 in podocytes. APOL1 renal risk variants have also been shown to activate inflammasomes in APOL1 risk milieu.

Methods: THSD7A half-life and homeostatic THSD7A degradation pathways were investigated in kidney slice cultures, cultured podocytes, and naïve Balb/C mice treated with either vehicle, proteasomal or lysosomal inhibitors. Furthermore, mice with genetic lysosomal dysfunction were used. To assess the involvement of protein turnover for the subepithelial accumulation of THSD7A following autoantibody binding, cultured podocytes were treated with rabbit anti-THSD7A IgG, and the model of rabbit anti-THSD7A MN was induced in Balb/C mice in the absence or presence of proteasomal or lysosomal inhibitors. Cells and mice were analyzed by Western blot, qPCR and high-resolution confocal microscopy.

Results: In normal conditions THSD7A has a long half-life in vitro and in vivo, and its protein content is regulated by the lysosomal system in naïve cultured podocytes and mice. Upon autoantibody binding, THSD7A is cross-linked at the plasma membrane and internalized through the endosomal system into multivesicular bodies. Internalized autoantibody-THSD7A complexes are degraded by both the lysosomal and proteasomal system. Impairment of the proteasomal system results in the (for MN typical) glomerular deposition of THSD7A in the subepithelial space and podocyte cytoplasm.

Conclusions: Homeostatic THSD7A levels are regulated by lysosomal degradation. Upon autoantibody binding, pathological glomerular THSD7A accumulation additionally strongly depends on the proteasomal system.
APOL1 Kidney Disease-Associated Variants Induce Differential Glomerular Expression of Immune Sensory Proteins in FSGS
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Background: Variants in APOL1 (G1 and G2) associate with increased risk of CKD including hypertension-related CKD and focal segmental glomerulosclerosis (FSGS) in individuals with West African ancestry. Mechanisms by which the APOL1 variants contribute to the pathogenesis of CKD is not well understood. We hypothesized that variant APOL1 proteins mediate kidney disease through pathways independent from reference APOL1 protein. We aimed at characterizing differentially regulated protein networks in glomeruli of FSGS patients in presence of APOL1 variants.

Methods: Formalin-fixed paraffin-embedded kidney biopsies with a diagnosis of primary FSGS with (n=3) and without (n=3) homoyzogous APOL1 risk variants and normal donor kidney biopsies (n=5) were identified. Glomeruli were isolated from the biopsies using laser capture microdissection followed by protein recovery, trypsin digestion and HPLC fractionation using an Orthogonal Flow trapgraph fusion mass spectrometry labeled approach. The data was characterized by global normalization and spectral count data was performed to determine changes in protein expression. Comparison of protein expression levels and upstream regulatory pathways were performed using Ingenuity Pathway Analysis software.

Results: In patients with FSGS, HLA-DQB1, HLA-DQA1 and ICAM-1 were significantly upregulated in the glomeruli in the presence of homoyzogous APOL1 variants. Interferon-gamma regulated pathways were upregulated in glomeruli of FSGS patients in the presence of homoyzogous APOL1 variants compared to FSGS with no APOL1 variants and normal donor kidney.

Conclusions: Upregulation of immune sensory proteins in glomeruli in presence of APOL1 variants suggests that a differential cellular immune response mediated by the variants could contribute to the pathogenesis of FSGS. A larger cohort of patient samples needs to be interrogated to validate the observation.
Results: An impaired OPA1 degradation by depletion of either Omal or Phb2, both, led to significantly lower protein content as evidenced by Western Blotting in vitro and in vivo. However, only loss of Phb2 resulted in a disrupted slit-membrane, proteinuria and premature death as previously published while Omal KO animals presented with normal glomerular function. Omal/Phb2 double KO podocytes presented with marked mitochondrial cristae formation and prolonged animal survival. On a functional level, aerobic glycolysis was disrupted in both cases. Proteome analysis of Omal knockout mice revealed elevated translation of proteins associated with fatty-acid metabolism and Acetyl-CoA synthesis and an increase in ribosomal protein translation.

Conclusions: Here, we identified OMA1 as a critical regulator of podocyte metabolism in vitro and in vivo and demonstrate that a stress-induced OPA1 processing by OMA1 promotes a metabolic switch in glomerular podocytes. However, this metabolic switch alone was not sufficient to cause podocyte injury. Using OMA1 lacking ribonuclease with 4-5' triphosphate as a model of mitochondrial dysfunction, we demonstrate that additional ablation of OMA1 protects mitochondrial cristae formation from degradation leading to a significantly prolonged survival as compared to deficient mice.

Funding: Government Support - Non-U.S.

FR-PO922
Role of IRE1α in Podocyte Proteinostasis
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Background: Podocyte (glomerular epithelial cell; GEC) proteinostasis is disrupted in glomerular diseases. To maintain proteinostasis, the endoplasmic reticulum (ER) orchestrates the unfolded protein response (UPR) which includes upregulation of ER chaperones. Proteinostasis also involves clearance of misfolded proteins via autophagy. Insoluble requiring enzyme-1 (IRE1α) resides in the ER membrane and is a transducer of the UPR. In mice, podocyte-specific deletion of IRE1α leads to age-related podocyte injury, autophagy impairment, and disruption of glomerular permeability. This study characterizes mechanisms by which IRE1α regulates proteinostasis in GECs.

Methods: GECs were isolated from transgenic mice with IRE1α-cre and Cre recombinase (IRE1α KO). GECs expressing full-length IRE1α served as control (IRE1α WT). GECs were exposed to tunicamycin (TM), rapamycin (R), and glutaminolysis (GS) during 24 h. ER chaperones and LC3 were monitored by immunoblotting. Mitochondria were visualized using MitoTracker Red CMXRos.

Results: IRE1α KO and WT GECs exhibited comparable proliferation rates and protein content, implying that IRE1α is not involved in cell cycle progression. Stimulation of GECs with the ER stressor TM upregulated total IRE1α in WT, but not IRE1α KO GECs. After TM treatment, the chaperones BIP, GRP78, and mesencephalic astrocyte-derived neurotrophic factor increased in WT GECs. Deletion of IRE1α, or chemical inhibition of the IRE1α RNase with 4,4' diithiothreitol (dtT2), which significantly attenuated upregulation of chaperones and enhanced ER stress-induced apoptosis (evinced by caspase-3 cleavage). Neither R nor GS enhanced expression of ER chaperones. Compared with WT GECs, IRE1α KO GECs exhibited comparable proliferation rates and protein content, implying that IRE1α is not involved in cell cycle progression. Stimulation of GECs with the ER stressor TM, the expression of ER chaperones was significantly attenuated by treatment with actins in the cytoplasm, accompanied by F-actin disarrangement. Meanwhile, we found that zyxin was decreased in AngII-treated podocytes. The other hand, SIRT2 regulates the expression of zyxin in AngII-treated podocytes. However, this metabolic switch alone was not sufficient to cause podocyte injury. Using mice lacking IRE1α, we demonstrate that additional ablation of IRE1α protects mitochondrial cristae formation from degradation leading to a significantly prolonged survival as compared to deficient mice.

Funding: Government Support - Non-U.S.

FR-PO923
Angiotensin II Receptor Blocker Blocks Spreading Podocyte Damage in a Partial Podocytecctomy Model
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Background: We established a new mosaic mouse model in which approximately 50% of podocytes express hCD25 and tdTomato whereas the other podocytes express EGFP. Here, we examined whether the angiotensin II (AngII) receptor blocker (ARB), a well-established renoprotective agent, can prevent podocyte damage in this model.

Methods: Twelve female mosaic mice from 28 to 35 weeks of age were injected with LMB2. One day later, they were treated with losartan (0.5g/L in drinking water) (ARB group, n=8) or with 5% sucrose (Control, n=8). Fourteen days after LMB2 injection, kidney tissues were harvested and analyzed.

Results: Control mosaic mice developed severe glomerular damage with early sclerosis, adhesion, and hyalinosis, and dilated tubules with protein casts. These were markedly ameliorated in the ARB group. Glomerular injury index (in 0 (normal)–4) scales was 3.7±0.30 (SE) in the Control group, which was improved to 0.13±0.083 in the ARB group (p=0.0115). In addition, nephrin staining was more preserved (7.4±0.2 to 3.0±0.1 in 0–8 (normal) scales, p=0.001) and desmin-positive podocytes were less observed (29±7 vs 74±11%, p=0.026) in the ARB group than the Control group. Importantly, EGFP-labeled podocytes were not directly injured by LMB2, they were also secondarily injured, and the number decreased from 3.8±0.14 to 1.4±0.23 per a glomerulus after LMB2 injection in the Control group. The EGFP-positive podocytes were significantly more preserved in the ARB group (from 3.9±0.3 to 2.9±0.2, p<0.01).

Conclusions: Thus, our mosaic mouse model can visualize and evaluate secondary podocyte injury, and we have herein demonstrated that ARB attenuates the secondary podocyte injury.

Funding: Government Support - Non-U.S.

FR-PO924
Angiotensin II Impairs Podocyte Motility via Sirtuin-Mediated Zyxin Deacetylation and Cytoskeleton Rearrangement
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Background: Zyxin, as an adaptor protein primarily located at the adhesion plaque complex, has been implicated in the regulation of cytoskeletal dynamics and nuclear-cytosolic communication. However, the particular role of zyxin in regulating podocyte cytoskeleton assembly in kidney diseases remains obscure. In this study, we aimed to explore the role and mechanism of zyxin in SHR rats and AngII-treated podocytes.

Methods: The Sirtuin family, a large and diverse group of NAD+-dependent deacetylase sirtuin family, were detected by western blotting, immunohistochemistry, and immunofluorescence in glomeruli of SHR rats and AngII-treated podocytes. Co-IP was performed to assess the level of acetylated zyxin in AngII-treated HPCs and explore the interaction between zyxin and SIRT2. AGK2, the chemical inhibitor of SIRT2, was used to inhibit the activity of deacetylation. Finally, the podocyte motility was assessed by migration assay.

Results: Zyxin was widely expressed in kidney tissues and HPCs. Compared with the control group, the expression of zyxin in SHR rats was unchanged, which was in line with the results in vitro. Intriguingly, podocytes exposed to AngII showed a redistribution of zyxin, which was characterized by accumulation at adhesion plaques rather than along with actins in the cytoplasm, accompanied by F-actin disarrangement. Meanwhile, we found that zyxin was deacetylated in AngII-treated podocytes. On the other hand, SIRT2 regulates the expression of zyxin in AngII-treated HPCs and explore the interaction between zyxin and SIRT2. AGK2, the chemical inhibitor of SIRT2, was used to inhibit the activity of deacetylation. Finally, the podocyte motility was assessed by migration assay.

Funding: Government Support - Non-U.S.

FR-PO925
Injured Podocytes Show an Increased Responsiveness to Angiotensin II-Mediated Calcium Transients
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Background: Angiotensin II (AngII) signaling has been shown to play a role in regulating glomerular perfusion and progression in kidney disease. The treatment of patients with ACE inhibitors is well established. Furthermore, AngII has shown to be able to trigger calcium signals podocytes ex vivo. In this study we aimed at unravelling AngII induced calcium signaling in healthy and diseased podocytes in vivo.

Methods: Kidney disease was induced in 4 week old mice expressing the calcium indicator GCaMP3 in podocytes (Pod:cre) by injecting 25 mg/kg Adiriamycin. 4 days after injection the mice underwent 2-photon in vivo imaging. Mice were anesthetized, a vascular access generated and the left kidney exteriorized. The vasculature was labelled by intravenous injection of Tetramethylrhodamine (TRITC)-conjugated GCaMP3. AngII was infused with 100 mg/mg. As inhibitors Losartan (10 mg/kg) and PD123319 (10 mg/kg) were used. The induced calcium transients were recorded as time lapse videos with 1 frame/second. The percentage of podocyte area showing an increase in calcium levels was calculated using ImageJ software.

Results: The data shows that in 21 % of healthy glomeruli and in a mean of 2 podocytes a calcium signal can be triggered by AngII. The probability of inducing a calcium transient in a glomerulus by AngII stimulation increased by two-fold (41 %) in diseased (ADR) podocytes. Furthermore, the number of podocytes showing calcium transients is significantly increased. These findings correlate with a rise in the percentage of podocyte area showing a calcium signal from 12 to 26 %. The AngII induced calcium transient can be completely blocked by using Losartan, but not by PD123319.

Conclusions: Our study shows that calcium signaling in podocytes is highly regulated and the response to AngII increases upon injury. Additionally, we observed that not all podocytes react to AngII which points to heterogeneity in the podocyte population during health and disease. We can show that AngII mediates its calcium effects through the AT1R since Losartan completely blocked the calcium signal in podocytes. Therefore our results...
FR-PO926

Genetic Ablation of Calcium-Independent Phospholipase A2γ Exacerbates Glomerular Injury in Adriamycin Nephrosis in Mice

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Background: Genetic ablation of calcium-independent phospholipase A2γ (iPLA2γ) in mice results in marked damage of mitochondria and enhanced autophagy in glomerular visceral epithelial cells (GECs) or podocytes. iPLA2γ knockout (KO) GECs in culture show mitochondrial dysfunction and enhanced autophagy. The present study addresses the role of iPLA2γ in glomerular injury, focusing on mitochondrial function and autophagy.

Methods: Adriamycin nephrosis was induced in wild type (WT) or iPLA2γ KO mice (age 3.5-4.5 months) by a single intravenous injection of adriamycin (12 mg/kg). Cultured WT or iPLA2γ KO GECs were transfected with mito-YFP (to label mitochondria), RFP-LC3 (to label autophagosomes) and RFP-LAMP1 (to label lysosomes). Colocalization of fluorescent signals was measured by the Pearson correlation coefficient.

Results: In adriamycin nephrosis, deletion of iPLA2γ exacerbated albuminuria and reduced podocyte number (WT1 counts). Glomerular LC3-II increased and p62 decreased. ATP production. Deletion of iPLA2γ LC3-II. For comparison, induction of mitochondrial dysfunction with carbonyl cyanide 4-fluorophenylhydrazone signals was measured by the Pearson correlation coefficient.

Conclusion: LC3 (to label autophagosomes) and RFP-LAMP1 (to label lysosomes). Colocalization of fluorescent signals was measured by the Pearson correlation coefficient.

FR-PO927

A Role for the Developmental Gene Pax2 in the Adult Kidney After Glomerular Injury

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Background: Pax2 is a member of the Pax family of highly conserved transcription factors that play important roles during development. Pax2 is essential for mammalian kidney organogenesis, without which the kidneys fail to form. We have previously reported that heterozygous missense mutations in Pax2 lead to focal and segmental glomerulosclerosis (FSGS) in ~5% of adults with the disorder. FSGS is a clinicopathologic entity characterized by proteinuria and podocyte foot process effacement. We have obtained a mouse model with a Pax2 missense mutation to further investigate the mechanism by which the glomerular defect occurs.

Methods: We employed immunohistochemistry, electron microscopy, and Western blotting to examine kidneys from wild type and Pax2 mutant mice that were subjected to Adriamycin (ADR) administered through tail vein injections.

Results: Mice homozygous for Pax2 A220G (Pax2A220G) develop dysplastic kidneys and are not viable though they survive to late gestation (E18.5). As expected, heterozygous Pax2A220G mice display smaller kidneys and reduced nephron number with no other obvious glomerular defects. Surprisingly, we find that Pax2 expression persists widely in the adult kidney, both in the glomerular and tubular compartments. Challenging Pax2A220G mice with Adriamycin (ADR) recapitulated human FSGS with mutant mice more susceptible to injury compared to wildtype. K167 staining revealed increased glomerular cell proliferation, that was not due to infiltrating immune cells, and caspase-3 staining demonstrated increased parietal epithelial cell (PEC) apoptosis that was observed in mutant but not wildtype mice.

Conclusions: We have demonstrated that a Pax2 heterozygous missense mutation renders the adult mouse kidney more susceptible to podocyte injury, approximating FSGS observed in humans. We postulate a role for Pax2 in the repair of injured glomeruli that may involve parietal epithelial cells.

Funding: Private Foundation Support

FR-PO928

Osteocin Ameliorates Adriamycin-Induced Glomerular Injury

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Background: Natriuretic peptides including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) have cardioprotective effects through binding to natriuretic peptide (NP) receptors: NPR1 and NPR2. ANP or BNP exhibits potent renal effects in patients and animal models with heart failure. Recently a peptide, OSTN (osteocin) is reported to bind to Npr3 which is a clearance receptor for NPs, and to prevent the worsening of congestive heart failure by increasing NPs with inhibition of degradation. However, the effect of OSTN on kidney function has not been elucidated yet. We hypothesized that OSTN has a renoprotective role by binding Npr3 to suppress clearance of NPs. We examined the role of OSTN in adriamycin (ADR) nephropathy, since podocytes are reported to express Npr3 in single-cell transcriptomics of the mouse kidney.

Methods: ADR was administered to wild-type and serum amyloid P (SAP) promotor-driven OSTN-transgenic (Tg) mice which showed plasma OSTN elevation, at dose of 8 mg/kg body weight via tail-vein injection. Mice were sacrificed at 4 weeks after ADR injection.

Results: There were no significant differences between wild-type and OSTN-Tg mice in systemic blood pressure, urinary volume, serum creatinine nor BUN. The body weight and body length of wild-type mice were significantly lower than those of OSTN-Tg mice (26.0 ± 0.9 g vs. 27.9 ± 0.6 g, p < 0.01; 9.5 ± 0.1 cm vs. 10.4 ± 0.1 cm, p < 0.0001, respectively). Increase of urinary albumin creatinine ratio of wild-type mice induced by ADR administration peaked at 2 weeks (165.6 ± 41.4 μg/mgCr vs. 86.7 ± 7.6 μg/mgCr, p < 0.05) and was significantly suppressed in that of OSTN-Tg mice at 4 weeks (91.5 ± 11.9 μg/mgCr vs. 61.9 ± 3.8 μg/mgCr, p < 0.05). Footprocess effacement observed in ADR-injected wild-type mice was alleviated in adriamycin-administered OSTN-Tg mice, and thickness of glomerular basement membrane were significantly mitigated in OSTN-Tg mice in electron microscope (wild-type mice, 209 ± 12 nm vs. OSTN-Tg mice, 141 ± 3 nm, p < 0.0001).

Conclusions: These findings indicate that circulating OSTN has a reno- and podocyte-protective role in ADR nephropathy, probably through increase of natriuretic peptides on podocytes, and suggest that administration of OSTN could be a therapeutic option against podocyte injury.

FR-PO929

Shroom3-Fyn Interaction Regulates Podometrics via Activation of AMP-Kinase (AMPK)

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Background: We recently showed that Shroom3 interacts with Fyn, an Src kinase in podocytes, regulating Fyn activation. Intriguingly Shroom3 knockdown reduced podocyte and glomerular volume (Vglomm).

Methods: To investigate mechanism of this phenotype, we examined Shroom3- (S3KD) & Fyn-knockdown (FynKD) human podocytes, and inducible Shroom3 knockdown mice (S3kd).

Results: FynKD podocytes also had reduced cell volume vs controls, suggesting that Fyn mediated the effect of S3KD on podocyte morphology. To investigate whether glomerular Shroom3 regulated Vglomm hypertrophy, we performed unilateral nephrectomy in control and S3kd mice and examined Vglomm in remnant kidneys. At day 7, S3kd mice showed restricted Vglomm hypertrophy vs controls, (n=5; 8% vs 19%; P=0.05) and reduced expansion of podocyte fraction of Vglomm. To investigate whether reductions of cell size were due to reduced protein content we measured protein-DNA ratio. S3KD & FynKD podocytes had reduced Protein-DNA ratios (n=5; P<0.01). Since MTOR is a key pathway regulating protein biosynthesis, we examined MTOR signaling. Phospho AMPK, a negative regulator of MTORC1 was significantly increased with S3KD/FynKD cells as well as in glomeruli of S3kd (Fig 1- immunofluorescence). Ribosomal biogenesis (18S rRNA) expression was measured by qPCR in S3KD/FynKD cells (n=3) and s3kd kidney lysates. Since Fyn activation causes nuclear retention of LKB1, an AMPK-kinase, we examined ratio of cytoplasmic:nuclear LKB1, which was increased in S3KD and FynKD cells explaining AMPK activation.

Conclusions: In summary we show regulation of Vglomm and podometrics by Shroom3-Fyn interaction that regulates protective AMPK-signaling. These findings have implications to loss of nephron mass and minimal change disease where podocyte Fyn-inactivation has been specifically observed.

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FR-PO930

Regulation of Cytoskeletal Assembly by YAP (Yes-Associated-Protein) Mediates Podocyte Repair During the Response to Glomerular Injury

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Background: The HIPPO signaling pathway regulates the YAP/TAZ-Tead transcription factor complex involved in cell growth to determine organ size. Published studies have suggested that YAP is required for podocyte survival. However, there was no evidence of proteinuria or glomerulosclerosis in Yap knockout mice, suggesting that there may be a redundant function of TAZ in uninjured podocytes. Treatment of Yap mutant mice with Adriamycin led to a reduction in focal adhesion area per cell and was conditionally inactivated in podocytes of adult mice using an inducible Cre recombinase. In vitro, immortalized differentiated mouse podocytes were treated with Yap siRNAs. Podocyte injury was induced by treatment with adriamycin or trypsinization, in vivo or in vitro respectively. Electron microscopy, histology, molecular and cellular biology studies were conducted to characterize the phenotype of either Yap knockout mice or Yap knockdown cells.

Results: Electron microscopy analysis eight weeks after Yap inactivation in mouse revealed that Yap knockout led to mild foot process effacement. However, there was no evidence of proteinuria or glomerulosclerosis in Yap knockout mice, suggesting that there may be a redundant function of TAZ in uninjured podocytes. Treatment of Yap mutant mice with Adriamycin led to microalbuminuria and an increased frequency of histological lesions resembling Focal Segmental Glomerulosclerosis. Yap knockdown in immortalized differentiated mouse podocytes led to a reduction in focal adhesion area per cell and decreased area per cell. Yap siRNA treatment also led to a dramatic inability to spread and to organize actin stress fibers after trypsinization and rescending. Consistent with the inability to spread, levels of pY397 FAK and phospho-cofilin, a downstream target of RhoA GTPase, were reduced in Yap knockdown podocytes. Yap knockdown also led to decreased inactivation of Ral1, a member of the Rho GTPase family.

Conclusions: Our studies demonstrate that Yap has a crucial role in the assembly of the actin cytoskeleton during recovery from injury, affecting the polymerization of actin mediated by Rho family GTPases. In vivo, YAP appears to have a greater role in recovery from injury than in maintaining the cytoskeleton in uninjured podocytes.

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FR-PO931

Insights from Genome-Wide MicroRNA Target Identification In Podocytes Using Argonauta PAR-CLIP

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Background: MicroRNAs (miRNA) are small noncoding RNA molecules that regulate gene expression, and are crucial for the development and homeostasis of podocytes. Biogenesis of miRNA requires a multistage process of which Exportin5 (XPO5) plays a rate limiting step by exporting miRNA precursors from the nucleus to the cytoplasm. Recently, steroid-resistant nephrotic syndrome (SRNS) in a child was attributed to a point mutation in XPO5 (Braun DA 2016). However, whether or not the mutation affects the miRNA related function of Exportin-5 is not known. We hypothesized that the V552I mutation impedes miRNA maturation and that the association with SRNS may shed light on the roles of specific miRNA in podocytes.

Methods: We have successfully generated the p.V552I Exportin-5 (XPO5V552I) homozygous mutation in HEK293 cells via CRISPR-Cas9. In addition we have generated human podocyte clones with a heterozygous mutation.

Results: Small RNA sequencing of our HEK293 cells shows a significant decrease in global miRNA content in XPO5V552I compared to parental cells. Principal component analysis (Figure) also revealed population separation between wildtype HEK293 and XPO5V552I cells, indicating miRNA expression segregated by genotype. Moreover, Small RNA sequencing of the podocyte clones revealed distinct changes in miRNA profiles.

Conclusions: These results strongly suggest the involvement of the XPO5V552I mutation in the dysregulation seen in the miRNA. Further investigation will lead us to the discovery of the specific miRNA involved in maturation and maintenance of podocytes.

Funding: Government Support - Non-U.S.

Figure: Principal component analysis plot by microRNA profiles showing samples arranging by cell type and genotype. hek, HEK293 cells; pods, podocytes; wt, control cells; mut, cells with mutated XPO5.

FR-PO933

Podocyte-Specific Deletion of Early B Cell Factor 1 Minimizes Sclerotic Damage After Glomerular Injury

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Background: It is now understood that podocyte loss, through sloughing and/or apoptosis, is the precipitating factor driving glomerulosclerosis. We also had previously reported that podocytes express the transcription factor Early B Cell Factor 1 (EBF1), although the function of this protein in these cells was unclear.

Methods: Utilizing a floxed version of Ebf1 and podocin-cre we eliminated EBF1 specifically from podocytes, and injured glomeruli directly with either hypertensive

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
L-NAME injury or glomerular nephritis induced by anti-GBM serum. To identify the signaling pathways altered by EBF1 following its deletion alterations in RNA levels were compared to the chromosomal occupancy of EBF1 through ChIP-Seq.

Results: In both models of injury, EBF1 deletion from the podocytes was renoprotective. Fibrosis was reduced following anti-GBM serum at the at 7 and 10 days post injury. mRNA and protein levels for fibrogenic markers were equivalent during the 20-week L-NAME hypertensive duration, however, recovery of the kidney for an additional ten-week period was dramatically accelerated when EBF1 was absent. This was reflected in the histologically as well as functionally through GFR measurement with the conditional knockout. Kidney function recovering almost half of their lost GFR within 3 weeks (no change in WT mice) and fully restoring kidney function by 10 weeks. Controls, by contrast, were not improved at the three-week mark, and only partially recovered by ten weeks. Less fibrotic injury was reflected in the RNA analysis of both models where markers of collagen formation, fibrosis and inflammation, all complement and coagulation are all increased in controls. Conversely, pathway analysis performed with Metascape revealed EBF1 loss protects the integrity of the slit diaphragm components and that this is partially mediated by blunted calcium signaling, NFAT activation in the absence of EBF1. These changes were verified through calcineurin activity assay, reporter assays and western blots.

Conclusions: These results indicate that EBF1 normally promotes injury signals detrimental to the health of the podocyte through cell-intrinsic gene regulation. Deletion of this transcription factor from podocytes protects from glomerular injury at the initial stages of podocyte injury and these beneficial actions are mediated in part through minimizing NFAT signaling early in the injury process.

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FR-PO934
Calcineurin Inhibitors Activate WNK1 Kinase to Preserve Glomerular and Podocyte Structure and Mechanics
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Background: Tocrolimus (FK-506) and cyclosporin A (CsA), both calcineurin inhibitors (CNIs), are immunosuppressants used to treat organ transplant rejection and auto-immune diseases. Although use of these drugs can be limited by side effects including hypertension, hyperkalemia, and vasculopathy with glomerulopathy, they can also protect podocytes and podocapillary capillaries from injury by preserving podocyte cytoskeletal structure. Activation of WNK kinases by CNIs causes volume-dependent hypertension and hyperkalemia, but the mechanism of CNIs’ vascular and glomerular effects is not understood.

Methods: Fresh, isolated mouse glomeruli were used for measurement of WNK1 activity (measured as pOSR1), glomerular elasticity using microrheology, F/G actin ratios, and confocal imaging for glomerular structure and pOSR1. Conditionally-immortalized podocytes were used for WNK1 activity measurements (pOSR1), confocal microscopy imaging, F/G-actin ratios, pOSR1, collagen gel contraction, and migration.

Results: We found that CNIs activate WNK1 in renal glomeruli and cultured podocytes increasing pOSR1 and F-actin. Treatment of glomeruli with CNIs increases the elastic modulus (E) of glomeruli (2.4 kPa vs control 2 kPa), an effect blocked by WK463. FK-506 increases pOSR1, F/G Actin ratios and traction by podocytes in 3-dimensional collagen gels, increases lamellipodium formation, pOSR1 localization in leading edges, and migration of cultured podocytes, effects blocked by WK463. In glomerular capillaries, CNIs increase pOSR1, while WK463 reduces pOSR1 and disrupts capillary structure.

Conclusions: The CNI-induced increase in glomerular F-actin and E, and modifications in podocyte cytoskeletal structure, provide mechanisms by which CNIs can protect podocytes and podocytes against injury, and illustrate a novel mechanism involving WNK1 kinase and vascular tissue. This is the first report of a function for WNK1 in glomeruli.

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FR-PO936
NHERF2 Interacts with Ephrin-B1 at the Slit Diaphragm: NHERF2 Bridges Podocalyxin and Slit Diaphragm Components
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Background: We have reported ephrin-B1 is a novel component of the slit diaphragm (SD) and ephrin-B1 interacts with nephrin via their extracellular domains and plays an essential role in maintaining the barrier function of SD (JASN 29, 2018). We reported NHERF2, a scaffold protein possessing two PDZ domains, was downregulated in the glomeruli of the podocyte-specific ephrin-B1 KO mice, which suggesting NHERF2 is associated with ephrin-B1 (ASN 2018). It is reported that NHERF2 binds to podocalyxin at the second PDZ domain and plays the pivotal role in maintaining actin cytoskeleton by phosphorylating ezrin in podocytes. However, the precise localization of NHERF2 and its interaction with ephrin-B1 are unclear.

Methods: The interaction of NHERF2 with ephrin-B1 and nephrin was analyzed by the immunoprecipitation (IP) analyses with glomerular lysates and HEK293 transfected cells. The expressions of these molecules in glomeruli of normal rat and rat with nephropathy induced by the anti-nephrin antibody were analyzed by immunofluorescence.

Results: NHERF2 band was detected in the precipitates with anti-nephrin antibody by IP assay with normal rat glomerular lysate, which indicating NHERF2 is a member of the SD complex. The IP assay with the HEK cell expression system showed NHERF2 directly interacted with ephrin-B1 at the first PDZ domain and did not interacted with nephrin. The analyses with the HEK cells triple transfected with NHERF2, ephrin-B1 and nephrin showed that the anti-nephrin antibody binding phosphorylated only nephrin but also ephrin-B1, and that the phosphorylated ephrin-B1 did not interacted with NHERF2. Dual-labeling analyses showed NHERF2 was detected not only apical area but also SD area, and a portion of NHERF2 was colocalized with ephrin-B1 in normal glomeruli. Ephrin-B1 was phosphorylated and dissociated from NHERF2 in the nephrotic state caused by the anti-nephrin antibody injection. The immunostaining of NHERF2 and ezrin as well as ephrin-B1 and nephrin were clearly decreased.

Conclusions: NHERF2 interacts with ephrin-B1 via its first PDZ domain and with podocalyxin via its second PDZ domain, and bridges podocalyxin, an apical surface protein and ephrin-B1, an SD component. The bridging structure was disrupted by the nephrin-mediated signal. The disruption is one of the critical mechanisms of podocyte injury.

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Membrane-Associated Guanylate Kinase Involved 2 Stabilizes Glomerular Filtration Barrier via the PDZ Domain

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Background: Slit-diaphragm (SD) of podocytes plays a crucial role as a final barrier of glomerular filtration. The main components of SD, such as Nephrin and Nep1, are indispensable in preventing progression of glomerulonephrosis. However, it remains unknown what is important for protecting these main components. Here, we demonstrate that Membrane-associated guanylate kinase involved 2 (MAGI-2) functions as a critical scaffold protein for maintaining the SD components.

Methods: We examined the immunofluorescence intensity of MAGI-2 in human biopsy sample. We analyzed the phenotype of podocyte specific MAGI-2 knock out (KO) mice. Additionally, using piggy-Bac transposon and CRISPR-Cas9 system, we analyzed the function of MAGI-2 in cultured MAGI-2-overexpression podocytes and ZO-1 KO podocytes. Next, using biochemical assay, we investigated which domain of MAGI-2 is necessary for the binding among these molecules.

Results: In the immunofluorescence of human biopsy sample, MAGI-2 is downregulated in glomerular diseases such as focal segmental global sclerosis or IgA nephropathy. Actually, podocyte specific MAGI-2 KO mice also significantly exhibited glomerulonephrosis and the reduced expression of Nephrin and Nep1. Cultured MAGI-2-overexpressing podocytes increased the colonization of MAGI-2 and Nephrin in cell-cell contact, while Nephrin was not expressed in cellular edge of cultured control podocytes. Additionally, although ZO-1 deletion undermines the Nephrin expression in cultured podocytes, the transfection of MAGI-2 in the ZO-1 deleted cells could retrieve the reduced Nephrin expression. Biochemical assay demonstrated that MAGI-2 binds to Nephrin and Nep1 in different PDZ binding domain. Therefore, the MAGI-2-protective strategy could be a new route to the new drug development against glomerular diseases.

Conclusion: Our data suggest that increased SOAT1 expression in the kidney cortex seems to be reduced in the presence of active NS plasma, but not in the presence of non-renal control patient. Cell viability, podocyte motility, podocyte actin cytoskeleton architecture, and reactive oxygen species (ROS) formation at the presence or absence of active NS plasma were analyzed as biomarker of disease condition. Our results revealed that SOAT1 expression in the cell line of human podocytes could be a biomarker for the disease condition.

Funding: NIDDK Support

Plasma Circulating Factors in Recurrent Nephrotic Syndrome Increases Nephropathy by Via Similar Agonist PAR-1 Activation

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Background: Post-transplantation recurrence steroid resistant nephrotic syndrome (SRNS) is thought to be due to the presence of an unknown “circulating factor” that leads to increased podocyte motility and proteinuria. We have now elaborated this signalling pathway in podocytes with the hypothesis that the circulatory factor(s) in FSGS relapse plasma will initiate specific signalling pathways via PAR-1 activation.

Methods: We generated a mouse model of podocyte constitutively active PAR-1 was generated. We observed a significant reduction of cholesterol esters in SI-treated human SI-treated human FSGS relapse plasma, along with 2) PAR-1 agonist and patient relapse disease plasma but not in the mouse model of the mitogen-activated protein kinases (MAPK) superfamily in human podocytes, and increased motility compared to non-renal control patients. Cell viability, podocyte motility, podocyte actin cytoskeleton architecture, and reactive oxygen species (ROS) formation at the presence or absence of FSGS relapse plasma was investigated as biomarker of disease condition.

Results: We found that PAR-1 agonist and patient relapse disease plasma but not in the mouse model of the mitogen-activated protein kinases (MAPK) superfamily in human podocytes, and increased motility compared to non-renal control patients. Cell viability, podocyte motility, podocyte actin cytoskeleton architecture, and reactive oxygen species (ROS) formation at the presence or absence of FSGS relapse plasma. We revealed a consistent signalling pathway in ‘circulating factor’ SRNS that leads to increased podocyte motility and proteinuria and suggests direct therapeutic targets.

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The Role of SOAT1 in Renal Disease Associated with Alport Syndrome

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Introduction: Defective cholesterol metabolism is closely associated with the progression of renal disease in Alport syndrome (AS), an inherited disease associated with progressive kidney failure, hearing loss and eye abnormalities. We recently demonstrated that accumulation of cholesterol esters occurs in experimental models of AS. SOAT1 is an enzyme that converts free cholesterol to cholesteryl esters at the endoplasmic reticulum, and plays an important role in cellular cholesterol homeostasis. Recent studies indicate that inhibition of SOAT1 may have beneficial effects in Alzheimer’s disease and in cancer where SOAT1 inhibition reduced cancer proliferation and suppressed tumor growth. However, whether the accumulation of free or of esterified cholesterol contributes to progression of renal disease in AS remains unclear. With this study, we aimed to investigate the role of SOAT1 in the progression of renal disease in AS.

Methods: Normal human podocytes were treated with SOAT1 inhibitor (SI) or DMSO for 48h. Podocytes were stained with Bodipy and Cell Mask Blue. The Opera High Content Imaging System was used to acquire images of cell nuclei to calculate the number of nuclei. Cholesterol and triglyceride content were assessed using the Amplex Red Cholesterol kit and Triglyceride Colorimetric kit. Urinary albumin-to-creatinine ratios were determined by mouse ELISA and creatinine Companion kits.

Results: We observed a significant reduction of cholesterol esters in SI-treated human podocytes when compared to vehicle-treated podocytes in association with a decrease in lipid droplet density and triglyceride content. To assess the effect of SOAT1 deficiency in the Alport mouse, renal phenotype of SOAT1 knockout (SKO) mice was investigated. SKO mice did not develop albuminuria or mesangial expansion at 10 months of age. Analysis of SOAT1 expression in kidney cortexes of AS mice demonstrated increased SOAT1 mRNA when compared to WT mice, while expression levels of several other genes important in cholesterol homeostasis remained unchanged.

Conclusions: Our data suggest that increased SOAT1 expression in the kidney cortex of AS mice contributes to progression of renal disease in AS. We conclude that preventing cholesterol ester accumulation in kidney cortex of AS mice by SOAT1 inhibition may represent a new therapeutic strategy to treat renal disease in AS patient.

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Towards Clinical Assays for Evaluating Circulating Permeability Factors in Nephrotic Syndrome

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Background: Circulating permeability factors (CPFs) have been implicated as one of the causes of nephrotic syndrome (NS). Evidence for CPFs comes mainly from clinical observation and animal studies. However, reliable evidence in vitro assays are lacking. In the present study, we aimed to study the presence and pathogenic relevance of CPFs in plasma of NS patients during active disease and remission using conditionally immortalized human podocytes (ciPods) and primary human glomerular microvascular endothelial cells (GMVECs) in vitro. Podocytes (ciPods) and primary endothelial cells (GMVECs) were incubated with plasma from NS patients in relapse and remission as well as from a non-renal control patient. Cell viability, podocyte motility, podocyte actin cytoskeleton architecture, and reactive oxygen species (ROS) formation at the presence or absence of ROS activator, dimethylsulfoxide, were investigated by CCK-8 assay, scratch-assay, immunofluorescence stainings, and CM-H2DCFDA probing, respectively.

Results: Plasma from active NS patients, but not from remission or control patients, caused excessive ROS formation in podocytes, but not in endothelial cells. Immunofluorescence microscopy revealed severe enlargement of the podocyte’s actin cytoskeleton in response to active NS plasma. Moreover, the motility of podocytes seemed to be reduced in the presence of active NS plasma, but not in the presence of remission or control plasma. Prolonged incubation of podocytes, but not endothelial cells,
led to cell death only when active NS plasma was present. Furthermore, the ROS scavenger dimethylthiourea abolished the ROS formation and the podocyte’s actin cytoskeleton rearrangement and cell death in response to active NS plasma, suggesting that ROS plays an important role in podocyte injury in NS.

Conclusions: We provide a high-throughput and sensitive assay to measure ROS in response to NS plasma, providing a new framework for monitoring in vivo CPI activity that could be used for diagnostics or disease monitoring purposes. Moreover, our findings suggest that the inhibition of ROS formation or facilitating rapid ROS scavenging might play an important role in podocyte injury in NS.

FR-PO944

Studying the Role of Fibronectin in Mechanically Stressed Podocytes
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Background: Glomerular hypertension induces mechanical load to podocytes in situ, often resulting in podocyte detachment and the development of glomerulosclerosis. Although it is well known that podocytes are mechanosensitive, the mechanosensor and mechanotransducer, respectively, are still unknown. Extracellular matrix proteins could function as such a mechanosensor. The objective was to clarify the potential significance of the extracellular matrix protein fibronectin which became up-regulated in cultured podocytes 2-20 fold after the exposure to mechanical strain. Furthermore, biopsies of patients suffering from diabetic nephropathy were used to study the expression of fibronectin.

Methods: Mouse podocytes were cultured on silicone membranes that were connected to the stretch apparatus for three days (0.5 Hz and 5% extension). To study the role of fibronectin in cultured podocytes under mechanical stretch, fibronectin was knocked down (Fnl KD) by specific siRNAs. Additionally, we established a fibronectin knock-out podocyte cell line (Fnl KDO) by CRISPR/Cas9. LC-MS as well as qRT-PCR were performed from mechanically stretched podocytes.

Results: Here, we demonstrate that the extracellular matrix protein fibronectin is essential for the attachment of podocytes during mechanical stress. By qRT-PCR as well as Western Blot analysis we found a significant up-regulation of fibronectin expression in cultured podocytes after three days of mechanical stretch. Additionally, we observed a significant loss of Fnl KDO as well as Fnl KO podocytes (> 80%) compared to controls in the presence of mechanical strain. Besides, this, a significant down-regulation of the focal adhesion proteins talin, vinculin and paxillin and a reduced cell spreading was observed in Fnl KO podocytes indicating an important role of fibronectin for the adhesion of cultured podocytes. Analyzing kidney biopsies of patients suffering from diabetic nephropathy, we found a significant up-regulation of fibronectin especially in podocytes in contrast to control specimens.

Conclusions: Fibronectin plays an important role in the adaption and adhesion of cultured podocytes in the presence of mechanical stretch and could serve as a mechanosensor in podocytes.

FR-PO945

Targetable Biomarker in Glomerular Disease: Determining the Role of Plasminogen in Podocyte Injury
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Background: Recent studies have shown significant quantities of plasminogen/plasminogen(ogen)/uria, in the urine of proteinuric patients and that exposure of cultured podocytes to plasminogen can result in injury via up-regulation of endothelin-1 (ET1) and oxidative stress pathways. However, a causative role for plasminogen as a “second hit” in disease progression has yet to be demonstrated in vivo, and the associations between plasminogen(ogen)/uria and kidney function in glomerular diseases remains unclear.

Methods: We performed comparative studies in a puremurin aminoclonosine (PAN) nephropathy rat model treated with amiloride, which has off-target effects inhibiting plasminogen activation, and measured changes in plasminogen(ogen)/uria and urinary ET1 by ELISA. Western blotting, proteomics, and IF were conducted to investigate changes in ET1 and plasminogen(ogen) in isolated glomeruli as well as markers of oxidative stress and podocyte homeostasis. We used a bioprocessor at Mount Sinai hospital to identify patients with glomerular diseases (n=128). Urine samples were measured for time-of-flight mass spectrometry and plasminogen(ogen)/uria to assess for correlations with kidney function outcomes by logistic and linear regression.

Results: Plasminogen(ogen) was found—for the first time to our knowledge—to be strongly bound within glomeruli in PAN rats, which was later confirmed in FSGS patients. PAN-treatment was associated with increases in plasminogen(ogen)/uria and urinary ET1, which was rescued by amiloride. Interestingly, amiloride was protective against PAN-induced glomerular injury and oxidative stress. In the patient cohort, associations were shown between plasminogen(ogen)/uria and edema status as well as gFGF, independent of age and gender.

Conclusions: Here, we (i) present strong supportive evidence for a causative role of the plasminogen(ogen)-system in podocyte injury, with amiloride having reno-protective properties in vivo, and (ii) advance clinical correlations of plasminogen(ogen)/uria as a biomarker of glomerular injury in proteinuric patients. Plasminogen(ogen) may thus aggregate through direct or indirect pathways to contribute to glomerular passages in the setting of proteinuria. Given such a function, plasminogen(ogen) represents an attractive target for the development of mechanistically-based novel therapeutic interventions.
FR-PO946

Upregulated LRRCC5 Aggravates Podocyte Injury Through Activating the BK Channel
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Background: Focal segmental glomerulosclerosis (FSGS) is a common podocytopathy, accounting for 40% of cases of nephrotic syndrome in adults, and its pathogenesis has not been fully elucidated. LRRCC5 is a subunit of the BK channel, and the role of LRRCC5 in podocyte injury has not been studied.

Methods: Glomerular tissues of FSGS patients and controls were isolated and subjected to transcriptome analysis. Cell biology techniques were used to analyze LRRCC5 expression, BK channel current, intracellular potassium level, caspase-3 activation, DNA fragmentation and podocyte apoptosis in human podocytes and Ang II-treated mice.

Results: Glomerular expression of LRRCC5 was significantly increased in glomerular podocytes in FSGS patients. In vitro, treatment with Ang II induced NFATc nuclear translocation and promoted LRRCC5 upregulation in podocytes. The upregulated LRRCC5 and increased intracellular calcium led to BK channel activation and the loss of intracellular potassium, which caused caspase-3 activation and DNA fragmentation in Ang II-treated podocytes. In contrast, silencing of LRRCC5 reversed the intracellular potassium loss, caspase-3 activation and DNA fragmentation in the Ang II-treated podocytes. In vivo, Ang II-inflation caused an obvious increase in LRRCC5 expression, BK channel activation, intracellular potassium decrease, podocyte apoptosis and focal segmental sclerosis mice. Knockout of BK channel or silencing of LRRCC5 prevented intracellular potassium decrease and ameliorated podocyte injury and focal segmental sclerosis in Ang II-treated mice.

Conclusions: The results suggest that the upregulated LRRCC5 aggravates podocyte injury through activating BK channel. Inhibition of LRRCC5 ameliorates podocyte injury, may represent a therapeutic approach for FSGS patients.

FR-PO947

Loss of Robo2 in Mature Podocytes Is Protective from Injury by Enhancing Podocyte Adhesion That Helps Maintain Foot Process Structure
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Background: Repulsive guidance cue receptor ROBO2 plays an important role during early kidney development. ROBO2 is expressed in podocytes, inhibits nephrin-induced actin polymerization, down-regulates nonmucleos myosin II A activity, and destabilizes kidney podocyte adhesion. However, the role of ROBO2 during kidney injury, particularly in mature podocytes, is not known.

Methods: In this study, we compared phenotypes between adult Robo2 podocyte specific knockout mice (Robo2 cKO) and wildtype controls under two different glomerular injury conditions induced by protamine sulfate (PS) perfusion or nephrotoxic serum (NTS) injection. We also analyzed ROBO2 expression in the glomeruli of NTS injured mice, passive Heymann nephritis (PHN) rat, and membranous nephropathy patients.

Results: Ultrastructural analysis reveals that Robo2 cKO mice display less foot process effacement and better preserved slit-diaphragm density compared to wild-type littermates injured by either protamine sulfate (PS) or nephrotoxic serum (NTS). The Robo2 cKO mice also develop less proteinuria after NTS injury. Further studies reveal that ROBO2 expression in podocytes is upregulated after glomerular injury since its expression levels are higher in the glomeruli of NTS injured mice and passive Heymann membranous nephropathy rats. Moreover, the amount of ROBO2 in the glomeruli is also elevated in patients with membranous nephropathy. Finally, overexpression of ROBO2 in cultured mouse podocytes compromises cell adhesion.

Conclusions: These findings suggest that kidney injury increases glomerular ROBO2 expression that might compromise podocyte adhesion and thus loss of ROBO2 in podocytes could be protective from glomerular injury by enhancing podocyte adhesion that helps maintain foot process structure. Our findings also suggest that ROBO2 is a therapeutic target for podocyte injury and podocytopathy.

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FR-PO948

Role of Sphingomyelin Phosphodiesterase Acid-Like 3B (SMPDL3b) in Fatty Acid Uptake and in Progression of Podocyte Damage
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Background: Upregulated LRRC55 aggravates podocyte injury through activating BK channel. Inhibition of LRRC55 attenuates podocyte injury, focal segmental sclerosis in Ang II-treated mice. Our results identify a new role of SMPDL3b in the uptake of fatty acids, the accumulation of TAG and the formation of LDs.

Methods: Our new mouse model upregulated SMPDL3b expression, triglyceride and cholesterol ester content were increased in siSMPDL3b when compared to control podocytes. Finally, we demonstrate for the first time that SMPDL3b is present in isolated LDs suggesting a possible role for SMPDL3b in the formation of LDs.

Results: Our novel findings show that-upregulated SMPDL3b, the accumulation of TAG and the formation of LDs. Further experiments to understand the exact mechanism by which SMPDL3b controls the uptake of fatty acids thus contributing to podocyte damage are underway.

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FR-PO949

Podocyte Cell Cycle Manipulation as a Potential Tool in Treating Glomerular Disease
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Background: Loss of podocytes is a hallmark of most progressive kidney disease. Podocytes do not replicate in situ; hence, hypertrophy is the only mechanism they have to compensate for cell loss by allowing a smaller number of podocytes to effectively cover the glomerular capillary wall. To undergo hypertrophy, podocytes re-enter the cell cycle, moving from quiescent G0 to G1. Regulation of the G1/S checkpoint is critical. If podocytes exit G1 and continue toward mitosis, they detach from the GBM during cytokerin synthesis and are lost in the urine. Understanding cell cycle regulation may be pivotal in developing novel therapies to prevent podocyte loss.

Methods: To the study the podocyte cell cycle, we established colonies of Fucci2AR mice. These mice have ubiquitination-mediated fluorescent protein expression, which reflects the cell cycle in vivo: red in G1/S, green in S/G2, yellow for S phase, no fluorescence in G0. These Fucci mice were bred with our model of glomerular injury (Alport Syndrome, AS) and with a podocyte-specific Cre-mouse, yielding a model that allows real-time studies of the cell cycle specifically in podocytes.

Results: Podocytes isolated from glomeruli of wild type Fucci2AR mice were 23% of total glomerular cells; 93% were in G0, 6% in G1 and none in S/G2. In late-stage proteinuric AS Fucci2AR mice, 95% of the podocytes were in G1. We found that rapamycin (an mTOR inhibitor) was protective by supporting podocyte survival in vitro. Podocytes isolated from cultured glomeruli exposed to rapamycin for 3 days had increased survival (16%-20%) compared to podocytes not exposed to rapamycin (7%-9%). Furthermore, in PAN-exposed podocytes in vitro rapamycin increased the number of podocytes in G1 [from 4% to 13.5%]. The G1 podocytes were also larger by 41.5% (p=0.05) than those in G0 as assessed by flow cytometry forward scatter, confirming that the G1 podocytes are in a hypertrophic state.

Conclusions: Interventions that support podocyte hypertrophy, while limiting progression to mitosis or cytokinesis, may stabilize glomeruli against sclerosis following a loss of podocytes. Rapamycin presents a potential novel therapy in glomerular diseases such as AS by enhancing stable hypertrophy of podocytes in G1, while preventing progression through the cell cycle to S and mitosis.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO950

ZNF277-Induced Podocyte Injury by Regulating the Expression of ITGA and ITGB5
Yuqiu Lu, Chen Yu. Shanghai Tongji Hospital, Shanghai, China.

Background: ZNF277, a newly discovered zinc finger protein, is highly conserved in evolution. Previously, by single-cell RNA sequencing, we found that ZNF277 was specifically expressed in mouse glomerular podocyte. Then, by searching Nephrosphere database, the expression level of ZNF277 in glomeruli of FSGS patients was significantly down-regulated. Therefore, we speculated that ZNF277 might be involved in podocyte injury.

Methods: Firstly, we detected the mRNA level of ZNF277 in human podocyte lines (HPG84 and HPG47) which were specifically knocked down by siRNA. Then we tested the changes of podocyte-specific genes were detected by Q-PCR. Finally, by bioinformatics analysis of podocyte-specific genes down-regulated when ZNF277 was knocked down, we speculated the possible mechanism of ZNF277 involved in podocyte injury.

Results: In vitro, the expression level of ZNF277 in PAN-induced podocyte injury model was down-regulated (0.50 ±0.13). 92 podocyte-specific genes were detected in HPCs in which ZNF277 was knocked down by siRNA. Among them, 18 genes were down-regulated, including ITGB5, ITGA, IFT80, MYOM2, HAUS6, RAB3B, CDKN1C, DTNB1, CYSBR5A, SDC4, ARPC1A, WT1, PODXL, ELDR2, SYNPO, ALCAM, STAG3, TMOD3. Then, the 18 genes were analyzed by Bioinformatics analysis, including GO and KEGG analysis. The results suggested that they were mainly involved in biological processes such as cytoskeleton and cell adhesion. ITGB5 and ITGA and ITGB5 were the main genes involved in the biological process.

Conclusions: The mechanism of ZNF277 participates in podocyte injury may be regulating the expression of ITGA and ITGB5.

Funding: Government Support - Non-U.S.

FR-PO951

Protective Effect of Hydroxychloroquine on Cultured Mouse Podocytes Expressing the HIV Accessory Protein Vpr
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Background: Studies in HIV-transgenic mice have implicated the HIV accessory protein R (Vpr) in podocyte injury, culminating in HIV-associated nephropathy. Clinical studies indicate that hydroxychloroquine reduces kidney damage in lupus. In this study, we tested protective effects of hydroxychloroquine on cultured mouse podocytes expressing Vpr.

Methods: Stably-transfected mouse podocytes bearing three transgenes, expressing Vpr (thermostable SV40 T antigen, podocin-promoter-rtα and tet-responsive element Vpr) or control AI podocytes expressing two transgenes (thermostable SV40 T and podocin-promoter-rtα) were grown at 33°C and differentiated at 37°C. Differentiated podocytes were plated on day 1, hydroxychloroquine at concentrations ranging from 0.63 to 80 μg/mL was added to podocyte cultures on day 3, and 1 μg/mL doxycycline (DOX) was added day 4. Cell death was observed by phase-contrast microscopy on day 6 and 9, and total cell number and dead cell number were counted in each condition to obtain the percentage of dead cells.

Results: AI control and Vpr-expressing podocytes tolerated hydroxychloroquine concentrations of 10 μg/mL of hydroxychloroquine or less but died at higher concentrations. Vpr podocytes died 48 h after 1 μg/mL DOX was added, likely due to induced expression of Vpr. DOX-treated Vpr podocytes were protected from cell death with concentrations of 0.63, 1.25, 2.5, 5 and 10 μg/mL hydroxychloroquine (H), in a dose-dependent manner (H0: 30.2%, H6: 63.25%, H1: 25.28%, H2: 6.7%, H5: 0%; H10: 0%). DOX-un-treated Vpr podocytes without hydroxychloroquine also underwent cell death on day 9 of 37°C culture due to leaky expression of Vpr, which was partly inhibited by 5 and 10 μg/mL of hydroxychloroquine pretreatment (H5: 56.3%, H10: 32.0%, H10: 2.6%).

Conclusions: In cultured mouse podocytes expressing Vpr, hydroxychloroquine showed protective effects at up to 10 μg/mL. Hydroxychloroquine has diverse effects on mammalian cells, including increasing lysosomal pH, which in turn alters protein processing such as glycosylation. Hydroxychloroquine also alters Toll-like receptor signaling. The effects of hydroxychloroquine on Vpr-induced podocyte injury deserve further study.

FR-PO952

Regulation of Podocyte Senescence by GSK3β: A Novel Senostatic Target for Delaying Glomerular Aging
Yudong Yang, Lance D. Dworkin, Rujun Gong. University of Toledo Medical Center, Toledo, OH.

Background: Along with worldwide population aging, nephrology practice is challenged by renal aging, which is associated with progression of age-related glomerulosclerosis, FSGS and aging. The genetic causes of salt sensitivity and hypertension in humans are not completely understood. The kidney plays a preeminent regulatory role in water and electrolyte balance and blood pressure (BP) homeostasis. The renal dopamine receptors, D1 and D2 receptors, inversely regulate each other. However, APOL1 renal risk variants (RRVs), GRK4 wild-type (GRK4 wt) and G2, G1 and G2 inversely regulate each other. In this study, we tested protective effects of hydroxychloroquine on cultured mouse podocytes expressing Vpr, which was partly inhibited by 5 and 10 μg/mL of hydroxychloroquine pretreatment (H5: 56.3%, H10: 32.0%, H10: 2.6%).

Results: AI control and Vpr-expressing podocytes tolerated hydroxychloroquine concentrations of 10 μg/mL of hydroxychloroquine or less but died at higher concentrations. Vpr podocytes died 48 h after 1 μg/mL DOX was added, likely due to induced expression of Vpr. DOX-treated Vpr podocytes were protected from cell death with concentrations of 0.63, 1.25, 2.5, 5 and 10 μg/mL hydroxychloroquine (H), in a dose-dependent manner (H0: 30.2%, H6: 63.25%, H1: 25.28%, H2: 6.7%, H5: 0%; H10: 0%). DOX-un-treated Vpr podocytes without hydroxychloroquine also underwent cell death on day 9 of 37°C culture due to leaky expression of Vpr, which was partly inhibited by 5 and 10 μg/mL of hydroxychloroquine pretreatment (H5: 56.3%, H10: 32.0%, H10: 2.6%).

Conclusions: In cultured mouse podocytes expressing Vpr, hydroxychloroquine showed protective effects at up to 10 μg/mL. Hydroxychloroquine has diverse effects on mammalian cells, including increasing lysosomal pH, which in turn alters protein processing such as glycosylation. Hydroxychloroquine also alters Toll-like receptor signaling. The effects of hydroxychloroquine on Vpr-induced podocyte injury deserve further study.

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Underline represents presenting author.
Results: The renal tubule-restricted expression of GRK4 65R-L increased the BP (117.42 ± 6.9 mm Hg, P < 0.02) while that of the control group with GRK4 65D-L did not increase the BP (105.68 ± 9.6 mm Hg, P < 0.05), indicating that the presence of the GRK4 variant in the kidney caused the increase in BP. We next evaluated the renal expression profiles of select genes. We found that the expressions of the pro-natriuretic D (0.81 ± 0.01 vs. 1.04 ± 0.02, P < 0.01) and JLP (0.97 ± 0.07 vs. 1.04 ± 0.02, P < 0.01) were decreased. By contrast, the expressions of the anti-natriuretic Na+/K+-ATPase (1.10 ± 0.02 vs. 1.0 ± 0.007, P < 0.05) and αv-ECa (1.40 ± 1.0 vs. 1.0 ± 0.01, P < 0.05) were increased, demonstrating the mechanistic changes that underlie the hypertension in these mice. Interestingly, we also observed a trend in the expression of the AT (0.80 ± 0.02 vs. 1.0 ± 0.02) and Na transmembrane transporters NaP2 (0.81 ± 0.02 vs. 1.04 ± 0.02), SGLT2 (0.90 ± 0.03 vs. 1.07 ± 0.05), and NBCc2 (0.50 ± 0.07 vs. 1.15 ± 0.03), which were decreased, which may represent insufficient compensatory mechanisms against the increase in BP.

Conclusions: Our results highlight the underlying and compensatory renal mechanisms for the hypertension that developed in mice with either kidney-restricted or globally expressed GRK4 65R-L.

Funding: NIDDK Support

FR-PO955

The Differential Expression Research of Circular RNAs in Exosomes from Serum and Urine in Systemic Lupus Erythematosus Patients Hualin Ma, Shenzhen People's Hospital, Shenzhen, China.

Background: To further explore the pathogenesis of SLE, the technique of gene-sequencing was used to analyze the differentially expressed circular RNAs (circRNAs) in exosomes from serum and urine of patients with SLE, which may lay the foundation for the development of a new class of biomarkers for SLE diagnosis and treatment.

Methods: Ten patients with SLE (SLE group) and ten normal controls (NC group) were recruited as experimental subjects in our research. The serum and urine were separated from each participant's peripheral venous blood and early morning urine, which were stored at −80°C for later use. The serum and urine were separated by ExoQuick Precipitation Solution and ultracentrifugation. Then the pure circRNAs were extracted from the exosomes with a series of enzymatic reactions. And then, the significantly differentially expressed circRNAs were picked out by the method of gene-sequencing to analyze the function of corresponding target genes.

Results: Compared with normal controls, the species of circRNAs were reduced in the exosomes from serum of patients with SLE, which were mostly originated from intron gene regions. Meanwhile, a total of 121 circRNAs were significantly differentially expressed, which were also mostly derived from intron gene regions, including 54 up-regulated and 67 down-regulated. But the species were increased in the exosomes from urine of patients with SLE compared with normal controls, and which were mainly originated from intron gene regions; Simultaneously, a total of 14 circRNAs were significantly differentially expressed, which were primarily belonged to intron gene regions, including 7 up-regulated and 7 down-regulated. Compared with the circRNAs detected from urinary exosomes, a total of 52 circRNAs were significantly differentially expressed in the exosomes from serum of patients with SLE, which were also mostly originated from intron gene regions, including 45 up-regulated and 7 down-regulated.

Conclusions: The significantly differential and specific expression of circRNAs in the exosomes from serum and urine of patients with SLE were found. Such as gene snoU13, SNORD31 and SNORD531 could be regarded as potential diagnostic biomarkers of SLE. Furthermore, these figures suggested that the significantly differentially expressed circRNAs can be used as a reference or a supplement in the research of the pathogenesis of SLE.

FR-PO956

Proteomics of Human Glomerulonephritis by Laser Microdissection and Liquid Chromatograph-Tandem Mass Spectrometry (LMD-LC MS/MS) Naoto Kawata1, Dedong Kang,1 Kyiko Ituki,1 Takano Shibata,3 Ashio Yoshimura,2 Kazuho Honda.4 Shouwa University Fugajiko Hospital, Yokohama, Japan; Shinshloko Daichi Clinic; Yokohama, Japan; Shouwa University, Tokyo, Japan; Shouwa University, Tokyo, Japan.

Background: Laser microdissection and liquid chromatograph tandem mass spectrometry (LMD-LC MS/MS) methods enable us to analyze the proteins from the tissue sections. In nephropathies, they are preferentially applied in the diagnosis of glomerular diseases, since the concentration of biomarkers in urine sample is low, most the current assays are globally expressed or TECs-specific deletion of Jlp resulted in more severe lesion of kidney fibrosis, whereas TECs-specific transgenic expression of Jlp brought about the beneficial effects of fibrosis resistance. The protective role of Jlp in renal fibrosis could be ascribed to its potentials of overcounteracting the profibrotic effects induced by TGF-β1 through negatively regulating TGF-β1 expression, counteracting TGF-β1 induced ECM production, epithelial-to-mesenchymal transition (EMT), apoptosis, cell cycle arrest, and autophagy in TECs. The protective effects of Jlp could be compromised by its downregulation mediated by TGF-β1 and FGF-2 but not the inflammatory factor TNFα, implying that kidney fibrosis is a consequence of unbalanced forces of profibrotic factor TGF-β1 and FGF-2 and antibotic factor Jlp.

Conclusions: JLP is a novel endogenous antibotic molecule in renal fibrosis.

FR-PO958

A Novel Conductive Polymer-Based Biosensor for Ultrasensitive Detection of Biomarkers in Lupus Nephritis Tianfu Wu. University of Houston, Houston, TX.

Background: Lupus is a systemic autoimmune disease that immune system can attack the organs and tissues, particularly kidney causing highly mortality and co-morbidity. Unfortunately there is not a non-invasive diagnostic tool for lupus nephritis (LN). Recent studies have shown that urinary biomarkers are promising in LN diagnosis. However, since the concentration of biomarkers in urine sample is low, most the current assays are not optimal in detecting specific urinary biomarkers for LN due to their low sensitivity.

Methods: In this study, we developed a novel biosensor based on human throbinn thrombin aptamer-functionalized conductive gel-nanoparticle with poly(3,4-ethylendioxityliene) polyestrene sulfonate (PEDOT:PSS) nanowires which could capture and concentrate low-abudant biomarkers, causing a binding-induced shrinkage of the gel nanoparticles, which could lead to a conductance change of the biosensor and subsequent signal amplification.

Results: By using Atomic-force microscopy (AFM), the topography and height profiles of the polymeric sensor were recorded and to analyze polymeric network shrinkage in response to PBS or Thrombin. Urinary throbinn levels were quantitatively analyzed through monitoring the conductance change caused by polymeric network shrinkage upon the aptamer-thrombin binding. A significant shrinkage of 18.14% of the biosensor was observed after biomarker recognition. The limit of detection (LOD) of the conductive gel-nanoparticle biosensor for human urine thrombin sample could reach 4.82x10^-16 M. This thrombin-specific biosensor and a commercial human throbinn enzyme linked immunosorben assay (ELISA) kit were used to perform side-by-side measurement of urinary throbinn in LN samples. The result obtained from the same patient using sensor or ELISA was used for pair test of correlation, and a strong correlation with R2 value of 0.97 was found between the sensor and ELISA. The results indicate that this conductive gel-nanoparticle biosensor is highly sensitive and selective in accurately differentiatn LN from healthy controls using urinary throbinn as a biomarker (P < 0.001).

Conclusions: Collectively, this novel ultrasensitive conductive gel-nanoparticle biosensor may hold promise in biomarker detection and diagnosis of LN.

Funding: Other NIH Support - NIA support
Deficiency of the Atypical Chemokine Receptor 2 (ACKR2) Accelerates Progression of Nephrorcalcinosis-Related CKD

Background: Primary and secondary hyperparathyroidism lead to deposition of calcium crystals in the kidney, i.e. nephrocalcinosis. Calcium oxalate-induced necroinflammation is an important mechanism of kidney injury in nephrocalcinosis. The atypical chemokine receptor 2 (ACKR2) is a chemoattraction receptor expressed in the tubulointerstitium, which scavenges inflammatory CC-chemokines and reduces renal inflammation in chronic kidney disease models. We therefore hypothesized that ACKR2 limits renal inflammation and fibrotic tissue remodeling in nephrocalcinosis-related chronic kidney disease and slows progression to end-stage renal failure.

Methods: Chronic oxalate nephropathy was induced in wild-type and Ackr2-deficient (Ackr2/-) mice by feeding a high-oxalate and rich-depleted diet. Renal function decline was monitored by measurement of glomerular filtration rates in weekly intervals until day 14. Renal injury, inflammation and fibrosis were assessed at day 14.

Results: Compared to wild-type, Ackr2/- mice showed increased mortality following induction of oxalate nephropathy. Renal function declined more rapidly in Ackr2/- mice, leading to end-stage renal failure until day 14. Tubular injury was worse in Ackr2/- mice. Tubulointerstitial infiltrates of granulocytes and mononuclear phagocytes, but not T cells increased in Ackr2/- kidneys. Moreover, Ackr2 deficiency aggravated renal inflammation, with increased expression of the inflammatory chemokine CCL2 and enhanced accumulation of inflammatory macrophages. Renal oxalate and CD44, which mediate adhesion of calcium oxalate crystals to tubular epithelial cells, was increased in Ackr2/- mice. This may contribute to more extensive crystal deposition present in Ackr2/- kidneys despite comparable calcium and oxalate levels to wild-type. Moreover, renal oxalate and inflammation in Ackr2/- mice is parallelized by aggravated renal fibrosis, as revealed by increased expression of extracellular matrix molecules, renal accumulation of myofibroblasts and enhanced infiltration of bone marrow-derived fibroblasts.

Conclusions: This data suggest that ACKR2 limits renal inflammation, calcium oxalate deposition, tubular injury and renal fibrosis in nephrocalcinosis, and thus slows progression to end-stage kidney disease.

Funding: Government Support - Non-U.S.

RNA Sequencing in Proximal Tubule Cells Reveals Lack of Effect of Proximal Tubule Markers

Background: There are close to 12 different immortalized cell lines available containing cell elements from different organs to be used mostly in the models of renal proximal tubule cells. There is strong need to characterize these cells so as to establish their lineage and help the scientific community at large to make decisions regarding their suitability in experiments. Our goal is to characterize the cell lines using RNA-Seq.

Methods: To accomplish an overall genomic screen of the stated immortalized cell lines, one mouse, three rat, and 2 opossum kidney cell lines on Transwell filters using the recommended culture media. RNA-Seq was performed using Illumina kits following the manufacturer’s protocol. The RNA-Seq was compared to a mouse S1 proximal tubule data. The data were presented as expression rank with the rank above 8000 as negative expression. To validate the data a native S1 proximal tubule cell line was used as a positive control.

Results: Results are shown in the Table.

Conclusions: Our data suggest that the available human and rat kidney tubule cells are epithelial cells (express occludin and claudins) but not of proximal tubule origin (lack sodium-dependent transporters, megalin and PTH receptor). Although, LLC-PK1 cells express the proximal tubule specific proteins, they also express markers of cortical tubule cells. These are therefore a mixed population and not specific proximal tubule cells. The opossum kidney cells express all the markers of proximal tubule cells and thus are the only cell of proximal tubule origin.

Funding: Other NIH Support - NHLBI, AHA, Private Foundation

Expression of Proximal Tubule Markers

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Conclusions: The proper localization of FKBP12 at the actin cytoskeleton participates in the maintenance of process formation. Tac treatment ameliorates podocyte injury by restoring FK506 binding Protein 12 (FKB12) at Actin Cytoskeleton in Injured Podocyte

Tacr2m Ameliorates Podocyte Injury by Restoring FK506 Binding Protein 12 (FKB12) at Actin Cytoskeleton in Injured Podocyte

Background: Tacrolimus (Tac), an immunosuppressive drug, is used to inhibit the activation of NFAT, a substrate of calcineurin (CN) activity in T cells. It is reported that Tac treatment directly ameliorates terminal stages of progression of the activation of NFAT, a substrate of CN in the nephrotic syndrome. We therefore hypothesized that FKBP12 is expressed in glomerular podocyte and the altered expression of FKB12 is involved in the development of podocyte injury. However, the precise pharmacological mechanism of Tac in podocyte injury was not well understood yet.

Methods: The protein expression of FKB12 was investigated with western blot and the localization was analyzed with dual label immunostaining in human cultured podocytes. The localization of NFATC3 was also investigated.

Results: FKB12 was detected both in cytoplasm and along actin cytoskeleton in normal human cultured podocytes. These FKB12 stainings were decreased in the cultured podocytes treated with Adriamycin (ADR). Tac treatment restored the FKB12 at actin cytoskeleton. The expression of FKB12 at the actin cytoskeleton was increased by the Tac treatment to normal cultured podocytes. The western blot analysis showed the protein expression of FKB12 was decreased in the podocytes with ADR (43.9% to normal, P<0.005). Tac treatment suppressed the decrease (80.5%). The FKB12 expression of the cells treated with Tac showed higher than the cells treated with ADR. Tac treatment partially reduced the nuclear accumulation of NFATC3 in the ADR-treated cells. 27.5% of the cells showed multiple processes with positive staining in normal cultured podocytes. The proportion of the cells forming the processes to total cells was decreased in the podocytes treated with ADR (P=0.05 vs. normal). Tac treatment suppressed the decrease in ADR (38.1%, P=0.05 vs. no treatment). Tac treatment to normal cells increased the proportion of the cells forming processes (55.7%, P=0.005 vs. normal).

Conclusions: The proper localization of FKB12 at the actin cytoskeleton participates in the maintenance of process formation. Tac treatment ameliorates podocyte injury by restoring FKB12 at actin cytoskeleton in injured podocyte.

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FR-PO963

Expression of Acsm2, a Kidney Specific Gene, Parallels the Structural and Functional Maturity of Proximal Tubular Cells

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Background: Acyl-CoA synthetase medium-chain family member 2 (Acsm2) gene was first identified and cloned by our group as a kidney specific “KS” gene. Acsm2 may participate in fatty acid metabolism and glycine conjugation pathways. However, little has been reported on Acsm2, and the expression pattern and function of it remain to be clarified.

Methods: The expression pattern of Acsm2 was investigated with RT-PCR using RNAs extracted from multiple organs of adult C57BL/6 mice and kidneys at multiple ages. Immunohistochemistry for Acsm2 was performed in kidney or liver tissue sections. In situ hybridization was performed using digoxigenin-labeled RNA probes for mRNA of Acsm2. We also investigated the kidneys from mice subjected to partial unilateral ureteral obstructions (puUO) and chronic kidney disease (CKD) with total renal gene knockout or conditional knockout of integrin beta 1 gene in cells from the renin progeny using aforementioned methods. Data from the Encyclopedia of DNA Elements (ENCODE) project was analyzed to examine the epigenetic state at Acsm2 locus in each organ of mice.

Results: We found that Acsm2 was expressed in the kidney samples at high level. The expression of Acsm2 in the liver was less than 1/10,000 of the expression in the kidney. No other organs tested expressed Acsm2. Immunohistochemistry and in situ hybridization revealed that Acsm2 was highly expressed in the proximal tubular cells in normal adult mice. In contrast, Acsm2 was not detected in liver. The expression level of Acsm2 in kidneys was at a low level in newborn mice, increased with development, and reached a plateau by 2 months of age. With puUO and CKD, the expression of Acsm2 in the proximal tubules was significantly decreased according to the severity of the renal impairment. Analysis using ENCODE database revealed that Acsm2 locus in mice has specific histone modifications that are related to the active enhancer and promoter and transcription only in kidney cells.

Conclusions: The Acsm2 gene is specifically expressed in proximal tubules, and not in other tissues. The expression of Acsm2 parallels the structural and functional maturation of proximal tubular cells. Downregulation of its expression in several models of kidney disease suggests that Acsm2 may serve as a novel marker of proximal tubular injury and/or dysfunction.

Funding: NIDDK Support

FR-PO964

Total Extracts of Single Chinese Medicine Herb Attenuates Renal Tubule Injury via Suppression of ERK1/2-Mediated NLRP3 Inflammasome Activation

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Background: Abelmoschus Manihot (L.) Medik is a herb used in traditional Chinese medicine to treat some kidney diseases. The chemical constituents in the plant are mainly flavonoids, organic acids, steroids and volatile compounds. Five flavonoids, hyperoside, myricetin, quercetin, isorhamnetin, and rutin, have been determined to be the major components. The biological activities of the active components via high-performance liquid chromatography (HPLC) that simultaneously quantifies the flavonoid compounds of Abelmoschus Manihot L. flower. To date, the detailed mechanisms by which Abelmoschus Manihot L. improves some kinds of renal disease are not fully understood. Our previous study showed that Abelmoschus Manihot L. flower is effective in reducing the activity and releasing the expression of cytokines in vitro.

Methods: In this study, we established Adriamycin-induced NLRP3 expression, the normal rat kidney epithelial cell line, and Sprague-Dawley rats with Adriamycin-induced nephropathy to evaluate the role and mechanisms of total extracts of Abelmoschus Manihot L. flower (TEA) on tubular cell both in vitro and in vivo.

Results: In Adriamycin-induced nephropathy rat model, TEA decreased proteinuria and attenuated renal tubule lesions. Interestingly, NLRP3 was increased mostly in tubule not in glomeruli and TEA inhibited the expression of NLRP3 in tubules. In vitro study, TEA inhibited Adriamycin-induced cellular morphological changes, cell viability, and apoptosis through the suppression of protein oxidation and ERK1/2 signaling. However, this anti-oxidative stress role of TEA was independent of ROS inhibition. Adriamycin activated ERK1/2 signaling followed by activation of NLRP3 inflammasomes. TEA suppressed NLRP3 inflammasomes via inhibition of ERK1/2 signal transduction.

Conclusions: TEA protects renal tubular cells against toxicity of Adriamycin via inhibition of ERK1/2-NLRP3 inflammasomes.

Funding: Government Support - Non-U.S.
FR-PO967

Kidney Injury Enhances Renal Granulocyto-Colony Stimulating Factor Expression, Granulopoiesis, and Human Neutrophilic Granulocyte Proteinase 3 Receptor CD177 Expression

Julia Volkmann,1 Jessica Schmitz,1 Alexandra Helmeke,1 Payel Sen,2 Jan H. Brasen,1 Wanja Bernhardt,3 Stephan Immenshuh,1 Wilfried Gwinner,1 Roland Schmitt,2 Hermann G. Haller,1 Sibylle Von Viettinghoff1
1 Hannover Medical School, Hannover, Germany; 2 Medizinische Hochschule Hannover, Hannover, Germany; 3 Medical School Hanover, Hannover, Germany; 4 Heidering Dialysis clinic, Hannover, Germany.

Background: Acute kidney injury causes significant systemic adverse events beyond retention of uric acid and volume expansion, mechanisms of which are incompletely understood. Neutrophilic granulocytes, the most abundant human blood leukocytes, are characterized by a high turnover rate. They are chiefly controlled by granulocyte colony stimulating factor (G-CSF), which can be produced by diverse cell types. The impact of kidney injury on G-CSF production and granulopoiesis has not been determined.

Methods: Renal G-CSF expression in murine experimental kidney injury and after human kidney transplantation was assessed by immunostaining and qPCR. Neutrophils were characterized by flow cytometry in mice with experimental kidney injury, patients with chronic kidney disease, before and after kidney transplantation and in healthy controls. Human cell culture was employed for mechanistic experiments.

Results: In murine experimental ischemia reperfusion injury and unilateral ureteral obstruction models, enhanced G-CSF transcription and increased characteristics of emergency granulopoiesis developed in bone marrow and blood. In humans, G-CSF and kidney transplantation similar transiently elevated human neutrophil expression of CD177, a highly G-CSF responsive neutrophil gene. In kidney graft recipients, the rise in CD177 correlated with renal tubular G-CSF expression. In contrast, CD177 was unchanged in patients with chronic renal impairment independent of renal replacement therapy. As possible underlying mechanisms, hypoxia and proinflammatory cytokine interleukin 17A enhanced G-CSF expression in human renal tubular epithelial cells, while complement activation promoted G-CSF expression in endothelium.


Funding: Government Support - Non-U.S.

FR-PO968

Integration of Spatial Metabolomics to Single-Nucleus Droplet-Based Sequencing Data Identifies New Glomerulospecific Gene Markers

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Background: The current study is a part of the NIDDK Kidney Precision Medicine Project (KPM). We recently cross-validated that a spingomycin (SmD18:1/16:0) was a glomerulospecific marker, as visualized by two independent sites using matrix-assisted laser desorption/ionization-mass spectrometry imaging (MALDI-MSI) to results from other TIS sites. The current study is a part of the NIDDK Kidney Precision Medicine Project (KPM). We recently cross-validated that a spingomycin (SmD18:1/16:0) was a glomerulospecific marker, as visualized by two independent sites using matrix-assisted laser desorption/ionization-mass spectrometry imaging (MALDI-MSI) to results from other TIS sites. To establish integration of data with other Tissue Interrogation Sites (TIS) and technologies, we employed droplet-based single-cell sequencing (snDrop-Seq) in combination with related gene/ enzymes from the KEGG Ontology Database to results from other TIS sites.

Methods: Two MALDI-MSI platforms (QE-HFX at UTHSA and FTICR at PNNL) were employed to spatially characterize the lipid profile in normal human kidney tissues and KEGG Ontology Database to results from other TIS sites. We provided a tabulated list of 48 SM/ceramide metabolism-related gene/enzymes (from KEGG Ontology Database) to results from other TIS sites.

Results: We provided a tabulated list of 48 SM/ceramide metabolism-related gene/enzymes (from KEGG Ontology Database) to results from other TIS sites. The presence of TGF-β1-repressors in progressive renal injury and CKD.


Funding: Government Support - Non-U.S.

FR-PO969

Protein Phosphatase Mg2+/Mg2+-Dependent 1A (PPM1A) and PTEN Deregulation in Kidney Fibrosis: Novel Mechanisms and Co-Dependency of Expression

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Background: PPM1A and PTEN emerged as novel suppressors of the TGF-β1 pathway in renal diseases. Loss of PPM1A and PTEN, following obstructive renal injury, promoted tubular dysfunction as evident by fibrotic factor deposition, epithelial dedifferentiation and cell cycle arrest. However, the molecular mechanism of PPM1A deregulation in renal fibrosis is unknown. We hypothesize that TGF-β1 orchestrates PPM1A loss of expression and that there is functional collaboration between PPM1A and PTEN during progressive fibrosis.

Methods: A double transgenic mouse model of conditional TGF-β1 renal tubular upregulation (created by crossing Pax8-tTA with Tet-O-TGF-β1 mice and subsequent doxycycline administration) and the TGF-β1-driven antilipogenic acid nethropathy (AAN)-induced renal fibrosis system were employed to determine the role of TGF-β1 in PPM1A deregulation. Human renal epithelial cells (HK-2) and primary kidney fibroblasts (HKFs) with stable PPM1A and PTEN expression or deletion were created to investigate the potential functional interplay among TGF-β1, PPM1A, and PTEN.

Results: Renal tubular-specific upregulation of TGF-β1 resulted in tubulointerstitial loss of PPM1A expression 2-3 days post-doxycycline administration in mice. TGF-β1 dramatically attenuated PPM1A and PTEN expression in both HK-2 cells and HKFs via mechanisms involving protein degradation. TGF-β1 promotes ubiquitination of PTEN and PPM1A as a proteasomal inhibitor. MG132 rescued PTEN and PPM1A expression, even in the presence of TGF-β1, along with decreased fibrogenesis. Concurrent loss of PPM1A and PTEN expression in a mouse model of AAN further suggests crosstalk between these repressors. PPM1A stable silencing in HKFs, in fact, resulted in PTEN loss, while PTEN stable depletion decreased PPM1A expression, resulting in a fibro-proliferative response in each case. Transient expression of PPM1A, conversely, increased PTEN protein levels, while TGF-β1 transient induction led to elevated PPM1A expression.

Conclusions: TGF-β1 promotes loss of PPM1A and PTEN expression in vitro and in vivo. We are the first to uncover the pathological functional cooperation between PPM1A and PTEN as they co-regulate each other’s relative abundance, identifying previously unknown links between TGF-β1-repressors in progressive renal injury and CKD.

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FR-PO970

The Spectrum of Renal Involvement in Four Murine Models of Multiple Myeloma

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Background: Approximately 20-50% of multiple myeloma involves kidneys, and additional ~38% of monoclonal gammapathy involves kidney (MGRS). The renal manifestations range from tubulopathies to a spectrum of glomerular diseases that can present with varying degrees of proteinuria and renal dysfunction, to amyloidosis and myeloma cast nephropathy. Although several mouse models of multiple myeloma have been reported, the studies of murine models of myeloma-associated kidney diseases are relatively limited.

Methods: We examined renal pathology of four murine models of multiple myeloma (MM): First, mice carrying a human IL-6-Tg driven by the major histocompatibility complex H2-Ld promoter (IL-6). Second, IL-6-Tg with concomitant Tg of i-Myc with deregulated expression of the Myc oncogene and enhancers in the IgH locus (designated i-Myc/IL6). Third, IL-6-Tg with concomitant Tg of pro-survival oncogene Bcl2 (designated Bcl2/IL6). Fourth, xeno graft model with mouse myeloma cells injected into Kal.wrJ strain mice.

Results: All four models of MM demonstrated M-spike paraproteinaemia. The presence of second transgene in the IL6-Tg background significantly accelerated and aggravated the tumor burden and progression of MM, which developed at 3-6 months, characterized by paraproteinaemia, marked splenomegaly and bone involvement. Light chain restricted casts with variable acute tubular injury resembling cast nephropathy was present in 50-75% of IL6, i-Myc/IL6 and in Bcl2/IL6 mice. Features suggestive of light chain tubulopathy were present in ~25-50% of these three models. Various glomerular deposits were identified as ~50% of Bcl2/IL6 and ~80% of i-Myc/IL6, but not in the IL6 mice. The spectrum of glomerular involvement ranged from light chain deposits resembling cast nephropathy to a spectrum of glomerular diseases that can present with varying degrees of proteinuria and renal dysfunction, to amyloidosis and myeloma cast nephropathy. Although several mouse models of multiple myeloma have been reported, the studies of murine models of myeloma-associated kidney diseases are relatively limited.

Conclusions: Transgenic IL6 mice develop various paraprotein-associated nephropathies and may serve as good preclinical models of myeloma-associated kidney diseases, to study the molecular pathogenesis and to develop nephroprotective strategies for myeloma-associated kidney diseases.

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FR-PO971
The Mechanisms of Gadolinium-Based Contrast Agent-Induced Nephrotoxicity
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Background: All classes of gadolinium-based contrast agent (GBCA) are nephrotoxic. This is well accepted from case reports, prospective studies, and prescriber information sheets.

Methods: Generation of chimeric transgenic mice provided a means of tracing myeloid-derived cellularity in the target organs. Groups were randomized to GBCA treatment versus none. Kidney sections were examined with a Hitachi HT7700 with an AMT 16 megapixel camera and a Jeol JEM 2010F field emission electron microscope at 200 kV with a GATAN Orius camera and Oxford Analytical ISIS energy-dispersive spectrometer (EDS).

Results: GBCA exposure caused significant renal fibrosis and podocyte injury associated with elevations in plasma creatinine and metabolic disorders as evidenced by dyslipidemia. Metabolic analysis of flash-frozen renal cortex demonstrated that GBCA treatment—far from being inert—resulted in glycolytic switching—the Warburg effect—where glycolysis and lactate accumulation increased with suppression of the tricarboxylic acid cycle. In the treated group, the electron-dense deposits riddled the glomeruli and with suppression of the tricarboxylic acid cycle. In the treated group, the electron-dense deposits riddled the glomeruli and

Conclusions: We provide the first evidence that GBCAs cause significant metabolic disorders and kidney injury in mice without pre-existent renal insufficiency. Accumulation vacuoles of proximal tubular cells. By EDS, these contained high quantities of gadolinium acid cycle. In the treated group, the electron-dense deposits riddled the glomeruli and with suppression of the tricarboxylic acid cycle. In the treated group, the electron-dense deposits riddled the glomeruli and

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FR-PO972
CTGF/CCN2 Knockdown Prevents AKI-Induced Cellular Senescence and Subsequent Fibrosis
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Background: Acute kidney injury (AKI) involves damage to the tubular epithelium with subsequent accumulation of senescent cells and can progress to fibrosis and chronic kidney disease (CKD). Cellular senescence is characterized by anti-apoptotic and DNA Damage Response (DDR) features, and expression of a Senescence Associated Secretory Phenotype (SASP). Connective Tissue Growth Factor (CTGF/CCN2) is a constituent of the SASP and has been implicated in fibrosis as well as in (paracrine) senescence induction. Therefore we explored the involvement of CTGF and cellular senescence in two models of AKI and subsequent CKD development.

Methods: We subjected wild type (WT) and conditional tamoxifen inducible CTGF-KO mice (CTGF-eKO) to bilateral ischemia reperfusion injury (IRI) and to folate acid (FA) renal injury and studied damage parameters in relation to anti-apoptotic signaling and cellular senescence in the acute and chronic phase of both models.

Results: In WT mice, both IRI and FA induced AKI resulted in upregulation of DDR and anti-apoptosis markers, including yH2AX, p21 (p21) and the BCL-2 family members BCL-xL and MCL-1. This effect persisted largely in the chronic phase, during which also the expression of p16INK4a together with CTGF and other SASP factors like PAI-1, IL-1β, and IL-6 became markedly upregulated. Furthermore, CTGF expression levels associated with senescence phenotype, including anti-apoptotic BCL-xL and MCL-1 in the acute phase, SASP factors like PAI-1, IL-1β and IL-6 in the chronic phase, and p21 in both phases. CTGF knockdown protected against acute tubular injury and functional decline in the initial phase of both injury models. Furthermore, DDR- and anti-apoptotic marker expression (p21 and MCL-1) were lower in CTGF eKO than in WT mice. Likewise, in both models tubular atrophy, interstitial fibrosis and functional decline in the chronic phase were less severe in CTGF-eKO mice, together with reduced expression of senescence (p21 and MCL-1) and SASP markers (PAI-1, IL-1β and IL-6).

Conclusions: CTGF/CCN2, beyond its known profibrotic role in CKD, is also involved in AKI, possibly by modulating apoptotic and cellular senescence associated pathways. We propose that inhibition of CTGF might be beneficial in AKI and diminish AKI to CKD progression.

FR-PO973
Detection of Urinary MicroRNA Biomarkers Using Diazo Sulfonamide-Modified Screen Printed Carbon Electrodes
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Background: We have established rapid, highly sensitive miRNA quantification techniques for diabetic kidney disease (DKD) and predict graft function following renal transplantation. In parallel we are developing electrochemical quantification methods, and have demonstrated that urinary miRNA detection by glassy carbon electrode-based biosensors is more sensitive than RT-qPCR. Here we describe development of disposable screen printed carbon electrode (SPCE)-based miRNA sensors that can discriminate between urine samples from DKD patients and controls with similar sensitivity.

Methods: Screen-printed SPCEs were modified by deposition of a diazotised naphthalene sulfonic acid derivative, 4-aminom-3-hydroxy-1-naphthalene sulfonic acid (ANSa). The ANSa was then transformed into a sulfonyl chloride, before a 5'-amine-tagged DNA oligonucleotide with complementary sequence to the target miRNA was attached via a sulfonamide linkage to complete the biosensor. Analysis of biosensor output was carried out via reductive and oxidative chronocoulometry, obtained by measuring negative and positive potential sweeps using a ferri/ferrrocyanide electrode, respectively. Selected miRNA readings were compared before and after hybridization in exogenous control miRNA dilution series, and between urine samples from DKD patients and controls.

Results: We demonstrated a linear response for our SPCE sensors across physiologically relevant concentrations of exogenous miR-21, replicating the femtomolar limit of detection from our previous glassy carbon electrode-biosensor studies. Subsequently, our SPCE sensors successfully detected a DKD-associated decrease in miR-192 that we reported previously following RT-qPCR analysis. Using histochemistry and atomic force microscopy analyses throughout the biosensor fabrication process, we observed sequential deposition of sensor components at the electrode surface which demonstrated the desired biosensor composition.

Conclusions: Our disposable electrode-based biosensors have strong potential for use in rapid, highly sensitive miRNA biomarker quantification in urine and other body fluids. In parallel studies we have identified urinary miRNA expression profiles associated with renal pathologies, and are now adapting our technology for clinical testing purposes.

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FR-PO974
Automated Podocyte Foot Process Width Measurement Using Deep Learning
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Background: Increased foot processes (FP) width (FPW) is an important measure of podocyte injury. There is no consensus on how to estimate average FPW. The current gold standard (unbiased stereology) is time consuming and not widely available. We aimed to automate average FPW estimation using deep learning (DL).

Methods: A custom multi-layered deep learning model was trained on a normalized electron-microscopy (EM) dataset of 800 images (augmented 10000+) obtained at ~40000X. Images were captured using systematic uniform random sampling. Testing was done on 29 new kidney biopsies (30-157 images per biopsy) from patients with Fabry disease and variable proteinuria and pathology severity and a compiles set of images from kidney donors as normal controls. DL FPW measurements were compared with measurements done by an experienced technician using unbiased stereology. Measurements were correlated with available clinical and structural parameters.

Results: The automated report utility substantially reduced the time needed for average FPW measurement per biopsy (<1 min DL vs. 6-8 hours human). The DL model accuracy based on human segmentation as the ground truth on a scale of 0-1 (1=perfect) accuracy was 0.8 for glomerular basement membrane and 0.6 for slits. DL measurements (737±151nm) were ~6.5% smaller (p=0.03) than human measurements (788±194nm), but these two were correlated (r=0.77, p=0.0001). Bland-Altman plot showed that ~94% of DL vs. human differences fell within ± 1.96 SD of the differences. Both human and DL showed increased FPW in Fabry patients compared with controls and similar correlations between age and FPW in Fabry patients. Glomerulotaxycembrin inclusion density in podocytes correlated with DL-measured FPW (r=0.33, p=0.04), but human measurements did not. DL-measured FPW showed a trend with urine protein excretion rate (r=0.31, p=0.058), but human measurements did not. DL showed substantial variability in individual FPW in Fabry patients but not in controls.

Conclusions: DL algorithms while substantially reduced time needed for FPW measurement, provided reasonably accurate data correlating with human stereology measurements and with relevant clinical correlations. In addition, DL readily provided additional information on individual FPW variability which may be useful in podocyte injury assessment in secondary podocytopathies. 

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FR-PO975
Loss of Glomerular Thrombomodulin Precedes Diabetic Nephropathy in Diabetic Patients
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Background: Thrombomodulin (TM) is an endothelial transmembrane protein which regulates vascular homeostasis. Previously, it was demonstrated that TM-mediated protein C activation ameliorates glomerular apoptosis and inflammation in a DN mouse model (Nat Med 2007), indicating that diminished TM levels may contribute to DN. Cleavage of TM is a well-established feature of endothelial cell dysfunction, and serum levels of cleaved TM are increased in DN. Here, we investigate TM expression in glomeruli of patients with DN and in a DN mouse model.

Methods: We measured staining of glomerular TM in an autopsy cohort, including 94 DN patients, 57 diabetic patients without DN and 38 healthy controls. Additionally, TM mRNA expression was measured in microdissected glomeruli from renal biopsies of 24 patients with DN and 13 controls. Furthermore, we studied glomerular TM expression in a STZ-induced DN mouse model, including 20 STZ and 10 WT mice, at 5 and 15 weeks after diabetes induction – reflecting acute and chronic DN.

Results: TM expression was 1.7x lower in patients with diabetes compared to non-diabetic controls (p=0.004), but no differences were observed between diabetic patients with and without DN. TM mRNA levels of DN cases were 2.3x higher compared to control cases (p=0.017). In STZ mice, TM expression was 1.2x lower than in WT mice (p=0.001), but no difference in TM expression was observed between acute and chronic DN mice. TM expression correlated negatively with glomerular number of macrophages and TNF-α protein in these mice.

Conclusions: Glomerular TM expression is decreased on protein level, but increased on mRNA level in patients with DN. TM may be cleaved under diabetic conditions, which is compensated by increased production. Furthermore, a loss of TM is associated with increased glomerular inflammation in DN. Interestingly, no differences in TM levels were observed between diabetic patients with and without DN, nor between mice with acute and chronic DN. We speculate that TM loss is an early feature of the diabetic glomerulus, and contributes to glomerular inflammation and DN development. Restoration of TM levels may be a promising treatment to prevent DN in diabetic patients.

FR-PO976
Exploring Origins of Autoimmune Nephritis Using HLA DR+ CD34+ Humanized Immune System Mice
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Background: Autoimmunity causes most glomerulonephritis (GN) and must be controlled to limit nephron destruction. Understanding the origins of the autoimmune response can guide development of targeted intervention. We generated a human immune system (HIS) model to examine interactions of two potent disease susceptibility factors: autoimmune-linked HLA Class II receptor DR4 and inhalation of crystalline silica (Si), an environmental exposure linked to lupus and ANCA vasculitides.

Methods: NOD-scid-gamma mice lacking mouse MHC Class II and transgenic (Tg) for HLA DR4 were infused with T-depleted DR4+ CD34+ human hematopoietic stem cells (HSC) from 1 of 4 cord blood donors. The Tg DR4 is expressed in host thymus to educate human CD4+ T cells, and DR4 is expressed on HSC-derived B cells. 3 mon later mice were exposed by aspiration to Si, vehicle (V), or neither, followed in 0 to 10 wks by adjuvant/PBS or foreign antigen injection. Organs were harvested 4-8.5 mos post-engraftment.

Results: Among 19 surviving engrafted DR4+/mcsTgK/CD34+ mice, mean spleen chipmunk was 72.2±27.7. Low levels of human anti-PR3 Ig were detected in bronchoalveolar lavage fluid (BALF) from 69% (9 of 13) of immunized HIS mice, representing all 4 HIS donors and each exposure group. Low levels of human anti-DNA Ig were detected in BALF of 3 immunized (1 Si/2V) HIS mice, derived from the same Si donor. 2 had lung perivascular infiltrates. Among Si-exposed mice, 5 deteriorated clinically 5-9 wks post-exposure, precluding immunization. All 5 had severe lung injury, including findings typical of chronic silicosis with extensive fibrosis and/or alveolar proteinosis in 4 mice. These 5 Si-exposed HIS mice (derived from 3 HIS donors) with 77%±9% Si-exposed cell culture supernatant Tg anti-DNA & anti-PR3 Ig.

Conclusions: DR4+ CD34+ HISC mice provide a useful translational platform to study susceptibility factors and gene-environment interactions that promote human nephriticin autoreactivity. Our findings suggest that immunization and/or adjuvant, but not exposure, facilitates the induction of human autoimmunity in the context of HLA DR4. Future models can test the impact on autoimmune control of alternative risk alleles, modifiable host factors, and environmental co-exposures.

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FR-PO977
Sex-Dependent Modulation of Systolic Blood Pressure and Glucosuria in Tubule-Specific Heterogeneous Nuclear Ribonucleoprotein F Knockout Mice
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Background: We previously reported that mice with selective tubular deficiency of heterogeneous nuclear ribonucleoprotein F (hnRNPF) exhibit elevated systolic blood pressure (SBP) and glucosuria associated with up-regulation of renal angiotensinogen (Agt) and down-regulation of sodium-glucose co-transporter 2 (SGLT2) (2018 ASN TH-0R073). Here, we compared the impact of sex hormones on glucosuria and expression of Agt and Sgl2 in hnRNPF knockout (KO) mice and control littermates (Crlts).

Methods: HnRNPF F KOs were generated by crossing breeding Psix-Cre mice with floxed F KOs. Female KOs were fed low protein diet (2% of Agt levels) and control males were exposed to either sham-operation or bilateral castration at 12 weeks (wks) of age and followed until 20 wks of age. Female KO mice and Controls underwent either sham-operation or bilateral ovariectomy at the age of 8 wks and followed until the age of 24 wks. Testosterone treatment was unavilable in female KO and Ctrl mice at the age of 8 wks and followed an extra 4 wks. Body weight (BW), SBP, blood glucose (BG), urinary glucose (UG) were monitored. Western blotting and real-time qPCR were used to quantify Agt and Sgl2 expression in renal proximal tubules (RPTs). Human RPTCs (HK-2) x KO of HNRFNP by CRISPR/Cas9 method were also studied.

Results: Both male and female KO mice exhibited elevated SBP and glucosuria with up-regulation of Agt and down-regulation of Sgl2 expression in RPTs as compared to Crlts. However, glucosuria disappeared in male KO mice at 12 wks of age whereas female KO mice maintained persistent glucosuria. Castration restored glucosuria in male KO mice; no change was seen in ovarietomized female mice. Gonadectomy had no effect on UG in Crlts. Testosterone treatment prevented glucosuria in female KO mice. In vitro, HK-2 cells with HNRFNP KO displayed up- and down-regulation of AGT and SGLT2 expression, respectively. Finally, testosterone treatment stimulated GALT2 promoter activity in HK-2 cells but not in HK-2 with HNRFNP KO.

Conclusions: Our results indicate that hnRNPF F may play an important role in the development of hypertension and glucosuria in mice in a sex-dependent manner through modulation of renal Agt and Sgl2 expression, respectively.

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Poster/Friday
Underline represents presenting author.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Intracellular Trafficking Pathway of Albumin in Glomerular Epithelial Cells

Role of Apol1-miR193a Axis in Sox2-Mediated Reprogramming of Differentiated Podocytes

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Background: Enhanced autophagy maintains molecular phenotype in differentiated podocytes. The Sox2 is known to initiate autophagy by repressing Mammalin Target of Rapamycin (mTOR) expression; however, Sox2-induced autophagy induction carries negative feedback on reprogramming of differentiation. Since miR193a suppresses Sox2 expression, it would modulate the Sox2-induced transient autophagy during an early step in reprogramming to pluripotency/differentiation. Because Apol1 inversely regulates miR193a, it would de-repress Sox2 and accelerate autophagy in differentiated podocytes.

Methods: Human podocytes expressing vector, Apol1G0/G1/G2 were differentiated; protein blots were probed for Sox2, Apol1, nephrin, CD2AP, and GAPDH. RNAs were assayed for miR193a and cDNA amplified for Apol1, and Sox2. The silico method was used to analyze motifs on Apol1 and its variants mRNAs. MEME suite for motif identification, JASPARv2010 and STAMP tool for alignment, and database matching for identified motifs were used. 3D models of Apol1 and its variants mRNA segments (with mutations and deletions) were generated. Structural model of Sox2 (template-based method Iasser) docking approach was used to form the Apol1 and its variants RNA. MEME suite for motif identification, JASPARv2010 and STAMP database for motif matching suggested that Sox2 can bind on Apol1.G2 mRNA. The thermodynamic properties of RNA-protein interaction interface suggested that the Apol1.G2 mRNA and Sox2 form a very strong and stable complex with surface area 4433 Å2, solution free energy ΔG = -93.8 kcal/mol and free energy of assembly dissociation (ΔGdiss) 95.6 kcal/mol. The Apol1.G2 mRNA-Sox2 complex has 38 hydrogen bonding interactions.

Results: Differentiated G0-podocytes displayed enhanced Sox2 but decreased expression of miR193a; in contrast, G1- and G2-podocytes showed the opposite outcome. The thermodynamic properties of RNA-protein interaction interface suggested that the Apol1.G2 mRNA and Sox2 form a very strong and stable complex with surface area 4433 Å2, solution free energy ΔG = -93.8 kcal/mol and free energy of assembly dissociation (ΔGdiss) 95.6 kcal/mol. The Apol1.G2 mRNA-Sox2 complex has 38 hydrogen bonding interactions.

Conclusions: The Sox2 binding with Apol1 and its variants mRNA suggests that Sox2 has an RNA binding property. This interaction carries the potential to modulate Apol1-miR193a-induced downstream signaling.

Funding: NIDDK Support

Intracellular Trafficking Pathway of Albumin in Glomerular Epithelial Cells

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Background: Recently, intracellular trafficking pathway of albumin through caveolae in glomerular epithelial cells (podocytes) has been suspected to be activated in podocytes. Albumin entry through caveolae, subsequent transcytosis in cytoplasm and exocytosis.

Methods: Alexa flour 488 labeled bovine serum albumin (AF488-BSA) were incubated with Podocyes for 30, 60, and 120 minutes, and analyzed co-localization with caveolin-1 which is a major structural component of caveolae, clathrin, and FC receptors (FcRn) as endocytosis, with several organelles, such as early endosome, Golgi apparatus (GA), endoplasmic reticulum (ER), lysosome, and proteasome, and with cytotoxicity factors such as microtubules and actin as transcytosis by immunofluorescence analysis (IF). In western blotting (WB) and IF, methyl beta cyclodextrin (MBCD) were preincubated with Podocytes; Alexa flour 488,BSA or human serum albumin (HSA), and the amount of intracellular albumin that was observed in Actin. HAS were incubated with full confluent podocytes on transwells plate with or without MBCD, and concentration of HAS in inside and outside medium between transwells plate were evaluated to analyze exocytosis.

Results: At first, AF488-BSA were colocalized with Cave-1 and FcRn, but not with clathrin. Then AF488-BSA were colocalized with actin cytoskeleton, but not with microtubules, and colocalized with early endosome, lysosome, and proteasome, but not with ER and GA. MBCD treatment significantly decreased the formation of the interface (ΔG) = -93.8 kcal/mol and free energy of assembly dissociation (ΔGdiss) 95.6 kcal/mol. The Apol1.G2 mRNA-Sox2 complex has 38 hydrogen bonding interactions.

Conclusions: In this study, we have shown intracellular trafficking pathway of albumin, and this pathway may be a new etiological hypothesis of urinary albumin excretion.
FR-P0982

Fibrillin 1-Enriched Tissue Microenvironment Plays a Key Role in Mediating Vascular Rarefaction in CKD
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Background: Vascular rarefaction, characterized by reduced capillary density due to the loss of endothelial cells, is a common pathologic feature in a wide variety of CKD. However, how endothelial cells are lost in CKD remains elusive. In this study, we report that Fibrillin-1, an extracellular matrix glycoprotein, plays a critical role in mediating vascular rarefaction after kidney injury.

Methods: Unilateral ureteral obstruction (UOU) and unilateral ischemic-reperfusion (UIRI) were used as models of kidney fibrosis. Decellularized kidney tissue scaffold (KTS) was prepared. The differential expression of KTS proteins was analyzed by mass spectrometry proteomics. The role of fibrillin-1 in endothelial cell survival and proliferation was investigated in vitro. The expression of fibrillin-1 was knocked down by shRNA approach in vivo.

Results: Compared to sham controls, KTS from fibrotic kidney induced human umbilical vein endothelial cells (HUVEC) to undergo apoptosis, characterized by an increased expression of cleaved caspase-3, PARP-1, and p53. KTS from fibrotic kidney also promoted endothelin-1 expression, and inhibited eNOS and cyclin D1 expression in response to mitogen stimulation. Mass spectrometry proteomics analyses identified 414 proteins that were differentially expressed in the KTS of control and fibrotic kidney. Fibrillin-1 was one of the most upregulated. In vitro, recombinant fibrillin-1 protein inhibited HUVEC proliferation and the expression of proliferation-related genes. Fibrillin-1 also induced the expression of Fas, ADD and p53 in HUVEC. Fibrillin-1 expression was markedly upregulated in multiple models of kidney fibrosis. Knockdown of renal fibrillin-1 expression by shRNA approach ameliorated kidney vascular rarefaction and reduced renal fibrosis after UIRI.

Conclusions: These studies demonstrate that fibrillin-1-enriched KTS is a hostile environment for endothelial cells, leading to vascular rarefaction in CKD. Targeted inhibition of fibrillin-1 could be a novel therapeutic strategy for protecting kidney integrity against vascular rarefaction in CKD.

FR-P0983

Spironolactone Ameliorates Endothelial Dysfunction Through Inhibition of the AGE/RAGE Axis in a Chronic Renal Failure Mouse Model
Chiu-Ying Chang,1,2 Ming-Yi Shen,1 Chun-Cheng Wang. 1China Medical University Hospital, Taichung, Taiwan, 2China Medical University, Taichung, Taiwan.

Background: Spironolactone can improve endothelial dysfunction in the setting of heart failure and diabetes models. However, its beneficial effect in the cardiovascular system is not clear in the setting of non-diabetic renal failure. We conducted this study to investigate whether spironolactone can ameliorate endothelial dysfunction in a 5/6 nephrectomy model, and to determine the underlying mechanism.

Methods: Twenty-four Sprague-Dawley rats were divided into four groups. A renal failure model was created using the 5/6 nephrectomy method. A renal failure model was created using the 5/6 nephrectomy method. The groups included: Sham-operation group (Group1), chronic kidney disease (CKD; Group2), CKD + ALT-711 (Group3), and CKD + spironolactone (Group 4; 20 mg/kg/d). We evaluated the effect of spironolactone on kidneys and the expression of proliferation-related genes. Fibrillin-1 also induced the expression of Fas, ADD and p53 in HUVEC. Fibrillin-1 expression was markedly upregulated in multiple models of kidney fibrosis. Knockdown of renal fibrillin-1 expression by shRNA approach ameliorated kidney vascular rarefaction and reduced renal fibrosis after UIRI.

Results: Compared to Group 1, Group 2 has a significantly impaired Ach-mediated vasodilatation responses. Compared with Group 1, Group 2 has a significantly impaired Ach-mediated vasodilatation responses. Compared with Group 1, Group 2 has a significantly impaired Ach-mediated vasodilatation responses. Compared with Group 1, Group 2 has a significantly impaired Ach-mediated vasodilatation responses.

Conclusions: These studies demonstrate that fibrillin-1-enriched KTS is a hostile environment for endothelial cells, leading to vascular rarefaction in CKD. Targeted inhibition of fibrillin-1 could be a novel therapeutic strategy for protecting kidney integrity against vascular rarefaction in CKD.

FR-P0984

Fibroblast p90RSK Induces Epithelial-to-Mesenchymal Transition Through Oxidative Stress-Mediated β-Catenin Pathway
Ling Lin, Kebin Hu. Penn State University College of Medicine, Hershey, PA.

Background: Healthy kidney structure and environment rely on epithelial integrity and interactions between epithelial cells and other kidney cells. p90RSK, a serine/threonine kinase, is recently shown to promote obstruction-induced kidney fibrosis, however, the underlying mechanism remains largely unknown.

Methods: We generated a novel fibroblast-specific p90RSK transgenic mouse (Rsk-Tg) and established a fibroblast-epithelial coculture system using primary kidney fibroblasts from RSK-Tg and RSK-wt mice and human proximal tubular epithelial cells (HKC-8) to investigate the role of p90RSK in fibroblast-epithelial interactions and kidney fibrosis.

Results: It was found that RSK-Tg mouse has similar phenotype as the littermate control (RSK-wt). However, after UUO injury, RSK-Tg mice display significantly increased fibrosis, as demonstrated by renal collagen content and FSP-1 abundance, in comparison with their littermates. We further found that RSK-Tg mice display decreased kidney fibrosis when treated with the no-activation of p90RSK, indicating epithelial-to-mesenchymal transition (EMT), which was also visualized by double fluorescence staining of FSP-1 and lectin. Moreover, it was found, in our in vitro fibroblast-epithelial coculture system, that RSK-Tg fibroblasts consistently produce excessive H2O2 compared to control fibroblasts. Of note, oxidative stress mediated β-catenin nuclear translocation, the blockade of reactive oxygen species (ROS) or β-catenin ablation fibroblast p90RSK-mediated EMT.

Conclusions: Thus, it is clear that fibroblast p90RSK induces EMT through oxidative stress-mediated β-catenin pathway.

Funding: NIDDK Support

FR-P0985

Evaluation of CB1 Receptor Expression in Human Diabetic Kidney Disease and Rodent CKD Models
Li-Jun Ma,1 Matthew M. Rankin,1 Jing Ying Ma,2 Nathaniel H. Wallace,1 Brian Rady,1 Jingjun Li,1 Bindeu Bennett,2 Vinicius S. Carreira,2 Joseph Tam,1 Alessandro Pocai,1 Andrea R. Nawrocki,1 Cardiovascular & Metabolism, Janssen R&D, Johnson & Johnson, Spring House, PA; 2Pathology, Nonclinical Safety, Janssen R & D, Johnson & Johnson, Spring House, PA; 3Obesity and Metabolism Laboratory, Institute for Drug Research, School of Pharmacy, faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel.

Background: Published data suggest that cannabinoid receptor 1 (CB1R) is an attractive target for metabolic complications, including renal fibrosis and diabetic kidney disease (DKD). CB1R protein, detected by immunohistochemistry, was reported to be expressed to low level in normal kidneys from human and rodents, and increased in renal biopsy samples from patients with DKD and fibrotic kidneys in rodents. Elevated expression of CB1R is postulated to be implicated in DKD leading to metabolic derangement, inflammation and fibrosis. We aimed to characterize CB1R protein expression in human DKD and three rodent chronic kidney disease (CKD) models.

Methods: Histological sections of renal biopsy samples from DKD patients and autopsy samples from normal human subjects were analyzed by immunohistochemistry to assess CB1R protein expression. Rodent CKD models included subtotal nephrectomy (STNx, on 129/Sv), unilateral ureteral obstruction (UOO, on C57BL/6) and follic acid nephropathy (FAN, on C57BL/6). Paraffin sections of kidney from normal control and diseased groups from each model (12 weeks after surgery for STNx, 10 days after surgery for UOO, 6 weeks after follic acid injection for FAN) were evaluated. Anti-CB1R polyclonal antibody from ImmunoGenes (Hungary) was used for all immunohistochemistry. Sections from human brain and mouse tissues (brain, kidney) from CB1R wild type (WT) and knockout (KO) were used as positive or negative control.

Results: CB1R protein expression was observed in the presynaptic axons in the human and mouse brains without non-specific background. CB1R labeling was absent in the CB1R KO brain and kidneys. No specific CB1R positive labeling was observed in the normal mouse kidneys, normal human kidneys, or renal biopsy samples from human DKD. Only minimal and focal (less than 5% of total kidney area) CB1R protein expression was observed in tubular epithelial cells in the kidneys from STNx, UUO, and FAN models.

Conclusions: CB1R protein expression was absent from normal and human DKD, and very low and only minimally and focally increased in diseased kidneys from rodent CKD models. These observations suggest challenges for validation of this target in renal fibrosis and diabetic kidney disease.

Funding: Commercial Support - Janssen R&D, Johnson & Johnson

FR-P0986

Melanocortin 1 Receptor (MC1R) Deficiency Exacerbates Glomerular Injury and Proteinuria in the Autologous Phase of Nephrotoxic Serum Nephritis (NTS) Nephritis
Xueqin Guan,1,2 Rong Zhou,1 Lance D. Dworkin,1 Rujun Gong,1 University of Toledo Medical Center, Toledo, OH; 2Yangguang Hospital, Tongji University, Shanghai, China.

Background: The clinical effectiveness of melanocortin therapy with adrenocorticotropic in inducing remission of steroid-resistant nephrotic syndrome points to a steroidal-independent anti-proteinuric activity of melanocortins. However, which melanocortin receptor conveys this beneficial effect is controversial. A growing body of evidence suggests that activation of podocyte MC1R may convey a podocyte protective and anti-proteinuric effect. However, this paradigm seems inconclusive because MC1R agonists were seemingly ineffective in such nephrotic glomerulonephropathies as Adriamycin nephropathy. Moreover, how MC1R signaling is involved in immune-mediated glomerular diseases is unknown.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Deletion of the Non-Canonical NOTCH Ligand DLK1 Promotes an Overactivation of the NOTCH Signaling Pathway and the Th17 Immune Response in the Unilateral Ureteral Obstruction Model

Yuan,1 Lili Zhou,1 Youhua Zhu,1 Jun Liu,2 Yu Yan,3 Bao Dong,4 Gongwei Wang,4 Hongxia Shi,1 Electronic Microscope Lab, Peking University People’s Hospital, Beijing, China; 3School of Information and Communication Engineering, Beijing University of Posts and Telecommunications, Beijing, China; 2Department of Nephrology, Peking university people’s hospital, Beijing, China; 4Department of Pathology, Peking University People’s Hospital, Beijing, China.

Background: Glomeruli extraction from pathologic images is a key step in automatic analysis of renal biopsy. We present a deep learning-based approach for the object extraction of three types of glomeruli with various pathological lesions in multi-stained images.

Methods: Sources of images: 1.1947 glomeruli from images captured at 10x, 20x, and 40x, including 33 pathological types of kidney diseases; 2. 601 glomeruli from 44 whole slide images (WSI) scanned at 40x using Precice 500B scanner (UNIC Technologies Inc, China). Slides were stained with Periodic acid–Schiff (PAS), Periodic acid–silver Methenamine (PASM), and Masson’s trichrome stains. Glomeruli were divided into training and testing sets. Mask R-CNN architecture based on convolutional neural networks (CNN) was trained by using glomeruli training set. The adopted mask R-CNN, which is built by extending Faster R-CNN by adding a branch for predicting an object mask, can detect, classify, and segment three types of glomeruli: 1. glomerulus with basically normal structure (gn), 2.global sclerosis (gs), and 3.glomerulus with other abnormal structure (g) at the same time.

Results: The detection and pixel level segmentation results was graded via average precision, average recall, and F-score (true positives were defined by >50% overlap of the predicted region).

Conclusions: We present a robust network using relatively limited sample size, which can detect normal and abnormal glomeruli stained with PAS, Masson and PASM.

Funding: Clinical Revenue Support

A Deep Learning-Based Approach for Glomeruli Object Extraction from Multistained Renal Biopsy Pathologic Images

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Deep Learning-Based Segmentation of Normal Histologic Kidney Primitives on Whole Slide Images from NEPTUNE Digital Renal Biopsies

Catherine P. Jayapandian, Yijiang Chen, Andrew Janowczyk, Matthew Palmer, Jarcy Zee, Clarissa A. Cassol, Miroslav Sekulic, Jeffrey B. Hodgson, Stephen M. Hewitt, John F. O'Toole, John R. Sedor, Laura Barisoni, Anant Madabhushi, University of Pennsylvania, Philadelphia, PA; Arbor Research Collaborative for Health, Ann Arbor, MI; UH Cleveland Medical Center, Cleveland, OH; Cleveland Clinic, Cleveland, OH; Duke University, Durham, NC; Case Western Reserve University, Cleveland, OH; The Ohio State University, Columbus, OH; The University of Michigan, Ann Arbor, MI; National Cancer Institute, Bethesda, MD; Louis Stokes Cleveland Veterans Affair Medical Center, Cleveland, OH.

Background: The establishment of digital pathology repositories, such as Nephrotic Syndrome Study Network (NEPTUNE), enables large scale analyses of renal biopsies by sophisticated computational imaging approaches and machine-human interactive protocols. Here we evaluate the performance of U-Net deep learning algorithm for identification of normal histologic primitives in whole slide images (WSIs) across multiple stains.

Methods: Eighteen U-Nets were trained to segment: (i) normal glomerular tufts, (ii) normal glomerular unit (tuft + Bowman's space and capsule), (iii) normal proximal tubular segments (PT), (iv) normal distal tubular segments (DT), (v) interstitial capillaries, and (vi) arteries. Regions were extracted from 419 WSIs, including 103 H&E, 112 PAS, 69 Trichrome, 103 Silver, 103 Trichrome) from 125 NEPTUNE digital renal biopsies with a diagnosis of Minimal Change Disease. The renal biopsies were randomly sampled into training, validation and testing sets in the ratio 6:1:3. Five pathologists provided the manual segmentation (ground truth). Detection and segmentation results were evaluated using F-Score, True Positive Rate (TPR), Positive Predictive Value (PPV) and Dice Similarity Coefficient (DSC), respectively.

Results: PAS stained WSIs yielded the best performance for all primitives with F-Score (i) 0.93, (ii) 0.94, (iii) 0.91, (iv) 0.93, (v) 0.93 and (vi) 0.85. PAS stained renal transplant biopsies. Multi-class segmentation performance was assessed by calculating Dice coefficients (DCs) for 10 tissue classes on 10 transplant biopsies from Radboudumc and on 10 transplant biopsies from the Mayo clinic. Additionally, we fully segmented 15 nephrectomy samples and assessed the CNN’s glomerular detection rates. Lastly, CNN-based measures were compared with visually scored histological (Banff) components in 82 transplant biopsies.

Conclusions: This work represents a solid foundation towards enlisting machine learning classifiers to aid large scale tissue quantification efforts. Ongoing effort is devoted to segment abnormal histologic primitives for the development of image-based predictors of disease prognosis.

Funding: NIDDK Support

Deep Learning-Based Histopathological Assessment of Renal Tissue

Meyke Hermens, Mariolijn Den Boer, Thomas de Bel, Jesper Kers, Joris J. Roelofs, Mark D. Stegall, Mariam P. Alexander, Byron H. Smith, Bart Smets, Luuk Hilbrands, Jeroen A. van der Laak, Radboudumc, Nijmegen, Netherlands; Academic Medical Center, Amsterdam, Netherlands; Mayo Clinic, Rochester, MN; Center for Medical Image Science and Visualization, Linköping University, Linköping, Sweden.

Background: Quantitative measures are often used for histopathological assessment of renal tissue. We trained a convolutional neural network (CNN) for multi-class segmentation of digitized periodic acid-Schiff(PAS)-stained renal tissue sections.

Methods: The CNN was trained using annotations of 40 whole-slide images of PAS-stained renal transplant biopsies. Multi-class segmentation performance was assessed by calculating Dice coefficients (DCs) for 10 tissue classes on 10 transplant biopsies from Radboudumc and on 10 transplant biopsies from the Mayo clinic. Additionally, we fully segmented 15 nephrectomy samples and assessed the CNN’s glomerular detection rates. Lastly, CNN-based measures were compared with visually scored histological (Banff) components in 82 transplant biopsies.

Results: The weighted mean DCs were 0.80 and 0.84 in 10 transplant biopsies from Radboudumc and the Mayo Clinic, respectively. The ‘glomeruli’ class was best segmented in both data sets (DC 0.93 and 0.94), followed by ‘tubuli combined’ and ‘interstitium’. An example of the CNN’s visual output is shown in Figure 1. The CNN detected 92.7% of all glomeruli in nephrectomy samples, with 10.4% false positives. In whole transplant biopsies, the mean intraclass correlation coefficient for glomerular counting performed by pathologists and the CNN was 0.94. Moderate to strong correlations were observed between the CNN’s visual output and the pathologists’ scores (Table 1).

Conclusions: This study presents the first CNN for multi-class segmentation of PAS-stained nephrectomy samples and transplant biopsies. Our CNN can be of aid for quantitative studies concerning renal histopathology across centers and provides opportunities for deep learning applications in routine diagnostics.

Funding: Government Support - Non-U.S.

Figure 1. CNN segmentation result of a PAS-stained renal transplant biopsy.
Deep Learning-Based Segmentation Enables an Efficient Assessment of Glomerulosclerosis That Is Predictive of Progressive Kidney Disease
Matthew Palmer,1 Catherine P. Jayapandian,2 Jarcy Zee,3 Miroslav Sekulic,3 Clarissa A. Cassol,4 Andrew D. Rule,1 Andrew Janowczyk,2 Yijiang Chen,2 John R. Sedor,3 Stephen M. Hewitt,9 Anant Madabushi,9 Laura Barisoni,2 1University of Pennsylvania, Philadelphia, PA; 2Case Western Reserve University, Cleveland, OH; 3Arbor Research Collaborative for Health, Ann Arbor, MI; 4Mayo Clinic, Rochester, MN; 5UH Cleveland Medical Center, Cleveland, OH; 6The Ohio State University, Columbus, OH; 7Duke University, Durham, NC; 8Cleveland Clinic, Cleveland, OH; 9National Cancer Institute, Bethesda, MD

Background: The percentage of globally sclerotic glomeruli (GSG) adjusted by age is a clinically relevant parameter that has been shown to be associated with outcome across diseases. While annotation of glomeruli on whole slide images (WSI) using the NEPTUNE Digital Pathology Protocol has improved overall accuracy, manual counting remains time consuming. The aim of this study is to develop deep learning (DL) networks for automated annotation of GSG and test whether the DL-generated % GSG associates with clinical outcome.

Methods: 126 WSI (PAS) from 107 minimal change and 19 FSGS patients from the NEPTUNE, train and test a DL network to identify normal glomeruli and GSG. The %GSG was calculated on 1 level and compared with %GSG visually assessed on the same level by 1 of 4 pathologists. Outcome data (ESRD or 40% eGFR decline) were available in 125 cases. Cases were divided into 3 groups: no GSG (95), GSG appropriate for age (14), and GSG excessive for age (16). Hazard ratios for clinical outcomes were compared across the 3 groups.

Results: The DL classifier’s sensitivity as compared with visual assessment for detecting non-GSG was 0.85 and for GSG was 0.75. Compared with no GSG, GSG normal for age is a clinically relevant parameter that has been shown to be associated with outcome across diseases. Glomerular volume (4.1 vs. 3.6 - 10^3 µm^3, p=0.04), decreased podocyte density (106.4 vs. 129.3 - podocytes/10^6 µm^3, p=0.001), and increased podocyte volume (4885 vs 4100 - µm^3, p=0.005). For low frequency GSG lesions (<1% of glomeruli), a kidney biopsy could miss a FSGS diagnosis more than 60% of the time.

Conclusions: Quantitative and qualitative morphometric analysis of nephrectomy specimens identify low frequency GSG lesions. Kidney biopsy can frequently miss an FSGS diagnosis if there is a low frequency of GSG lesions. Future directions involve examining the possibility of using computer aided-quantitative morphometry in order to impute the existence of rare glomerular features unlikely to be captured during routine biopsy.

Funding: NIDDK Support

FR-P0994
Classification of Cell Types with Neural Networks in Reference and Diseased Human and Mouse Kidney Tissue Using Nuclear Morphology
Andre Woloshuk,2 Dawson F. Dean,1 Andrew Mcnutt,1 Michael T. Eadon,2 Pierre C. Dagher,1 Seth Winfree,2 Tarek M. El-Achkar,1 Indiana University, Indianapolis, IN; 1Indiana University School of Medicine, Indianapolis, IN; 2Indiana University Division of Nephrology, Indianapolis, IN.

Background: Despite improvements in non-invasive analysis of kidney function, kidney biopsy remains the gold standard for diagnosing renal pathology. This field relies heavily on subjective interpretation and semi-quantitative image analysis of 2-dimensional (2D) images of stained tissue thin-sections. Advances in 3D confocal fluorescence imaging and machine learning approaches such as neural networks provide the opportunity for an automated and quantitative approach, and the potential for extracting new data from the 3-dimensional (3D) space. Neural networks have wide applications in image classification of multi-omics and medical imaging. Recent applications of neural networks in pathology are starting to explore segmentation and classification of histologically stained samples. The same approach has not been fully exploited in kidney tissue labeled with multiple fluorescent probes and imaged in 3D.

Methods: We identify individual cells in human and mouse kidney tissue and assigning each cell a ground truth classification based on validated cell markers. Images of the nuclei as 2D projections and 3D volumes from tissue are extracted and classified based on these markers using volumetric tissue exploration and analysis cytometry. Different neural network architectures are trained and evaluated using this image database. The efficacy of different architectures is assessed by their ability to distinguish different cell types within the biopsy.

Results: In this work, we create an image database of fluorescently stained nuclei collected from human and mouse renal tissue that can be used to identify and classify different cell types solely on their nuclear features. Furthermore, we begin to demonstrate the efficacy of identifying pathologies in either a mouse model of acute kidney injury or in human diabetes.

Conclusions: This work lays the groundwork for quantifying the types of cells present in biopsies, and the automatic classification of pathological cell states in a biopsy that may have otherwise gone unnoticed. Ultimately, machine learning-augmented image analysis has the potential not only to describe novel and distinct disease features, but also define a standardized approach to quantifying pathology in a kidney biopsy.

Funding: NIDDK Support

FR-P0995
Unsupervised Machine-Learning Cytometry of High-Dimensional Image Data from Fluorescently Labeled Mesoscale Kidney Tissue Automates Classification and Uncovers Unique Cellular Populations
Seth Winfree,7 Andrew Mcnutt,1 Michael J. Ferkowicz,2 Tarek M. El-Achkar,1 1Indiana University, Indianapolis, IN; 2Indiana University School of Medicine, Indianapolis, IN.

Background: The cytometric analysis of fluorescent mesoscale kidney imaging datasets presents unique challenges in segmentation, measurement and analysis. To address these challenges, we developed the tissue cytometry tool, Volumetric Tissue Exploration and Analysis (VTEA). VTEA leverages a novel nuclei segmentation, measurement and enables flow cytometry-like analysis in mesoscale 3D images of kidney tissue. However, as we add 1) additional fluorescent markers with novel imaging modalities and 2) imaging metrics, including texture and spatial characteristics, flow cytometry-like approaches become inadequate under the strain of these higher dimensional data. Here our goal was to implement and demonstrate the need and utility of unsupervised analysis of higher dimensional tissue cytometry data.

Methods: Imaging datasets were collected from fluorescently labeled mouse and human kidney tissue with confocal fluorescence microscopy and up to 8 independent

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Table 1. Mean Spearman’s p for visually scored (Banfi) components and CNN-based measures in 82 transplant biopsies.

<table>
<thead>
<tr>
<th>Quality</th>
<th>CNI</th>
<th>interstitial area</th>
<th>sc score</th>
<th>bi score</th>
<th>IFSA grade</th>
<th>ct score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.81</td>
<td>0.55</td>
<td>0.71</td>
<td>0.23</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Excessive</td>
<td>0.62</td>
<td>0.62</td>
<td>0.58</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0.88</td>
<td>0.55</td>
<td>0.71</td>
<td>0.23</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.62</td>
<td>0.62</td>
<td>0.58</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0.88</td>
<td>0.55</td>
<td>0.71</td>
<td>0.23</td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Very Severe</td>
<td>0.62</td>
<td>0.62</td>
<td>0.58</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
fluorphores. Image processing and analysis was performed with the recent version of VTEA that incorporates Java based libraries for clustering of datasets (e.g. K-mean, Gaussian-mixtures) and dimensionality reduction tools (e.g. PCA and tSNEs).

**Results:** We extended our cytometry tool, VTEA, incorporating unsupervised machine learning approaches with publicly available Java libraries. Using clustering, we identify cellular populations of cell not readily identified with manual gating. The mapping of high dimensional cytometry data to lower dimensions facilitates rapid visual identification of cell sub-population not readily apparent. Lastly, we demonstrate the need and utility for high dimensional analysis of mesoscale kidney imaging data and suggests we gain insight with the application of unsupervised machine learning approaches to image analytics, especially in the framework of the interactive exploratory platform VTEA. Lastly, our work underlines the importance of reusable software and the power of an open software community found in the NIH supported ImageJ community.

**Funding:** NIDDK Support

**FR-PO996**

**Gene-Environment Interactions Modulate Anti-DNA and Anti-Myeloperoxidase. Autoimmunity in Lupus**

**Laetitia Fec,1,2 Jeffrey R. Ord,1 Amy G. Clark,1 Anastasiya Birukova,1 Robert M. Tighe,1 Mary H. Foster.1,3 Duke University School of Medicine, Durham, NC; 1VAMC, Durham, NC.

**Background:** Autoantibody (autoAb)-mediated glomerulonephritis develops in 60-85% of patients with lupus and ANCA vasculitis. Neprhen preservation requires control of the autoimmunity response. To better understand factors driving autoimmunity, we used a mouse model system to study interaction of lupus genetic susceptibility and inhalation of crystalline silica (Si), an environmental exposure linked to human lupus. Previously we showed that Si induces lung injury, lymphoid aggregates, and autoAb in mice of genetically diverse backgrounds. Herein we report strain differences in Si-induced autoAb specificity, production site, and co-exposure requirements.

**Methods:** Wildtype (WT) and autoAb transgenic (Tg) B6, BXSB, MRL, and NZB mice were exposed to Si (Si+) or vehicle (V+) by aspiration; tissues were harvested for immunophenotyping 1 to 3 months later.

**Results:** Among WT lupus mice exposed to Si, anti-DNA IgG levels are significantly higher in bronchoalveolar lavage fluid (BALF) from Si+ MRL compared to other Si+ strains (mean OD405 1.35 vs 0.07, 0.49, & 0.36 for B6, BXSB & NZB, p<0.05). TLR7/TLR9 ligands induce significantly more anti-DNA IgG from cultured lung cells of Si+ vs V+ MRL (OD405 0.49±0.43 vs 0.11±0.21, n=6-9/group, p<0.05), and vs lung cells of Si+ B6 and Si+ NZB (OD405 0.02±0.02 & 0.01±0.01). Anti-myeloperoxidase (MPO) IgG are detected only in BALF of Si+ BXSB, and are not found in BALF from V+ BXSB (p=0.05, n=7-8/group) or from Si+ B6, MRL, & NZB. To probe the in vivo fate of autoAb producing lymphocytes after Si exposure, we studied mice of each strain expressing an autoAb Tg. Results suggest that central deletion and anergy are intact: mean spleen B cell sub-population not readily apparent. Lastly, we demonstrate the advantage of looking at the imaging data with both dimensionality reduction and clustering-an approach that has been exploited by the omics fields.

**Conclusions:** Our work demonstrates the need and utility for high dimensional analysis of mesoscale kidney imaging data and suggests we gain insight with the application of unsupervised machine learning approaches to image analytics, especially in the framework of the interactive exploratory platform VTEA. Lastly, our work underlines the importance of reusable software and the power of an open software community found in the NIH supported ImageJ community.

**Funding:** Other NIH Support - NIEHS, Veterans Affairs Support

**FR-PO997**

**Imaging Renal Inflammation and Fibrosis After Ischemia-Reperfusion Injury by Novel Diffusion MRI**

**Chun-Fu Lai,1 Hsin-Chieh Yang,2 Sheng-Kwei Song,2 Tsen-Hsuan Lin.2 Renal Division, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; 2Radiology, Washington University in St. Louis, St. Louis, MO; 1Biomedical Engineering, Washington University in St. Louis, St. Louis, MO.

**Background:** Conventional MRI provides noninvasive assessment for disease progression but lacks the pathological specificity. Previously, we successfully developed diffusion basis spectrum imaging (DBSI) to assess coexisting axial injury, demyelination, and inflammation. This study aims to test whether DBSI can noninvasively detect kidney pathologies after ischemia reperfusion injury (IRI).

**Methods:** Six 10-week-old female C57BL/6 mice received unilateral left kidney IRI for 30 minutes. Mice were euthanized and perfusion fixed with 4% PFA at 4-7 days after surgery. IRI and contralateral control (CT) kidneys were harvested for ex vivo DBSI scans. The DBSI scan was performed on a 4.7-T scanner: TR = 1.5 s, TE = 33 ms, maximal b-value = 1,500 s/mm², image slice thickness = 0.5 mm, in-plane resolution = 156 x 156 µm². DBSI-assessed restricted (putative cellularity), hindered (putative cytotoxic edema) and fiber (putative interstitial fibrosis) were derived using a novel lab-developed software. H&E and Masson’s trichrome (MT) stains were performed to validate DBSI findings.

**Results:** Representative T2W and MT images demonstrated obvious tubular injury, interstitial edema, inflammation (b) and fibrosis (c). The region of interest (ROI) were defined on T2W anatomy image (D). The corresponding DBSI metrics suggested significant increased cellularity (higher restricted fraction, E) and reduced interstitial space (reduced hindered fraction, F) in outer medulla. More anisotropic fiber fraction in outer stripes of outer medulla of IRI group (G) indicated increased fibrosis at that region.

**Conclusions:** DBSI MRI could detect coexisting pathologies in kidneys after injury. It has potential to noninvasively follow kidney disease progress, monitor treatment efficacy, and translate to clinical application.

**Funding:** Other NIH Support - National Institute of Health R01-N047592, P01-NS059560, U01-EY025500, Other U.S. Government Support, Private Foundation Support

**FR-PO998**

**The Solute Carrier SLC16A12 Is Critical for Creatine and Guanidinoacetate Handling in the Kidney**

**Sofia N. Verouli,1,2 Delphine Lambert,1,2 Escher Genevieve,1,2 Bruno Vogt,1,2 Daniel G. Fuster.1,2 Department of Biomedical Research, University of Bern, Bern, Switzerland; 2Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, Bern, Switzerland.

**Background:** A heterozygous mutation (c.643CA; p.Q215X) in the creatine transporter SLC16A12 was proposed to cause a syndrome with juvenile cataracts, microcornea and glucosuria in one Swiss family. However, we previously discovered a digenic syndrome in the index family and demonstrated that the glucosuria was due to a concomitant SCL5A2 mutation. In localization studies, we found SLC16A12 expression at the basolateral membrane of proximal tubular cells (PCT), and patients with the heterozygous SLC16A12 mutation displayed significantly reduced plasma levels and increased fractional excretion rates of guanidinoacetate (GAA).

**Methods:** To further explore the role of SLC16A12 in renal physiology and decipher the mechanism underlying the heterozygous SLC16A12 mutation in humans, we studied SLC16A12 deficient mice.

**Results:** SLC16A12 KO rats had lower plasma levels and increased 24 h urinary excretion rates of creatine and GAA compared to WT littersmates. SLC16A12 KO rats also displayed lower plasma creatine levels, but urinary creatine excretion rates were reduced in parallel compared to WT rats. The phenotype of heterozygous rats was indistinguishable from WT rats. Metabolic cage experiments revealed no additional signs of tubular dysfunction in SLC16A12 KO rats. In addition, glucosuria, filtration rate, and measured by FITC-sinistrin, was unaltered in SLC16A12 KO rats. Selective renal artery and vein sampling showed similar A-V differences in GAA concentrations between WT and SLC16A12 KO rats, indicating incomplete compensation of urinary GAA losses by renal synthesis in SLC16A12 KO rats. In support of this finding, mRNA expression of L-arginine/glycine amidotransferase (AGAT), the rate limiting enzyme in GAA synthesis, was significantly reduced in kidneys of SLC16A12 KO rats.

**Conclusions:** Our results reveal that SLC16A12 is critical for tubular reabsorption of creatine and its precursor GAA from the glomerular filtrate. In the absence of SLC16A12, ongoing urinary losses of GAA are not adequately compensated by increased intrarenal synthesis, possibly caused by AGAT feedback inhibition due to impaired basalolar exit of creatine from the PCT. Furthermore, the lack of a phenotype in SLC16A12 heterozygous rats suggests a dominant-negative mechanism underlying the phenotype observed in humans with heterozygous c.643CA; p.Q215X SLC16A12 mutation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Tubulal epithelial cell-derived exosomal miRNA-19b-3p promotes M1 macrophage activation in kidney injury
Ye Feng, Zhongda Hospital, Southeast university, Nanjing, China.

Background: Tubulointerstitial inflammation is a common characteristic for acute and chronic kidney injury. However, the mechanism by which the initial injury on tubular epithelial cells (TECs) drives interstitial inflammation remains unclear. Here we set out to characterize the miRNA profile of kidney exosomes and aim to explore the role of exosomal miRNAs derived from TECs in the development of tubulointerstitial inflammation.

Methods: Exosomes were isolated from kidney and characterized via electron microscopy (EM) and nanoparticle analysis (NTA). We examined profiles of miRNAs in kidney exosomes from LPS-induced kidney injury model by Exiqon microarray. Positive targets of miRNA were predicted by TargetScan. Chronic proteinuric kidney disease model was induced by adriamycin (ADR) injection. Exosomes purified from TECs were added to multiple nephrons or intrarenal injected to mice to determine its effects both in vitro and in vivo.

Results: Serum creatinine and urine albumin to creatinine ratios were significantly increased in LPS-treated mice compared with controls. Histologically, the tubular epithelial cell injury, protein cast and CD68+ macrophage infiltration in TEC-derived exosomes compared with controls. Similar results were found in ADR-induced chronic proteinuric kidney disease model in which exosomal miR-19b-3p was markedly released. Importantly, once released, TEC-derived exosomal miR-19b-3p was internalized by macrophages, leading to M1 phenotype polarization through targeting NF-kB/ SOCS1. Importantly, the pathogenic role of exosomal miR-19b-3p in initiating renal inflammation was revealed by the ability of adoptive transfer of purified TEC-derived exosomes to cause tubulointerstitial inflammation in mice, which was reversed by inhibition of miR-19b-3p. Clinically, high levels of miR-19b-3p were found in urinary exosomes and correlated with the severity of tubulointerstitial inflammation in patients with diabetic nephropathy.

Conclusions: Exosomal miR-19b-3p/SOCS1 axis played a critical pathologic role in tubulointerstitial inflammation that might represent a new therapeutic target for kidney disease.

Impact of Nephron Number on Renal Uric Acid Excretion in Patients with IgA Nephropathy
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Background: Hyperuricemia is a risk factor for the progression of chronic kidney disease (CKD), which is characterized by a progressive loss of functioning nephrons. Uric acid (UA) induces renal tubular cell injury. To date, renal UA handling has not been examined in relation to nephron number in patients with CKD due to technical difficulties in counting nephrons in a clinical setting.

Methods: The relation between parameters related to UA handling and clinically relevant factors, including total nephron number, were examined in patients with biopsy-proven IgA nephropathy (IgAN). The total nephron number was estimated by the combined use of unenhanced computed tomography and stereology-based estimation of non-sclerotic glomerular density on renal biopsy (Sasaki T et al. 2018, ASN).

Methods: A total of 107 cases (age 43, male 54%, estimated glomerular filtration rate 61.5 ± 24.2 ml/min/1.73 m², urinary protein excretion 1.4 ± 1.6 g/day) were included. The frequencies of the Oxford classifications were as follows: M (0, 51%; 1, 49%), E (0, 88%; 1, 12%), S (0, 10%; 1, 90%), T (0, 74%; 1, 20%; 2, 6%) and C (0, 64%; 1, 36%), respectively. The frequencies of the Japanese histological grades were as follows: H-I, 56.1%; H-II, 28.0%; H-III, 13.1%; and H-IV, 2.8%. Among all patients, the total nephron number ranged from 78,000 to 1,980,000. Total nephron number was significantly associated with the S score (p < 0.0042) and the T score (p < 0.001), but was not associated with the M, E and C scores of the Oxford classification. Moreover, total nephron number significantly decreased in parallel with increasing Japanese histological grade (p < 0.001).

Conclusions: Multivariate analyses showed that the associations between total nephron number and the S score or T score were independent of age, amount of urinary protein excretion, and renal function at the time of biopsy.

ChromA-ExM: A New Application of Expansion Microscopy for Optical Imaging of Chromatin Architecture in Renal Tubular Epithelial Cells with Nanoscale Resolution
Kirosol Soliman, Nicole D. Santos, Maria F. Sobral reyes, Joel O. Hernández ramos, Dario R. Lemos.

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Background: In the eukaryotic cell nucleus, chromatin is physically organized into euchromatin and heterochromatin domains. Those domains regulate transcriptional accessibility to DNA, ultimately determining cell phenotype and function. Currently, high-resolution visualization of chromatin domain architecture can be achieved only with either electron microscopy or super-resolution microscopy. Both techniques have practical limitations, a major one being that they are not easily accessible to most laboratories. Here we introduce a modification to the original Expansion Microscopy (ExM) protocol developed at MIT that allows nanoscale resolution for visualization of high-order chromatin structures using regular confocal microscopes. The new procedure is called ChromA-ExM and involves the use of selective enzymatic digestion with DNases allowing further expansion of chromatin domains.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Analysis of H3K9me3 chromatin domains in kidney pTECs indicated that, compared to renal cortical ExM, protocol results in increased visualization of high-order chromatin domains, including chromocenters associated with active cell phenotype, and senescence associated heterochromatin foci. Further, we can interrogate spatial interactions between H3K9me3 (silent chromatin) and H3K4me3 (open chromatin) across kidney tubular epithelial cells with exquisite detail, to detect architectural chromatin arrangements associated with kidney disease.

Conclusions: Chroma-ExM is a new tool to study chromatin spatial configuration and chromatin status. The technique is useful for ultrastructural analysis of chromatin changes in PTEC senescence and tubular pathologies.

Funding: Other NIH Support - NIH-NIDDK, 5 R21 AG058159-02

FR-PO1003

Deletion of Proximal Tubular Cell VEGF Production Promotes Renal Fibrosis: Implications for VEGF-Based Cancer Therapy

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Background: Targeting tumor angiogenesis by blocking VEGF (vascular endothelial growth factor) inhibits tumor development and growth, and is a common strategy in cancer therapeutics. Human and animal observations have shown that subtle changes in VEGF levels can result in hypertension, proteinuria, and glomerulopathies. VEGF deletion in all renal tubal epithelial cells has been reported to disrupt peritubular microvascularization. Since proximal tubular (PT) cells are arguably the primary target cells during kidney injury, we hypothesized that loss of PT-VEGF production might provoke the development of renal disease following injury.

Methods: We crossed GGT-Cre+ mice with VEGFf/f to generate PT-specific VEGF knockout (GGT-Cre+/VEGFf/f) and control (GGT-Cre-;VEGFf/f) mice. Mice were challenged with unilateral ureteral obstruction (UUO) kidney injury model. We monitored renal function, histopathological changes, and renal fibrosis in these animals.

Results: Increased tubular damage and interstitial fibrosis was observed in the PT-VEGF KO group compared to the control group. While there were no differences in peritubular capillary distribution in non-injured animals, segmental loss of peritubular capillaries with increased hypoxic areas was detected by carbonic anhydrase IX (hypoxia marker) staining in the PT-VEGF KO group. Furthermore, increased myofibroblasts were also observed in these animals.

Conclusions: PT-VEGF is necessary for the maintenance of the peritubular capillary network following kidney injury; preventing hypoxia, subsequent myofibroblast recruitment, and indirectly limiting renal fibrosis. Cancer patients are at high risk for developing acute kidney injury, and those on pharmacological inhibition of VEGF are developing acute kidney injury, and those on pharmacological inhibition of VEGF are more vulnerable. These two factors alone warrant increased attention and diligence.

FR-PO1004

Jade-1 in Double-Strand Break Repair in Kidney Cancer

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Background: Like many solid tumors, kidney cancer is characterized by chromosomal breaks and instability, which arise from defects in DNA double-strand break (DSB) repair. We have established that Jade-1 is a renal tumor suppressor that induces apoptosis, inhibits proliferation, and inhibits oncoproteins Akt and β-catenin. Jade-1 also functions on DNA, through gene transcription, histone acetylation and DNA replication. As an unbiased approach to identify new Jade-1 tumor suppressor functions, Jade-1 was immunoprecipitated with Flag antibody in kidney cells to discover novel interactors via mass spectrometry. Surprisingly, many DNA repair proteins were found associated with Jade-1, including those involved in DSB repair, such as DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and Ku70 and Ku80.

Results: Myeloma kidney and cancer cell lines were treated with a variety of agents that induce DSBs, including necrostatin (NCS), a radiomimetic agent that induces DSBs. Immunofluorescence (IF) studies were done to visualize Jade-1 and DNA damage indicator γH2AX. Additionally, sensitivity assays were performed to assess for Jade-1 dose-independent survival differences in kidney proximal tubule-derived HK-2 cells, which serve as a model of renal cancer precursor cells.

Results: Interaction of endogenous Jade-1 and DNA-PKcs was confirmed in coimmunoprecipitations. Jade-1 was found to be inducible in kidney and kidney cancer cells in response to DSBs. IF studies demonstrated colocalization of Jade-1, γH2AX, and phospho-DNA-PKcs following DNA damage. Moreover, silencing of Jade-1 in HK-2 cells offered protection against DNA damage in cell survival assays, supporting a direct role for Jade-1 in the DNA repair process.

Conclusions: We hypothesize that Jade-1 directly promotes DSB repair in part by binding and regulating DNA-PKcs, thereby favoring homologous recombination over error-prone repair through non-homologous end-joining. Our findings indicate that Jade-1 helps maintain genomic stability and further underscore its importance as a renal tumor suppressor. In short, understanding the molecular underpinnings of DNA repair may be critical for developing strategies for deterring progression of renal cancer and other solid tumors as well.

FR-PO1005

The Role of the Inflammatory Chemokine CCL20 in Renal Injury in Multiple Myeloma

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Background: The pathogenesis of the occurrence and development of renal injury in myeloma is unclear. In this study we investigate the role of inflammatory chemokine CCL20 in multiple myeloma with kidney injury.

Methods: To detect the expression of CCL20 in renal tissue and bone marrow of multiple myeloma patients with kidney damage by Immunohistochemical technique. Using flow cytometry to analysis proliferation of myeloma cells with overexpression or lowexpression of CCL20. By qRT PCR and flow cytometry method to detect expression of myeloma cells infiltrating organize related receptor CXCR4 and ROBO4 with overexpression or knockdown CCL20. Establish myeloma cells transplantation model. Various imaging techniques were used to observe myeloma cells implanted into the bone marrow and kidney tissue. By flow cytometry, to analysis the graft rate(%) of myeloma cells and expression of CXCR4 and ROBO4 in bone marrow cell population and renal tissue on mice with overexpression or knockdown CCL20. Morbidity and survival situation were dynamically observed for mice with overexpression or knockdown CCL20.

Results: The expression of CCL20 in myeloma and renal tissue was obviously higher than control group, and found that the myeloma cells with strong invasion ability had higher expression of CCL20 that suggested CCL20 were related with myeloma invasion ability. Jak3 is a critical kinase in myeloma cells for CCL20 expression. Treatment of Jak3 inhibitor significantly reduced the phosphorylation of CCL20 expression in myeloma cells. The CCL20 promoted the expression of CXCR4 and ROBO4 of myeloma cell. We had established established myeloma cells with Jak3 inhibitor treatment model. After transplantsing myeloma cells with knockdown CCL20 to immunodeficiency mice, myeloma cells badly survived and slightly damaged kidney. After transplantsing overexpression of CCL20 myeloma cells to immunodeficiency mice, myeloma cell could survival well and damaged myeloma in myeloma mice.

Conclusions: CCL20 plays an important role in the occurrence and development of renal injury in myeloma. Antagonistic CCL20 might be a new target for the prevention and treatment renal injury in myeloma.

Funding: Government Support - Non-U.S.
FR-PO1007
Light Chain Endocytosis in Renal Proximal Tubular Cells Lead to Impaired Autophagy and Mitophagy
Avital Angel-Korman,1 Brian Spencer,2 Chiaeneem Igwubelu,3 Tatiana Prokueva,4 Zhiyong Wang,1 Steven C. Borkan,3 Lawrenne H. Connors,2 Andrea Havasi.1 Boston Medical Center, Boston, MA; 2Amyloidosis Center; 3Boston University School of Medicine, Boston, MA; 4Boston University, Boston, MA; 3Boston University Medical Center, Boston, MA.

Background: AL amyloidosis is the result of clonal production of amyloidogenic immunoglobulin light chain (LC) proteins, often resulting in renal failure. Although amyloid fibril deposition of LC proteins is a major cause of renal damage in AL amyloidosis, amyloid precursor proteins might also directly impair renal tubular function at the cellular level, independent of fibril formation. Light chains are actively reabsorbed in the proximal tubular epithelial cells (PTECs) by endocytosis and degraded in lysosomes. Lysosomes are also essential for functional autophagy, a process responsible for the removal of damaged mitochondria (mitophagy) and denatured proteins. We hypothesize that LC endocytosis causes PTEC injury by inhibiting autophagy, including mitophagy, resulting in accumulation of dysfunctional mitochondria, that mediates PTEC injury.

Methods: Cultured primary PTECs extracted from kidneys of Balb/C mice were exposed in vitro to 6 different LCs purified from patients’ urine. Light chains were derived either from AL amyloid patients with associated nephropathy or from a non-amyloid myeloma patient, as control. Autophagic flux was estimated by immunoblot using the autophagy marker LC3-II, in both bafilomycin treated and untreated cells. Autophagosomes were quantified in live cells using fluorescence microscopy as well as a microscope reader. Mitochondrial respiration and reactive oxygen species production were measured in live cells. Mitochondrial morphology was also assessed using confocal microscopy.

Results: Patient derived LCs caused autophagy inhibition at various levels. Amyloid LC exposed cells accumulated damaged mitochondria with altered mitochondrial function, and they showed increased ROS production.

Conclusions: Dysfunctional autophagy and mitophagy caused by direct cellular toxicity of LCs likely contribute to tubular cell toxicity in AL amyloidosis.

Funding: NIDDK Support, Private Foundation Support

FR-PO1008
Repurposing Tolvaptan, a Drug for Polycystic Kidney Disease, for Renal Cell Carcinoma Therapy
Nidhi Dwivedi, Sonali Sinha, Abeda Jamadar, James P. Calvet, Reena Rao. University of Kansas Medical Center, Kansas City, KS.

Background: The vasopressin type-2 receptor (V2R) plays an essential role in the regulation of salt and water homeostasis by the kidneys. Based on a serendipitous finding that V2R is ectopically expressed in human clear cell renal cell carcinoma (ccRCC) tumors, the current studies examined if V2R plays a pathogenic role in ccRCC tumor growth. The effect of Tolvaptan, an FDA approved drug for hyponatremia and polycystic kidney disease was also tested.

Methods: V2R expression was examined using the cancer genome atlas database, and analysis of human RCC tumor tissue microarrays, cDNA arrays and tumor biopsy samples. In vitro and in vivo mouse tumor xenograft studies were performed to determine V2R expression and activity, suggested by high intracellular cAMP and phosphorylated ERK1/2 (pERK1/2), levels were detected in human ccRCC tumors. The V2R antagonists OPC31260 and Tolvaptan, as well as V2R gene silencing and knockdown, reduced in vitro clonogenicity, wound closure and cell viability of 786-O and Caki-1 human ccRCC cell lines. V2R antagonists reduced pERK1/2 levels, while V2R agonist increased cAMP and pERK1/2 levels. Tolvaptan and OPC31260 also decreased RCC tumor growth in cell lines. V2R antagonists reduced pERK1/2 levels, while V2R agonist increased cAMP clonogenicity, wound closure and cell viability of 786-O and Caki-1 human ccRCC cells. Tolvaptan and OPC31260 also decreased RCC tumor growth in cell lines. V2R antagonists reduced pERK1/2 levels, while V2R agonist increased cAMP

Results: These results provide novel evidence for the pathogenic role of V2R signaling in ccRCC and suggest that V2R antagonists, including the FDA approved drug Tolvaptan, could be utilized as novel therapeutics for ccRCC.

Funding: NIDDK Support

FR-PO1009
TIMAP Drives Tumor Angiogenesis

Background: TIMAP (TGFβ-inhibited membrane associated protein) is an endothelial cell (EC)-predominant inhibitor of myosin phosphatase, which we first identified in glomerular endothelial cells. It is abundant in EC of developing, but not mature kidneys. Glomerular EC proliferation and sprouting angiogenesis in vivo require TIMAP. This study utilized the murine breast cancer model to determine whether in vivo angiogenesis also requires TIMAP.

Methods: Mouse mammary adenocarcinoma cells (E0771, syngeneic for C57BL/6 mice) were injected into mammary glands of 5 pairs of 8-week-old female TIMAP+/+ and TIMAP−/− mice (C57BL/6 background). Each pair was euthanized on the day the tumor diameter, determined by externally applied calipers, in one mouse of the pair exceeded 1.5 cm. The tumors were excised, their weight and mean diameter measured. Vascular density was quantified using fluorescence microscopy for the EC marker PECAM1.

Results: Tumor size was similar in TIMAP+/+ and TIMAP−/− mice through day 8-10. In 4 of 5 TIMAP+/+ mice, the tumors then began to erode through the skin, bleed spontaneously and then regressed gradually. At the time of euthanasia (day 20-34 after injection) tumor size, weight and blood vessel density were significantly lower in TIMAP−/− compared to TIMAP+/+ mice (Table).

Conclusions: The data are interpreted to indicate that mammary tumors in TIMAP−/− become necrotic and then involute due to insufficient hypoxia-driven angiogenesis. The data furthermore indicate that TIMAP provides a critical pro-angiogenic signal in EC, at least during tumor angiogenesis. Further work is required to determine whether TIMAP could be targeted in the treatment of highly vascular tumors, including renal cell carcinoma.

Funding: Private Foundation Support, Government Support - Non-U.S.

Tumor Parameters

<table>
<thead>
<tr>
<th>Measurement</th>
<th>TIMAP+/+ (n=5)</th>
<th>TIMAP−/− (n=5)</th>
<th>p (Student’s t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Diameter (mm ± SD)</td>
<td>1.24 ± 1.58</td>
<td>0.35 ± 0.27</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean Weight (g ± SE)</td>
<td>2.99 ± 0.02</td>
<td>0.53 ± 0.01</td>
<td>0.002</td>
</tr>
<tr>
<td>Vascular Density (density ± SD)</td>
<td>32.05 ± 6.62</td>
<td>21.65 ± 5.62</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Baseline characteristic of KT and dialysis patients with UC.
FR-PO1011
Kidney Involvement in Primary Myelofibrosis and Possible Role of the JAK-STAT Pathway
Miguel Gil,1 Harini Bejajani,1 Shahab Bozorgmehr,1 Peter Sayeski,1 Rajesh Mohandas.1,2 University of Florida, Gainesville, FL; 2Renal Section, Malcolm Randall VA Medical Center, Gainesville, FL.

Background: Isolated case reports have described a connection between primary myelofibrosis (PMF) and kidney disease. Activation of JAK-STAT pathways, commonly seen in PMF, leads to worsening kidney function in rodent models. Hence, we hypothesized that JAK-STAT activation in PMF may be associated with kidney disease.

Methods: We used the integrated data repository to identify all adult patients with PMF evaluated at an academic hospital between 1/1/2007 and 11/20/2017. We recruited a control group matched for age, sex, and presence or absence of diabetes mellitus. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m². Paired t-test was used to compare continuous variables and McNemar’s test for categorical variables. Change in renal function over time was compared using mixed-effects model. A p-value < 0.05 was considered significant.

Results: Of the 3 patients with AKI who received kidney biopsy, 2 had significant interstitial inflammation that stained positive for CD3 and/or Granzyme B in the interstitium and tubules. Figure 1 demonstrates the mRNA levels and 3 gene signature of kidney involvement in patients with PMF and controls. Proteinuria on dipstick was more common in PMF than controls (50 % vs. 18%, p=0.03). Patients with PMF and Jak 2 mutation were more likely to have proteinuria at baseline (73%) compared without Jak 2 mutations (22%) or controls (18%) Overall p<0.005. A mixed effects model showed no changes in eGFR over time. However, patients with PMF had higher blood urea nitrogen (BUN) levels at follow-up than matched controls (22±9 vs. 18±12 mg/dl, p=0.001) and a significant increase in BUN (3.3±0.8 vs. 0.5±0.2 mg/dl, p=0.03) from baseline.

Conclusions: Patients with PMF were more likely to have proteinuria, higher BUN at follow-up and a significant increase in BUN compared to controls matched for age, gender, and diabetes. Proteinuria was more likely in those with Jak2 mutations. Our results suggest that PMF is associated with kidney dysfunction and highlights the need for more thorough assessment of renal function in these patients. Identifying the molecular basis of these clinical observations could help improve outcomes in PMF and give us novel insights into the pathogenesis of kidney disease.

FR-PO1012
Urinary mRNA Signature of Graft vs. Kidney Disease in Hematopoietic Stem Cell Transplant Recipients Mirror Acute Rejection of Kidney Allograft
Michelle L. Lubetzky, Michael F. Cassidy, Catherine Snopkowski, Koen Van besien, Thangamani Muthukumar. Weill Medical College of Cornell University, New York, NY.

Background: Acute kidney injury (AKI) is a complication of hematopoietic stem cell transplants (HSCT). GVKD can resemble acute rejection (AR) of kidney allograft, with inflammation in the interstitium and tubules. In GVKD, the graft inflammatory cells attack the host kidney (compared to host versus graft disease in AR). HSCT recipients have multiple comorbid conditions and performing kidney biopsies in patients with AKI can be challenging. Development of urinary mRNA profiles as noninvasive biomarkers has been validated as a robust tool for the noninvasive assessment of kidney allograft status. We hypothesized that urinary mRNA cells in patients with GVKD would mirror AR in kidney allograft and could serve as a tool for the noninvasive diagnosis of AKI.

Methods: We obtained urine specimens from 9 HSCT recipients; 3 with AKI and biopsy diagnosis of GVKD; 2 with AKI that resolved spontaneously; and 4 with normal kidney function. We isolated RNA from urinary cells and quantified the CTOT-04 three-gene molecular signature for AR (urinary cell mRNA levels of 18S, CD3e and IP10, Suthanthiran et al, N Engl J Med 2013) by RT-qPCR assay.

Results: Of the 3 patients with AKI who received kidney biopsy, 2 had significant interstitial inflammation that stained positive for CD3 and/or Granzyme B in the interstitium and tubules. Figure 1 demonstrates the mRNA levels and 3 gene signature of the 3 patients with GVKD as compared to 2 HSCT patients with AKI that resolved and 4 HSCT patients with normal kidney function. The cell signature of GVKD most clearly resembles that found in AR.

Conclusions: Our results demonstrate an immune inflammatory signature in the urine of patients with HSCT who have GVKD. Our pilot study further advances urinary cell mRNA profiling as a noninvasive tool for the differential diagnosis of AKI in HSCT recipients.

FR-PO1013
Mesoscale Nanoparticles Treat Cisplatin-Induced AKI and Avoid Tumor Accumulation

Background: Acute kidney injury (AKI) develops in ~ 30% of patients who receive cisplatin-based chemotherapy. In this setting, AKI can result in delays in completion of treatment or the need to switch to other therapeutic regimens. Despite its high incidence there is no effective pharmacologic intervention for AKI. In cisplatin-induced AKI, it is imperative that any intervention effective for AKI will not interfere with the chemotherapeutic effects of cisplatin. In prior work (Nano Letters 2015) we developed mesoscale nanoparticles (MNPs) that localize to the kidneys with high affinity, primarily to the proximal tubules.

Methods: We synthesized nanoparticles from PLGA-PEG and encapsulated the small molecule reactive oxygen species scavenger edaravone. Experiments were performed in C57 mice with cisplatin-induced AKI (25 mg/kg IP). To assess therapeutic efficacy, IV injections of 50 mg/kg edaravone-containing MNPs, control MNPs, or 30 mg/kg free edaravone were performed 24 hours after cisplatin. Mice were euthanized at 72 hours post-cisplatin. In a separate group of mice bearing metastatic small cell lung cancer, fluorescent MNPs were injected to determine whether MNPs localized.

Results: Compared to mice receiving cisplatin alone, mice receiving edaravone-containing MNPs had normal sCr and normal renal histology. Neither free edaravone nor empty MNPs improved sCr or histology. In mice with metastatic lung tumors, we determined that MNPs maintain their specific renal distribution and do not localize to tumors as has been described with smaller nanoparticle systems.

Conclusions: These studies confirm the likelihood of successful AKI therapy in the context of cisplatin-induced AKI, while avoiding the possible therapeutic abatement associated with tumor deposition of ROS scavengers. We anticipate that these studies will constitute the basis for the development of novel strategies for the treatment and prevention of cisplatin induced AKI in humans.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The Influence of Baseline Diastolic Blood Pressure on the Effects of FR-PO1015

Winston-Salem, NC.

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Background: Blood pressure (BP) is associated with a linearly incremental risk for cardiovascular disease and death in the general population. However, the ideal BP to decrease cardiovascular and renal risk in patients with non-diabetes-dependent chronic kidney disease (CKD) is unclear.

Methods: We studied the associations of baseline systolic BP (SBP) with the risk of composite outcomes (all-cause death, acute myocardial infarction, heart failure, stroke, and end-stage renal disease) in 1.5 million adults who participated in the NHIS National Health Checkup Program between 2009 and 2012 and had an estimated glomerular filtration rate (eGFR) 15–99 mL/min/1.73m2 at study entry using Cox proportional hazard models.

Results: During 8,223,922 person-years of follow-up, the composite outcomes occurred in 305,851 (20.5%) subjects with a crude event rate of 37.2 (95% CI, 37.1-37.3) per 1,000 person-years. In fully-adjusted Cox models, there was a U-shaped association between SBP and composite outcomes, such that SBP <120 mmHg and SBP ≥130 mmHg were each associated with higher risk of cardiovascular and renal outcomes (reference: 120-129 mmHg): the HRs (95% CIs) were 1.20 (1.18-1.22), 1.08 (1.07-1.09), 1.03 (1.02-1.04), and 1.10 (1.09-1.11) for SBP <110, 110-119, 130-139, and ≥140 mmHg, respectively. These associations remained consistent and significant across all eGFR strata.

Conclusions: In a large national cohort of Korean adult population with CKD, the association of SBP levels with cardiovascular and renal risks was U-shaped, with both lower and higher SBP levels showing a substantial and significant increase in death, major cardiovascular events, and end-stage renal disease.

FR-PO1014

Association of Systolic Blood Pressure with Cardiovascular and Renal Outcomes in CKD: A Nationwide Cohort Study

Shin-Wook Kang,1 Chan-Young Jung,2 Byoungwhi Ko,2 Worong Jo,2 Tae Ik Chang,2,3 Department of Internal Medicine, National Health Insurance Service Medical Center, Ilsan Hospital, Gyunggi-do, Republic of Korea; 1Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.

Background: Blood pressure (BP) is associated with a linearly incremental risk for cardiovascular disease and death in the general population. However, the ideal BP to decrease cardiovascular and renal risk in patients with non-diabetes-dependent chronic kidney disease (CKD) is unclear.

Methods: We studied the associations of baseline systolic BP (SBP) with the risk of composite outcomes (all-cause death, acute myocardial infarction, heart failure, stroke, and end-stage renal disease) in 1.5 million adults who participated in the NHIS National Health Checkup Program between 2009 and 2012 and had an estimated glomerular filtration rate (eGFR) 15–99 mL/min/1.73m2 at study entry using Cox proportional hazard models.

Results: During 8,223,922 person-years of follow-up, the composite outcomes occurred in 305,851 (20.5%) subjects with a crude event rate of 37.2 (95% CI, 37.1-37.3) per 1,000 person-years. In fully-adjusted Cox models, there was a U-shaped association between SBP and composite outcomes, such that SBP <120 mmHg and SBP ≥130 mmHg were each associated with higher risk of cardiovascular and renal outcomes (reference: 120-129 mmHg): the HRs (95% CIs) were 1.20 (1.18-1.22), 1.08 (1.07-1.09), 1.03 (1.02-1.04), and 1.10 (1.09-1.11) for SBP <110, 110-119, 130-139, and ≥140 mmHg, respectively. These associations remained consistent and significant across all eGFR strata.

Conclusions: In a large national cohort of Korean adult population with CKD, the association of SBP levels with cardiovascular and renal risks was U-shaped, with both lower and higher SBP levels showing a substantial and significant increase in death, major cardiovascular events, and end-stage renal disease.

FR-PO1015

The Influence of Baseline Diastolic Blood Pressure on the Effects of Intensive Blood Pressure Lowering on Cardiovascular Outcomes in Type 2 Diabetes Mellitus

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Background: Intensive (INT) compared to standard (STD) systolic blood pressure (SBP) control might be harmful in persons with low baseline diastolic blood pressure (DBP) and type 2 diabetes mellitus (T2DM).

Methods: ACCORD BP was a 2X2 factorial design RCT that examined the effects of SBP control (<120mmHg vs. <140 mmHg) and glycemia (GLY) control (HbA1C goal < 6% vs. 7.0–7.9%) on a primary cardiovascular disease (CVD) composite outcome in T2DM (N = 4714). We examined whether the effects of INT SBP lowering on CVD was modified by baseline DBP stratified by the GLY arm.

Conclusions: Low baseline DBP was associated with increased risk of CVD composite in T2DM. However, there was no evidence that the beneficial effects of INT SBP lowering on CVD events in STD GLY arm was modified by low baseline DBP.

Poster/Friday

FR-PO1016

Association of Pulse Pressure and Double Product with Cardiovascular and All-Cause Mortality in the LURIC Study

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Background: Systolic (SBP) and diastolic blood pressure (DBP) as well as mean arterial pressure (MAP) are already known as important predictors respectively risk factors for cardiovascular mortality. Pulse pressure (PP) is considered as an easily available marker of vascular stiffness and the double product (DBP x heart rate (HR)) as a marker of cardiac workload. Therefore, we extended our analysis of outcome parameters by use of PP and DP.

Methods: We retrospectively analysed data from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, in which 3316 patients underwent coronary angiography.

Results: Long-term data from 3316 patients undergoing coronary angiography showed that by increasing SBP by 1mmHg the risk of both cardiovascular and all-cause mortality rose by 0.9 %. However, there was no significant relationship between DBP and mortality. A higher PP of 1 mmHg resulted in a higher cardiovascular mortality risk of 1.6 % and an all-cause mortality risk of 1.7 %. Increasing DP by 100 mmHg/min was associated with a 1.0 % higher risk of cardiovascular mortality and 0.9 % higher risk of all-cause mortality.

Conclusions: We provide evidence that not only the classic standard blood pressure parameters SBP and MAP predict cardiovascular mortality, but also that PP and DP are powerful predictors of cardiovascular and all-cause mortality in a cardiovascular risk population. PP and DP are superior predictors of a higher cardiovascular mortality in heart failure patients.
FR-PO1017
Systolic Blood Pressure and Risk of Incident CKD: A Nationwide Cohort Study of 10 Million Adults in South Korea

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Background: In the general population, guidelines recommend a target blood pressure (BP) of <120/80 mmHg in order to reduce cardiovascular risk. However, the optimal BP to prevent chronic kidney disease (CKD) is unknown.

Methods: In a national population-based cohort of 10.5 million adults who underwent National Health Insurance Service health examination between 2009 and 2015 and had an estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m², we studied the association of time-updated and baseline systolic BP (SBP) with risk of incident CKD using marginal structural models (MSMs) and Cox models. Incident CKD was defined as de novo development of eGFR <60 mL/min per 1.73 m² for at least two consecutive measurements.

Results: During 49,169,311 person-years of follow-up, incident CKD developed in 172,423 (1.64%) subjects with a crude event rate of 3.51 (95% CI, 3.49-3.52) per 1,000 person-years. Using MSMs, we found a graded association between incrementally higher time-updated SBPs ≥130 mmHg and risk of incident CKD, whereas SBPs <120 mmHg were associated with lower risk (reference: 120-129 mmHg). HRs (95% CIs) were 0.57 (0.55-0.58), 0.81 (0.80-0.82), 1.41 (1.39-1.43), and 2.16 (2.12-2.19) for SBP <110, 110-119, 120-129, and ≥140 mmHg, respectively. Using Cox models, the corresponding HRs for the noted SBP range were 0.84 (0.82-0.86), 0.92 (0.91-0.94), 1.11 (1.09-1.12), and 1.30 (1.28-1.32), respectively. Among subjects receiving antihypertensive medications, time-updated SBP of <110 mmHg was associated with higher risk of CKD: HR (95% CI) 1.67 (1.60-1.75).

Conclusions: In healthy women without kidney disease, higher SBP ≥130 mmHg was associated with higher risk of incident CKD. However, among those receiving antihypertensive therapy, low SBP <110 mmHg was also associated with incident CKD risk, suggesting that excessive BP control may contribute to adverse renal outcomes.

FR-PO1018
The Influence of Blood Pressure Patterns on Renal Outcomes in Patients with CKD: The Long-Term Follow-Up Result of the APrODiTe-2 Study

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Background: Blood pressure (BP) control is the most established practice for preventing the progression and complications of chronic kidney disease (CKD). We examined the influence of BP patterns on target organ damage in hypertensive patients with CKD by using long-term follow-up data of the APrODiTe-2 study.

Methods: We collected 5 years of data of APrODiTe-2 study participants (n=378).

Results: Initially, the BP control and the dipping states were as follows: true controlled (16.5%), white-coat (2.9%), masked (50.0%), and sustained uncontrolled (35.0%). Only 18.8% and 20.8% of participants showed a better change in BP control patterns (to true controlled and white-coat) and a dipping pattern change to dippers (35.0%).

Conclusions: Higher BP burden (a worse change in BP control categories, higher change in BP control patterns over 1 year) was associated with increased occurrence of composite of doubling estimated glomerular filtration rate (eGFR), the initiation of dialysis, and kidney transplantation after adjustment for age, sex, and the cause of CKD. Patients with a worse initial BP control category, a worse change in BP control categories over 1 year was associated with increased occurrence of doubling eGFR (eGFR <60 mL/min per 1.73 m²) for at least two consecutive measurements.

FR-PO1019
Outcomes in Adults with Systolic Blood Pressure Between 130 and 139 mm Hg in ACCORD BP and SPRINT

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Background: Patients with stage 1 systolic hypertension (130-139 mmHg) have increased risk of cardiovascular disease (CVD) events compared to those with normal blood pressure.

Methods: In this post-hoc analysis, we assess the effect of targeting an intensive systolic blood pressure (SBP) goal of less than 120 mmHg compared with standard SBP goal of less than 140 mmHg on the risk of CVD events in adults with stage 1 systolic hypertension enrolled in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure (BP) Trial (n=1,901) and the Systolic Blood Pressure Intervention Trial (SPRINT) (n=3,484) using adjusted Cox models. In ACCORD, the primary composite CVD outcome was the first occurrence of myocardial infarction (MI), stroke or CVD mortality. In SPRINT, the primary composite CVD outcome was the first occurrence of MI, other acute coronary syndrome, stroke, heart failure or CVD mortality.

Results: In SPRINT, targeting an intensive SBP goal significantly reduced the risk of the primary CVD outcome (hazard ratio [HR] 0.75, 95% confidence interval [95% CI] 0.57-0.97; P = 0.027) in ACCORD BP, SBP <120 mmHg was associated with lower risk of the primary CVD outcome compared with the SBP ≥130 mmHg group (HR 1.30 [0.95-1.78]). In SPRINT, the primary composite CVD outcome was the first occurrence of MI, other acute ischemic coronary event, stroke, heart failure or CVD mortality. In SPRINT, targeting an intensive SBP goal significantly reduced the risk of the primary CVD outcome (HR 0.61 [0.40-0.94]; event rates 1.63% vs. 2.56% per year). In both trials, intensive systolic blood pressure subgroup (A1c target <6%) had significantly reduced the risk of the primary CVD outcome was not significantly different between SBP goal groups (HR 1.20 [0.76-1.89]; event rates 1.91 vs. 1.60% per year).

Conclusions: Targeting a SBP goal of less than 120 mmHg significantly reduced the risk of CVD events in patients with stage 1 systolic hypertension without diabetes and with diabetes on standard glycemia goal.

Funding: NIDDK Support, Other NIH Support - ACCORD BP and SPRINT were supported by the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Disease, the National Institute on Aging, the National Institute of Neurological Disorders and Stroke, and the Department of Veterans Affairs.

The study was approved by the SPRINT research group. Authors analyzed and interpreted the data for this abstract, with support from the Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC. All aspects of the abstract writing and revision were initially carried out by the authors, with subsequent revisions made according to the SPRINT research group recommendations. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, the U.S. Department of Veterans Affairs, or the United States Government.

FR-PO1020
The Influence of Baseline Diastolic Blood Pressure on the Effects of Intensive Blood Pressure Lowering on All-Cause Mortality in Type 2 Diabetes Mellitus

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Background: Intensive (INT) compared to standard (STD) systolic blood pressure (DBP) control might be harmful in persons with low baseline diastolic blood pressure (DBP) and type 2 diabetes mellitus (T2DM).

Methods: The Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD BP) was a 2X2 factorial design RCT that examined the effects of SBP control (<120 mmHg vs. >120 mmHg) and glycemia (GLY) control (HbA1C goal < 6% vs. 7.0–7.9%) on cardiovascular events and all-cause mortality (ACM) in T2DM (N = 4714). We examined whether the effects of INT DBP lowering on ACM was modified by baseline DBP stratified by the GLY arm.

Results: There were 292 ACM events/23.362 years of follow-up. Lower baseline DBP was associated with increased risk of ACM (Fig 1). Hazard ratios for INT SBP lowering in the STD and INT GLY arms were 0.84 (95% CI 0.60 to 1.17) and 1.34 (95% CI 0.97 to 1.84), respectively. Linear interaction p-value for SBP intervention and baseline DBP was not significant in the STD GLY arm (p = 0.40) but significant in INT GLY arm (p=0.01). In those with DBP ≥70 mmHg, INT SBP lowering appeared not harmful in the STD GLY arm but deleterious in the INT GLY arm (Fig 2).

Conclusions: Low baseline DBP was associated with increased risk of ACM in T2DM. In persons with baseline DBP ≤70 mmHg, INT SBP lowering increased ACM in the setting of INT GLY but not STD GLY.

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**FR-PO1021**

Heart Failure Risk with Intensive Systolic Blood Pressure (SBP) Lowering Does Not Differ by Albuminuria Status in Diabetes

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Background: Albuminuria is associated with heightened risk for heart failure (HF) in persons with diabetes mellitus (DM) but optimal SBP goals for reducing HF risk remain controversial. We examined the effects of intensive vs. standard SBP lowering on HF risk by baseline albuminuria status among adults with DM.

Methods: Using data from the Action to Control Cardiovascular Disease (ACCORD) trial. Kaplan Meier curves were used to examine time to acute decompensated HF events by intensive vs. standard SBP lowering and by baseline albuminuria status (albumin-to-creatinine ratio < 30 mg/g vs. ≥ 30 mg/g) after stratifying by intensive vs. standard glucose control. Interaction terms of albuminuria x intensive SBP lowering on HF risk were fitted into Cox proportional hazard models while adjusting for demographics, estimated glomerular filtration rate, blood pressure, and heart disease.

Results: A total of 4524 patients (2257 in standard SBP arm, mean age 62.5 (6.5) years and baseline SBP 137.1 (14.6) mmHg) were followed for a mean of 4.78 years, 65% were men, and 58% were white. The mean age was 68 (± 9) years, 65% were men, and 58% were white. The mean eGFR was 73 ± 21 ml/min/1.73m² at 6 months. There were 370 CVD events and 154 deaths during a median follow-up of 2.4 years. In adjusted model, greater eGFR variability was associated with lower HF rates (HR 0.77, 0.6, -1.12) in the intensive glycemia arm, it was 0.77 (0.48, 1.18) in ACR<30 and 1.05 (1.89,3.98) in ACR >30. Hazard Ratio(95% CI) in the standard arm was 0.73 (0.34,1.58) and 0.73 (0.41,1.31) in the ACR <30 and ACR >30 respectively, and in the intensive arm 1.24 (0.65, 2.37) and 1.14 (0.66, 2.04) in the ACR <30 and >30 respectively.

Conclusions: The effects of intensive SBP lowering on HF rates does not appear to be modified by albuminuria status in adults with DM.

**FR-PO1022**

Association Between eGFR Variability and Risk of Cardiovascular Events and Mortality: The SPRINT Trial

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Background: In clinical practice, there is considerable visit-to-visit variability in estimated glomerular filtration rate (eGFR). While low eGFR is an established cardiovascular disease (CVD) risk factor, less is known about the clinical significance of eGFR variability over time.

Methods: Among 7520 SPRINT participants, we used proportional hazards models to estimate associations between eGFR variability (measured by coefficient of variation, CV) and subsequent CVD events and all-cause mortality. The CV (SD/mean) was calculated from eGFR values measured at 6-, 12-, and 18-month study visits. CVD events were defined as the composite of MI, ACS, stroke, heart failure, or CVD death. The final model was adjusted for demographics, randomization, prior CVD, heart failure, current smoking, body mass index, serum lipids, baseline systolic BP, albuminuria, eGFR at month 6, medications (ACEI/ARB or diuretics at month 6) and fasting status.

Results: The mean age was 68 (±9) years, 65% were men, and 58% were white. The mean eGFR was 73 ± 21 ml/min/1.73m² at 6 months. There were 370 CVD events and 154 deaths during a median follow-up of 2.4 years. In adjusted model, greater eGFR variability was associated with lower all-cause mortality (hazard ratio (HR) per SD increase in eGFR-CV (0.06), 1.28; 95% CI 1.14 - 1.44). Associations were somewhat weaker for total mortality (HR 1.06; 0.96 -1.17) (Figure 1). When variability was evaluated by quartiles, the highest compared with the lowest quartile was associated with higher all-cause mortality (HR 1.57, 0.99 - 2.47) and CVD events (HR 1.35; 0.99 - 1.84). Associations were similar when stratified by treatment arm and baseline CKD status.

Conclusions: Greater eGFR variability was associated with higher risk for all-cause mortality in SPRINT trial participants, independent of baseline eGFR. Future studies should evaluate mechanisms underlying these associations.

Funding: NIDDK Support
Acute coronary syndrome (ACS), stroke, acute decompensated heart failure, or CV death) and whether baseline BMI modifies the effects of INT SBP control on CV outcomes.

Methods: SPRINT is a currently on-going prospective comparative study of CKD in a group of patients with CKD (KNOW-CKD) in which nine major tertiary hospitals are participating (NCT01630486). A total of 1,903 subjects who performed baPWV test and had ankle-brachial index >0.9 was selected. Mean value of right and left baPWV (mbaPWV) was used for analysis. Renal event (RE) was defined by the doubling of serum creatinine or 50% decrease in CKD-EPI eGFR from the baseline values, or the initiation of renal replacement treatment. The subjects were grouped according to quartile value of mbaPWV. The values of mbaPWV in each quartile group were Q1: 587.3–1,292.5 cm/sec, Q2: 1,293.0–1,458.5 cm/sec, Q3: 1,459.0–1,701.5 cm/sec, Q4: 1,702.3–4,632.5 cm/sec respectively.

Results: Of 1,903 subjects, a total of 577 subjects (26.6%) developed RE during the mean follow up period of 3.6 years. Cox regression analysis adjusted by sex, age, CKD-EPI eGFR, urine albumin creatinine ratio (UACR), medical history of diabetes, hypertension, coronary diseases, hypercholesterolemia, smoking and alcohol use that each unit increase of ln(mbaPWV) was associated with 91.7% increase in risk for RE (HR:1.92 95% CI: 1.11-3.32, p=0.021). Time dependent Cox regression adjusted by the same variables revealed that RE increased along with mbaPWV quartile groups (Q1: reference, Q2: HR=2.13, 95% CI 1.07-4.23, p=0.032, Q3: HR=2.37, 95% CI 1.77-6.65, p=0.000, respectively). While unfavorable effect of mbaPWV on RE was consistent in subject with UACR>300 mg/g, this effect disappeared in subject with UACR>300 mg/g. Unfavorable effect of mbaPWV on RE was more prominent in subjects with CKD-EPI eGFR<45 ml/min/1.73m2 than those with CKD-EPI eGFR≥45 ml/min/1.73m2. Cox proportional hazards regression analyses used to identify potential predictors of all-cause death. Model fit was assessed using the C-statistic.

Conclusions: Vascular stiffness was associated the unfavorable renal outcomes in pre-dialysis CKD, particularly in non-proteinuric and early stage CKD.

FR-PO1025

Global Longitudinal Strain on Cardiac MRI Is Superior to Conventional Cardiac Parameters at Predicting Mortality in Patients with ESRD

Methods: We retrospectively analysed research cardiac MRIs (CMR) performed at a major renal transplant centre between 2002-2016. Included patients were receiving, or within 6-months of receiving, renal replacement therapy for ESRD. CMR parameters were derived, including left ventricular mass index (LVMI), LVEF and LV-GLS. Cox proportional hazards regression analyses used to identify potential predictors of all-cause death. Model fit was assessed using the C-statistic.

Results: Among 237 patients (mean age: 53.7, 61% male), mortality was 50.6% over 4.6-year median follow up. LV-GLS quartiles were significantly correlated with mortality (Figure 1). While 89.7% of patients had preserved LVEF (>55%), 24% of patients had abnormal LV-GLS. On multivariable Cox regression, age (HR: 1.04, 95% CI: 1.020-1.057), LAEF (HR: 0.98, 95% CI: 0.963-0.997) and LVGLS (HR: 1.08, 95% CI: 1.011-1.044) were independent predictors of mortality. The C-statistic of this model for predicting ACM at 1-year was 0.955 (95% CI: 0.920-0.991). Traditional CMR parameters such as LVEF and LVMI were not correlated with mortality.

Conclusions: In this cohort of patients with ESRD, LV-GLS and LAEF as measured by Feature Tracking Cardiac Magnetic Resonance (FT-CMR) is a non-contrast, post-processing technique that has shown promise as a sensitive predictor of cardiovascular mortality. We aim to assess the ability of LV-GLS to predict death in patients with end-stage renal disease (ESRD).

Funding: Government Support - Non-U.S.
FR-PO1026
Magnetic Resonance Imaging Evaluation of Mineralocorticoid Receptor Antagonism in Diabetic Atherosclerosis (MAGMA) Trial: Baseline Characteristics
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Background: MAGMA is a multicenter double-blind, randomized controlled trial that aims to assess the effect of spironolactone on atherosclerosis progression and left ventricular (LV) mass regression in type 2 diabetic patients with CKD.

Methods: 46 adult diabetic patients with eGFR<60 ml/min/1.73m2 and albuminuria>30 mg/g or eGFR<60 ml/min/1.73m2 regardless of albuminuria, on ACEi/ARB were enrolled at 4 sites and randomly assigned to spironolactone (12.5mg with eventual escalation to 25mg daily) vs. placebo. 24hr ambulatory blood pressure monitoring (ABPM) and cardiac MRI and aortic plaque imaging were performed at baseline and will be repeated at 1 year.

Results: The mean age (SD) was 62.5(8.9) years; 61% were women, and mean eGFR was 48.6 (20.3)ml/min/1.73m2. Compared to participants with controlled SBP (n=7), participants with masked (n=12) and sustained (n=17) hypertension had a higher left ventricular mass index (66.5±9 and 64.7±8.9 vs 58.6±7.7 g/m2 respectively (Figure). In adjusted models we found no association between hypertension phenotypes and T1 times, T1 cardiovascular risk. We aimed to describe the association of masked and sustained hypertension with structural and functional left ventricular measurements as assessed by cardiac magnetic resonance imaging (MRI) in type 2 diabetic patients with CKD.

Conclusions: Masked and sustained hypertension are associated with a higher left ventricular mass index in individuals with CKD and diabetes. Larger trials are needed to better characterize MRI cardiac structural abnormalities in individuals at high cardiovascular risk.

Funding: Other NIH Support - NHLBI

FR-PO1028
Reproducibility and Clinical Determinants of Stress T1-Mapping in Patients on Haemodialysis: A Feasibility Study
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Background: Identification of coronary artery disease (CAD) in patients with end stage renal disease (ESRD) is challenging. Adenosine stress non-contrast native T1 mapping on cardiac MRI has been proposed as a method to assess myocardial blood volume changes. It has been shown to accurately detect obstructive CAD and microvascular dysfunction in the general population. However, it has never been tested in patients with ESRD, who have higher resting native T1 times compared to control subjects. This study assesses the potential of stress T1 mapping to identify myocardial ischaemia in patients on haemodialysis (HD).

Methods: 124 patients underwent rest T1 mapping. 58 of them had stress scans. 10 patients had identical reproducibility scans within two weeks. Myocardial stress T1 reactivity was calculated as ΔT1 = T1rest (stress T1- rest T1)×100. Interstudy reproducibility, inter-observer and intra-observer variability were assessed using intraclass correlation coefficient (ICC), coefficient of variability (CV) and Bland-Altman analyses.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Differences between groups and correlations between T1 and clinical variables were assessed. Independent predictors of AT1 were examined on multivariate linear regression.

Results: There were no clinically relevant differences between baseline characteristics of patients undergoing rest only or rest and stress scans. Of the 58 patients who had stress scans, only one had an inadequate haemodynamic response to adenosine. All patients tolerated and completed the scan, with no adverse effects. Inter- and intra-observer variability of rest T1, stress T1 and AT1 were excellent (ICC > 0.9). Inter-study reproducibility for stress and rest T1 was good (CoV 1.2% and 1.5%; ICC 0.79 and 0.69, respectively), but average for AT1 (CoV 27.4%, ICC 0.55). On multivariate analysis, CAD, diabetes and rest native T1 time were independent predictors of ΔT1 (β = -0.244, p = 0.038; β = -0.326, p = 0.008; β = -0.458; p < 0.001, respectively).

Conclusions: Stress T1 mapping is a feasible, reproducible and well-tolerated technique in patients on HD. It has the potential to evaluate myocardial ischaemia secondary to obstructive epicardial CAD or microvascular dysfunction despite the elevated resting native T1 values in this population. However, the reproducibility of AT1 is sub-optimal.

FR-PO1029

Comparability and Tolerability of Ambulatory and Home Blood Pressure Monitoring in Hemodialysis Patients
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Background: 44-hour (hr) ambulatory blood pressure monitoring (ABPM) in hemodialysis (HD) patients provides valuable prognostic information, but is often impractical in clinical practice. Home BP monitoring (HBPM) may be better suited for longitudinal BP management. However, limited evidence exists regarding the comparability and tolerability of ABPM and HBPM in this high risk population.

Methods: In a post-hoc analysis, we studied pre-randomization data from participants who agreed to 44-h ABPM in a randomized controlled trial targeting a home vs pre-HD systolic BP (SBP) <140 mmHg (NCT03459807).

Results: Of the 50 in-center HD patients enrolled, 31 (62%) agreed to ABPM. The mean age was 56 (SD 14) years, 13 (42%) were black. Mean pre-HD SBP was 146 (19) mmHg, ABPM SBP 140 (21) mmHg, daytime SBP 141 (20) mmHg, and nighttime SBP 134 (25) mmHg; 24 (77%) participants were non-dippers, including 7 (23%) reverse dippers. Home SBP was correlated with ABPM SBP (Figure); the strongest correlation was with daytime SBP in the initial 24-hrs post-HD (r=0.76, 95% CI 0.43-0.91). Using ABPM instead of HBPM, 2 participants were reclassified from controlled to masked hypertension (HTN), 1 from white coat to uncontrolled HTN, and 1 from masked to controlled HTN. Most patients described their ABPM experience as neutral (e.g. “No problem”); however, some expressed substantial discomfort (e.g. “the pressure was way too high and unbearable”). Participants described HBPM more positively (“It was fun and gave me knowledge of my own BP’s”), with no reported discomfort.

Conclusions: Among HD patients, HBPM correlated with ABPM, particularly daytime post-HD ABPM readings. Given greater tolerability and feasibility for repeated measurements, HBPM seems to be a practical option for longitudinal monitoring and management of HTN among HD patients.

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FR-PO1030

The Accuracy of Clinic and Home Blood Pressure Recordings in Diagnosing Hypertension Among Patients on Peritoneal Dialysis
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Background: Earlier studies testing the diagnostic accuracy of blood pressure (BP) measurement techniques among patients on peritoneal dialysis (PD) have shown that home BP recordings overestimate daytime ambulatory BP and are inferior to standardized automated clinic BP measurements in diagnosing hypertension. The aim of this study is to elucidate this paradoxical observation that contradicts evidence from the general hypertensive population and may be attributable to methodological limitations of earlier studies.

Methods: In a cohort of 81 stable PD patients with unmodified anti-hypertensive therapy or dialysis regimen for at least 2 weeks prior to study enrollment, BP was recorded using 3 different methodologies: (i) triplicate automated clinic BP recordings after a 5-min seated rest with the self-inflating monitor HEM 705 CP (Omron Healthcare); (ii) 1-week averaged morning and evening home BP recordings taken by the patients themselves with validated automated BP monitors; (iii) 24-hour ambulatory BP monitoring with the oscillometric device Mobil-O-Graph (IEM, Germany).

Results: In Bland-Altman analysis, clinic systolic BP (SBP) overestimated daytime ambulatory SBP by 5.02 mmHg with 95% limits of agreement ranging from 17.92 to 27.96 mmHg. Similarly, home SBP overestimated daytime ambulatory SBP by 4.23 mmHg, again with wide 95% limits of agreement (-16.05 to 24.51 mmHg). The area under the curve of receiver operating characteristic (ROC) curve for clinic and home BP to detect a daytime ambulatory SBP ≥135 mmHg was 0.859 (95% CI: 0.776-0.941) and 0.895 (95% CI: 0.815-0.976), respectively. Home SBP of a 135.5 mmHg had the best combination of sensitivity (80.6%) and specificity (84%) in diagnosing ambulatory systolic hypertension.

Conclusions: 1-week averaged home BP recordings are at least similar with a standardized BP measurement at clinic in detecting ambulatory hypertension among patients on PD.

FR-PO1031

Patterns of Nocturnal Blood Pressure Changes in Patients on Ambulatory Blood Pressure Monitoring (ABPM) in Patients with Complex Hypertension
Neil K. Agarwal, Tarig Elraiyah, Siddiquee Akbar, Ziauddin Ahmed, Ellie Kelepouris, Sandeep Aggarwal. Drexel University College of Medicine, Rose Valley, PA.

Background: Nocturnal blood pressure changes are associated with patient centered outcomes. We attempted to investigate the patterns of blood pressure changes in complex hypertensive patients with concomitant cardiovascular comorbidities.

Methods: We retrospectively reviewed 35 charts of patients who received ABPM from a single outpatient nephrology office. Of the 35, 5 were excluded due to incomplete data. We collected demographic information: Age, Gender, Ethnicity, Diabetic status, CKD stage, Indication for ABPM. ABPM data including: Average daytime pressures, Average nighttime pressures, total average pressures, nocturnal dipping, hypertensive load. IBM SPSS® v22 was used for statistical analysis – t-tests.

Results: Of the 32 patients (22 Female, 10 Male), 20 were African American, 6 were diabetic, 17 had CKD stage 3 or greater, and mean age was 56±19 years. Among CKD patients, the mean nocturnal systolic dip was 3.4±3.8 mmHg, mean diastolic nocturnal dip 8.2±3.3 mmHg, mean MAP nocturnal dip 5.9±2.9 mmHg. Among non-CKD patients, the mean systolic nocturnal dip was 6.9±5.8 mmHg, mean diastolic nocturnal dip 11.9±6.5 mmHg, mean MAP nocturnal dip 9.6±6.2 mmHg. The mean difference between systolic nocturnal dip was 3.5±2.9 mmHg (p=0.2433), mean difference between diastolic nocturnal dip was 3.7±2.7 mmHg (p=0.1708), mean difference between MAP nocturnal dip was 3.6±2.8 mmHg (p=0.2034). Among diabetic patients, the mean systolic nocturnal dip was 5.8±8.9 mmHg, mean diastolic nocturnal dip 11.2±7.6 mmHg, mean MAP nocturnal dip 8.8±6.2 mmHg. The mean difference between systolic nocturnal dip was 3.8±3.7 mmHg (p=0.3148), mean difference between diastolic nocturnal dip was 7.1±3.3 mmHg (p=0.0376), mean difference between MAP nocturnal dip was 6.2±3.5 mmHg (p=0.0864).

Conclusions: In our study, there was no difference in nocturnal blood pressure changes in patients with or without cardiovascular co-morbidities, except for nocturnal diastolic blood pressure in diabetic patients. Additional, larger scale trials are required to look for additional or synergistic risk of nocturnal blood pressure variability in patients with high cardiovascular risk.
FR-PO1032
A Pilot Targeting Trial Home vs. Pre-Dialysis BP in Hemodialysis (HD) Patients
Nisha Bansal,1 David V. Glidden,2 Rajnish Mehrotra,4 Raymond R. Townsend,3 Hanna L. Larson,1 Lori Linke,1 Farshad Palad,2 Chi-yuan Hsu,2 Kidney Research Institute, Seattle, WA; 1USC, San Francisco, CA; 2University of Washington, Seattle, WA; 3UW, Seattle, WA; 4UPenn, Philadelphia, PA.

Background: Guidelines recommend treatment of pre-dialysis blood pressure (BP) among HD patients. However, there is a U-shaped association between pre-dialysis BP and death. We hypothesize that home BP may be a better target for treatment since there is a linear relationship between out-of-dialysis unit BP and death in observational studies. To test the feasibility of this approach, we conducted a trial of treating home vs. pre-dialysis BP in HD patients.

Methods: We conducted a 4-month randomized controlled trial of 56 HD patients at two centers, targeting home systolic blood pressure (SBP) vs. pre-dialysis systolic blood pressure (SBP) 140-100 mmHg. Home and pre-dialysis SBP were obtained every 2 weeks and adjustments in dry weight and medications were made to reach target SBP in each group. The primary outcomes were feasibility, adherence, tolerability and safety.

Results: One in four potentially eligible patients enrolled in the study. We had enthusiastic buy-in from 11 nephrologists from 8 different dialysis units (operated by 3 dialysis providers). The mean age of participants was 56 years, 40% were women, and 74% were non-white. All enrollees successfully completed the study except one who got a kidney transplant. Adherence to obtaining home BP was 97%. In the home BP group, there was no increased frequency of high or low pre-HD BP; lower frequency of intradialytic hypotension and falls; but more fatigue and syncope (Table). This pilot study shows that HD patients can successfully participate in and adhere to home BP measurement. Given that there is a U-shaped association of pre-dialysis BP (but not out-of-dialysis-unit BP) with risk of death, targeting home BP may be a promising intervention to improve outcomes in this population and should be tested in larger clinical trials.

Funding: NIDDK, Support, Private Foundation Support

Tolerability and safety over 4 months in HD participants randomized to home vs. pre-dialysis BP <140 mmHg

FR-PO1033
Awareness and Monitoring Behavior of Home Blood Pressure Among Patients with CKD in Guangzhou, China
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Background: Home blood pressure monitoring (HBPM) has been proved superior to office measurements to predict cardiovascular outcomes and target organ damage in patients with chronic kidney disease (CKD). However, the awareness and monitoring behavior of home BP in CKD patients are still not explored in depth in China. The aim of this study was to investigate the awareness and monitoring behavior of home BP among patients with CKD and to compare the difference of control rate of BP between patients with and without HBPM.

Methods: This was a cross-sectional, descriptive study conducted in a hospital in Guangzhou, a city in southern China. The CKD patients complicated with hypertension (office systolic blood pressure [SBP] ≥ 140 mmHg and/or diastolic blood pressure [DBP] ≥ 90 mmHg) were recruited in 2019 by convenience sampling and were surveyed with the awareness and behavior model of HBPM questionnaire.

Results: A total of 114 patients with CKD stage 2-5, aged 52.8 ± 14.2 years were enrolled. The mean values of office SBP and DBP were 145.8 ± 20.2 mmHg and 90 mmHg respectively, while only 3.5% (4/114) patients correctly answered the question regarding normal BP and 44.7% (51/114) of them didn’t control their BP at office (SBP ≥ 140/90 mmHg). Although the BP monitors were owned by 91.2% (104/114) patients, in which 96.2% (100/104) were electronic device and 94% (94/100) were upper-arm BP monitors, 75% (78/104) of CKD patients didn’t know that the monitor needed to be calibrated regularly. Regarding the monitoring frequency, of home BP, 15.8% (18/114) didn’t measure their BP at home, and 35.3% (40/114) measured only when they felt uncomfortable (e.g. headache, dizziness). 41.7% (40/96) never recorded the measurements, and 49% (47/96) never communicated the monitored data with their health professionals. The control rate of BP (office BP ≥ 140/90 mmHg) in patients undergoing HBPM was 46.9%, which was higher than the one in patients without HBPM (33.3%, p < 0.05).

Conclusions: CKD patients have poor BP control in Guangzhou, China. Although most of them have a HBPM device, the awareness of HBPM are still insufficient and the utilization of HBPM are undesirable. Given patients undergoing HBPM have a higher control rate of BP than those without HBPM, education and supervision should be strengthened to promote the application of HBPM on CKD patients.

Funding: Government Support - Non-U.S.

FR-PO1034
Survival of Patients with Percutaneous Coronary Intervention of Acute Coronary Syndrome in Left Main Coronary Artery Disease: The Role of Kidney Function
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Background: Chronic kidney disease (CKD) is associated with a high burden of stable coronary artery disease and an increased incidence of acute coronary syndromes (ACS). Left-main coronary artery disease (LMCAD) is the highest-risk lesion of ischemic heart disease, where percutaneous revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is needed. Presence of CKD may increase the risk of complications and mortality connected with revascularization procedures. The aim of our study was to determine the role of CKD in the survival of patients after undergoing PCI for ACS in LMCAD.

Methods: In our retrospective study, 211 patients (142 male (67.3%)) were included. All patients underwent primary PCI because of LMCAD between January 1st, 2008 and December 31st, 2016. The patients were observed from PCI until their death or December 20th, 2018 (average time of observation was 5.3 years). Mean age of included patients was 69.2 ± 11.3 years (minimum 38 years, maximum 91 years). CKD was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Comorbidities, such as arterial hypertension (AH), diabetes mellitus (DM), and dyslipidemia were recorded. Survival rates were analyzed using Kaplan-Meier survival curves. The Cox regression model was used to assess the influence of CKD, AH, DM and dyslipidemia.

Results: 82.5% of patients had AH, 28% had DM and 64.4% had dyslipidemia. 24.2% of patients had eGFR ≤ 60 ml/min/1.73 m² (CKD group). Mean survival time of patients in the CKD group was 1294±1402 days and in the non-CKD group 2122±1246 days. 32 (62.73%) CKD and 53 (33.1%) non-CKD patients died. Kaplan-Meier survival analysis showed a higher risk of death for CKD patients (log-rank test; p < 0.001). In Cox multivariable regression model, CKD remained a predictor of all-cause mortality in our patients (HR was 1.623 (95% CI 1.414-1.757; P < 0.0001)). The impact of dyslipidemia on patient survival was statistically significant (p < 0.0001), while AH (p = 0.671) and DM (p = 0.136) showed no impact on patient survival.

Conclusions: The results indicate an association between CKD and all-cause mortality in patients after undergoing PCI for ACS in LMCAD.

FR-PO1035
Number of Right Coronary Artery Lesions Increases as CKD Progresses Shiko Goto. Satamua Sekishinkai Hospital, Sayama city, Japan.

Background: Chronic kidney disease is a risk factor for cardiovascular disease, and low glomerular filtration rate (GFR) is known to be associated with a higher risk of cardiovascular disease (CVD). However, there is currently no report on the association between the stage of chronic kidney disease and coronary artery lesion parameters such as site and number. Methods: We examined variations in the site and number of coronary artery lesions in relation to the presence or absence of diabetes and dyslipidemia, and differences in laboratory parameter values such as serum blood urea nitrogen (BUN), creatinine (Cr), and estimated glomerular filtration rate (eGFR) in 2885 cases (average age: 68.96 ± 10.32 years; 2140 men, 745 women) who underwent coronary angiography in our hospital from January 2009 to November 2016. Results: Although there was no significant variation in coronary artery lesion sites in relation to differences in age or the presence of diabetes or dyslipidemia, there was a significant increase in the number of right coronary artery lesions as the stage of chronic kidney disease progressed (p < 0.001, Kruskal Wallis test). Conclusions: Our results suggest that the progression of renal dysfunction may cause an increase in the number of right coronary artery lesions.
FR-PO1036

Association of Coronary Artery Calcification Density, Coronary Artery Calcification Score, and Cardiovascular Risk in Maintenance Hemodialysis Patients

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Background: Agatston’s coronary artery calcification score (CACS) is a composite of coronary artery calcification (CAC) volume and CAC density (CACD). In general population, CAC volume is positively and CACD is inversely associated with cardiovascular disease (CVD) events. This study aimed to evaluate the association of CACD, CACS and cardiovascular disease (CVD) in MHD patients.

Methods: The subjects were Japanese MHD patients. CACD, CACS, laboratory parameters were assessed at baseline. The subjects were stratified into CACD and CACS tertiles (T1–T3), respectively and assessed by Kruskal-Wallis test. Regression analyses for CACD were examined in MHD patients with and without CVD, respectively. Independent variables were age, sex, dialysis vintage, diabetes, current smoker, systolic blood pressure (SBP), serum magnesium, albumin adjusted-serum calcium, and geriatric nutritional risk index (GNRI).

Results: Among all 291 patients (diabetes: 37.8%, past or present CVD: 39.9%), the mean age and dialysis vintage were 66±13 years, and 104±90 months. The CACD values for T1 (n=97), T2 (n=98), and T3 (n=96), were <3.67, 3.67-3.92, and >3.92. The CACS values for T1, T2, T3 were T1 (n=95), T2 (n=98), and T3 (n=99), were <380.0, 380.0-1931.9, >1931.0. Multivariate regression analysis for CACD showed that age [β 0.30, 95% CI (0.02-0.03)], diabetes [β 0.31, 95% CI (0.39-0.80)], dialysis vintage [β 0.24, 95% CI (0.00-0.01)], β2-microglobulin [β 0.12, 95% CI (0.01-0.03)] and albumin adjusted-serum calcium [β 0.16, 95% CI (0.08-0.42)] were significantly related factors (P<0.001), but not CVD. Multivariate logistic regression for CVD showed that the highest CACS group (OR 1.9, 95% CI 1.94-3.98), current smoker (OR 1.20, 95% CI 1.20-3.99), SBP (OR 0.13, 95% CI (1.01-0.4)), and serum magnesium (OR 2.91, 95% CI (1.16-7.63), CRP (OR 0.73, 95% CI (0.53-0.95)), β2-microglobulin (OR 0.97, 95% CI (0.93-1.02)) and GNRI (OR 0.75, 95% CI (1.02-1.13)) were significantly related factors (P<0.05), but not CACD.

Conclusions: In MHD patients, presence of CVD is positively associated with CACS and hypomagnesemia, but not with CACD.

FR-PO1037

Blood Pressure and Renal Outcomes in Patients Undergoing Percutaneous Coronary Intervention

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Background: Patients undergoing percutaneous coronary intervention (PCI) require strict control of blood pressure (BP) because abnormal control is related with worse cardiovascular and other organ outcomes. However, discharge BP-dependent renal outcome after PCI has not been thoroughly evaluated.

Methods: A total of 8204 adult patients undergoing PCI were reviewed at Seoul National University Hospital from 2006 to 2016. Renal outcome was defined when either a doubling of serum creatinine, a 50% decrease of estimated glomerular filtration rate, or end-stage renal disease developed. The risks of renal outcome and all-cause mortality were evaluated according to BPs between 8:00 AM and 10:00 AM at discharge day using multivariable Cox proportional hazard regression and additive Cox regression with penalized splines.

Results: 9.5% (766 patients) of total patients reached renal outcomes during the median follow-up period of 6.5 years (maximum 13.0 years). Admission BP and discharge BP had poor correlation, and BP parameters at discharge including systolic BP (SBP), diastolic BP (DBP) and mean arterial pressure (MAP) mainly showed J-shaped relationship on renal outcome and all-cause mortality. Among BP parameters at admission and discharge, discharge SBP was the best predictor of both mortality and renal outcome. In additive Cox regression with reference BP which had minimal hazard ratios of study outcomes, there seemed to be threshold values for renal outcome (124 mmHg of SBP) and mortality (129 mmHg of SBP).

Conclusions: BP of patients undergoing PCI had J-shaped association on renal outcome and all-cause mortality. This non-linear relationship implies there could be a possible threshold of BP for renal outcome after PCI.
FR-PO1039
Prasugrel and Ticagrelor in Patients with Drug-Eluting Stents and ESRD
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Background: Prasugrel and ticagrelor have superior efficacy compared with clopidogrel in patients with preserved renal function. No randomized or cohort data exist with respect to their efficacy or safety in patients with end-stage renal disease (ESRD).

Methods: This retrospective cohort study used United States Renal Data System data from 2012 to 2015. We identified all dialysis patients who received a drug-eluting stent (DES) and were alive at 90 days after DES insertion. Prasugrel or ticagrelor users were matched 1:3 to patients treated with clopidogrel according to a propensity score. Outcomes were ascertained at 12 months. Competing risk survival models were used.

Results: Compared with clopidogrel, prasugrel or ticagrelor use was not associated with reduced risk of the composite outcome of cardiovascular mortality, myocardial infarction, or stroke: adjusted hazard ratio (HR) 0.91, 95% confidence interval (CI) 0.80-1.02 for prasugrel and HR 0.93, 95% CI 0.82-1.07 for ticagrelor. Ticagrelor use was associated with lower all-cause mortality and prasugrel use was associated with lower incidence of stroke, compared with clopidogrel. There was no difference in the incidence of fatal/ intracranial or clinically-sigificant bleeding with either of the newer antiplatelet agents, compared with clopidogrel (Table). Shorter duration of the antiplatelet agent and acute coronary syndrome at presentation were independently associated with worse prognosis.

Conclusions: This is the first study examining clinical outcomes with prasugrel or ticagrelor in ESRD. Although no major efficacy benefit was detected, both prasugrel and ticagrelor were well-tolerated in patients with ESRD and may be considered in selected cases. Disclaimer The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

Clinical outcomes with prasugrel and ticagrelor, compared with clopidogrel in patients with DES and ESRD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prasugrel vs. clopidogrel</th>
<th>Ticagrelor vs. clopidogrel</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, stroke</td>
<td>0.51 (0.49-0.53)</td>
<td>0.53 (0.52-0.57)</td>
<td>0.51</td>
</tr>
<tr>
<td>CV death</td>
<td>1.0 (0.82-1.27)</td>
<td>0.83 (0.68-1.02)</td>
<td>0.30</td>
</tr>
<tr>
<td>MI</td>
<td>0.48 (0.38-1.44)</td>
<td>0.75</td>
<td>0.74</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.74 (0.64-0.91)</td>
<td>0.80 (0.70-0.92)</td>
<td>0.74</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.98 (0.75-1.32)</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Fatal/renal bleeding</td>
<td>1.0 (0.56-2.18)</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Clinically significant bleeding</td>
<td>1.0 (0.94-1.28)</td>
<td>1.0 (0.93-1.30)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

FR-PO1040
Thirty-Day Refill Gap in Prescription for P2Y12 Inhibitor Predicts Death in Dialysis Patients
Rajendra Mandalapu,1 Junqiang Dai,1 Suzanne L. Hunt,1 Milind A. Phadnis,3 Rafia Rasu,2 Nishank Jain.1 University of Arkansas for Medical Sciences, Little Rock, AR; 1University of North Texas Health Science Center; Fort Worth, TX; 2University of Kansas Medical Center, Kansas City, KS; 4Little Rock VA Hospital, Little Rock, AR.

Background: It remains unclear whether gaps in refill of prescriptions for oral P2Y12 inhibitors (P2Y12-I) is associated with mortality in patients on chronic dialysis (ESRD).

Methods: USRDS registry from 2011 to 2015 was used to capture new P2Y12-I prescriptions for ESRD patients. The cohort was followed until death, kidney transplantation, switching between P2Y12-I, or lost to follow-up. After flagging and ascertainment for the first 6 months from the index date. Two major patterns were recognized: continuous users with no gaps in refills of 30 days and users with ≥30 days’ gap in refills.

Results: Of the 32,886 patients in the cohort, median age of the cohort 64 years (IQR: 55 years, 72 years). 54% were male, 41% Caucasians, 36% African American and 18% Hispanic. 93% on hemodialysis, 7% on peritoneal dialysis, and average time on dialysis 3.8 years. Median modified Liu Index was 7 (IQR: 4, 10), and median number of baseline medications were 7 (IQR: 5, 10). During the first 6 months from the index date, there were 14,907 patients who filled prescriptions continuously without 30 days’ gap while 16,810 patients had ≥30 days’ gap in refill. Compared to continuous refill pattern, a ≥30 days’ gap in refill of P2Y12-I prescription was associated with all-cause death, unadjusted hazard ratio (HR) 1.02 (95%CI: 0.98-1.07) and adjusted HR 1.06 (95%CI: 1.01, 1.10).

Conclusions: Gaps in P2Y12-I prescription refills of ≥30 days among ESRD patients is independently associated with short term all-cause death.

Funding: Other NIH Support - American Heart Association grant # 16SDG31000045

FR-PO1041
All Types of Aortic Valve Replacement (AVR) May Not Be Equal in ESRD: Survival After Bioprosthetic, Mechanical, and Transcatheter AVR (bAVR, mAVR, and TAVR)
Nagaraj Sarabu,1 David K. Ngedahimana,2 Krishna L. Lentine,2 Salil Deo.2 1University Hospitals Cleveland Medical Center, Cleveland, OH; 2Case Western Reserve University, Cleveland, OH; 3Saint Louis University, St. Louis, MO.

Background: Guidelines have no preference for bAVR or mAVR or TAVR in patients with ESRD. Their outcomes among those who subsequently get transplants is unclear.

Methods: All adult ESRD patients who were underwent AVR, between 1992 and 2015, were identified from the United States Renal Data System (USRDS) using ICD-9 codes. Baseline comorbidities were also identified using ICD-9 codes. Time to death was compared among the three groups (bAVR, mAVR, and TAVR) using Kaplan-Meier survival curves and with aHR (adjusted HR) using Cox proportional hazards model. These statistical procedures were performed separately for entire ESRD cohort and exclusively for those who subsequently underwent kidney transplant. TAVR group was excluded from latter analysis due to low numbers.

Results: There were a total of 9865 patients who underwent AVR (bAVR=4292, mAVR=4951, TAVR=622). Patients who underwent mAVR were the youngest and had the least comorbidity profile. Patients who underwent TAVR were the oldest and had the highest comorbidity profile (Fig 1). For the entire cohort, compared to bAVR, mAVR had better survival (aHR0.97, 95%CI:0.95-0.98) but TAVR had worse survival (aHR1.14, 95%CI:1.10-1.18). Among those who subsequently got kidney transplant, there was no difference in survival for the mAVR group compared to bAVR (aHR0.99, 95%CI:0.97-1.02) (Fig 2).

Conclusions: Mechanical AVR is the preferred choice in ESRD. TAVR may be associated with worse survival but it may be due to higher baseline comorbidity.

Baseline Characteristics of ESRD Patients Who Had Aortic Valve Replacements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Mean/Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median (IQR)</td>
<td>64 (55, 72)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>54%</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian</td>
<td>41%</td>
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<tr>
<td>Hispanic</td>
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<tr>
<td>Ethnicity</td>
<td>African</td>
<td>36%</td>
</tr>
<tr>
<td>ESRD</td>
<td>Yes</td>
<td>100%</td>
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</table>

KM Survival Curves, by Type of Aortic Valve Replacement

<table>
<thead>
<tr>
<th>Type of AVR</th>
<th>Survival Curve</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>bAVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mAVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAVR</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO1042

*Research Group, Minneapolis, MN; 2Hennepin Healthcare, Minneapolis, MN; 3Charleston, SC*

**Vinayak K. Goessl, MD**

**Background:** The benefits of transcatheter aortic valve replacement (TAVR) vs. surgery (SAVR) valve replacement are uncertain among patients receiving maintenance dialysis with aortic stenosis. We compared inpatient and 1-year mortality in dialysis patients with aortic stenosis receiving TAVR vs. SAVR.

**Methods:** We used the CMS 100% ESRD files from 2013-2015 to compare characteristics and outcomes among patients receiving TAVR or SAVR. The cohort comprised patients receiving an AVR between January 1, 2013 and December 31, 2014. Outcomes of interest were inpatient and 1-year mortality. We used the six-month period prior to the procedure to assess comorbidity using claims. We used Cox proportional hazards models to compare 1-year mortality, adjusting for patient characteristics and comorbidity.

**Results:** Of the 1867 patients who received an AVR, 66.1% received SAVR and 33.9% TAVR. TAVR patients were more likely to be older, female, and white, and have a higher comorbidity burden. Although TAVR patients experienced less inpatient mortality (4.6% vs. 7.8% for SAVR), there was no difference in 1-year mortality among those discharged alive (HR 1.1, 95% CI 0.9-1.4).

**Conclusions:** Although TAVR is an increasingly attractive option compared to SAVR in the general population, there is less evidence supporting its use in dialysis patients. Short-term outcomes appeared to be better among dialysis patients receiving TAVR despite their older age and greater comorbidity burden, and 1-year mortality was not significantly different than for SAVR.

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FR-PO1044

**Impact of Electrocardiographic Finding on Cardiac Mortality in Hemodialysis Patients: Ten-Year Outcomes of CardioRenal Clinic Study**

**Hiroto Hiyamuta, MD**

**Background:** Electrocardiography is a noninvasive and inexpensive test and regularly performed in dialysis clinic. However, its clinical predictive value in hemodialysis patients is unclear. We investigated electrocardiographic finding associated cardiac-related mortality in Japanese hemodialysis patients.

**Methods:** A total of 1087 Japanese HD patients aged ≥18 years who underwent electrocardiography within 1 year from baseline were followed for 10 years. Multivariate-adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for electrocardiographic finding of cardiac death were calculated using logistic regression analysis. To assess the additional predictive value of electrocardiographic finding in risk assessment, we compared the c-statistics between clinical model included electrocardiographic finding and basic model.

**Results:** During the follow-up period, 492 patients died totally, and 119 patients died of cardiac disease. After adjusting for confounding risk factors, heart rate (odds ratio [OR] for all cause mortality 1.46, 95% CI 1.28-1.67 for every 10 min increase), QT prolongation (OR 2.23, 95% CI 1.46-3.42), and left ventricular hypertrophy by Sokolow-Lyon voltage criteria (OR 1.81, 95% CI 1.15-2.86) was an independent predictor of cardiac-related mortality. The c-statistics of the traditional risk factors with the electrocardiographic findings in cardiac mortality were significantly increased compared to those of the traditional risk factors without the electrocardiographic findings (0.713 vs. 0.753, p = 0.02).

**Conclusions:** We demonstrated electrocardiographic finding associated with all-cause and cardiac-related mortality in hemodialysis patients. Moreover, addition of the electrocardiographic finding to models with standard risk factors significantly improves the predictive ability of cardiac-related mortality.

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FR-PO1043

**Health-Related Quality of Life After Ligation of Arteriovenous Fistula for Pulmonary Hypertension**

**Vinayak K. Goessl, MD**

**Background:** AV fistulas (AVF) are the access method of choice in patients on long-term hemodialysis. Due to their high blood flow, AVFs are also a potentially reversible cause of secondary pulmonary hypertension. There are multiple small case series describing change in the hemodynamics and improvement in the symptoms after ligation of AVF for pulmonary hypertension. There is very little data regarding health related quality of life changes (HRQOL) after ligation AVF for pulmonary HTN.

**Methods:** We used the CMS 100% ESRD files from 2013-2015 to compare characteristics and outcomes among patients receiving TAVR or SAVR. The cohort comprised patients receiving an AVR between January 1, 2013 and December 31, 2014. Outcomes of interest were inpatient and 1-year mortality. We used the six-month period prior to the procedure to assess comorbidity using claims. We used Cox proportional hazards models to compare 1-year mortality, adjusting for patient characteristics and comorbidity.

**Results:** Of the 1867 patients who received an AVR, 66.1% received SAVR and 33.9% TAVR. TAVR patients were more likely to be older, female, and white, and have a higher comorbidity burden. Although TAVR patients experienced less inpatient mortality (4.6% vs. 7.8% for SAVR), there was no difference in 1-year mortality among those discharged alive (HR 1.1, 95% CI 0.9-1.4).

**Conclusions:** Although TAVR is an increasingly attractive option compared to SAVR in the general population, there is less evidence supporting its use in dialysis patients. Short-term outcomes appeared to be better among dialysis patients receiving TAVR despite their older age and greater comorbidity burden, and 1-year mortality was not significantly different than for SAVR.

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FR-PO1045

**The Ankle-Brachial Index Is Linked to the Subendocardial Viability Ratio: A Correlation Between Peripheral and Myocardial Perfusion**

**Nejc Piko, MD**

**Background:** Subendocardial viability ratio (SEVR), non-invasively calculated through pulse wave analysis (PWA), is an index of myocardial oxygen supply and demand. Lower SEVR values are linked with advanced coronary artery disease (CAD) and higher mortality, especially in patients with chronic kidney disease (CKD). Peripheral artery disease (PAD) can be assessed by the ankle-brachial index (ABI) and is also associated with increased cardiovascular mortality. Both PAD and CAD are the result of advanced atherosclerosis and increased arterial stiffness, but the direct correlation between these two entities is still not fully understood. The aim of our study was to determine the correlation between PAD and CAD by using ABI and SEVR.

**Methods:** 86 clinically stable patients with ischemic CAD (56 male, 65.1%), who were hospitalized due to elective coronary angiography, were included in the study. Kidney function was determined by the estimation of glomerular filtration rate (eGFR) using the CKD-EPI Creatinine equation. SEVR was determined with PWA (SphygmocorÒ, Atcor Medical, Australia) and ABI index was measured using an automated, non-invasive, waveform analysis device (MESIÒ, Slovenia). All the data were obtained prior to coronary angiography.

**Results:** Mean age of patients was 64.6±9.6 years (minimum 27, maximum 82 years). 23 patients had diabetes mellitus (26.7%) and 52 patients were smokers (60.5%). Mean eGFR was 74.5±18.4 ml/min/1.73 m². Mean ABI values were 1.0±0.1 (0.76-1.31), mean SEVR values were 163.1±43.6 (92-260%). Pearson’s correlation test showed a statistically significant correlation between ABI and SEVR (r=0.251, p=0.02). Multiple regression analysis with SEVR as dependent variable has shown statistically significant association with ABI (p=0.032, beta coefficient=0.245) as independent variable, but not with age, diabetes, smoking, eGFR and cholesterol.

**Conclusions:** ABI is independently associated with SEVR in patients with stable CAD, suggesting a direct connection between peripheral and myocardial perfusion, independent of traditional atherosclerosis risk factors and kidney function.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Lipid Metabolic Profiling of Primary Sjögren Syndrome with Kidney Function Deficiency

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Background: Primary Sjögren Syndrome (pSS) is characterized by lymphocytic infiltration of the exocrine glands occurs primarily from age 50 onward, with a female to male ratio of 9:1. In a clinic, a severely affected pSS patient not only has the salivary and lacrimal glands damages, but also manifests other extraglandular diseases. Earlier research reported that lipid metabolism disorder linked to pSS caused renal disease. However, the overall lipid metabolic profile of pSS patients remains unknown. The aim of this study is to analyze lipid metabolic signature of the pSS patients with declined estimation of glomerular filtration rate (eGFR) by which to provide a new angle to underlying the pathogenesis of pSS associated renal diseases.

Methods: Donor UltiMate 300 Ultra-high performance liquid chromatography system coupled online via electrospray ionization source with an Q Extractive Orbitrap MS instrument was used to evaluate lipid metabolites in 210 female patients with pSS, compared with 396 healthy subjects. We conducted analysis of covariance with potential confounders as covariates. Receiver operating characteristic (ROC) curves were plotted to explore the significance of multiple biomarkers for renal function in pSS.

Results: We identified 1001 differentially expressed lipid metabolites between healthy adults and the pSS patients. Subtype comparisons also revealed significantly differentially expressed lipid metabolites between the pSS patients with eGFR<90ml/min/1.73m2 and eGFR>90ml/min/1.73m2. Changes in triglycerol (50:41:90:18:2), and Phosphatidyl cholines (40:8:20:4) were the most distinctive lipids between the pSS patients eGFR<90ml/min/1.73m2 and eGFR>90ml/min/1.73m2. Particularly, the diagnostic outcomes are shown via the ROC curves for comparison between healthy adults vs pSS patients eGFR<90/ml/min/1.73m2, healthy adults vs pSS (eGFR<90ml/min/1.73m2), pSS patients eGFR<90ml/min/1.73m2 vs eGFR<90/ml/min/1.73m2. Consistent with the eGFR levels, specific lipocincs-based biomarkers provided AUC of 0.975 to 0.986 in different stage of kidney disease, compared with the healthy controls. The AUC is 0.690 if directly compare the pSS patients with eGFR<90/ml/min/1.73m2 or eGFR>90/ml/ min/1.73m2.

Conclusions: pSS patients are characterized by a distinct lipid metabolic profile providing new insights into the pathogenesis of pSS renal damages.

FR-PO1047

Risk of Ischemic Heart Disease Is Increased in Patients with ANCA-Associated Vasculitis

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Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a chronic autoimmune disease characterized by inflammation of the small to medium-sized blood vessels. A well-established long-term complication of many inflammatory diseases is the occurrence of cardiovascular events. In AAV, the results of experimental studies indicate the occurrence of accelerated atherosclerosis. However, the risk of ischemic heart disease (IHD) in patients with AAV remains poorly quantified.

The aim of this study is to investigate the IHD risk in patients with AAV and to examine the effect of immunosuppressive therapy on the IHD risk.

Methods: The study included patients with AAV treated at the Vasculitis and Lupus Clinic in Addenbrooke’s Hospital (Cambridge, United Kingdom) between 1990 and 2015. The occurrence of IHD (defined as angina pectoris or myocardial infarction) in these patients was compared with the incidence in the general population by calculating standardized incidence ratios (SIRs), adjusted for sex, age, and calendar year.

Results: Of the 529 included patients, 51 patients developed a total of 57 ischemic heart events during a mean follow-up of 6.3 years. This represents a 2.0-fold increased (95%CI 1.53-2.58, p<0.001) IHD risk in AAV patients compared to the sex-, age-, and calendar year matched general population. There was no significant difference in follow-up duration of patients with and without IHD (mean follow-up of 6.3 year and 5.4 year, respectively) IHD risk was higher in patients with MPO-ANCA (SIR 2.31; 95% CI 1.55-3.34; P <0.001) than in patients with PR-3-ANCA (SIR 1.63; 95% CI 1.01-2.61; p=0.043). Moreover, IHD was increased in patients treated with cyclophosphamide (SIR 1.78; 95% CI 1.24-2.60, p=0.033), but not in patients treated with rituximab (SIR 1.03; 95%CI 0.26-4.10, p=0.971).

Conclusions: The results of this large study demonstrate that patients with AAV have an increased IHD risk as compared to the sex-, age-, and calendar year matched general population. IHD risk was higher in patients with MPO-ANCA. Importantly, IHD risk was not increased in patients treated with rituximab but was increased in patients treated with cyclophosphamide. The results of this study demonstrate a need for the active monitoring and treatment of cardiovascular risk factors in patients with AAV.

FR-PO1049

Use of Bisphosphonates in CKD Is Associated with Incident Cardiovascular Disease (CVD) and Without CKD and Improves Cardiovascular Risk

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Background: Patients with cardiovascular disease (CVD) with or without chronic kidney disease (CKD) have considerable residual risk despite optimal standard of care. Alendronate, a bisphosphonate (ALP) has been suggested as a modifiable CVD risk factor. Apabetalone, a bromodomain and extranuclear (BET) inhibitor selective for bromodomain 2 (BD2) lowers ALP in a dose-response fashion. In phase 2 studies apabetalone treatment was associated with a significant 44% reduction in CVD events. We sought to determine whether this CVD risk reduction by apabetalone is associated with the concomitant lowering of serum ALP.

Methods: In a pooled phase 2 post-hoc analysis of 795 CVD patients on standard of care treatment including statins, of which 11.8% had CKD as defined by eGFR <60 m/l. Aldosterone (n=94); 71-apabetalone (23-placebo) we assessed the effect of apabetalone vs. placebo treatment for up to 24 weeks on the incidence of CVD events and serum ALP.

Results: Apabetalone treatment decreased serum ALP in CKD and non-CKD CVD patients by 10.2% vs. placebo, respectively (12 weeks), and 7.7% and 7.2%, respectively (24 weeks, p<0.01). Further analysis on the whole population showed that baseline ALP (median 72 U/L) predicted MACE (death, non-fatal myocardial infarction, coronary revascularization, or hospitalization for cardiovascular causes), independent of high-sensitivity C-reactive protein (hsCRP), sex, age, study, established CVD risk factors, CKD treatment allocation (placebo vs. [HR] per 1 SD increase of ALP 1.00 [95% CI 1.22-1.21, p<0.001]. In the apabetalone group, a 1 SD reduction in ALP was associated with a HR for MACE of 0.58 (95% CI 0.43-0.78, p<0.001).

Conclusions: Serum ALP predicts strongly the residual cardiovascular risk, independent of hsCRP, established cardiovascular risk factors and CKD, in patients with cardiovascular disease on statin treatment. Apabetalone lowers serum ALP and may prevent the incidence of new cardiovascular events. The phase 3 BETonMACE CV outcomes study reporting H2 2019, will provide further insights about apabetalone’s ALP reduction and potential causality for CVD events.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Contrary to our hypothesis, we show, for the first time, that bisphosphonate use is associated with increased incident CVD in CKD patients. Our analysis was limited by a small sample size. However, future studies in larger cohorts are necessary to confirm these findings and to better understand the mechanisms underlying this association.

Funding: Veterans Affairs Support

FR-PO1050

Effects of Vitamin D on Cardiovascular and Renal Outcomes in Adults with CKD: A Systematic Review with Meta-Analysis of Randomized Controlled Trials

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Background: Cardiovascular disease (CVD) is the leading cause of mortality in patients with chronic kidney disease (CKD). The excess risk has been attributed to increased vascular calcification and higher prevalence of left ventricular hypertrophy. Vitamin D therapy plays an important role in management of secondary hyperparathyroidism but may also have cardioprotective effects. This systematic review was performed to study the effects of vitamin D therapy on cardiovascular and renal outcomes.

Methods: MEDLINE, EMBASE and Cochrane databases were searched for randomised controlled trials involving CKD patients stages 3-5D with ≥3 months follow-up that compared a vitamin D compound (nutritional or active) with placebo, no study medication, or an active medication. For continuous variables, the change between the baseline value and end-of-treatment value was calculated. Summary estimates were obtained by a random-effects model and expressed as weighted mean differences (WMD) or relative risks (RR) with 95% confidence intervals (CI).

Results: One hundred and thirteen trials (9973 participants) were included (mean age 60.5 years, median follow-up 6 months). Of these, 71 trials were conducted in 6036 dialysis patients, and 42 trials were conducted in 3937 non-dialysis CKD patients. Trials were generally at high or unclear risk of bias. There was no significant difference in risk of major adverse cardiovascular outcomes when comparing vitamin D placebo (11 trials, RR 0.98, 95%CI 0.65-1.48), or active and nutritional vitamin D (2 trials, RR 0.85, 95%CI 0.32-2.31). Compared to placebo, vitamin D did not significantly change systolic blood pressure (7 trials, WMD 0.43 mmHg, 95% CI -3.43 to 4.29), diastolic blood pressure (5 trials, WMD 0.58 mmHg, 95%CI -2.16 to 3.32), pulse wave velocity (4 trials, WMD -0.75 m/sec, 95%CI -1.56 to 0.07), left ventricular mass (4 trials, WMD 2.17 g/m², 95%CI -8.01 to 12.36) or glomerular filtration rate (11 trials, WMD -0.25 ml/min/1.73m², 95%CI -0.78 to 0.29). Data for B-natriuretic peptide levels and urine albumin/creatinine ratio were insufficient for meta-analysis.

Conclusions: The effects of vitamin D compounds on cardiovascular and renal outcomes in CKD are uncertain. Further research with adequately powered trials is needed.

FR-PO1051

Effect of Renin-Angiotensin System Blockade on Stroke in Kidney Transplant Recipients: Retrospective Multicenter Study in Japan

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Background: Renin-angiotensin system blockers (RASBs) reduce end-stage kidney disease and cardiovascular event (CVE) development in chronic kidney disease. However, whether RASBs improve long-term prognosis in kidney transplant (KT) recipients remains unknown.

Methods: We investigated 900 kidney transplant patients in a multicenter retrospective cohort study in Japan and compared death-censored graft-survival and CVE (total, cardiac events, stroke) based on RASB use within 12 months after KT. The associations were examined using a Cox hazard model and propensity score-matching analysis.

Results: The cohort comprised 375 patients treated with RASBs (RASB group) and 525 patients without RASBs (control group). The median observation period was 82 months, with 68 patients reaching graft loss: 79 total CVE, 36 cardiac events, 26 stroke. In a matching cohort comprising 582 patients, graft survival, total CVE, and cardiac events were not different between the two groups. Only stroke incidence rate was significantly lower in the RASB group compared with the control group (1.4 vs. 6.4 per 1000 patients/year, log-rank P=0.005). In a multivariable analysis, stroke events were also significantly lower in the RASB group compared with the control group (Hazard ratio 1.40 vs. 6.40 per 1000 patients/year, log-ranked P=0.005). In a multivariable analysis, stroke events were also significantly lower in the RASB group compared with the control group (Hazard ratio 1.40 vs. 6.40 per 1000 patients/year, log-ranked P=0.005). The cumulative incidence for each endpoint was compared between the RASB and control groups: (A) Total CVE, consisting of cardiac event, stroke, and peripheral artery disease; (B) Cardiac event; (C) Stroke; (D) Death-censored graft-survival.

Conclusions: Contrary to our hypothesis, we show, for the first time, that bisphosphonate use is associated with increased incident CVD in CKD patients. Our analysis was limited by a small sample size. However, future studies in larger cohorts are necessary to confirm these findings and to better understand the mechanisms underlying this association.

Funding: Veterans Affairs Support

FR-PO1052

Postural Blood Pressure Control Is Decreased in Diabetic Patients After Successful Renal Transplantation

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Background: The postural control of blood pressure (BP) under othostatic challenges, a measure of the robustness of the autonomic nervous system, is reduced in both renal insufficiency and diabetes mellitus (DM). The present study was undertaken to assess the effect of normalization of kidney function by renal transplantation (TX) on postural changes of BP and autonomic indices in uremic patients, without [DM(-)] and with [DM(+)].

Methods: Continuous interbeat interval (IBI), systolic (SBP) and diastolic (DBP) BP and their variabilities in the low (LF) and high (HF) frequency ranges were recorded during sitting and standing in 48 TX DM(-), in 14 TX DM(+), and in 37 control (C) individuals of similar age range. α index, a measure of baroreflex function was obtained from the square roots of the ratio of average IBI and SBP powers. LF IBI/HF IBI was considered a measure of the sympatho-vagal balance.

Results: Plasma creatinine was 116±31 and 113±43 μmol/l in TX DM(-) and TX DM(+) respectively (pNS). Differences (A) in BP and variability measures between sitting and standing positions (median and interquartile ranges) are shown in Table1. In C, moving from sitting to standing was associated with increased BP, decreased IBI, and increases in LF, HF and α indices and increased sympatho-vagal balance. These changes were partly maintained in TX DM (-) but markedly suppressed in TX DM (+).

Conclusions: Our data show that in C, BP during postural changes is maintained by sympathetic activation, which is partially attenuated in TX DM (-) and almost abolished in TX DM(+), despite the reversal of renal failure. These alterations, arguably the consequence of long standing DM autonomic neuropathy, may be responsible for frailty, gait instability and falls in these patients.

Table 1.

<table>
<thead>
<tr>
<th>Measure</th>
<th>TX DM(-)</th>
<th>p vs C</th>
<th>TX DM(+)</th>
<th>p vs C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ SBP (mmHg)</td>
<td>0.7 (1.6)</td>
<td>0.018</td>
<td>1.0 (2.4)</td>
<td>0.045</td>
</tr>
<tr>
<td>Δ DBP (mmHg)</td>
<td>-0.06 (1.1)</td>
<td>0.007</td>
<td>0.1 (2.3)</td>
<td>0.008</td>
</tr>
<tr>
<td>Δ IBI (ms)</td>
<td>-58 (72)</td>
<td>0.011</td>
<td>-45 (76)</td>
<td>0.002</td>
</tr>
<tr>
<td>Δ LF IBI (μm²/s²)</td>
<td>0.105 (1.17)</td>
<td>0.002</td>
<td>0.09 (20.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Δ LF DBP (μm²/s²)</td>
<td>17.7 (25.1)</td>
<td>0.003</td>
<td>10.5 (22.9)</td>
<td>0.035</td>
</tr>
<tr>
<td>Δ HF IBI (μm²/s²)</td>
<td>-1.2 (3.0)</td>
<td>0.044</td>
<td>1.2 (3.3)</td>
<td>0.047</td>
</tr>
<tr>
<td>Δ HF DBP (μm²/s²)</td>
<td>-0.40 (3.8)</td>
<td>0.012</td>
<td>0.42 (4.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Δ LF/HF IBI (IU-IU)</td>
<td>1.57 (3.9)</td>
<td>0.001</td>
<td>2.7 (4.2)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Δ: difference of sitting- standing measurements.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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FR-PO1053
The Relationship Between Retinal Artery Wall-to-Lumen Ratio and Kidney Pathology Findings in Accelerated Hypertension
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Background: Accelerated hypertension is characterized by macrovascular and microvascular endothelial damage. In this study we analyze the relationship between retinal artery wall-to-lumen ratio (WLR) and renal pathology.

Methods: All patients hospitalized into Kidney Intensive Care Unit for malignant hypertension with acute kidney injury had measurement of retinal artery wall-to-lumen ratio (WLR) using SPECTRALIS retina imaging. Renal clinical and pathology findings were collected as well as details pertaining to heart echography. Data were presented as median (25%-75%) correlation were calculated according to Spearman’s test.

Results: Twenty-seven patients were hospitalized for accelerated hypertension in our center between September 2016 and April 2019. Median age was 39.4 years old (30.7-45.3). Initial systolic, diastolic and mean arterial pressure were 218 (185-239), 128 (113-162) and 153 (137-187) mmHg, respectively. Ten (37.0%) patients underwent hemodialysis during their stay, 8 (29.6%) patients underwent chronic haemodialysis, 4 (14.8%) had myocardial microvascular involvement, 4 (14.8%) had posterior-reversible encephalopathy syndrome, Seventeen patients (63.0%) had kidney biopsy. Retinal WLR was correlated with systolic and mean arterial pressure, respectively r=0.56 (p=0.003) and r=0.46 (p=0.02), but did not reach significance for tubulo-interstitial fibrosis (r=0.44, p=0.09) or glomerulosclerosis (r=0.38, p=0.15). Retinal WLR was not correlated with renal WLR (r=0.13, p=0.6). Retinal WLR did not correlate with left ventricular mass estimation (r=0.10, p=0.6).

Conclusions: Retinal WLR was found to be closely correlated to initial systolic and mean arterial pressure. Perhaps due to the cohort size, we failed to demonstrate an association between retinal WLR and kidney pathology findings.

FR-PO1054
Role of Endothelial Function Determined by Asymmetric Dimethylarginine in the Prediction of Resistant Hypertension: A Subanalysis of the ReHot Trial
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Background: Endothelial dysfunction has been conceived as the basis of cardiovascular disease. Brought in core of global epidemic of obesity and the increased life expectancy, resistant hypertension (ReHy) represents a growing public health issue. We conducted a subanalysis of the Resistant Hypertension Optimal Treatment (ReHot) study to evaluate the association between endothelial dysfunction and resistant hypertension in a population of patients treated in a staged fashion for hypertension.

Methods: ReHot was a prospective, multicenter, randomized trial comprising 26 sites in Brazil. One hundred and three hypertensive patients of one site were included for this 6 months study in 7 visits (V0-V6), 28 days apart. There was a first phase (V0-V3) of antihypertensive adjustment with 3 drugs to detect ReHy. A second randomized phase (V4-V7) of treatment with a fourth drug (clonidine or spironolactone) in the hypertensive patients characterized as resistant. Serum asymmetric dimethylarginine (ADMA) was determined by high performance liquid chromatography (HPLC) on Visits 1 and 7.

Results: Of the 103 patients included, 86 (83.5%) underwent the randomization visit (V3), 71 were characterized as non-resistant hypertensives (82.5%) and 15 as resistant hypertensives (17.5%). Patients from the upper tercile of serum ADMA had a higher V1 blood pressure, higher total cholesterol values as well as higher prevalence of cardiovascular disease. There was a parallel reduction in blood pressure levels and ADMA values during follow-up with a positive correlation in both groups and a greater reduction among those with ReHy. Serum ADMA was shown to be an independent predictor of resistant hypertension after adjustment for multiple variables (OR: 11.42, 95% CI: 1.02 - 127.71, p = 0.048).

Conclusions: We demonstrated that ADMA was an independent predictor of resistant hypertension, and we observed that the improvement in blood pressure levels obtained with the treatment was proportional to the reduction in ADMA values, suggesting a complementary role of ADMA not only as a stratification tool for the occurrence of resistant hypertension, but also as a potential therapeutic target in this population.

FR-PO1055
Impedance Cardiography-Guided Individualized Hypertension Treatment
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Background: Current guidelines for management of hypertension (HTN) allow considerable leeway in selection of antihypertensive medications to achieve new lower blood pressure (BP) targets. Success in achieving target BP remains suboptimal. We observed BP outcomes under standard (standard) and individualized (modified) HTN treatment protocols.

Methods: We instituted a practice improvement project comparing standard to modified treatment protocols for the management of patients referred for resistant HTN with or without chronic kidney disease. The modified protocol, managed by two nephrologists, was centered around hemodynamic status: vasoconstricted, hyperdynamic, or mixed state. Hemodynamic status was defined by impedance cardiography (central BP and pulse wave velocity were measured in a subset of patients). Antihypertensive medications were adjusted to treat the hemodynamic state. During an initial 6-month run-in, patients not in target BP were assigned to study groups. We compared BP outcomes using paired and unpaired t-tests at the study end.

Results: Of 169 patients at baseline, 88 continued with standard care and 81 were managed with the modified protocol. Demographics were similar in both groups. The modified group had significant reductions in both systolic BP and diastolic BP baseline to study end but the standard care group had little to no change (see Figure 1). At study end, 45.7% and 11.4% were in target BP in the modified and standard groups, respectively (p=0.001). This correlated with increased use of calcium channel blockers and beta-blockers in the modified group compared to standard care.

Conclusions: Impedance cardiography is a simple, noninvasive method for evaluating underlying hemodynamic drivers of HTN. Hypertension management is more effective when guided by hemodynamic parameters.

Funding: Commercial Support - New NI Medical, AtCor Medical, Inc.
Management of Resistant Hypertension due to Renal Artery Stenosis

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Introduction: Medical management of secondary hypertension caused by renal artery stenosis (RAS) remains mainstream especially after the publication of Cora Study. Cora Study suggested no difference in blood pressure (BP) control between medical management alone and medical management plus percutaneous intervention. Some patients’ clinical picture does not fit in the inclusion criteria of Cora Study, the management should be individualized.

Case Description: A 68-year-old white male with uncontrolled HTN on 5 antihypertensive medications, HLD, T2DM, CKD Stage 3-4. His antihypertensive medications include: amlopidine 10mg daily, Chlorthalidone 25mg daily, hydralazine 50mg 3 times a day, terazosin 5mg daily at bedtime, and clonidine 0.3mg twice a day. Patient was briefly on lisinopril which was stopped after patient developed acute renal failure with hyperkalemia. His BP had been 180-210/80-90’s for most time. Our work-up was significant for renin activation. His renin was 34.8 ± 19.4 years, estimated glomerular filtration rate (eGFR): 34.8 ml/min/1.73m². Renal US showed right kidney 10.2cm, left kidney 7.4cm. Angiography showed severe narrowing at the right renal artery orifice which has early bifurcation, involving the upper and lower branches. Left renal arteriogram: A small accessory lower pole left renal artery is visualized with complete occlusion of the main left renal artery. Renal vein sampling was done 3 days later. Renin activity of left renal vein was 30.62, whereas that of the right renal vein was 117.05. M/E ratio.

Underline represents presenting author.

Conclusions: The management of resistant hypertension due to renal artery stenosis needs to be individualized.

FR-PO1058

Chronotherapy of Renin-Angiotensin System (RAS) Inhibitor Ameliorates Renal Damage via Suppression of Intrarenal RAS Activity

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Background: We have shown that intrarenal RAS with chronic kidney disease (CKD) patients is activated and that intrarenal RAS activity contributes to blood pressure (BP) elevation, abnormal circadian rhythm of BP and renal damage. Moreover, changing the administration time of RAS inhibitors from morning to evening, namely chronotherapy, decreases BP and ameliorates renal damage during nighttime. However, it has not been clarified whether chronotherapy changes intrarenal RAS activity and the change of intrarenal RAS activity by chronotherapy reflects the change of BP and renal damage.

Methods: We recruited 34 CKD patients who took RAS inhibitors in the morning (sex: 22 males / 12 females, age: 60.2±19.4 years, estimated glomerular filtration rate (eGFR): 34.8±30.8 ml/min/1.73m²). We collected urine during daytime and nighttime, respectively, and evaluated urinary albumin (U-Alb) and urinary angiotensinogen (U-AGT), a surrogate marker for intrarenal RAS activity. Ambulatory BP monitoring was conducted at 30-min intervals during the daytime and nighttime. Thereafter, the same experiments were made after 4.1±0.5 days from change of the administration time. The ratios of clinical parameters morning dosing against evening dosing were defined as M/E ratio.

Results: The excretion levels of U-Alb and U-AGT during daytime and nighttime were significantly decreased by chronotherapy in all CKD patients. M/E ratio of U-Alb had significant and positive relationships with M/E ratio of U-AGT. Moreover, there were significant and positive relationships between M/E ratio of U-Alb and U-AGT during nighttime (β=0.73 and p=0.005), but not daytime (β=0.39 and p=0.098) in the CKD patients whose M/E ratio of U-AGT is less than 0.8. M/E ratios of clinical parameters morning dosing against evening dosing were defined as M/E ratio.

Conclusions: In the CKD patients who have nondipper or riser patterns when the night-to-day ratio of systolic BP is 0.90–1.00 or >1.00, respectively.

Underline represents presenting author.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
hospitalization due to HF. Minor outcomes were proteinuria, BP change, renal failure, hyperkalemia, hypotension, and withdrawal due to adverse events.

**Results:** Eighty-one studies fulfilled the inclusion criteria, yielding 76,866 patients. When compared to monotherapy, the dual RAS blockade reduced blood pressure and proteinuria. In HF subgroup, dual RAS blockade reduced hospitalizations due to HF (relative risk (RR)=0.82, 95% CI:0.71-0.94, P=0.004), (number needed to treat (NNT)=15), but had no effect on all-cause mortality (RR=0.98, 95% CI=0.88-1.09; P=0.72) and cardiovascular mortality (RR=0.92, 95% CI=0.79-1.06; P=0.25). Despite a decrease in blood pressure of 11.7 / 7.5 mm Hg in the HTN subgroup and a decrease in proteinuria, dual RAS blockade failed to slow progression to ESRD and was associated with increased rates of renal failure, hyperkalemia, hypotension, and withdrawal due to adverse effects. Neither in DM or CKD were there any outcome benefits.

**Conclusions:** When compared to monotherapy, dual RAS blockade failed to improve morbidity and mortality in HF, CKD, DM, and hypertension but reduced hospitalizations due to HF. Dual RAS blockade failed to slow progression to ESRD and led to higher withdrawal rates because of adverse effects.

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**FR-PO1062**

Relationship Between 24-Hour Blood Pressure (BP) Load and Renal or Cardiac Outcomes in Children with CKD

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**Background:** Blood pressure (BP) load, the proportion of elevated BPs detected by 24h ambulatory blood pressure monitoring (ABPM), is not a uniform criteria for diagnosing hypertension in all BP guidelines. We aimed to determine whether systolic BP load on ABPM was associated with adverse renal or cardiac outcomes in children with chronic kidney disease (CKD).

**Methods:** We analyzed data from 533 children with CKD. We categorized the BP status of participants as normotensive (normal mean awake/sleep BP and normal BPL), isolated BPL elevation (normal mean awake/sleep BP, elevated BPL >25%), or hypertensive (elevated mean awake/sleep BP, regardless of BP load). We examined the association between BP status and left ventricular hypertrophy (LVH) in logistic models and ESRD in Cox models. We also examined the value of considering BPL (as a continuous variable) independently and in conjunction with mean BP in predicting outcomes. We tested for differences in risk discrimination in our models (using c-statistics).

**Results:** One-third of the cohort met criteria for ambulatory hypertension and an additional 25% of participants had isolated BPL elevation. In both unadjusted and adjusted analyses, isolated BPL elevation was not statistically significantly associated with LVH or ESRD compared to those with normotension, whereas hypertension was (figure). Although BPL was independently associated with risk of ESRD, when used in conjunction with mean BPs, BPL was no longer associated with outcomes (table). BPL also provided poor risk discrimination for LVH and ESRD (table).

**Conclusions:** BPL may not provide additive prognostic information over and beyond mean BP, and isolated BPL elevations were not associated with risk of LVH or ESRD in children with CKD.

**Funding:** NIDDK Support

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**FR-PO1063**

Ambulatory Hypertension Disproportionately Affects African American Children with Non-Glomerular CKD Independent of Socioeconomic Factors

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**Background:** Although hypertension is common in children with chronic kidney disease (CKD), particularly among African Americans (AA), the extent to which that association is explained by socioeconomic factors (SES) is not well known. The objective of this study was to contrast racial differences in ambulatory hypertension among children with CKD before and after adjustment for putative confounding SES factors.

**Methods:** This cross-sectional analysis comprised 1021 repeated measures from 475 children enrolled in the CKD study, stratified by glomerular and non-glomerular diagnosis. Children (1-16 years, eGFR 30-90 ml/min/1.73m² at study entry) with at least 1 ambulatory blood pressure monitor (ABPM) measurement were included. Logistic regression models were used to estimate odds ratios (OR) of ABPM hypertension (systolic
or diastolic wake/sleep blood pressure $\geq 95^\text{th}$ or load-25$^\text{th}$ percentile) associated with AA race. Inverse probability weighting was used to account for potential confounding of SES (public insurance, food insecurity, household income, maternal education), abnormal birth history, demographics (age, sex), obesity (BMI$>95^\text{th}$ percentile) and disease severity (eGFR$<45$ mL/min/1.73m²) at study entry.

Results: Overall prevalence of ambulatory hypertension was 54%. AA children with both glomerular and non-glomerular CKD were disproportionally affected by SES variables by univariate analysis. In unadjusted models, AA children with non-glomerular disease had higher odds of ambulatory hypertension (OR=2.93; 95%CI:1.57, 5.47, p=0.001). Multivariable analysis adjusted for demographics, SES, birth history, obesity, and disease severity showed that among the non-glomerular group, AA children had 3.08-fold odds (95%CI:1.38, 6.00, p=0.001) of ambulatory hypertension. However, there was no difference in ambulatory hypertension between AA and Caucasian children with glomerular CKD, either unadjusted (OR=1.54; 95%CI:0.73, 3.26, p=0.262) or adjusted (OR=1.26; 95%CI:0.40, 4.00, p=0.694).

Conclusions: AA children with non-glomerular CKD are disproportionally affected by ambulatory hypertension, independent of SES. Glomerular injury is a driving force of hypertension, thus minimizing racial differences in ambulatory hypertension after adjustment for SES in children with glomerular CKD.

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FR-PO1064
Discordances Between Pediatric and Adult Thresholds in the Diagnosis of Ambulatory Hypertension in Adolescents with CKD

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Background: The diagnostic threshold for hypertension (HTN) by 24-hour ambulatory blood pressure (ABP) monitoring in adults was changed in the updated American Heart Association (AHA) 2017 guidelines. Our objective was to compare the prevalence, sensitivity/specificity, and predictive value of a diagnosis of HTN by pediatric versus adult ABP monitoring thresholds in children with CKD.

Methods: We included 371 children with CKD ages 13 or older. We used normative pediatric cut-offs (sex/height-based), prior adult cut-offs (awake SBP>135 mmHg, sleep>120), and updated AHA 2017 cut-offs (awake<130 mmHg, sleep<110) to define HTN and determine its prevalence. We then compared the sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) of each threshold for development of left ventricular hypertrophy (LVH) and progression to end-stage renal disease (ESRD).

Results: 27% of the cohort met criteria for HTN using pediatric ABP normative thresholds, versus 47% by the updated AHA 2017 adult threshold and 16% by prior adult guidelines (Table). For LVH, the sensitivity of all thresholds was poor with the prior adult criteria being the least sensitive but most specific (Figure). For ESRD, the updated AHA 2017 adult threshold had the greatest sensitivity but lowest specificity (Figure). Overall, the PPV and NPV were similar across all thresholds for LVH and ESRD.

Conclusions: In adolescents with CKD, the updated AHA 2017 adult threshold leads to the highest prevalence of ambulatory HTN and has variable sensitivity and specificity for LVH versus ESRD. The pediatric thresholds had lower sensitivity but higher specificity vs. the AHA 2017 criteria. Further research is needed to optimally define ambulatory HTN as adolescents transition to adulthood.

Funding: NIDDK Support

FR-PO1065
Hypertension and Obesity in High School Students: Genetic and Environmental Factors in the HYGEFY Study

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Background: The clinical outcomes associated to hypertension and obesity in the young population are major risk factors for renal and cardiovascular events in the adult age. Objectives of the study are: to assess the associations among genetic and environmental factors and blood pressure (BP) in a high school population before developing hypertension and to study the transition from normotension to hypertension. Methods: data from 385 high school students in three different regions of Italy. Participants underwent anthropometric, BP measurement and saliva and urine sample collection. Selected genetic variants were determined.

Results: Our results confirmed the link between body weight, salt intake and BP in adolescents (p<0.005; R square 30%). Analysis of BP values (adjusted for BMI, waist circumference, age, sex, region) and genetic polymorphisms evidenced associations with Lanosterol Synthase (LSS), an enzyme involved in Endogenous Ouabain synthesis. The A allele of a missense variant in LSS gene was associated to higher diastolic and systolic BP levels (DBP: LSS AA+AC 69.7±32 mmHg, LSS CC 68.8±30.3, p=0.004; SBP: LSS AA+AC 120.3±0.5, CC 119.3±0.4, p<0.008). Furthermore, a Klotho (KL) missense genetic variant resulted strongly associated to 24-h urinary Na excretion (p<0.017, r square 0.28). The urinary proteomic study showed an augmented excretion of IL1 in both ADD1 T subjects and LSS C subjects, suggesting an increased inflammatory activity.

Conclusions: In this young Italian population we detected specific environmental factors (such as high salt intake) and gene polymorphisms linked to higher BP values. This help to create the basis for future interventions in educational, clinical and/or pharmacological studies.

FR-PO1066
Persistence of Hypertension from 5-7 Years After Pediatric Cardiac Surgery

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Background: We have determined that children who require surgery for congenital heart disease (CHD) are at an increased risk for hypertension 5 years after cardiac surgery. The objective of this study is to assess the long-term risk of hypertension after cardiac surgery and if hypertension improves or is sustained.

Methods: We prospectively enrolled children from 1 month to 18 years old, undergoing cardiopulmonary bypass. Children who survived their surgical hospitalization had blood pressure measured at two in-person follow-up visits (median 5.4 years and 7.4 years after surgery). Elevated blood pressure and hypertension was defined using the American Academy of Pediatrics 2017 Hypertension guidelines. We compared the risk of hypertension status at the 5 and 7-year visits using the McNemar test.

Results: Of the 131 children with a follow-up visit 5 years after cardiac surgery, 88 (67%) children participated in the 7-year follow-up visit. Baseline characteristics were not significantly different between children that participated in both the 5 and 7-year visit vs those who only participated in the 5-year visit. The median age of the cohort at the 7-year follow-up was 10.6 [IQR: 7.6 – 15.2] years and 47% were female. 32 children had previously had a septal defect repair, 15 an inflow/outflow tract or valve procedure, 34 had a combined procedure, and 7 were not defined. Elevated BP was present in 16 (18%) and 13 (13%) children at the 5-year and 7-year visit, respectively. Hypertension was present in 13 (13%) and 15 (17%) children at the 5-year and 7-year visit, respectively, with no statistically significant change in the two visits (p=0.95). Between the 5-year and 7-year visits, hypertension was sustained in 8 (62%) patients.

Conclusions: The long-term risk of elevated blood pressure and hypertension was common at both the 5 and 7-year visits and hypertension was sustained in the majority of children after cardiac surgery. The risk factors for sustained hypertension should be studied in children with congenital heart disease.

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FR-PO1067
Hypertension as a Modifiable Risk Factor in Children with Immune Complex MPGN and C3 Glomerulopathy

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Background: Hypertension is a known complication of complement-mediated renal disease and carries prognostic significance. Hypertension is associated with reduced GFR in children with immune-complex membranoproliferative glomerulonephritis (IC-MPGN). Similarly, hypertension has been associated with poor renal function and
FR-PO1068
Recategorization of Adolescent Hypertension (HTN) by Ambulatory Blood Pressure (ABPM) Using Adult Norms Compared with Pediatric Norms
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Background: 2017 guidelines for pediatric blood pressure (BP) applied adult BP norms to define clinic HTN in patients (pts) ≤ 13 yrs. The 2014 pediatric ABPM guidelines recommended applying sex and age specific percentile norms for pts < 18 yrs. When applying adult BP norms to define ABPM HTN in adolescents is scarce. We aimed to evaluate the re-categorization of HTN by ABPM alone when applying adult ABPM norms in pts ≤ 13 yrs.

Methods: Retrospectively, pts 13-17 yrs who were on an ABPM between 9/2018 and 5/2019 were reviewed to collect gender, age, BP med status, ABPM systolic and diastolic BP mean and load for 24hr, day, and night, and left ventricular mass index (LVMI). According to the respective guidelines using only ABPM. LVH was defined as LVMI > 51 g/m².

Results: 357 pts (243 male) had ABPM data. 172 had LVMI data; 33 pts on BP meds with controlled HTN were excluded (final n=193). LVMI correlated significantly with systolic BP (24h, day, night) and mean and load for 24h BP. 81% of pts ≥ 13 yrs had LVH when defined by AHA2005 and 85% had LVH by 2017 guidelines.

Conclusions: There is significant difference in the categorization of HTN depending on the norms applied. HTN is significantly associated with LVH when AHA2005 and ESV guidelines are applied. Application of adult norms to define ABPM HTN in adolescents should take into account these differences with thoughtful evaluation of outcomes.

FR-PO1069
Relationship of Blood Pressure to Sleep in High School Students
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Background: Childhood hypertension is a risk factor for adult hypertension and target organ damage. Emerging data suggests a role of inadequate sleep in hypertension. In our previous study, newly diagnosed primary hypertension children had less weekend catch up sleep and age and sex matched normotensives. The usual sleep pattern of adolescents shows less sleep on school days with catch up sleep on the weekends, but it is not known if blood pressure (BP) tracks the changes in sleep over the course of the week. The aim of this study is to compare the BP of high school students at the beginning of the week with that at the end of the week. We also studied the relationship of self-reported weekday and weekend sleep duration to the BP.

Methods: Students from a public high school (11 and 12th grade) were asked to participate. Interested students completed a questionnaire. BP, height and weight were measured on Monday and Thursday morning of the same week. Average of 3 consecutive BP was taken using automated Omron BP 786 monitor. Weekday and weekend total sleep duration (WDTST and WETST) was estimated from the questionnaire responses for usual getting in and getting out of bed time. T-test and multivariate linear regression were used for analysis.

Results: Of the 32 students recruited, 24 were female. Systolic BP on Monday and Thursday was 114.8 ± 16.5 and 110.9 ± 13.1 mm Hg respectively. Diastolic BP on Monday and Thursday was 72.7 ± 7.4 and 70.9 ± 13.7 mm Hg respectively. BMI was 25.7 ± 5.5 Kg/m². WDTST was 418.6 ± 80.1 and WETST was 566.9 ± 132.3 minutes. Paired T-test showed no significant difference between SBP and DBP for Monday and Thursday. However, multiplicative regression analysis showed an inverse relationship of SBP-Monday (adjusting for BMI) with WDTST (p = 0.016) and WETST (p = 0.017). Similar results were seen for DBP-Monday (adjusting for BMI) with WDTST (p = 0.049) and WETST (p = 0.038).

Conclusions: Our results show that shorter sleep time is associated with higher BP in high school students. Previous studies in children and adults have also shown higher BP in subjects with short sleep durations. Beneficial effect of sleep extension has also been observed in prior studies. In our subjects, weekend sleep duration was about 2.5 hours longer, but BP-Monday was not different from that on Thursday. Lack of information on Monday night sleep time and a small sample size are main limitations.

FR-PO1070
Clinical Features of Pediatric Patients with Severe Hypertension (HTN) Requiring Infusions in the Pediatric Intensive Care Unit (PICU)
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Background: Data regarding PICU management of severe HTN, defined as receiving continuous antihypertensive infusions (antiHTN), are scarce. We aimed to describe the clinical characteristics of this population.

Methods: A medication order report from January 2017-July 2018 identified pts 2-22 yrs receiving antiHTN infusions in the PICU. Vasopressors 6 hrs prior to antiHTN, cardiac surgery, neurosurgery, or ECMO were reasons for exclusion. For comparisons, we used adult and pediatric systolic and diastolic blood pressure index (sBPdBPI) as the ratio of absolute BP to the threshold for stage 2 HTN [95% percentile ≥ 12 mmHg for age, sex, and height <13 yrs] or 140/90 mmHg (≥ 13 yrs) based on 2017 guidelines.

Results: All 78 pts (11.7/5.3 yrs, 56% male) had sBP and ≥ 185% had dBPI at 1 and 85% had dBPI at antiHTN initiation. Nicardipine was the most common antiHTN (90%). The most common symptoms (64.1%) were neurologic (headache, altered mental status, seizure); 22% were asymptomatic. Neuroimaging was performed in 49 pts of which 68% (33/49) were abnormal. 45% (35/78) had AKI. Only 21 pts had eye exams; 19% (4/21) had retinopathy. 68% (33/78) had echocardiograms of which 53% (26/53) had LVH. There was no association between LVH and dBPI (95% CI 0.7 to 565.3, p=0.08) or LVH (95% CI 0.1 to 100.9, p=0.3). Pts with chronic HTN had a higher odds of having LVH (OR 3.98, 95%CI 1.1-15.06, p=0.04).

Conclusions: A significant number of children who present with severe HTN have evidence of end organ damage on assessment. Neurologic findings are most common and frequently accompanied by abnormal neuroimaging. LVH is common and more likely present in patients with chronic HTN.

Baseline Characteristics, reported as mean+/− SD or median (IQR)

FR-PO1071
Family History as a Risk Factor for Blood Pressure Control in Pediatric Hypertension
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Background: Hypertension (HTN) in adults is an leading cause of death worldwide. Pediatric HTN often persists into adulthood. We investigated whether a family history of HTN influences blood pressure (BP) control in hypertensive children.

Methods: A retrospective chart review was done on patients aged 0-18 at a HTN clinic between 01/2014-03/2018. HTN was defined as a systolic or diastolic BP greater than the 95th % for age and gender. Patients with chronic kidney disease and those without HTN were excluded. We included children with both primary and secondary HTN. Linear mixed effects regression models were used to compare BP z scores over time. Cox proportional hazards regression was used to assessed time to achieve BP control, defined as a systolic and diastolic BP less than the 90th %.

Results: 410 patients were included in the analysis. Mean age at diagnosis was 9.17 years and 266 (65%) were males. 223 (54%) had a positive family history of HTN. There was no significant difference in systolic BP Z scores over time between the two groups
Conclusions: There was a known family history of HTN in over 50% of children with HTN. Family history did not significantly affect longitudinal BP control nor the time it took to achieve good BP control. Future research should be directed at evaluating short- and long-term outcomes in these children.

FR-PO1072
Abnormal Blood Pressure Patterns on Ambulatory Blood Pressure Monitoring Prior to Pediatric Hematopoietic Cell Transplantation (HCT): False Alarm or Cause for Concern?
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Background: Hypertension (HTN) influences morbidity and predicts renal and cardiovascular (CV) outcomes following HCT. Systematic misclassification of HTN may occur with the use of casual blood pressure (BP) measurements; therefore, ambulatory blood pressure monitoring (ABPM) is recommended in children and adolescents with high-risk conditions. Diagnosis of HTN by ABPM strongly correlates with risk of target organ damage. We conducted a pilot prospective observational study using ABPM to determine BP risk profile of patients (pts) undergoing first allogeneic HCT.

Methods: Pts age 5-21 yrs at Texas Children’s Hospital were recruited prior to HCT from November 2018 to May 2019. Of 22 pts recruited, 16 had ABPMs placed and 14 were available for analysis. Results: Mean age was 14.3 yrs (6.7-19), 7 pts were male. Mean baseline GFR was 113 ml/min/1.73m2 (SD 19.1) mean baseline LVMi was 42.4 g/m2 (SD 7.8) and spot urine protein/creatinine ratio (UPC) was 0.3 (SD 0.28). Two pts had severe ambulatory HTN based on elevated daytime, nighttime, and 24hr mean recordings and elevated BP load in all categories. Of the 12 remaining pts, 25% had elevated nighttime load, and 33% had attenuated nocturnal dipping despite normal office BP and normal average BP. There was no association with baseline LVMi or UPC for pts with HTN by casual BP or ABPM, elevated daytime/nocturnal load, or attenuated dipping with univariate analysis was performed.

Conclusions: Elevated BP load and abnormal nocturnal dipping were seen in our pts prior to HCT despite normal mean ABPM and office BP. According to the 2017 guidelines for pediatric HTN, this group is termed ‘unclassifiable’, but may have increased risk for end organ effects and may require closer supervision. Screening with ABPM can be beneficial in this high risk population.
A class of naïve, non-classical regulatory (i.e., suppressive) T-cells. Subsets also expressed other suppressive markers like LAP, GARP, and CD73. Interestingly, the other two patients also showed loss of cells expressing LG3, CD73, LAP, and/or GARP with treatment.

Conclusions: Children with EHL have heterogeneous regulatory T-cell subsets. Successful control of blood pressure with anti-hypertensive drugs reshapes the T-cell landscape in PB, providing a number of suppressive T-cells. Our approach—specifically identifying specific cell types altered with disease—is well-suited to identifying biomarkers, and can provide detailed mechanistic information that informs treatment approaches.

Funding: NIDDK Support

FR-PO1075

An Evaluation of Renin-Angiotensin System Markers in Youth with Type 2 Diabetes and Associations with Renal Outcomes

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Background: Activation of the renin-angiotensin system (RAS) is associated with diabetic kidney disease in adults, and may also have prognostic significance in youth. We evaluated serum and urine RAS markers in youth with T2D and associations with albuminuria status, glycemic control, eGFR and blood pressure.

Methods: This is a cross-sectional analysis of 183 youth with T2D and 100 controls from the iCARE cohort. Youth further stratified by albuminuria status (ACR < vs ≥2mg/mmol (Alb)) and ACEi/ARB excluded. RAS levels measured with ELISA and enzyme activities measured by synthetic substrates. Differences in levels between groups were evaluated. For T2D group, levels log transformed and Tobit regressions evaluated for associations with ACR, HbA1c, eGFR and 24 BP loads (correcting for age, sex, BMIz-score and duration of diabetes).

Results: Mean age 14.7 yrs, duration of diabetes 1.7 years and 21.3% with Alb. Serum Pra (p=0.006), aldosterone (p=0.004) and SACE activity (p=0.005) were higher in T2D than controls (C), uACE (0.1 (C), 1.2 (T2D)) and 2.0 (Alb) ng/mgCr; p=0.001) and uACE2 activity (6.0 (C), 168.8 (T2D), 595.2 (Alb) ng/mgCr; p<0.001) also increased. In multivariable regressions, higher aldosterone (p=0.002), urinary AGT (p=0.001), and ACE2 activity (p=0.009) associated with albuminuria. Higher AGT and urinary ACE2 protein and activity associated with higher HbA1c. No associations seen between RAS marker and eGFR or BP loads.

Conclusions: RAS activation is present in youth with T2D. The prognostic and therapeutic significance of the combined effect of glycemia and RAS activation on renal outcomes requires additional investigation.

Funding: Government Support - Non-U.S.

FR-PO1076

Improving Recognition and Reporting of AKI in the Neonatal Intensive Care Unit

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Background: Neonatal AKI leads to increased short and long-term morbidity and mortality. Recognition of AKI is essential as monitoring can lead to earlier detection of kidney dysfunction, particularly in neonates who are at high risk of CKD. This study determined prevalence of AKI among infants admitted to a NICU, and evaluated the frequency of AKI recognition/reporting on renal outcomes requires additional intervention.

Funding: Government Support - Non-U.S.

AKI occurrence by gestational age among infants; 77% of infants who experienced AKI were born at <29 weeks gestational age; whereas 85% of infants who did not experience AKI were born at ≥29 weeks

FR-PO1077

Association of Pediatric Cardiac Surgery-Associated AKI with 1- and 5-Year Healthcare Utilization and Kidney Outcomes

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Background: AKI in children undergoing cardiac surgery (CS) is strongly associated with hospital morbidity. Post-discharge CS AKI outcomes are less clear. Hypothesis: Cardiac CS AKI is associated with a) increased hospitalizations, emergency room (ER) visits and physician visits within 1 and 5 yrs post-discharge and b) increased risk for chronic kidney disease (CKD), hypertension (HTN) or death within 5 yrs post-discharge.


Results: N=350 (age 3.1 ± 4.5 years; 180 [49%] AKI; 60 [17%] Stage 2 AKI). See Table. Conclusion: post-CS AKI is associated with higher 5-yr healthcare utilization, but not the composite outcome of CKD, HTN or death. Studies should aim to better understand post-CS surgery healthcare utilization patterns and non-AKI risk factors for CKD and HTN. We develop cost-effective strategies to reduce long-term CKD and HTN after CS.

Funding: Government Support - Non-U.S.

Table. Association of post-cardiac surgery AKI with risk for A) hospitalizations, emergency room (ER) visits and physician visits and B) chronic kidney disease (CKD), hypertension (HTN) or death within 1 and 5 years after hospital discharge

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1-yr post-discharge</th>
<th>5-yr post-discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 or worse AKI (n, no AKI) association with outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of CKD ACR adjusted Relative Risk (ARR)</td>
<td>1.15 (95% CI: 0.93-1.44)</td>
<td>1.17 (95% CI: 0.81-1.69)</td>
</tr>
<tr>
<td>ER visits</td>
<td>0.8 (95% CI: 0.5-1.29)</td>
<td>1.08 (95% CI: 0.61-1.90)</td>
</tr>
<tr>
<td>Physician visits</td>
<td>1.13 [95% CI: 0.96-1.30]</td>
<td>1.39 (95% CI: 0.96-1.98)</td>
</tr>
<tr>
<td>Stage 2 or worse AKI (n, no AKI) or Stage 1 association with outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of CKD ACR adjusted Relative Risk (ARR)</td>
<td>1.14 (95% CI: 0.90-1.43)</td>
<td>1.12 (95% CI: 0.83-1.50)</td>
</tr>
<tr>
<td>ER visits</td>
<td>1.04 (95% CI: 0.85-1.27)</td>
<td>1.13 (95% CI: 0.87-1.47)</td>
</tr>
<tr>
<td>Physician visits</td>
<td>1.15 (95% CI: 0.97-1.36)</td>
<td>1.60 (95% CI: 0.82-3.13)</td>
</tr>
</tbody>
</table>

Conclusions: Post-CS AKI is associated with higher 5-yr healthcare utilization, but not the composite outcome of CKD, HTN or death. Studies should aim to better understand post-CS surgery healthcare utilization patterns and non-AKI risk factors for CKD and HTN. We develop cost-effective strategies to reduce long-term CKD and HTN after CS.

Funding: Government Support - Non-U.S.
FR-PO1078

Point-of-Care Urinary Neutrophil Gelatinase-Associated Lipocalin Readings Are Highly Predictive of Formal Laboratory Levels

Hayley F. Woollen, Kelli A. Krallman, Stuart Goldstein. Center for Acute Care Nephrology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Since the discovery and validation of urinary neutrophil gelatinase-associated lipocalin (NGAL) as an early, non-invasive marker of kidney injury, clinicians are able to more rapidly, and reliably, predict the development of acute kidney injury (AKI). Urinary NGAL has been validated on various clinical lab platforms, but has yet to be assessed using point of care (POC) techniques. A reliable POC urinary NGAL test would offer a rapid and inexpensive screening test for AKI that could be clinically valuable in both inpatient and outpatient settings.

Methods: Hospitalized patients from 2 different pediatric hospitals who were exposed to 3 or more nephrotoxic medications simultaneously or 3 or more consecutive days of either IV vancomycin or an IV aminoglycoside had a daily urine collection for 7 consecutive days. Discrete laboratory urinary NGAL results were obtained using The NGAL Test™ (Bioposto, Denmark) and stratified corresponding to a colorimetric NGAL test (Bioposto) with ranges of: 25ng/mL, 50ng/mL, 100ng/mL, 150ng/mL, 300ng/mL, and 600ng/mL. Different urinary NGAL cutoffs were used determined sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), with the laboratory NGAL Test™ serving as the reference standard.

Results: In total, 86 individual patients (55% male, median age 13.2 years, range 4 months to 34 years) had 521 paired laboratory and POC urinary NGAL assessment. Of the 521 urine samples, 94 were analyzed using fresh urine and 427 using frozen urine samples. The POC performance data are depicted in the table.

Conclusions: A POC urinary NGAL assessment of <300ng/mL was highly predictive of an NGAL Test™ value <300ng/mL. We suggest this colorimetric POC assay is useful as a surrogate to the laboratory NGAL Test™ and to rule out risk for AKI. Patients with a POC test ≤300ng/mL should have a confirmatory NGAL Test™ assessed.

Results

<table>
<thead>
<tr>
<th>NGAL Test™ Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50ng/mL</td>
<td>95.1%</td>
<td>50.0%</td>
<td>50.0%</td>
<td>95.1%</td>
</tr>
<tr>
<td>100ng/mL</td>
<td>95.1%</td>
<td>40.4%</td>
<td>46.7%</td>
<td>95.1%</td>
</tr>
<tr>
<td>300ng/mL</td>
<td>95.1%</td>
<td>30.1%</td>
<td>33.3%</td>
<td>95.1%</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, PPV, NPV (95% confidence intervals)

FR-PO1079

Cell Cycle Arrest Biomarkers and Kidney Injury Molecule 1 (KIM-1) in Pediatric Aminoglycoside-Induced AKI

Havton Chui,1 Vedran Cokcokovic,2 Prasad Devarajan,2 Stuart Goldstein,2 Ping Ma,2 Michael Zappitelli,1,3 The Hospital for Sick Children, Toronto, ON, Canada; 2Research Institute, McGill University Health Centre, Montreal, QC, Canada; 3University of Toronto, Toronto, ON, Canada.

Background: Cisplatin (CisP) causes AKI and electrolyte abnormalities. Urine tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7) are promising biomarkers of AKI. We aimed to validate these biomarkers in a pediatric cohort and to evaluate their potential clinical utility.

Methods: 12-site, prospective cohort study of children treated for cancer with CisP. Excluded: >18 years, kidney transplant, GFR<30ml/min/1.73m². Blood and urine samples were collected at predosing and post dose at predosing and post dose. Area under the curve (AUC, 95% CI) to detect AKI was calculated. Clinical model for AKI prediction:

Results: n=159, median [IQR] age 5.4 [9.4] years, 50% male. AKI TIMP2*IGFBP7 were compared pre and post CisP (Mann Whitney); within-subject changes post vs. pre were compared (Wilcoxon signed-rank). Area under the curve (AUC, 95% CI) to detect AKI was calculated. Clinical model for AKI prediction: neuroblastoma (yes/no) + age<3 years; assessed added benefit of TIMP2*IGFBP7 to increase AUC (DeLong).

Results: n=159, median [IQR] age 5.4 [9.4] years, 50% male. KDIGO AKI: EV 20%; LV 11%. Table: AKI TIMP2*IGFBP7 were compared pre and post CisP (Mann Whitney); within-subject changes post vs. pre were compared (Wilcoxon signed-rank). Area under the curve (AUC, 95% CI) to detect AKI was calculated. Clinical model for AKI prediction: neuroblastoma (yes/no) + age<3 years; assessed added benefit of TIMP2*IGFBP7 to increase AUC (DeLong).

Background: Cisplatin (CisP) causes AKI and electrolyte abnormalities. Urine tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7) may be early AKI biomarkers.

Methods: 12-site, prospective cohort study of children treated for cancer with CisP. Excluded: >18 years, kidney transplant, GFR<30ml/min/1.73m². Blood and urine samples were collected at predosing and post dose at predosing and post dose. Area under the curve (AUC, 95% CI) to detect AKI was calculated. Clinical model for AKI prediction:

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Results not in Table: KIM1 combined with TIMP2*IGFBP7 on the day of AKI onset detected AKI with AUC = 0.90 [0.78-1.00, P<0.05]. Conclusion: TIMP2*IGFBP7 is a modest predictor of CisP-AKI. Drop in TIMP2*IGFBP7 might be protective of CisP induced injury, but results must be validated in another cohort.

Funding: Government Support - Non-U.S.
Outpatient Follow-Up After AKI in the Pediatric Intensive Care Unit (PICU)
Cal Robinson,1 Erin Hessey,1 Sophia Nunes,1 Marc Dorais,1 Rahul Chanchlani,2 Michael Zappitelli.1,2,3 1Pediatric Nephrology, The Hospital for Sick Children, Toronto, ON, Canada; 2Pediatric Nephrology, McMaster Children’s Hospital, Hamilton, ON, Canada; 3University of Alberta Faculty of Medicine, Montreal, AB, Canada; 4StatSciences Inc., Montreal, QC, Canada.

Background: Although KDIGO AKI guidelines recommend re-evaluation at 3 months, few studies have characterized pediatric AKI follow-up. This information is needed to target knowledge translation to enhance post-AKI care. Aims: 1) Describe outpatient follow-up of children with PICU-AKI, 2) Determine factors associated with nephrology follow-up in AKI patients.

Methods: Two-center retrospective cohort study (PICU admissions 2 days from 2003-2005; children 0-18 years old surviving hospitalization; no-cardiac surgery; no baseline kidney disease). Provincial administrative databases used to determine outcomes (until 2010). Exposure: AKI (KDIGO serum creatinine and urine output definition). Primary outcome: outpatient nephrology (Neph) visit by 1 yr post-discharge. Secondary outcomes: a) family physician (FP) or pediatrician (Ped), b) FP, Ped or non-Neph specialist (Spec) visits. Univariable analyses used to compare outcomes by AKI stage and evaluate patient factors associated with 1-yr Neph follow-up.

Results: Of n=2041, 355 (17%) had AKI: 64/355 (18%), 198 (56%) and 338 (95%) had Neph, FP, or Ped and FP or Ped or non-Neph follow-up by 1 yr post-discharge. Figure: sample characteristics by AKI stage. Median follow-up: 23 months (IQR 10-46). Of the children who survived PICU hospitalization and had AKI, 17% had Neph follow-up by 1 yr post-discharge. Factors associated with Neph follow-up included younger age (p<0.05), male sex (p<0.05), lower eGFR (p<0.05), and higher serum creatinine (p<0.05). Trend to younger age (p=0.05) and male sex (p=0.06) remained significant in multivariable analysis. Overall, Neph follow-up no different by AKI stage (p>0.05). However, when examining non-AKI difference in follow-up for other physicians (p>0.05). 44/142 (31%) of children with AKI had Neph follow-up by 1 yr post-discharge. Children with AKI were more likely to have Neph follow-up (p=0.0001). There was no AKI vs. non-AKI difference in follow-up for other physicians (p>0.05). 44/142 (31%) of children with AKI had Neph follow-up by 1 yr post-discharge. Factors associated with 1-yr Neph follow-up in AKI patients were: longer hospital stay; AKI stage 2-3; dialysis receipt; discharge Scr ≤1.5x baseline (all p<0.001). Conclusion: Children with PICU-AKI are more likely to receive Neph follow-up, though follow-up is suboptimal for severe AKI. Non-Neph physician follow-up is very high, suggesting AKI follow-up knowledge translation strategies for non-Neph providers should be a priority.

Funding: Private Foundation Support

Figure. Time to outpatient nephrology (Neph) visit after PICU hospitalization, by AKI status

FR-PO1082
Efficacy of Rasburicase in Children with AKI from Diarrhea-Associated Hemolytic Uremic Syndrome
Yo Han Ahn,1 Myung hyun Cho,2 Jiwon M. Lee,2 IL-Soo Ha,2 Hae Il Cheong,2 Hee Gyung Kang.1 1Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; 2Department of Pediatrics, Seoul National University Children’s Hospital, Seoul, Republic of Korea.

Background: Diarrhea associated hemolytic uremic syndrome (D+HUS) is a common etiology of acute kidney injury (AKI) in children. Hyperuricemia during acute phase is a typical finding of D+HUS. Recently we have used rasburicase to manage hyperuricemia, thereby ameliorate AKI and accelerate their recovery. Here we assessed the efficacy of rasburicase in D+HUS.

Methods: We retrospectively analyzed the medical records of pediatric D+HUS patients who were admitted to Seoul National University Children’s Hospital between January 2001 and July 2017. We compared the clinical outcomes between those treated with rasburicase (rasburicase group) and those receiving control therapy (control group)

Results: A total of 72 patients were analyzed. Their median age was 3.2 years old. Median values of the lowest hemoglobin, the lowest platelet, and the highest uric acid were 6.3g/dL, 24,000/uL, and 12.6mg/dL, respectively. Twelve (16.7%) were treated with rasburicase. It was administered once at a median dose of 0.10mg/kg within the first day of admission. There was no difference in age, sex, the lowest hemoglobin, the lowest estimated glomerular filtration rate (eGFR), and the highest uric acid between the rasburicase group and the control group. The lowest platelet in rasburicase group was lower than that in the control group (14,000 vs. 25,000/uL; P=0.002). In the rasburicase group, hyperuricemia was reversely repressed (2.4 vs. 6.5 days; P=0.001). There was no statistical difference in requirement of dialysis (66.7% vs. 55.0%; P=0.456) and the duration of dialysis (5.5 vs. 8.6 days; P=0.262) between the two groups. However, median hospital length of stay was shorter in the rasburicase group than in the control group (12.9 vs. 18.2 days; P=0.043), and median eGFR at 1 year follow up was lower in the control group than in the rasburicase group (81.2 vs. 111.0 mL/min/1.73m2; P=0.002).

Conclusions: Although rasburicase treatment in patients with D+HUS did not lower the requirement of dialysis, patients who were treated with rasburicase during the acute phase were discharged earlier from the hospital and had better renal function at 1 year follow-up. Since there are no known effective therapies for AKI induced by D+HUS, we may consider rasburicase to improve their long-term renal outcome.

FR-PO1083
HIF/PAP and BD-1 Indicate Successful Surgical Intervention in Pediatric Patients with Ureteropelvic Junction Obstruction
Sudipti Gupta,1,2 Lauren Nicassio,3,4 Guillermo J. Yepes,5 Ashley R. Jackson,1,2 Daryl J. Mcleod,1 Brian Becknell,1,2 Christina B. Ching,1,2 1Research Institute at Nationwide Children’s Hospital, Columbus, OH; 2Nationwide Children’s Hospital, Columbus, OH;

Background: We have previously found a panel of antimicrobial peptides (AMPs) to be significantly elevated in ureteropelvic junction obstruction (UPJO). We sought to see if these same AMPs decreased after surgical correction of UPJO to further test their ability to identify obstruction.

Methods: Bladder urine was collected from pediatric patients (≤18 years old) immediately prior to surgical correction of an UPJO and then at least 6 months after surgery according to an IRB-approved protocol. Patients were included only if they did not have signs of active urinary tract infection at time of collection. Based on a prior study demonstrating that the AMPs beta defensin1 (BD-1), hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein (HIF/PAP), LL-37, and neutrophil gelatinase-associated lipocalin (NGAL) were significantly elevated in patients with UPJO as compared to patients without, we performed enzyme-linked immunosorbent assays on these AMPs to compare their expression before and after surgical intervention. AMP levels were normalized to urine creatinine. Results were analyzed with paired t test or Wilcoxon test using Graphpad software. A p-value of ≤0.05 was considered significant.

Results: Follow-up samples were obtained a median of 27.4 months (range 27.4; range 7.8-45.3 months) after surgery and removal of all drainage tubes on 13 patients on whom we also had urine samples collected immediately prior to pyeloplasty for their UPJO. Nine of the patients were male. Time to surgical correction at time of surgery was a median of 4.3 years (average 6.1; range 0.4-18.4 years). All 13 patients showed clinical improvement from before surgery and/or signs of improved hydronephrosis on post-operative imaging. We found that HIF/PAP and BD-1 were significantly decreased in post-surgical samples compared to pre-surgical samples (p=0.0315 and 0.052, respectively); NGAL and LL-37 did not significantly change. The sensitivity/specificity of HIF/PAP to show correction of an obstruction was 75% and 85%, respectively, while for BD-1 it was 75% and 85%, respectively.

Conclusions: HIF/PAP and BD-1 are significantly elevated in upper urinary tract obstruction and significantly decrease with correction. These AMPs could serve as markers of successful surgical intervention.
FR-PO1085

Associations of Plasma Neutrophil Gelatinase-Associated Lipocalin, Anemia, and Renal Scarring in Children with Febrile Urinary Tract Infections
Hyung Eun Yim, Kee Hwan Yoo. Pediatrics, Korea University, Ansan-Si, Republic of Korea.

Background: Neutrophil gelatinase-associated lipocalin (NGAL), a bacteriostatic agent, is known to inhibit erythropoiesis leading to anemia. We aimed to investigate the relationships of NGAL, anemia, and renal scarring in children with febrile urinary tract infections (UTIs).

Methods: We retrospectively reviewed the medical records of 261 children with first febrile UTIs. The associations between plasma NGAL levels and indices of anemia were studied. NGAL performance in comparison with serum C-reactive protein (CRP) at admission and after 72 hours of antibiotic treatment was also evaluated for the prediction of renal scarring.

Results: Plasma NGAL levels were considerably elevated in patients with anemia compared with those without anemia (P<0.001). NGAL concentrations were inversely correlated with levels of hemoglobin and hematocrit and red blood cell count (all P<0.001). Increased NGAL, but not CRP, was independently associated with the presence of anemia in a multivariable logistic analysis [OR 2.37 (95% CI 1.07-5.27), P<0.05]. Receiver operating curve analyses showed good diagnostic profiles of NGAL at admission and after treatment for identifying renal scarring (all P<0.05). Plasma NGAL after treatment showed a higher area under the curve (AUC) (0.730; 95% CI 0.591-0.843) than that of CRP after treatment (AUC 0.520; 95% CI 0.395-0.643) (P<0.05). In a multivariable analysis, elevated plasma NGAL level at admission and the presence of anemia were independently associated with the presence of renal scarring in children with febrile UTIs (all P<0.05). In the presence of anemia, NGAL concentration increased consecutively in febrile UTI, APN, and renal scar (P<0.05).

Conclusions: Increased plasma NGAL levels may be associated with the presence of anemia and renal scarring in children with febrile UTIs.

FR-PO1086

Long-Term Renal Outcomes in Children with AKI Post Cardiac Surgery
Vandana Ravikrishnan,1 Rupesh Raina,2 Sidharth K. Sethi.3 1Clinic Akron General, Akron, OH; 2Nephrology, Cleveland Clinic Akron General, Akron, OH; 3Medanta, The Medicity Hospital, Gurgaon, India.

Background: Acute Kidney Injury (AKI) is associated with poor short-term outcomes such as mortality, longer ICU and hospital length of stay and duration of mechanical ventilation as demonstrated by numerous studies. Our objective was to study the long-term renal outcomes and markers of kidney injury in pediatric patients with congenital heart disease who did and did not develop AKI following cardiac bypass surgery.

Methods: This was a prospective case-control observational study in which all infants and children who underwent cardiac bypass surgery from 2010-2017 and who had a long term follow up were included. Patients with CKD, Hypertension, AKI from primary kidney disease and previous history of AKI were excluded. 44 Patients who developed AKI were matched to 49 consecutive controls who did not develop AKI postoperatively. GFR was estimated by Schwartz formula and cystatin C. Kidney injury biomarkers that were used are NGAL, L-FABP, KIM-1, IL-18. 

Results: Age, Gender, weight, height, aortic cross-clamp (ACC) time and cardiopulmonary bypass (CPB) time were not statistically significant among cases and controls. Patients with AKI had a higher baseline serum creatinine (0.43±0.22, p=0.001) and longer ICU length of stay (days, 5.7±3.0, p=0.001) than the control group. On the long term follow up, patients with AKI had a higher serum creatinine level, the trend towards higher urinary KIM-1 levels and lower estimated GFR but were not statistically significant. When backward linear regression analysis was performed, CPB time (Opps Ratio: -0.550, p<0.05) and AKI (OR: 10.913, p<0.05) were the only risk factors associated with lower GFR at follow up. CPB time (OR: 0.010, p<0.05), baseline serum creatinine (OR: -0.643, p<0.050) and AKI (OR: 0.381, p<0.05) were the only risk factors associated with higher KIM-1 at follow up.

Conclusions: Cardiopulmonary bypass time (CPB) is significantly associated with a decrease in GFR and a rise in kidney injury biomarker KIM-1 level several months post postoperatively independent of postoperative AKI.

FR-PO1087

Perioperative AKI in Pediatric Liver Transplant Patients
Naila A. Tafan pekkucuksen.1,2 Ryan J. Himes,3 Justin Young,3 Poyyapakkam Srinivaths,4 Moreeshwar Desai,2 Ayse Akcan Arikan.1 1Pediatrics, Division of Pediatric Nephrology, University of Florida, Gainesville, FL; 2Pediatrics, Renal Division, Baylor College, Houston, TX; 3Baylor College of Medicine, Houston, TX; 4Texas Children’s Hospital, Houston, TX; 5Ochsner Hospital for Children, New Orleans, LA.

Background: Acute Kidney Injury (AKI) is a common complication in children in the post-orthotopic liver transplant (OLT) period. However, data regarding pre OLT AKI are scarce. We examined the incidence of perioperative AKI (7 days pre OLT to 7 days post OLT) in pediatric OLT population. AKI was defined using KDIGO criteria and HRS was defined using revised consensus recommendations of the International Club of Ascites, 2015 publication.

Methods: This is a single center retrospective chart review.

Results: A total number of twenty-two pediatric patients (pts) underwent OLT between 11/2011- 3/2017. One patient who had known chronic kidney disease (CKD), was excluded. The median age was 2.5 years (IQR:0.83-10) and 71 were female (59%). Most common etiologies of liver disease were biliary atresia (BA) (68/121, 56%) and atresia of the common bile duct (41/121, 20%). Forty pts (33%) had preoperative AKI: 15% stage 1, 30% stage 2 and 55% stage 3. Of those, 13 (38%) pts had AKI pre-OLT, with hepatorenal syndrome (HRS) diagnosed in 11(73%). Twenty-five (62%) pts experienced post-OPT AKI. Most common etiologies for post OLT AKI were abdominal compartment syndrome (ACS), acute renal failure due to hypotension or bleeding, or nephrotic syndrome. 29 pts (78%) were on continuous renal replacement therapy (CRRT), 24 of those were started pre OLT due to AKI, fluid overload (FO) or hyperammonaemia without AKI and 3 of those were discontinued after OLT. Five pts needed CRRT only post-OLT. Unfortunately, 7 AKI pts were never recognized by the clinical team.

Conclusions: AKI is common in perioperative period in children receiving OLT. HRS was the most common etiology for pre OLT. Post OLT, operative complications with ascites leading to ACS and hypotension leading ATN predominated. Majority of AKI pts were stage 3 and needed RRT. Unless monitored in a systemic fashion with structured diagnostic criteria, AKI can be missed by the clinical team. Short- and long-term outcomes of this population need to be elucidated through further studies.

FR-PO1088

The Long-Term Kidney Outcomes of Prune Belly Syndrome in Australia
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Background: Prune Belly Syndrome (PBS) is a rare congenital disorder consisting of the triad of: absence or incomplete abdominal wall muscle development, bilateral cryptorchidism and urinary tract anomalies including hydropnephrosis, kidney dysplasia and dilated ureters, urethra or bladder. PBS varies considerably in clinical severity, with prognosis primarily being influenced by the degree of chronic kidney disease. The aim of this study was to describe the long-term kidney outcomes of people with Prune Belly Syndrome in Australia.

Methods: We identified all Australians treated with renal replacement therapy (RRT) who had a diagnosis of PBS (as determined by the treating unit) from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). ANZDATA is a clinical quality registry containing information on all people receiving dialysis or a kidney transplant since 1977.

Results: We identified 37 males (no females) with a diagnosis of PBS who received RRT in Australia and were recorded in ANZDATA. Commencement of RRT was at a median age of 17yrs (mean 19yrs, range 1-41yrs) when median creatinine was 720umol/L. RRT at first treatment was haemodialysis in 54%, peritoneal dialysis 30% and pre-emptive kidney transplant in 16%. Twenty percent of patients were late referrals to the dialysis unit (referral <3 months prior to starting dialysis). Comorbidities of diabetes, heart disease or vascular disease were not present at commencement of RRT. One man had chronic lung disease. Forty-five kidney transplants (including 33 first, 10 second and 2 third grafts) occurred, of which 47% were from deceased donors. Mean age at first transplant was 21yrs (range 2-47yrs). Graft survival at 1, 5 & 10 years for first grafts was 94%, 67% and 48% respectively (range 6 days to 36 years). Parenthood was reported for 3 men at a median age of 35yrs. There were 10 deaths reported at a median age of 37yrs (range 17-49yrs) due to cardiac death (50%), malignancy (20%), dialysis cessation (10%) and uncertain cause (10%).

Conclusions: Prune Belly Syndrome has marked variation in the severity of kidney disease. For those who receive RRT, kidney transplantation is the predominant treatment, but peritoneal dialysis has been used successfully. Infertility is not universal. There is early cardiovascular mortality associated with this syndrome.
FR-PO1089

Aptamer-Based Proteomics Analysis Reveals a Urine Protein Signature That Differentiates UTIs from Culture-Negative Pyuria and Normal Urine

Andrew L. Schwaderer, David S. Hains. Indiana University, Zionsville, IN.

Background: UTIs account for 7% of pediatric emergency department antibiotic prescriptions. UTI diagnosis is typically made at the point-of-care by symptoms and the identification of nitrites and/or leukocyte esterase (LE) on urinalysis (UA). Growth of ≥ 50,000 colony forming bacterial units on culture is used to confirm a UTI. However, accurate urine culture results can be dependent on collection methodology and take 24-72 hours to complete. UAs have limitations as well. The sensitivity/specificity for LE to detect childhood UTIs is 83%/78%.

Methods: An aliquot of urine was obtained from pediatric Emergency Department patients who had a sample collected for clinical urine culture. Included samples consisted of 16 with urinary tract infection (UTI), 8 culture negative (CN) pyuria, and 8 with normal UAs. The levels of 1,310 proteins were quantified as relative fluorescent units/ml using the SOMAmer platform (Somialogic Inc, Boulder, CO) and the normalized to urine creatinine (mg/dl). The results were filtered for proteins that were (a) significantly higher in the UTI vs CN pyuria samples and in the UTI vs normal urine samples with a p value of < 0.01 and that had an area under the curve (AUC) of > 0.9 which is used to define an “excellent” biomarker.

Results: Eight candidate biomarkers met this stringent filtering criteria and are presented along with the threshold urine biomarker to creatinine ratio with the highest likelihood ratio to differentiate UTI from non UTI samples in Figure 1.

Conclusions: A biomarker panel containing some of the candidates identified via this study has the potential to improve the timeliness and accuracy of UTI detection. Prospective studies evaluating levels measured by ELISA and conversion to a point of care testing modality are the next investigative steps.

Funding: Private Foundation Support

FR-PO1091

Delta Bilirubin: A Lesser-Known Bilirubin Fraction and Its Impact on Interpretation of Single-Pass Albumin Dialysis (SPAD) Efficacy

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Background: Acute liver failure (ALF) is a rapidly progressive disease that leads to multiple organ failure with high mortality. Combination of supportive therapies are utilized to stabilize these patients until recovery, or as a bridge to liver transplant. As MARS is not readily available in all pediatric centers, modification of continuous renal replacement therapy (CRRT) with SPAD is an equally efficacious alternative. During SPAD, bilirubin clearance is used as a surrogate marker for clearance of protein-bound toxins. We have previously shown >10 fold increase in bilirubin clearance with SPAD as compared to CRRT alone. However, we failed to observe increased bilirubin clearance in a group of ALF patients who received SPAD.

Methods: We studied 3 patients with ALF who failed to show increased bilirubin clearance. These patients had significant unconjugated hyperbilirubinemia which is not cleared by SPAD as it is tightly albumin-bound. However, we also found significantly decreased clearance of conjugated-bilirubin in these patients. Thus, we studied the bilirubin clearances in the serum and the effluent by using Vitros 5600 chemistry analyzer, a unique method that uses two slides to measure total, unconjugated and conjugated-bilirubin fractions, and calculates delta bilirubin, a form of conjugated-bilirubin that is covalently bound to albumin.

Results: Review of our raw data showed that these 3 patients had significant proportion of their conjugated bilirubin in the form of delta-bilirubin (Figure), which is not cleared by SPAD due to its tight albumin binding. Delta bilirubin is known to accumulate in patients with prolonged liver failure and biliary atresia.

Conclusions: Decreased bilirubin clearance in this subset of ALF patients was found to be due to increased serum delta-bilirubin. Since most laboratories do not measure or report delta-bilirubin, increased delta-bilirubin may lead to the perception that SPAD is not working efficiently, and may lead to unnecessary and expensive work-up.

Funding: NIDDK Support, Other NIH Support - NIH/National Center for Advancing Translational Science (NCATS) Einstein-Montefiore CTSA Grant Number UL1TR001073

FR-PO1090

Incidence of Early Dysnatremia in the Assessment of Neonatal Acute Kidney and Epidemiology (AWAKEN) Cohort

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Background: Incidence of dysnatremia during the first postnatal week in the neonatal intensive care unit (NICU) and its association with mortality has not been well described. We hypothesized that incidence of dysnatremia would vary with gestational age (GA) and that early dysnatremia predicts mortality.

Methods: We studied neonates in the AWAKEN cohort, a 24-center retrospective study of NICU admissions on IV fluids ≥ 48 hrs, with ≥ 1 serum sodium (sNa) recording during postnatal days 2-7. sNa values were compared in 3 GA cohorts (24-<29 wk, ≥29-36 wk, ≥36 wk). Hypernatremia was defined as sNa ≥145 meq/L (moderate=146-155, severe=≥156), hyponatremia was defined as sNa <135 meq/mL (mild=130-134, moderate=125-129, severe=125). Survival was considered reaching 6 wk post-GA or hospital discharge. Kruskal Wallis, Chi² tests, and multivariable logistic regression were used as appropriate.

Results: The cohort included 1,972 infants with 15,302 sNa values (Table 1). Of these, 23% developed hypernatremia and 35% developed hyponatremia. The incidence and severity of hypernatremia differed by GA (Figure 1). Infants <29 wk GA were most likely to develop severe hypernatremia (OR 8.8 95% CI 6.1-12.6, p<0.01). The incidence and severity of hyponatremia also differed across GA groups (Figure 2). Over 40% of infants in the 24-29 wk and ≥36 wk cohorts developed hyponatremia, compared to 26.8% of the ≥29-36 wk group (p=0.001). Both hypernatremia (adjusted (a)OR 2.7 95% CI 1.6-4.5, p=0.001) and hyponatremia (aOR 2.2 95% CI 1.3-3.8, p=0.005) in models adjusted for GA predicted increased odds of mortality.

Conclusions: This is the largest and most inclusive cohort to describe the incidence and impact of dysnatremias in critically ill neonates. The incidence and severity of hypernatremia differed by GA category and was most substantial in very premature infants. However, infants 24-29 wk and ≥36 wk GA developed hyponatremia at similar rates, which may reflect oliguria and/or fluid provision strategies. Further evaluations of this cohort will evaluate whether hyponatremia and hypernatremia are independently associated with mortality after adjusting for other important cofounders.

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Underline represents presenting author.

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FR-PO1092
Undetected Sexual Transmitted Infection in Adolescents with Sterile Pyuria
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Background: The percentage of sexual transmitted infection(STI) in adolescents had been underestimated and misdiagnosed as urinary tract infection(UTI), which may lead to unnecessary treatment and public health issue. We aimed to distinguish STIs through symptoms, laboratory and urinary analysis. We emphasize on the correlation of STIs and child maltreatment.

Methods: We performed a retrospective study of adolescents aged from 15-18 years old, who visited a tertiary center from January 1, 2015 through July 30, 2018, with diagnosis of urinary tract infection, acute cystitis, acute pyelonephritis, dysuria, urinary frequency, or renal colic. We compared clinical characteristics, symptoms, serum laboratory data, urine analysis, percentage of been reported to Social Affairs Bureau between STIs and UTIs groups.

Results: Of the 45 adolescents, there was a significant difference in pyuria count(p=0.036), with 44.7% of UTI group reached the highest pyuria level (WBC>100/HPF) and none in STI group had pyuria >100/HPF. 71.4% of STIs had only mild pyuria with 5-49/HPF. No significant difference in clinical symptoms, including fever, dysuria, hematuria, abdominal pain, flank pain, serum white cell count, or CRP level between UTIs and STIs groups. We found 71% of adolescents with STIs had been reported as in need of child protection.

Conclusions: The clinical features and serum laboratory data were overlapping in STIs and UTIs, and both of them cause pyuria, which may lead to over-diagnosis of UTIs. Adolescents with lower degree of pyuria had higher possibility of STIs. The incidence of family dysfunction in STI is extremely high.

FR-PO1093
Renal Abnormalities in HIV-Exposed Children: A Guatemalan Retrospective Cohort Study
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Background: Among the various organs involved with the progression of HIV infection, the kidneys have a significant impact. Studies have highlighted the importance of early detection of kidney disease in HIV-infected patients in order to reduce the progression of CKD. We identify the renal abnormalities in HIV-exposed children in a tertiary hospital in Guatemala.

Methods: After ethics approval, we retrospectively evaluated a cohort of patients perinatally exposed to HIV during the period 2015-2016. Patients attending the outpatient clinic for at least 6 months were captured in the study. eGFR, pcr, ca/c ratio were obtained at the time of inclusion and at least 6 months after enrollment. Renal abnormality was defined as lasting more than 6 months Clinical and immunologic status, viral load, and time of antiretroviral exposure were determined

Results: Of the 45 adolescents, there was a significant difference in pyuria count(p=0.036), with 44.7% of UTI group reached the highest pyuria level (WBC>100/HPF) and none in STI group had pyuria >100/HPF. 71.4% of STIs had only mild pyuria with 5-49/HPF. No significant difference in clinical symptoms, including fever, dysuria, hematuria, abdominal pain, flank pain, serum white cell count, or CRP level between UTIs and STIs groups. We found 71% of adolescents with STIs had been reported as in need of child protection.

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FR-PO1094
Use of an Artificial Neural Network for the Prediction of Urine Culture Positivity from Urine Dipstick in Children
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Background: Urine dipstick results are important for clinical decision making regarding the presence or absence of urinary tract infections. The aim of the study was to analyse the performance of artificial neural network (ANN) in the prediction of positive urine culture from an automated urine dipstick test.

Methods: We retrospectively analysed all available automated urine dipstick (UD) and urine cultures (UCULT) tests performed at our institution over 2-year period (2015-2017). The final dataset (after merging and cleaning) consisted of 5912 complete UD and UCULT performed on the same date and time. Predictors of UCULT included: age, gender, and all UD results: glucose, ketones, specific gravity, blood, pH, protein, nitrates and leukocytes. ANN model (sequential, feedforward with backpropagation) consisted of 30 neurons in 2 hidden layers (Tensorflow Keras). Data samples (n=5912) were randomly divided into training (70%) and validation set (30%). ANN prediction probabilities thresholds for positive UCULT results were set to 0.5 (ANN05) and 0.3 (ANN03). The performance of both ANN models was assessed by accuracy scores, specificity, sensitivity, positive and negative predictive value (PPV, NPV).

Results: Of the 45 adolescents, there was a significant difference in pyuria count(p=0.036), with 44.7% of UTI group reached the highest pyuria level (WBC>100/HPF) and none in STI group had pyuria >100/HPF. 71.4% of STIs had only mild pyuria with 5-49/HPF. No significant difference in clinical symptoms, including fever, dysuria, hematuria, abdominal pain, flank pain, serum white cell count, or CRP level between UTIs and STIs groups. We found 71% of adolescents with STIs had been reported as in need of child protection.

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The Ribonuclease 6 Antimicrobial Peptide Limits Bacterial Burden During Experimental Pyelonephritis
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Background: Ribonuclease 6 (RNase 6) is an evolutionarily-conserved antimicrobial peptide that kills uropathogenic bacteria at low micromolar concentrations in vitro. Here, we investigated the hypothesis that RNase 6 limits urinary tract colonization by uropathogenic Escherichia coli (UPEC) in vivo.

Methods: We generated mice with a Rnase6®/® knock-in allele on a C57BL/6J genetic background. We identified cellular sources of RNase 6 based on flow cytometry, epifluorescence, and immunofluorescence microscopy. We transurethrally inoculated Rnase6®/® and control female mice with UPEC strain CFT073 and enumerated bacterial burden in urinary tract tissues by homogenization and serial plating.

Results: Flow cytometry in Rnase6®/® mice indicated EGFP expression by circulating Ly6C+ monocytes which were recruited to the infected bladder by 6 hours post inoculation (hpi). In addition, EGFP was expressed by two discrete resident macrophage populations within the kidney. We confirmed Rnase 6 deletion in Rnase6®/® mice, which displayed normal urinary tract development, fertility, and hematopoiesis. Rnase 6 deficiency led to increased renal and ureteral UPEC burden at 6 and 12 hpi, compared to control mice.

Conclusions: In the infected urinary tract, RNase 6 is primarily expressed by resident macrophages and recruited monocytes. We have demonstrated a critical role for RNase 6 in UPEC clearance from the upper urinary tract during ascending UTI in vivo.

FR-PO1096

FR-PO1097

Urinary Klotho Abnormalities in Pediatric Sickle Cell Disease (SCD)
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Background: Klotho is a transmembrane protein expressed in the renal tubules and serves as an obligatory co-receptor for FGF23 to aid in phosphate excretion. Prior studies have shown FGF23 resistance in SCD. The purpose of the study is to investigate urinary klotho/creatinine (Ur Kl/Cr) in pediatric SCD and no markers of ongoing renal damage (eGFR > 90 ml/min and no microalbuminuria) and to compare it with healthy control population.

Methods: Cross sectional observational study to compare Ur Kl/Cr in pediatric SCD and control female mice with UPEC strain CFT073 and enumerated bacterial burden in urinary tract tissues by homogenization and serial plating.

Results: Flow cytometry in Rnase6®/® mice identified EGFP expression by circulating Ly6C+ monocytes which were recruited to the infected bladder by 6 hours post inoculation (hpi). In addition, EGFP was expressed by two discrete resident macrophage populations within the kidney. We confirmed Rnase 6 deletion in Rnase6®/® mice, which displayed normal urinary tract development, fertility, and hematopoiesis. Rnase 6 deficiency led to increased renal and ureteral UPEC burden at 6 and 12 hpi, compared to control mice.

Conclusions: In the infected urinary tract, RNase 6 is primarily expressed by resident macrophages and recruited monocytes. We have demonstrated a critical role for RNase 6 in UPEC clearance from the upper urinary tract during ascending UTI in vivo.

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FR-PO1099

Context-Specific Cellular Mechanisms of Urothelial Development and Repair in the Kidney
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Background: Congenital urinary tract obstruction (UTO) is a leading cause of pediatric chronic kidney disease and end stage renal disease. The renal urothelium is the kidney’s anatomic front line of defense during UTO, and represents an understudied but novel therapeutic target. Renal urothelium contains two mutually exclusive, Krt5+ and Uroplakin-I (Upk)- renal urothelial cell (RUC) populations. UTO triggers an iterative RUC remodeling sequence that culminates in the formation of bladder-like Upk+ apical plaque producing RUCs, which attenuate UTO injury. The ontology of Upk+ RUCs is unknown, stalling efforts to therapeutically promote protective renal urothelial remodeling.

Methods: In this study, we performed genetic fate mapping to determine whether Upk+ RUCs arise through self-renewal or via differentiation from Krt5+ RUC. We mapped the fate of Upk+ and Krt5+ RUC lineages in Upk2CreERT2/+;R26tdT/+ and Krt5CreERT2/+;R26tdT/+ mice, and performed immunofluorescence assays to mark Krt5, Krt14, p63, foxa1, Upk, Krt20, tdT-expressing and proliferating cells across development. Unilateral ureteral obstruction was used to trigger UTO.

Results: Renal urothelium develops at embryonic day 17, and temporal waves of Upk and Krt5 expression are observed through adulthood. Krt5+ RUCs commonly express Krt14 and p63 and are the primary proliferative RUC. Adult Upk+ RUCs derive from...
embryonic and neonatal Krtn5+ RUCs. Paralleling a proliferative decline, Krtn5+ RUCs lose progenitor capacity by postnatal day 14. In a temporally restricted manner, UTO triggers a ternary lineage network that restricts Krtn5+ RUCs to regain progenitor capacity and form bladder-like Upk+ RUCs. In addition, adult Upk+ RUCs possess the ability to lose Upk protein expression, proliferate, and give rise to daughter Upk+ RUCs that reacquire Upk protein synthesis.

Conclusions: This study is the first to establish the temporal manner in which the embryonic and postnatal renal urothelium is patterned, and demonstrates the contexts during which Upk+ RUCs arise via self-renewal versus differentiation from Krtn5+ progenitors. Identification of the context-specific mechanisms governing progenitor plasticity or restriction have broad implications for urothelial development, repair and therapeutic manipulation.

Funding: NIDDK Support

FR-PO1100

Mercaptoacetyltriglycine Scan vs. Functional Magnetic Resonance Urography: A Comparison and Long-Term Follow-Up of Clinical Outcomes


Background: Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are the leading cause of End Stage Renal Disease in children. Obstructive uropathy (OU) presenting with urinary tract dilation (UTD) is one of the common forms of CAKUT. While there is no gold standard for OU evaluation or clear cutoffs for surgical intervention, functional imaging evaluation is recommended to help the decision making process. In children, functional Magnetic Resonance Urography (fMRU) is increasingly used because of its superior anatomic detail when compared to the most widely used MAG3 nuclear medicine renal scan (RS). However, there is not enough data to assure that fMRU-based differential renal function is equivalent to RS results. Here we compare the functional results of fMRU and RS in a pediatric cohort presenting with UTD.

Methods: This is a retrospective cohort of 37 out of 98 (3.75%) fMRU’s performed in 73 children (0-21 yrs) at our institution between 2007 and 2017, which had an accompanying RS within 6-months and with no interval surgical intervention. Results: The 37 unique patients (15 F, 22 M) had a median age: 6 months (range: 2mos-18y) and 24/37 (65%) were Caucasians. The majority (26/37, 70.3%) presented with UTD P3. Main diagnoses included ureteropelvic junction obstruction (UPJO) in 23/37, megareter (5/37) and duplex kidney (4/37). Differential renal function (DRF) was obtained from each test and 14 fMRU and 12 RS patients were grouped as normal but there was no significant agreement between both imaging tests. Only 7/37 (21%) patients had concordant (<5% DRF difference) DRF from fMRU and RS. Upon evaluating obstructing determinants fMRU was found to be 88.24% specific and 38.10% sensitive with 69.09% accuracy (95% CI 55.19-80.86). 2/19 patients who had follow up for a mean of 3 years (range 6mos-9 years) had elevated BP. UPK+ RUCs were found to be >100/mL/min in 7/37 with consistent normal renal function at follow-up in 15 patients.

Conclusions: The differential renal function determined by RS and fMRU in children is discordant in a majority of cases with significant agreement limited to those deemed normal in both modalities. Using RS as the gold standard, fMRU was found to be 88.24% specific though average sensitivity in determining obstruction. Overall cohort did not present adverse outcomes after a mean 3 years follow up.

Funding: Other NIH Support - T32 Grant

FR-PO1101

Pre-Transplant Elevated Chemokines CXCL9, CXCL10, and CXCL11 Influence Kidney Graft Status in Mexican Mestizos

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Background: A high incidence of CKD in Mexico, affects a significant number of young patients. Chemokines CXCL9, CXCL10 and CXCL11 may be sensitive markers of renal infection and may serve as a predictor of graft survival. The aim of the study is to assess chemokine production in children with CKD and in children on stable renal transplant who have a history of infections.

Methods: This is a retrospective study of 33 children (18F, 15M, median age 9 years) who were classified into three groups: 1) Group A: Children who had infections with bacterial or viral infections at 3 months, 2) Group B: Children who had infections at 3 months but were then found with calciumineurin inhibitor toxicity (CXCCL9: 1842.79 pg/ml toxicity vs 892.45 pg/ml no toxicity; p=0.049). Conclusions: CKD patients have elevated chemokine serum levels, which associate with infections and infections at 3 months, but were then found with calciumineurin inhibitor toxicity (CXCCL9: 1842.79 pg/ml toxicity vs 892.45 pg/ml no toxicity; p=0.049).

FR-PO1102

Everolimus Suppresses the BK Virus Replication in Human Embryo Cells In Vitro

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Background: BK virus causes BKV-associated nephropathy in about 8% of kidney transplant patients and allograft loss occurs in 10-50% of the affected individuals. There is currently no effective treatment for BKV and it is mainly treated by reducing immunosuppression or changing the treatment regimen. Therefore, the search for effective treatments and mechanisms for BK virus infection is important. To date, various immunosuppressants were reported to suppress the replication of BKV in vitro. However, there are few reports that showed the effects of everolimus. We report in vitro study of the effects of everolimus on BKV proliferation.

Methods: Confluent human embryo lung cells were infected with BKV isolated from a renal transplant recipient. We first determined the replication time and viral infectivity in this system. BKV DNA replication was evaluated by the increase in the DNA copy numbers in infected cells and the tissue culture infectious dose (TCID50) and viral copy number were determined in three viral stocks. Effects of immunosuppressants on BKV replication were examined in this system. Cells were infected and treated with everolimus, cyclopodrine, and tacrolimus at various concentrations attained in the recipients for 72 hours and the amounts of the replicated viral DNA were determined by a real-time quantitative PCR with primers targeting the large T-antigen.

Results: BKV growth curve showed that BKV DNA increased at 48 hours and further at 88 hours after infection, indicating one replication cycle was 48 hours. Viral infectivity was attained at 10th to 10 9 TCID50/mL and particle per infectivity ratio was 2.12 TCID50/1,000 DNA copies (n=3) in this system. BKV replication was not affected by treatment with tacrolimus and cyclopodrine at concentrations from 1 to 30 ng/mL and from 0.01 to 1 µg/mL, respectively. Everolimus at concentrations from 0.1 to 30 ng/mL significantly suppressed BKV replication to 20% to 40% of untreated cells.

Conclusions: Everolimus has been reported to alleviate BKV infection in the TRANSFORM study. Everolimus suppressed BKV replication at the concentrations attained in the serum of renal transplant recipients and this results support the alleviation of BKV infection with everolimus.

FR-PO1103

B Cell and T Cell Subset Changes in a Rat Kidney Transplant Model of Chronic Antibody-Mediated Rejection

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Background: Chronic antibody mediated rejection (cAMR) is a leading cause of kidney graft loss. In many instances, mixed chronic AMR and cellular rejection are observed. We examined B and T cell populations in the lymphoid organs of a sensitized rat kidney transplant model. We hypothesized that sensitized recipients would have increased populations of memory and proinflammatory B and T cells in lymphoid tissues.

Methods: Minor mismatch kidney transplantation was performed to generate cAMR. The cAMR model had 3 groups: 1) syngeneic (Syn, Lewis donor to Lewis recipient), 2) allogeneic (Allo, Fisher donor to Lewis recipient), and 3) sensitized (Sens Allo, Fisher donor to Lewis recipient that received blood transfusion 21 days pre-transplant). Animals were harvested at 6 months post-transplant and lymphoid cells were analyzed by flow cytometry.

Results: Sensitized recipients demonstrated increased numbers of nonswift and memory B cells in the bone marrow compared to allogeneic recipients (Figure 1). Sensitized recipients demonstrated increased numbers of splenic CD4+ T cells compared to allogeneic recipients. However, splenic CD8+ T cells and T regulatory cell numbers were similar between sensitized and allogeneic recipients. Additionally, splenic T follicular helper (Tfh) cells were elevated in sensitized recipients compared to allogeneic recipients. Conclusion: We show sensitized kidney transplant recipients with cAMR develop increased populations of memory B cells and CD4+ T cells, including Tfh cells. The interactions of CD4+ T cells, including Tfh cells, with B cells promote the generation of memory B cells and antibody production and support a role for T and B cells in chronic rejection.

Funding: Other NIH Support - KL2 award
FR-PO1104

Ex Vivo Exposure to IL-6 and TNFa Improves Proliferation of Regulatory T Cells Without Impairing Their Function and Lineage Stability

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Background: Clinical trials testing the efficacy of regulatory T cell (Treg) therapy in kidney and liver transplantation are underway. The survival and function of the infused Tregs in the inflammatory environment of the recipient are key determinants of the safety and efficiency of Treg therapy. We sought to investigate the impact of ex vivo exposure to IL-6 and TNFa on Treg proliferation, phenotype, and function.

Methods: First, we isolated CD4+ CD25+ CD62L+ Tregs from C57BL/6J mice lymph nodes using fluorescence activated cell sorting (FACS). We stimulated the Tregs with anti-CD3/CD28 beads in the presence of IL-2, with or without IL-6 and TNFa and monitored Treg proliferation over a 10-day period. In addition, we adoptively transferred IL-6 and TNFa exposed NOD.BDC2.5 TCR transgenic Tregs into NOD.CD28KO mice. Similarly, we setup ex-vivo cultures of human CD4+CD25+CD127+ Tregs isolated from peripheral blood mononuclear cells of healthy donors. Finally, we profiled both murine and human Tregs using flow cytometry, luminescence, bisulfite conversion and pyrosequencing.

Results: We observed that C57BL/6J mouse Tregs exposed to IL-6 and TNFa have increased proliferation (136+/-28 versus 110+/-50 fold; n=3, p=0.02), expressed Foxp3 and Helios and remained demethylated at the Treg specific demethylated region (TSDR). Adoptive transfer of IL-6 and TNFa exposed NOD.BDC2.5 TCR transgenic Tregs protected NOD.CD28KO recipients from diabetes. Similarly, ex-vivo exposure to IL-6 and TNFa increased proliferation of human CD4+ CD25+ CD127+ Tregs (24+/-13 versus 5+/-1 fold; n=3, p=0.04). IL-6 and TNFa exposed human Tregs remained FOXP3+ HELIOS+, did not produce pro-inflammatory cytokines such as IL-2, IL-4, IFNγ or IL-17, and maintained demethylated TSDR. Finally, IL-6 and TNFa exposed human Tregs maintained their suppressive function against pre-activated CD4+ T effector cells, similar to their non-exposed Treg counterparts.

Conclusions: Our results demonstrate that Treg exposure to IL-6 and TNFa enhances their proliferation without negatively impacting their lineage stability and suggests that Tregs positively respond to these cytokines by increasing their proliferation as a way to scale to inflammation. This property may be exploited to improve therapeutic Treg manufacturing for transplantation.

Funding: Other NIH Support - NIAID Support, Private Foundation Support

FR-PO1106

Angiotensin-(1–7) Attenuates Tacrolimus-Induced Apoptosis in Human Renal Proximal Tubular Epithelial Cells

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Background: Tacrolimus (FK-506) is used clinically to reduce the rejection rate in patients with kidney transplantation; however, the nephrotoxicity induced by tacrolimus remains a serious clinical problem. Although tacrolimus-induced nephrotoxicity might be involved renin-angiotensin system, but the role of angiotensin-(1–7) (Ang-(1–7)) has not been completely understood. The present study was aimed to investigate the renoprotective effects of Ang-(1–7) in tacrolimus-induced renal tubular injury.

Methods: To investigate the molecular mechanisms underlying tacrolimus-induced renal tubular cell injury, human proximal tubular epithelial (HK-2) cells were treated with tacrolimus (75 µM) in the presence or absence of Ang-(1–7) (1 µM) and Mas receptor antagonist A779 (1 µM). Cell viability was examined using WST-1 assay. Cell cycle arrest was assessed by the protein expression of cyclin B1, phospho-Cdc2 (Tyr 15) and phospho-Histone H3 (Ser 10).

Results: Treatment of tacrolimus decreased cell viability in a dose or time-dependent manner in HK-2 cells. In addition, treatment of tacrolimus decreased the protein expression of cyclin B1, phospho-cdc2 and phospho-Histone H3 in cytosol and nuclear fraction compared with control, indicating that cells arrested at G2/M phase. Moreover, tacrolimus induced the expression of nuclear factor-κB (NF-κB) signaling, pro-apoptotic markers Bax and cleaved caspase-3 and necrotic cell death marker cleaved PARP1, as well as attenuated the anti-apoptotic marker Bcl-2 in HK-2 cells. However, these changes were attenuated by pretreatment with Ang-(1–7), while co-treatment with A779 abolished the effect of Ang-(1–7). In addition, tacrolimus increased tumor necrosis factor-α converting enzyme (TACE) and decreased angiotensin-converting enzyme 2 (ACE2) expression in HK-2 cells, while pretreatment with Ang-(1–7) or A779 significantly inhibited or enhanced these effects, respectively.

Conclusions: NF-κB signaling and cell cycle arrest at G2/M phase might be mediated in tacrolimus-induced apoptosis. Also, tacrolimus increased TACE expression, which could mediate the vicious cycle of decreasing ACE2. However, Ang-(1–7) protects the cell viability by suppressing apoptosis and necrosis via Mas receptor in tacrolimus-induced HK-2 cells.

FR-PO1107

Whole Blood vs. Packaged Red Blood Cell-Based Perfusion in Normothermic Machine Perfusion of Kidneys


Background: With a rapidly growing gap between supply and demand for donor kidneys, transplant centres look to utilize extended criteria donors to meet the demand. Normothermic machine perfusion (NMP) is a novel preservation method that offers opportunities for graft evaluation and therapeutic interventions not possible with traditional methods. Although NMP offers advantages compared to cold storage preservation, it is not yet a standard practice in transplant centers. In this study, we evaluate the performance of whole blood perfusion versus NMP in a porcine kidney model.

Results: In a porcine model, we observed that whole blood perfusion resulted in lower oxygen consumption, higher glomerular filtration rate, and lower blood lactate levels compared to NMP. Additionally, whole blood perfusion preserved the histological integrity of the kidneys better than NMP.

Conclusions: Whole blood perfusion may be a viable alternative to NMP in kidney transplantation, offering improved graft function and reduced ischemic injury.
hypothemic methods. With higher metabolic demand, NMP requires an oxygen carrier for efficient tissue oxygenation, and the most common choice is packed red blood cells or leukocyte-depleted blood. We aim to investigate the effects of whole blood compared to packed red blood cell-based NMP perfusate on graft perfusion and inflammation.

Methods: Porcine kidneys were recovered and perfused with our pressure controlled NMP system (NMP FORTESSA™ X-20) for 12 hours. The NMP system is primed with a modified plasmalyte (crystalloid) solution and either whole donor blood or washed donor packed red cell perfusate. Perfusion is supplemented with heparin, glucose, and insulin over time through infusions. Perfusion and urine samples are collected for analysis throughout perfusion.

Results: Both groups experienced comparable mean renal blood flow consistently over 12 hours of perfusion, with a trend showing increased renal blood flow in whole blood perfusates (whole blood: 719±27.5ml/min; packed red blood: 639±28.6ml/min). No significant differences in perfusate pH were detected. Pro-inflammatory cytokines TNF-alpha and IL-10 were significantly increased in whole blood compared against packed red cell-based perfusate. Anti-inflammatory cytokine IL-10 was also significantly increased in whole blood compared to packed red cell-based perfusate.

Conclusions: Both whole blood and packed red blood cell-based perfusates demonstrated equivalent perfusion resistance and perfusate biochemistry in a porcine model of kidney normothermic machine perfusion. With the presence of leukocytes in whole blood-based perfusates, there was a significant increase in perfusate cytokines, including both pro-inflammatory cytokines TNF-alpha and IL-6 and anti-inflammatory cytokine IL-10. However, the physiological significance of perfusate cytokine presence still requires further study through histological evaluation and a transplant model with long term follow up.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO1108
Downregulation of Alloraft 25-Hydroxyvitamin D3 1 Alpha-Hydroxylase Is an Early Biomarker for Rejection in Kidney Transplantation
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Background: 1a, 25(OH)2 vitamin D3 (1a,25VitD3) results from both renal and extrarenal 25-Hydroxyvitamin D3 1 alpha-hydroxylase (1a-HOase) activity. Renal 1a-HOase is classically associated with mineral metabolism whereas extrarenal 1a-HOase exhibits immunomodulatory effects. Vitamin D deficiency may also be prevalent in the immediate post-transplant period. In the present study, we investigated the relationship between cytokine secretion, graft 1a-HOase expression, renal cortical epithelial cell injury (RCEC), and alloraft rejection in a pig model of kidney transplantation and in cultured human RCEC.

Methods: Outbred Yorkshire pigs underwent autotransplants or mismatched allogeneic kidney transplants as we described (Transplant Immunol 42:40). No immunosuppression was used. The vitamin D axis was assessed 72 hours post transplant. The effect of 1a,25VitD3 and 25VitD3 on T cell proliferation and epithelial-mesenchymal transformation (EMT) were investigated using cultured RCEC.

Results: Circulating levels of 1a,25VitD3 and 25VitD3 were increased and decreased, respectively, in 30 pigs following auto (n=5) or allotransplantation (n=25). Alloraft 1a-HOase was decreased in rejection showing a negative correlation with the extent of rejection (Bland: r=-0.712, p<0.01) and renal function (BUN: r=-0.706, p<0.01; creatinine: r=-0.673, p<0.05). Additionally, IL17 and IFNγ were upregulated, and 1, 25-hydroxyvitamin D3 24-hydroxylase was downregulated in rejecting 1a-HOase was mainly expressed in RCEC. Activating cultured RCEC with cytokines gave a two-fold increase of CHOP abundance and a 70-fold increase of spliced XBP1 abundance in cell lysates. Parallel immunofluorescence analysis showed CsA-induced nuclear E-cadherin (E-cad) and tight junction protein-1 (TJP1), whereas 1a,25VitD3 attenuated cytokine induction of EMT, as well as normalized expression of E-cad and TJP1. When compared to 25VitD3, 1a,25VitD3 exhibited a 50-fold greater suppression of T cell proliferation.

Conclusions: Alloraft 1a-HOase expression may predict alloraft rejection, not the circulating 1a,25VitD3. Alloraft 1a-HOase may play a key role in the prevention of alloraft rejection.

Funding: Private Foundation Support

FR-PO1109
Inhibition of Spleen Tyrosine Kinase Decreases Donor-Specific Antibody Levels in a Rat Model of Presensitization
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Background: Antibody mediated rejection (ABMR) is the leading cause of allograft failure post transplantation and there is currently no available effective treatment. Orthotopic kidney allografts from Fischer F344 DU (F344) to Lewis RT1 I (LEW) rats is a well-established model for chronic allograft nephropathy. The aim of this study was to determine if LEW pre-sensitized with F344 whole blood produced donor specific antibodies (DSA); and whether inhibition of SYK with Fostamatinib had efficacy in reduction of circulating DSA levels.

Methods: Male LEW rats were transfused with whole blood from male F344 rats. Transfused LEW rats were treated with 40mg/kg of Fostamatinib or vehicle by oral gavage twice daily for 14 days from 7 days (early treatment), or 11 days (late treatment) post transfusion. Serum MFI levels for IgG DSA levels were determined on a BD LSRRFORTESSA™ X-20.

In our experiment the first time F344 to LEW whole blood transfusion has been described as a pre-sensitization model. Transfused LEW rats developed IgG DSA. Early treatment was implemented at onset of IgG antibody production (day 7), and late treatment where IgG antibody production was established and nearing peak levels (day 11) (Fig1a).

In our experiment early treatment with Fostamatinib significantly decreased circulating IgG levels (Fig1b), late treatment, when antibody levels were established was not effective (Fig1c).

Conclusions: In conclusion, we have shown that treatment of pre-sensitized LEW rats with selective SYK inhibitor Fostamatinib at the start of IgG antibody production significantly reduced levels of circulating IgG DSA. Cytotoxic IgG antibodies have a well-established role in ABMR. This indicates a potential use of Fostamatinib as a treatment option for pre-sensitized patients requiring renal transplant or following development of a de novo DSA.

Funding: Government Support - Non-U.S.
FR-PO111
Blockade of PKCδ in Donor Kidneys Protects Against Cold Ischemia-Reperfusion Injury in Kidney Transplantation
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Background: Ischemia-reperfusion injury (IRI) is an inevitable consequence of kidney transplantation. PKCδ has been reported to contribute to mitochondrial pathway of apoptosis during cell stress, but role of PKCδ in kidney IRI remains unknown. This study aims to evaluate the role and regulation of PKCδ in cold storage with renal transplantation.

Methods: C57BL/6 mice kidneys were preserved in an ice bath for 0.5, 4, 8, 10 or 14 hours in University of Wisconsin solution (UWS) and transplanted into syngeneic recipients. Renal injury and regeneration were examined at 24 hours or day 6 after transplantation. The responses of kidneys from wild-type and PKCδ-null mice were examined and compared. Rat proximal tubular cells (RPTC) were exposed to hypothermia at 4°C for 4 hours and then cultured with complete medium in 37°C. Mitochondria morphology was examined under confocal microscopy and mitochondria dysfunction was evaluated by Cytochrome C release and Bax translocation. Active and kinase-dead PKCδ were transfected to determine the role of PKCδ in RPTC cells.

Results: Post-transplant injury in WT kidneys was mild when cold storage time was longer than 4 hours, but the injury increased notably with 8 hours and longer cold storage. Ki-67+ tubules peaked at 8 hours of cold storage, while longer cold storage suppressed post-transplant tubular proliferation. PKCδ was activated during cold storage as indicated by its phosphorylation at Y311 and proteolysis. WT kidneys with 10 hours cold preservation showed variable damage and tubular apoptosis at 24 hours after transplantation. In comparison, PKCδ-KO kidneys had significant less injury and better tubular proliferation. Furthermore, PKCδ-KO kidneys had improved kidney repair and function as life-supporting kidney at day 6 when native kidneys were removed from recipient. Consistently, pharmacological inhibitors of PKCδ also prevented early post-transplant injury at day 1. In RPTC cells, mitochondrial fragmentation and leakage were involved in cold storage injury. Mitochondrial injury and cell death were inhibited by PKCδ kinase-dead mutant but were aggravated by active PKCδ fragment.

Conclusion: Blockade of PKCδ in donor kidneys and mediates subsequent renal IRI during kidney transplantation. Inhibition of PKCδ may alleviate subsequent kidney injury during cold storage and benefit subsequent renal transplantation. Funding: NIDDK Support, Veterans Affairs Support

FR-PO1112
Developing an Imaging Mass Cytometry-Based Injury Panel to Define the Pathogenesis of Delayed Graft Function
Zachary FR-PO1112

FR-PO1113
Differential Control of COX-2 Expression in Macula Densa Cells Under Calcineurin Inhibition by Cyclosporine A

Background: Calcineurin inhibitors such as cyclosporine A (CsA) are in use as immunosuppressive drugs to prevent rejection of transplanted organs. Despite positive outcomes, side effects such as decreased GFR and overall functional and structural deterioration during cold kidney may affect the kidney. Among the causes, interactions of vasoactive systems have been considered. We therefore studied how CsA may cause dysregulation of key juxtaglomerular signaling components.

Methods: Wistar rats received vehicle or 25mg CsA/kg b.w. for 14d. Organs were perfused and embedded for morphology. Cultured macula densa (MD) cells were exposed to CsA (5 µM) and angiotensin II (AngII; 1 µM) for 6 or 24h. Tissues or cells were immunohistochemically studied for renin, COX-2, NFAT subtypes 1 to 4, p38 MAPK, CREB, NF-κB, and activating p38 MAPK and CREB phosphorylation. Inhibitors p38 MAPK (SB203580; 10 µM) and AngII (1.9-fold) were added to CsA (5 µM) induced IRI kidneys experience early anti-inflammatory changes conducive to improved kidney function post injection of adipose-derived regenerative cells (ADRC). The mechanism on how these cells induce reparative effects during IRI remains elusive. We investigated ADRC-derived effects within the injured kidney at early timepoints.

Methods: In vitro models were developed for inducing programmed cell death (apoptosis—TNFα, ATP depletion; necroptosis—TNFα, ATP depletion, zVAD) and cell stress (autophagy—serum starvation, TGFβ; ER stress—serum starvation, tunicamycin) pathway activation in human proximal tubule HK2 cells. Antibodies showing specificity by IF were conjugated to heavy metals to be used for IMC.

Results: HK-2 cells showed reduced viability under cell death conditions (control 95 ±/−0.9%; apoptosis 46.3 ±/− 5.9%; necroptosis 66.6 ±/− 5.9%). Validated antibodies showed significant differences under injury vs control conditions, including: apoptosis (anti-Casp3: 9.5 ±/− 2.5% vs 0.8 ±/− 0.3%); necroptosis (anti-pMLKL: 17.9 ±/− 5.1% vs 2.8 ±/− 0.7%); autophagy (anti-p62: 29.8 ±/− 7.4% vs 7.1 ±/− 1.9%); and ER stress (anti-Grp94: 21.0 ±/− 0.6% vs 2.0 ±/− 0.7%). All 4 antibodies retained staining by IF in a tumor-associated interstitial nephritis kidney biopsy.

Conclusions: We now have 35 validated antibodies, including the 4 described above, to simultaneously quantify injured tubular and vascular cell populations and their frequency of interaction with immune subtypes. We will perform IMC with this expanded panel of antibodies on transplantation biopsies from 16 deceased donors (7 with subsequent DGF) and 15 living donors as healthy controls.

Funding: NIDDK Support

FR-PO1114
Non-Cultured Adipose-Derived Regenerative Cells Limit Early Inflammation and Fibrosis in Renal Ischemia-Reperfusion Injury
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Background: Studies in our rat model of ischemic reperfusion injury (IRI) demonstrate improved kidney function post injection of adipose-derived regenerative cells (ADRC). The mechanism on how these cells induce reparative effects during IRI remains elusive. We investigated ADRC-derived effects within the injured kidney at early timepoints.

Methods: In vitro models were developed for inducing programmed cell death (apoptosis—TNFα, ATP depletion; necroptosis—TNFα, ATP depletion, zVAD) and cell stress (autophagy—serum starvation, TGFβ; ER stress—serum starvation, tunicamycin) pathway activation in human proximal tubule HK2 cells. Antibodies showing specificity by IF were conjugated to heavy metals to be used for IMC.

Results: ADRC-treated kidneys expressed lower levels of inflammatory gene CXCL12 and significantly lower protein levels of granulocyte macrophage colony-stimulating factor (both p<0.05). In addition, a consistent increase in cytotoxic T-lymphocyte-associated protein 4 (CTLA4) receptor was charaterized. ADRC treated kidneys had half of vehicle controls contained higher levels of CD45+ leukocytes. Assessment of leukocyte infiltrate indicated a trend of higher infiltrate in vehicle control kidneys compared to ADRC kidneys at 48 hours with significant apparent differences by 1-week post IRI (p<0.05).

Conclusions: Collectively, gene, protein expression and histological evidence suggest that ADRC treated IRI kidneys experience early anti-inflammatory changes conducive to the inhibition of fibrogenesis. Funding: Private Foundation Support, Government Support - Non-U.S.
Methods: THP-1 cells were seeded in the presence of TNF-α at different time-points (3, 6, and 24 hours) and concentrations (5, 10, and 20 ng/ml). Cells were pretreated for 30 minutes with 1 μM of the A2AR agonist ZM241385 before TNF-α was added and samples were analyzed by Real-time PCR.

Results: TNF-α significantly augmented the expression of A2A but not A2B at all pretreatment periods, reaching the maximum increase at a concentration of 10 ng/ml at 3 hours of treatment (p<0.001). TNF-α also induced the expression of TLR-β3 and the M2 marker CD163 at 18 and 24 hours (figure 1A). Interestingly, the expression the M1 macrophage marker CD86 decreased with TNF-α and the M1 marker CD163 at 18 and 24 hours (figure 1B) and concentrations (5, 10 and 20 ng/ml). Pretreatment with ZM241385 abolished the effect of TNF-α. A2A receptor is involved in M2 macrophage activation by TNF-α. In fact, induction of CD163 expression by IL-10 (p=0.0006) was partially but significantly blocked by ZM241385 (31.4% increase blocked, p=0.018). We did not detect any effect of IL-10 on TLR-β3.

Conclusions: Our results suggest TNF-α induces macrophage M2 switching and TLR-β3 expression through A2a receptor activation.

Funding: Government Support - Non-U.S.

FR-PO1116

Dual Treatment of CD40 Silencing or Mesenchymal Stem Cells Infusion with Sub-Therapeutic Doses of Cyclosporine Effectively Prevents Acute Rejection in an Allogenic Model of Renal Transplantation

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Background: Previous studies in our group showed partial protective effect of cosilencing silencing with a siRNA-CD40 or MSC infusion in life sustaining model of rat renal allograft transplant. This study was designed to investigate the combination of CD40 silencing or MSC infusion with suboptimal doses of Cyclosporine in this renal allograft model.

Methods: In this model, rats were randomly allocated into different groups: Non-Treated (n=10); Scrambled siRNA (n=10); Cyclosporine (control full dose, 5 mg/kg/day) (n=9); CsA1/2 (sub-therapeutic, 2.5 mg/kg) (n=5); MSC, group treated with two MSC doses at day -7 and day 0 (n=8); siRNA-CD40 (500 ug) (n=5); CsA1/2+siRNA-CD40 group (500 ug) (n=5); CsA1/2+MSC group (n=5). Histological analysis of lymphoid infiltration of CD40 treated mice was performed from Wistar to Lewis rats, with 21 days of follow up. Survival, renal function, conventional histology and immunohistochytemetry (CD68 cells, CD3 cells, glomerular and peritubular capillary Cd4) were analyzed in all groups.

Results: Monotherapy either with CsA1/2, siRNA-CD40 or MSC showed slight improvement in all the described parameters as compared to Non-treated or Scrambled groups. The combined treatment using CsA1/2+MSC or CsA1/2+siRNA-CD40 displayed significant amelioration of these parameters compared to monotherapy groups. Interestingly, the CsA1/2+siRNA-CD40 group presented a clear reduction of glomerular and peritubular Cd4 deposition and the degree of Cd3 infiltrate, reaching similar values to Cyclosporine full dose group.

Conclusions: In conclusion, siRNA or MSC combined with sub-therapeutic doses of Cyclosporine offered better prevention in allograft rejection and survival than monotherapy groups. But was the CsA1/2+siRNA-CD40 group that gave the greatest protection both in the cellular and humoral arms, perhaps by an additive effect.

Funding: Government Support - Non-U.S.

FR-PO1117

Contrasting Effects of Conventional Immunosuppressants in Establishing Murine Transplantation Tolerance

Haruki Katsumata,2,1 Satoshi Miyairi,2 Toshihito Hirai,1 Kan Saiga,2 Masayoshi Okumi2,3 Yasuyuki Ishii,1 Takashi Yokoy,1 Kazunari Tanabe,1 The Jikei University School of Medicine, Minato-ku, Japan; 2Uozu, Toccyo Women's Medical University, Tokyo, Japan; 3University of Tokyo Medical University, Meiko Park, CA; 2Tokyo Women's Medical University, Shinsukuba, Japan; 3REGIMUNE Corporation, Tokyo, Japan.

Background: Tacrolimus (TAC) is one of the most commonly used calcineurin inhibitors (CNIs) for immunosuppression maintenance after kidney transplantation. It inhibits immune responses by suppressing T-cell receptor signaling and downstream expression of interleukin-2. An inhibitor of the mammalian target of rapamycin (mTOR-I) and mammalian target of rapamycin (mTOR-I) inhibitors (EVL) shows immunosuppressive activity by inhibiting other pathways. Since, regulatory T cells (Treg) function depends on interleukin-2 signaling, CNIs can affect their suppressive potentials. However, mTOR-I has a weaker effect on Treg proliferation. We previously reported an approach to induce mixed chimerism by sublethal irradiation and injection of responder cells with liposomal formulation of alpha-galactosylceramide (RGI-2001) and CD40 ligand (4DCL40). We evaluated the impact of TAC or EVL on chimerism establishment and Treg in this regimen.

Methods: Recipient mice were treated with either TAC or EVL from day 1 to day 14 and CD122 mAb donor mice, in addition to the regimen using sublethal irradiation, and a single injection of RGI-2001 and anti-CD40 antibodies. Then, we analyzed the proportion of donor cells and Treg in peripheral blood mononuclear cells. Isolated Treg were co-cultured with the mixture of host T cells and T-activator CD3/CD28 by selecting 4-day culture, the proliferation of responder cells was analyzed by flow cytometry.

Results: In immunosuppressive drug-dosing phase, chimerism was comparably enhanced by TAC and EVL. Following drug discontinuation, TAC-treated mice exhibited a gradual decrease in the donor cell proportion. In contrast, EVL-treated mice sustained long-term robust chimerism. Treg of TAC-treated mice showed lower proliferation and low suppressive activity than EVL-treated mice.

Conclusions: TAC negatively impacted the regimen by interfering with Treg proliferation and activation.

Funding: Government Support - Non-U.S.

FR-PO1118

Anti-CD40 (Iscalimab) Treatment Results in Preserved Allograft Histology in Non-Human Kidney Transplantation Compared with Calcineurin Inhibitors

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Background: The CD40-CD154 costimulatory pathway has been implicated in the pathology of transplant rejection, and blockade of this interaction using anti-CD40 antibodies significantly prolongs renal allograft survival in non-human primates (NHPs). Further, recent clinical data indicated that the anti-CD40 mAb Iscalimab (CFZ533) demonstrated comparable efficacy and superior renal function versus tacrolimus in de novo calcineurin inhibitor (CNI)-free kidney transplantation. One possible explanation for superior renal function was that Iscalimab treatment may have resulted in improved graft quality compared to CNIs, a notion supported by data from a small number of patients from the aforementioned clinical phase II study.

Methods: To further examine this notion, allograft histology from baseline and up to one hundred days post-transplanted NHP kidney allografts from transplanted animals treated with Iscalimab, anti-CD154 mAb, Cyclosporine A, PCK inhibitors or FTY720 were reviewed and scored in a blinded fashion by a pathologist according to the Banff classification.

Results: In addition, we performed molecular analyses of these samples. Our analyses indicated that the quality of allografts as defined using total, inflammatory and fibrotic BANFF scores, from Iscalimab treated animals was superior to that observed in animals dosed with all other immunomodulatory and immunosuppressive agents. This was also reflected in the molecular analyses of allograft biopsies showing that CFZ533 was more likely to preserve the gene expression profile of baseline tissue following transplantation compared to other drugs.

Conclusions: Collectively our data indicated that prevention of allograft rejection by Iscalimab appears to be associated with higher graft quality compared to other drugs, including CNIs.

Funding: Commercial Support - Novartis Pharmaceuticals AG

FR-PO1119

T Cell-Specific mir-17-92 Knockout Improved Skin Graft Tolerance by Modulating T Follicular Helper Cell Development and Regulatory T Cell Activity

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Background: T follicular helper (Tfh) cells provide crucial signals to germinal center (GC) B cells supporting GC B cell proliferation. Tight control of Tfh cells prevents self-tolerance. Regulatory T (Treg) cells play a critical role in maintaining self-tolerance and controlling the magnitude of physiologic immune response. The Treg transcription factor forkhead box P3 (Foxp3) works in concert with other co-regulator molecules to determine suppressive phenotype of Treg. MicroRNA-17-92 (miR-17-92) has been shown in our previous study to regulate the suppressive effect of Treg on mice EAE models. The knockout of Mir-17-92 increased the immunosuppressive activity of Treg.

Methods: We generated T cell specific mir-17-92 knockout (mir-17-92-/-) mice, followed by skin transplantation. B6 miR-17-92-/- and B6 wild type littermates were used as recipients of BALB/c skin grafts. By bioinformatics study, possible targets of mir-17-92, related to Treg function was evaluated. In addition, we performed a MLR (mixed lymphoid reaction) by co-culture donor APC with recipient derived T cells.

Results: The sirolimus-treated, mir-17-92-/- mice showed less Tfh cells, less GC B cells and the less plasma cells as compared with those in the sirolimus-treated, wild type mice. Consistent with the reduction germinal center response, skin histological analysis revealed a lower mean histopathology score. Moreover, mir-17-92 knockout enhance the suppression function of Tfh. Th1 and Th17 are decreased in the miR-17-92-/- mice.
Moreover, T cells from miR-17-92 -/- mice demonstrated a donor antigen-specific hyporesponse in vitro.

Conclusions: We found that the skin graft survival was significantly better in the sirolimus-treated, miR-17-92 -/- mice, unveiling the future therapeutic potential of microRNA manipulation in transplantation.

Funding: Government Support - Non-U.S.

FR-POI120

Examining a Novel Emerging Immune Checkpoint in Kidney Transplant Recipients

George J. Kavalavan, Amar D. Desai, Anil K. Chandraker, Sudipta Tripathi, Brigham and Women’s Hospital, Boston, MA.

Background: The balance between T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) and its co-receptor CD226 function as an ‘immune checkpoint’ with immunomodulatory functions in both T and NK cells. Immunomodulation is mediated through the balance of TIGIT/CD226 binding with the ligands CD155 and CD112. Interaction of CD226 with the ligands CD155 and CD112 co-stimulates T cell, whereas TIGIT exerts the opposite effect and inhibits T cell response. This ligand/receptor network plays an important role in various autoimmune diseases and cancer, but its role in transplantation remains unclear. We examined the expression levels of TIGIT, CD226 and their ligands CD155 and CD112 in kidney transplant recipients (KTR) and healthy controls (HC) to understand the relevance of TIGIT/CD226 co-signaling in transplantation.

Methods: Blood samples were collected from 23 HC and 68 KTR and cell surface expression of CD226, TIGIT, CD155 and CD112 and other cell markers on peripheral T and NK cells were determined by flow cytometry.

Results: We observed that in the KTR group both T and NK cell populations showed a significant decrease in TIGIT and an increase in CD226 expression compared to HC. Interestingly, in the KTR CD4+ T cells showed a significant increase in CD226 expression whereas CD8+ T cells showed a significant decrease in TIGIT expression. Both these changes lead to an increase in IFNγ production and a pro-inflammatory environment. The predominant peripheral CD16+ NK cells also showed an inflammatory phenotype with both increased CD226 expression and decreased TIGIT expression and also showed a significant increase in the expression of both the ligands CD155 and CD112 in comparison to HC.

Conclusions: Increased expression of CD226 in both T and NK cells and increased expression of its ligands CD155 and CD112 on NK cell populations were observed in KTR, suggesting a pro-inflammatory phenotype and a plausible NK-T cell-cell interaction in the periphery. The TIGIT/CD226 axis may be potential targets for reducing the alloimmunity response mediated by T and NK cells.

FR-POI121

Dissecting the Role of Adipocyte Na-K-ATPase Signaling in Attenuating Experimental Uremic Cardiomyopathy by Adipose Tissue Transplantation

Komal Sohni, Marshall University Joan C. Edwards School of Medicine, Huntington, WV.

Background: Adipocytes contribute to systemic diseases has become an important topic. We have recently demonstrated that administration of NaKtide, antagonist of Na/K-ATPase (NKA) signaling, coupled to adipocyte specific promoter adiponectin can improve adipocyte phenotype. In experimental uremic cardiomyopathy, uremic toxin exposure, as an ‘immune checkpoint’ with immunomodulatory functions in both T and NK cells. Immunomodulation is mediated through the balance of TIGIT/CD226 binding with the ligands CD155 and CD112. Interaction of CD226 with the ligands CD155 and CD112 co-stimulates T cell, whereas TIGIT exerts the opposite effect and inhibits T cell response. This ligand/receptor network plays an important role in various autoimmune diseases and cancer, but its role in transplantation remains unclear. We examined the expression levels of TIGIT, CD226 and their ligands CD155 and CD112 in kidney transplant recipients (KTR) and healthy controls (HC) to understand the relevance of TIGIT/CD226 co-signaling in transplantation.

Methods: Blood samples were collected from 23 HC and 68 KTR and cell surface expression of CD226, TIGIT, CD155 and CD112 and other cell markers on peripheral T and NK cells were determined by flow cytometry.

Results: We observed that in the KTR group both T and NK cell populations showed a significant decrease in TIGIT and an increase in CD226 expression compared to HC. Interestingly, in the KTR CD4+ T cells showed a significant increase in CD226 expression whereas CD8+ T cells showed a significant decrease in TIGIT expression. Both these changes lead to an increase in IFNγ production and a pro-inflammatory environment. The predominant peripheral CD16+ NK cells also showed an inflammatory phenotype with both increased CD226 expression and decreased TIGIT expression and also showed a significant increase in the expression of both the ligands CD155 and CD112 in comparison to HC.

Conclusions: Increased expression of CD226 in both T and NK cells and increased expression of its ligands CD155 and CD112 on NK cell populations were observed in KTR, suggesting a pro-inflammatory phenotype and a plausible NK-T cell-cell interaction in the periphery. The TIGIT/CD226 axis may be potential targets for reducing the alloimmunity response mediated by T and NK cells.

FR-POI122

Human Donor-Specific Regulatory T-Cell Line Function Is Mediated Through the Adenosinergic Pathway

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Background: We have previously shown that regulatory T cell lines generated and expanded from transplanted individuals have the capacity to induce longterm allograft survival in an animal model and suppress human donor specific effector T cell responses in vitro. In murine models targeting the CD39/73 adenosinergic pathway is associated with long-term graft function and reduced graft versus host disease severity. Little is known about how this pathway functions in human regulatory T cells.

Methods: 45 kidney transplant recipients were included in the study and 19 T-cell lines were generated from 17 patients by stimulating PBMCs with mismatched donor-derived HLA-DR allopeptides. T-cell lines were immunomophenotyped with fluorochrome conjugated human anti-CD39 and anti-CD73 and analyzed using Flowjo. Involvement of the adenosinergic pathway by using Adenosine A2A receptor (A2AR) antagonist.

Results: The functional characterization of the ex vivo expanded T-cell lines was determined by assessing their immunosuppressive function to inhibit antigen specific and non specific T cell proliferation. We observed that all ex vivo expanded T-cell lines were able to substantially inhibit donor antigen specific T cell proliferation. Expression of both CD39 and CD73 in our T-cell lines, both related to the adenosinergic pathway. Inhibition using the A2AR antagonist Istradefylline resulted in abrogation of suppression and increase in an antigen specific T cell proliferation (Figure).

Conclusions: Our results suggest that the CD39/CD73 adenosinergic pathway is important in the function of regulatory T cells and therapies targeting CD39 and CD73 may enhance human regulatory T cell function.

FR-POI123

Increased Mitochondrial Metabolic Enzymes Are Associated with Superior Kidney Function After Normothermic Ex Vivo Kidney Perfusion: A Proteomics Study

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Background: Normothermic ex-vivo kidney perfusion (NEVKP) is associated with significantly improved graft function following transplantation in comparison to static cold storage (SCS). We hypothesized that NEVKP would induce key alterations in the molecular mechanisms central to superior graft function.

Methods: Porcine kidneys were removed following 30 minutes of warm ischemia, and then subjected to either SCS or NEVKP (n=5 each) for 8 hours prior to auto-transplantation. Kidney biopsies were collected at time zero, upon reperfusion, and at POD3. We conducted an unbiased proteomics analysis by LC-MS/MS on Q-Exactive Plus tandem mass spectrometer. Subsequent analyses were performed using MaxQuant, Perseus, R, pathDIP, mirDIP, and NaViGATOR.

Results: Kidney function was significantly improved with NEVKP compared to SCS. We observed that the CD39/CD73 adenosinergic pathway is important in the function of regulatory T cells and therapies targeting CD39 and CD73 may enhance human regulatory T cell function.
Comparison with external datasets of ischemia reperfusion injury, and datasets related to other models of acute and chronic kidney injury confirmed that many of the molecular changes observed in these datasets are expected to be reversed or attenuated by NEVKP.

**Conclusions:** The proteome-level changes associated with NEVKP demonstrate that the preservation of major metabolic pathways, and of cell polarity and integrity may be pivotal mechanisms by which NEVKP results in improved graft function.

**FR-PO1124**

**Role of Interferon-y Associated Chemokines and FOXP3+ T Cells in BK Virus Nephropathy**

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**Background:** BKV reactivation has been associated with increased expression of interferon-y (IFNγ) induced chemokines and increased levels of granulocyte b, cytotoxic T cell molecule. Histological findings of BK virus nephropathy (BKVN) have been compared to those with acute cellular rejection (ACR) but the role of FOXP3 has not been studied. We hypothesized that heightenned expression of IFNγ associated chemokines and lower expression of FOXP3 would be prognostic of 3-year outcomes in BKVN.

**Methods:** To address this hypothesis, we studied absolute mRNA copies of MIG, IP-10, CD3, granzyme B, FOXP3 and 18SrRNA in biopsy matched urine cell pellets of 51 BKVN and 33 ACR patients using a standard curve method in real-time quantitative PCR assay. Continuous variables were compared using Mann-Whitney test and logistic regression was used to determine if urine mRNAs were predictive of graft loss in BKVN patients.

**Results:** We found that urinary cell mRNA for interferon-y inducible chemokines IP-10 was higher and mRNAs for CD3, GB and FOXP3 were lower in BKVN cohort compared to ACR cohort. Ratio of IP-10:CD3 mRNA in urinary cells was significantly higher in BKVN cohort versus ACR cohort. Urinary cell mRNA for IP-10, MIG and GB were associated with increased risk of 3 year graft loss.

**Conclusions:** We conclude that BKVN is associated with increased levels of IP-10 and lower levels of CD3 as compared to ACR and the ratio of IP10:CD3 mRNA can be used to distinguish inflammation associated with BKVN from that of ACR. Urinary cell mRNA levels of IFNγ associated chemokines are associated with 3-year graft loss.

**FR-PO1125**

**Proteomics of Laser-Captured Microdissected Glomeruli and Tubulointerstitial Remodeling of Kidney Allografts with Antibody-Mediated Rejection**

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**Background:** Kidney transplantation is the optimal treatment for end-stage kidney disease, but most grafts fail prematurely. Antibody-mediated rejection (AMR) accounts for >50% of graft loss. AMR is caused by antibodies against HLA and non-HLA antigens in two main renal compartments: glomeruli and tubulointerstitium. We hypothesized that compartment-specific proteome alterations may uncover the mechanisms of early antibody-mediated injury.

**Methods:** We performed laser-capture/microdissection to isolate glomeruli and tubulointerstitium from FFPE kidney biopsies, and subjected samples to proteome analysis. We compared 7 biopsies with AMR with 23 matched ‘non-AMR’ biopsies with T-cell rejection or acute tubular necrosis. Primary human glomerular microvascular endothelial cells (HGMEC) were studied in vitro.

**Results:** We identified 2026 proteins in glomeruli and 2399 in tubulointerstitium (FDR<0.01). 120 proteins were differentially expressed (p<0.05) in AMR vs. non-AMR glomeruli and 180 in the tubulointerstitium. Proteins involved in HLA-mediated antigen presentation were increased in AMR. Proteins decreased in AMR were basement membrane components, and belonged to processes such as extracellular matrix (ECM) and cytoskeleton. Reduced glomerular protein levels of LAMC1, NPHS1, and PTPRO in AMR was verified by immunostaining. Levels of ECM proteins correlated directly and significantly (R=0.7; p<0.05), suggesting co-regulation in AMR. Protein expression of CCT8 (cytoskeleton dynamics) and CALU (protein folding) significantly and directly correlated with histological features of AMR, namely glomerulitis and peritubular capillaritis (q=0.017). Protein-protein interaction and pathway analysis of ourglomerular protein signature revealed enrichment of inflammatory pathways, such as IL-8 signaling. Stimulation of HGMECs with anti-HLA class I antibody increased the secretion of IL-8 and MCP-1 cytokines.

**Conclusions:** Basement membranes are often remodeled in late chronic AMR and are the targets of non-HLA antibodies, suggesting that our findings may represent early, important alterations in AMR. Targeting early ECM changes in AMR may represent a new therapeutic opportunity.

**Funding:** Government Support - Non-U.S.

**FR-PO1126**

**A Proteomic Atlas Depicting the Changes in Small Urinary Extracellular Vesicles Throughout Kidney Transplantation**

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**Background:** Extracellular vesicles (EVs) have come into the research focus of many life sciences. Urinary EVs, specifically since they can be collected noninvasively, hold the prospect of harboring valuable biomarkers to complement renal biopsies. We aimed to establish a concise atlas of the urinary EV protein content and its changes during living donor transplantation as a resource for the investigation of both the biological processes affected by renal transplantation and the identification of potential biomarkers as indicated by our first correlation analyses.

**Funding:** Government Support - Non-U.S.

**Table 1:** Association of urine mRNA profiles with graft loss at 3 years following BKVN

<table>
<thead>
<tr>
<th>Sample</th>
<th>MIG/CD3</th>
<th>IP-10/CD3</th>
<th>GB/CD3</th>
<th>FOXP3/CD3</th>
</tr>
</thead>
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<tr>
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<td>1.5</td>
<td>1.2</td>
<td>1.6</td>
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<td>1.2</td>
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</tbody>
</table>

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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DNA Methylation Profiling Reveals Epigenetic Differences Before and After Acute Rejection-Induced Allograft Dysfunction
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Background: The incidence of acute rejection (AR) has declined to <15% in the first year after renal transplantation but remains a risk factor for allograft nephropathy and determination of allograft fate. DNA methylation regulates gene expression and persists after removal of the stimulus. Here, we analyzed dynamic changes in the methylation landscape before and after AR-induced allograft dysfunction.

Methods: In this two-cohort study, we followed-up with identical patients who successively experienced end-stage renal disease, renal transplantation with allograft function or dysfunction, and final hemodialysis. Peripheral blood mononuclear cells from the same patients were collected at different time points and used for microarray analysis of changes in DNA-methylation status.

Results: In contrast to the allograft-stable cohort, AR accelerated changes in DNA-methylation patterns. Pathway analysis revealed that hypermethylated areas associated with genes were related to T cell receptor, nuclear factor-kappa B, and mammalian target of rapamycin signaling in the AR-induced allograft-dysfunction group, which differed from pathways associated with hypomethylated areas. Moreover, AR altered the methylation status of genes related to epigenetic modification, and in a mouse model of AR, the DNA-methyltransferase inhibitor decitabine ameliorated renal allograft-related inflammatory injuries by enhancing regulatory T cell activities through inhibiting DNMT1 and suppressing T helper 1/2/17.

Conclusions: These results revealed that AR after renal transplantation reshapes the DNA-methylation landscape, with hypermethylated genes associated with AR, and suggested inhibition of DNA methylation as a potential therapeutic approach for AR after organ transplantation to improve allograft survival.

Funding: Government Support - Non-U.S.
CNI trough level) had an additive effect (88% AKI incidence among patients with both risk factors vs. 25% incidence among RTRs with neither risk factor, P=0.004).

Conclusions: RTRs have a higher risk of AKI following cardiac surgery compared with non-RTRs with otherwise similar characteristics. Among RTRs, DD-RTRs and those with higher preoperative CNI trough levels are at highest risk.

Funding: NIDDK Support

FR-PO1130

Transcatheter vs. Surgical Aortic Valve Replacement in US Renal Transplant Patients

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Background: Renal Transplant (RT) patients are a high risk group for surgical aortic valve replacement. Few data exist on the comparative outcome of renal transplant patients with aortic stenosis receiving transcatheter (TAVR) vs. surgical (SAVR) aortic valve replacement.

Methods: The CMS 100% ESRD files from 2013-2015 were used to find RT patients receiving TAVR or SAVR, and to compare inpatient death and adjusted 1-year mortality. The cohort comprised patients receiving TAVR or SAVR 1/1/2013-12/31/2014. Patients with endocarditis or multivalve SAVR were excluded. A six-month period prior to the valve replacement procedure was used to assess comorbidity from claims. Post-discharge mortality rates were estimated and Cox proportional hazards models were used to compare post-discharge 1-year mortality, adjusting for patient characteristics and comorbidity.

Results: Table 1. TA VR vs. SA VR, Transplant Patients

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Table 1. TAVR vs. SAVR, Transplant Patients

FR-PO1131

Development and Validation of a Risk Score for the Prediction of Cardiovascular Disease in Kidney Transplant Recipients

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Background: Cardiovascular disease (CVD) is a major cause of death in kidney transplant (KT) recipients. It is clinically important to estimate the risk of CVD after a KT.

Methods: A derivation cohort contained 387 KT recipients underwent KT at Kyushu University Hospital from January 2006 to December 2012. A prediction model was retrospectively developed and risk scores for CVD were investigated via multivariable logistic regression. The internal validation of the prediction model was estimated via the c-static and the external validation was calibrated via the Hosmer-Lemeshow goodness of fit test using a validation cohort containing 332 KT recipients underwent KT at Kyushu University Hospital.

Results: In derivation cohort 34 patients (8.8%) had CVD events during the observation period. Age, CVD history, diabetic nephropathy, dialysis vintage, and serum albumin at 12 months after KT were significant predictors of CVD. A prediction model consisting of integer risk scores demonstrated good discrimination (c-statistic 0.80) and goodness of fit (Hosmer-Lemeshow test P = 0.78). In a validation cohort containing 332 KT recipients the model demonstrated moderate discrimination (c-statistic 0.70) and goodness of fit (Hosmer-Lemeshow test P = 0.94), suggesting external validity.

Conclusions: This simple model for predicting CVD after kidney transplantation was moderately accurate and useful in clinical situations. In also suggested that nutritional status was an influential risk factor for CVD in KT recipients.
Cardiovascular Disease After Kidney Transplantation: A Nationwide Study in South Korea
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Background: Cardiovascular disease (CVD) is the most common cause of death in end-stage renal disease (ESRD). Kidney transplantation (KT) is an effective treatment for ESRD, and is known as lowering risk for CVD compared to the ESRD patients on the transplantation waiting list. However, there is a lack of large-population studies especially for Asians.

Methods: We analyzed the nationwide health insurance database of South Korea and identified patients who received kidney transplantation from the year of 2007 to 2015. Patients who were under 20 years of age, had previous CVD identified, or had multigraft transplantation were excluded from the study. As controls, ESRD and GP groups were extracted after same exclusion and matching with KT recipients by age, sex, and inclusion year. CVD was defined as major cardiovascular events (MACEs) consisted of myocardial infarction, ischemic stroke, and all-cause mortality.

Results: During the study period, a total of 13,179 patients received KT. After exclusion, 4,156 KT recipients were selected. The same number of ESRD and GP control were extracted after matching. Mean age was 41.3 ± 10.2 years and 55.2% were men in all 3 groups. KT recipients had similar proportions of diabetes and hypertension and a lower proportion of dyslipidemia compared with the ESRD controls, although significantly higher co-morbidities than GP controls. The total number of MACEs was 76 (3.7 per 1000 person-year) in KT recipients, 377 (21.7 per 1000 person-year) in ESRD, and 51 (2.5 per 1000 person-year) in GP. KT recipients had significantly lower MACE risk (adjusted HR 0.81, 95% CI 0.52–1.27, p = 0.365). When subgroup analysis of age, sex, diabetes and hypertension was performed, similar trends were observed regardless of subgroups.

Conclusions: In this study, we found that the KT recipients had a lower risk of newly onset MACE after transplantation compared to patients maintaining dialysis in Korea, and showed a similar MACE risk compared to the general population.

Pre-Transplant Body Mass Index as a Risk for Late Post-Kidney Transplant Hypertension: A Propensity Score Weighting
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Background: Body mass index (BMI) at the time of kidney transplantation (KT) is associated with post-transplant hypertension (HTN). However, imbalance between comparison groups can distort the result.

Methods: Kidney transplant recipients from a single center were divided into obesity (BMI < 25 kg/m²) and non-obesity with BMI ≥ 25 kg/m², respectively. Baseline pre-transplant characteristics of both groups were balanced by propensity scores (PS) with weighting method leading to new study populations. Association between BMI and post-transplant systolic (SHTN) and diastolic HTN (DHTN) defines as systolic (SBP) and diastolic blood pressure (DBP) ≥ 130 and 80 mmHg, respectively at 1.5 year among this new study population was examined by multiple logistic regression.

Results: Of all 70 patients, mean agesSD was 52.7±11 years old, 58.6% were male, and 31% were obese. Mean BMI was significantly higher in obese than non-obese groups (34.1±3.8 vs 24.7±3.4, mean difference 9.4, 95% CI 7.5, 11.3). Several baseline characteristics between 2 groups are different. After adjusting PS weights with generalized boosted model to balance covariates (Figure 1), obese group has 7.09 and 9.21 times higher the odds of having SHTN and DHTN, respectively compared to non-obese group (SHTN: OR 7.09; 95% CI 1.19, 42.17; DHTN: OR 9.21; 95% CI 2.13, 39.77). After adjusted for race, age, gender, type of induction immunosuppression, type of KT, the association remains (SHTN: OR 5.53; 95% CI 4.12, 741.02; DHTN: OR 12.33; 95% CI 2.23, 68.15).

Conclusions: With PS as a balancing method to examine inference, pre-transplant obesity remains one of the risks for post-transplant HTN. Pre-transplant weight should be controlled to mitigate poorer transplant outcomes.
Detection of BK Virus in Renal Allograft Biopsies by RNA In Situ Hybridization RNAscope® Assay
Francesca Costigliolo,1 Kara A. Lombardo,2 Lois J. Arend,2 Avi Z. Rosenberg,4 Andres Matoza,2 Naima Carter-Monroe,3 S.M. Bagnasco,4 Pathology, Johns Hopkins University, Baltimore, MD; Johns Hopkins Medical Institutions, Baltimore, MD; Johns Hopkins Hospital, Baltimore, MD; Johns Hopkins University, Baltimore, MD; Veterans Administration Maryland Health Care System, Baltimore, MD; The Johns Hopkins School of Medicine, Baltimore, MD.

Background: BK polyomavirus associated nephropathy (BKVpyV) remains a cause of graft loss in kidney transplant recipients on immunosuppressive therapy, and its diagnosis relies on identification of BK virus in the renal allograft biopsy based on positive immunohistochemical stain for the viral SV40 large-T antigen. Real time PCR (qPCR) and in situ hybridization (ISH) for BK DNA can also be used to identify BK in kidney tissue. Aim of this study was to evaluate RNAscope®, a novel-next generation technique for in situ hybridization with probes designed to increase the signal-to-noise ratio to visualize RNA transcripts, for the detection of BKv RNA in allograft biopsies.

Methods: SV40 IHC stain (Santa Cruz, Ventana System) and RNAscope® ISH (following Advanced Cell Diagnostics manufacturer protocol), were performed on serial paraffin embedded tissue sections of kidney allograft biopsies. The number of tubules showing positive SV40 nuclear staining was compared to the number of tubules showing positive RNAscope® ISH signal in each biopsy, paired, 2 sides t-test, linear regression, Pearson.

Results: From 2010 to 2018, a diagnosis of BKpyV was made on 32 allograft biopsies from 30 renal transplant recipients (66% Caucasian, 58% male, average age at biopsies 3.3 years). Median time of diagnosis per transplant was 366 days (range 21-1577), median serum creatinine at diagnosis was 1.6 mg/dl (range 0.84-3.48 mg/dl), and median serum creatinine at 120 days after KT was 1.3 mg/dl (range 0.85-3.95 mg/dl). We excluded 3 biopsies (median age of recipient was 63, 20 and 19 years) with median serum creatinine at 120 days after KT was 2.9 mg/dl (range 1.5-3.6 mg/dl). Pearson correlation coefficient of average number of BKv positive tubules detected by RNAscope® and SV40 IHC stain was r=0.74 (P<0.01). Weak correlation was seen between the level of BK viremia and showed trend for higher incidence of BK viremia.

Conclusions: Our data suggest that RNAscope® ISH may be comparable to SV40 for detection of BKv in renal allograft biopsies.

Assessment of the Banff Working Group Classification of Definitive BK Polyomavirus Nephropathy
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Background: The Banff Working Group on Polyomavirus Nephropathy (PVN) proposed a classification of definitive PVN based on polyomavirus replication/oblod level and the extent of interstitial fibrosis. This study is to test the classification using independent cohorts of patients with PVN in renal allograft biopsies, and to analyze the significance of other variables that may play a role in the outcome of PVN, namely presence of tubulointerstitial inflammatory infiltrates (TIBMD) and peak level of plasma BK particles by PCR.

Methods: Four institutions participated in this study. Patients with kidney allograft biopsy-proven PVN with at least 24 months follow up were identified. Clinical data was captured and biopsies were scored according to the Banff PVN classification. Statistical analysis was performed using multivariable logistic regression and analysis of covariance (ANCOVA) to assess dichotomous and continuous outcomes, respectively.

Results: 145 patients met the criteria for the study. 25 (17%) biopsies were classified as Class 1, 67 (46%) as Class 2, and 53 (36%) as Class 3. Serum creatinine levels were elevated and similar regardless of class, with Class 1 mean 1.78 mg/dl, Class 2 1.62 mg/dl, and Class 3 1.78 mg/dl. At the time of diagnosis biopsy the median change in Scr was parallel across classes of PVN (increase in Scr 0.60, 0.52, and 0.60 respectively, p=0.57). At 24 months, median Scr change from baseline increased numerically, as also seen in other reports (increases 0.45, 0.75 and 1.2, p=0.29). In this cohort overall graft failure was 22% (compared to 30% previously reported), and was equally distributed amongst classes (25%, 20% and 25%). TBMD were found in a subset of all PVN classes (10%, 10% and 15%), and were associated with a trend toward worse outcomes (p=0.15). The highest mean number of plasma BK particles was seen in PVN Class 3, but was not statistically different from other classes.

Conclusions: The proposed classification of PVN is promising for evaluation of allograft biopsies; however, the classes do not stratify and identify patients at increased risk of allograft loss. Additional normal parameters need to be identified to determine risk for adverse allograft outcome.

The Incidence of BK Viremia Among Recipients Who Received Kidney Transplants (KT) from Hepatitis C-Infected and Uninfected Donors
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Background: Our previous data showed KT from hepatitis C virus (HCV) infected donor to non-infected recipients might be associated with higher incidence of BK viremia. Methods: One hundred and ninety-two deceased KT recipients (74 HCV infected (D+R-) and 55 HCV negative (D-R+) donor) to HCV negative recipients were included. Outcome was defined as time to incidence BK viremia which 1) was detectable in blood specimen by PCR ( BK viremia≥21,2) was greater than 10,000 copies/mL (high BK viremia≥9). We performed time to event analysis from KT to 120 days after KT with unadjusted and thymoglobulin dose adjusted Cox regression model.

Results: The mean age at KT was 52±11 years old and 80% were African-American. Table shows the baseline characteristics of HCV D+R- and D-R- groups. The median number of the highest viral copies was tended to be 5-fold higher in HCV D+R- group median viral copies range (IQR): 3,239-303,823 copies/mL than D-R- group (median:4,356; IQR:2.931-15,219 copies/mL;P=0.45). Figure shows the probability of the (high) BK viremia over the follow-up time. Compared to D-R-, HCV D+R- group showed a higher incidence of BK viremia (p=0.03). We found no significant difference in the average number of BKv-positive tubules detected by RNAscope® ISH (r=0.250, P=0.012) or RNAscope® ISH (r=0.255, P=0.014).

Conclusions: Additional parameters need to be identified to determine risk for adverse allograft outcome.

Nocardiosis in Renal Transplant Patients
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Background: Kidney transplant (Tx) patients are chronically immunosuppressed and are at increased risk for opportunistic infections, including the gram positive rod Nocardia. Nocardiosis is rare, with an incidence of 0.4%-3.6% in solid organ Tx recipients. The disease is difficult to diagnose, and targeted therapy is required for treatment. In kidney Tx patients specifically, information on the incidence and risk factors for Nocardia infection
is limited. To address this issue in a large at-risk population, we utilized the United States Renal Data System (USRDS) to investigate the incidence and risk factors for *Nocardia* in over 200,000 kidney Tx patients. Sequelae of allograft failure or rejection after infection was also examined.

**Methods:** Demographics, clinical risk factors, *Nocardia* diagnosis, and allograft failure following *Nocardia* infection were queried in kidney Tx patients from the USRDS using ICD-9 codes and CMS Form 2728. Generalized linear models incorporating the number of person years at risk were used to examine risk factors for *Nocardia* and the adjusted relative risks (aRR) and 95% confidence intervals were determined.

**Results:** We queried 203,233 kidney Tx patients and 657 (0.32%) were diagnosed with *Nocardia*. Pneumonia was the most frequent presentation (15.2%) followed by brain abscess (8.4%). Factors that increased the risk for *Nocardia* included granulomatous disease (aRR=7.65), history of allograft rejection (4.82), tacrolimus use (2-4.5), and age > 65 years (2.31). Azathioprine use (0.73), hepatitis C (0.56) and tobacco use (0.74) were associated with decreased risk. Patients with nocardiosis had associated high percentages of graft failure (67.28%) and kidney rejection (60.58%).

**Conclusions:** In this large kidney Tx population, nocardiosis affected 0.3% of patients and presented most often as pneumonia or brain abscess. A history of granulomatous disease, allograft rejection, and tacrolimus use increased the risk for infection, presumably due to higher rates of immunosuppression associated with these comorbid events. This study may improve early recognition of nocardiosis in kidney Tx patients.

**FR-PO1139**

Cytomegalovirus Prevention Strategies and the Risk of BK Polyomavirus Viremia and Nephropathy

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**Background:** Polyomavirus BK (BKV) is the cause of polyomavirus-associated nephropathy resulting in premature graft loss. There are limited data regarding the role of cytomegalovirus (CMV) infection and its prevention in developing BK virus viremia and PVAN.

**Methods:** In a prospective study, we analyzed 267 consecutive renal transplant recipients previously enrolled to 2 randomized trials evaluating different CMV prevention regimens with routine screening for BKV and CMV. Of these, 59 received valganciclovir and 100 valacyclovir prophylaxis, 48 patients were managed by preemptive therapy.

**Results:** At 3 years, the incidence of BKV viremia and CMV was 28% and 5%, respectively. CMV DNAemia developed in 55% and CMV disease in 6%. Both BKV viremia (42% vs. 23% vs. 21%, P=0.006) and PVAN (12% vs. 2% vs. 2%, P=0.011) were increased in patients treated with valacyclovir prophylaxis compared to valacyclovir and preemptive therapy. Using multivariate Cox proportional hazard regression, valacyclovir prophylaxis was independent predictor of BKV viremia (hazard ratio [HR]=2.38, P=0.002) and PVAN (HR=4.73, P=0.026). In contrast, the risk of subsequent BKV viremia was lower in patients with antecedent CMV DNAemia (HR=0.5, P=0.018).

**Conclusions:** These data suggest that valganciclovir prophylaxis is associated with increased risk of BKV viremia and PVAN. CMV DNAemia did not represent a risk for BKV.

**Funding:** Government Support - Non-U.S.

**FR-PO1140**

Serum Albumin Levels Prior to Kidney Transplant Predicts Post-Transplant BK and Cytomegalovirus Infections

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**Background:** Post-transplant Infections are a common cause of morbidity and mortality in kidney transplant recipients (KTRs). Prior studies have shown that pre- and post-transplant hypoalbuminemia are associated with graft failure and all-cause mortality. Others suggested that low post-transplant albumin is linked to cytomegalovirus (CMV) infections. These studies suggest serum albumin levels could indicate post-transplant infection risks. Our study evaluated the association between pre-transplant serum albumin and post-transplant BK Virus (BKV) and Cytomegalovirus (CMV) infections in KTRs.

**Methods:** We used our university database to identify adult KTRs transplanted between 01/01/2005 and 12/31/2015. All subjects had serum albumin measured within 45 days before the transplant. We categorized all KTRs into three pre-transplant albumin levels: Group 1: normal serum albumin ≥2.5-3.9 g/dL, Group 2: moderate hypoalbuminemia 2.5-3.9 g/dL, and Group 3: severe hypoalbuminemia < 2.5 g/dL. We used incidence models per 100 person-years and Cox proportional hazards to compare outcomes between groups.

**Results:** 1717 patients were included in the study. Of those, 36.2% (n=622) were identified as group 1, 62.3% (n=1070) as group 2, and 1.4% (n=25) as group 3. Albumin groups differed by age, cause of end-stage renal disease, BMI, induction immunosuppression and maintenance immunosuppression with tacrolimus vs other, all with a p-value less than 0.001. Incidence of BKV viremia for group 1 was 2.2 per 100 person-year which was lower, compared with group 2: 4.6/100 person-year and group 3: 9.9/100 person-year; as well as for CMV viremia, group 1: 1.75/100 person-year, group 2: 2.7/100 person-year and group 3: 3.6/100 person-year. The adjusted relative hazard for BK was also higher for group 2 (HR=5.2, 95% CI [2.15, 5.2]) and group 3 (HR=2.3, 95% CI [1.04-4.9]) compared to group 1. A similar trend was found for CMV for group 2 (HR=1.1, 95% CI [0.77-1.53]) and group 3 (HR=1.4, 95% CI [0.43-4.5]).

**Conclusions:** Our results suggest that the degree of hypoalbuminemia pre-transplant is directly correlated with the risk of BKV and CMV post-transplant. Proper screening and management of hypoalbuminemia may be helpful in reducing the future risk of these infections.
FR-POI141
BK Virus Surveillance and Outcomes
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Background: Polyoma virus associated nephropathy (PyVAN) caused by BK virus (BKV) occurs in 1-10% of kidney transplant recipients (KTR). Due to lack of effective treatment options, early screening for BKV replication is the most important tool to improve outcomes. Proposed screening strategies are based on consensus guidelines but protocols vary across centers. We report the outcomes in a single center with an intensive BKV screening protocol.

Methods: We performed a retrospective analysis of KTR between Jan 2014 and Nov 2017. We obtained monthly plasma BKV DNA PCR in the first year and every other month in the 2nd year after transplant. A BKV load of >1000 copies/mL was considered positive. Information regarding incidence, treatment and outcomes of patients with BKV, rejection episodes and graft and patient survival was collected.

Results: Among 144 KTR, data were available for 138. There were 34 (25%) patients who developed BKV during a median 2.6-year follow-up period. Baseline characteristics of patients with BKV and no BKV were similar except that more patients in BKV group were on maintenance steroids (62% vs 32%, P = 0.004). Median time from transplant to detection of BK viremia was 139 days (range 34-743). Of those who developed viremia, 30 (88%) developed BKV in 1st year. Median initial and peak viral loads were 7762 copies/mL (Range, 1044-862,198) and 26200 copies/mL (Range 1145-5,000,000) respectively. Six patients developed high grade BKVPyVAN. Almost all patients (32/34) were managed with reduction in immunosuppression (IS). The initial IS reduction was MMF in 16 patients, CNI in 8 patients and 7 patients required reduction in both CNI and MMF. IVIG was used in 1 patient.

Conclusions: Intensive BKV screening in the 1st year post kidney transplant allows for early detection to guide IS management with excellent graft outcomes. Few patients develop BK viremia in the 2nd year and a less intense monitoring can be considered in 2nd year. Larger trials are needed to determine the optimum frequency of BKV monitoring.

FR-POI142
Efficacy and Safety According to Dose of Valganciclovir for Cytomegalovirus (CMV) Prophylaxis in Transplantation: Network Meta-Analysis Using Recent Data
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Background: Valganciclovir is importantly used to prevent post-transplant CMV infection among kidney transplantation patients. However, the dose of such drug being used still remains controversial since the continuous use of such drug decrease kidney function and induces leukopenia in some of the cases. Accordingly, the purpose is to measure the appropriate dose of the drug required for preventing CMV using network meta-analysis.

Methods: We searched the Cochrane Central Register, OVID MEDLINE and Pubmed until April 15, 2019. Studies evaluating among valganciclovir 900 mg, 450 mg and controls were evaluated. We performed direct and indirect network meta-analysis using Bayesian models and generated rankings of the different dose of valganciclovir agents by generation mixed treatment comparison (GeMTC).

Results: Twenty-three studies involving 3,478 participants were eligible. As a result of analyzing among three groups, following completion of the research, the analysis revealed that the glomerular filtration rate, graft loss, tacrolimus level, antibody mediated rejection, fungal, and Candida infection rates were not different among groups. Compared with control, there was no difference between low dose 0.79 [95% CrI, 0.50-1.40] and standard dose 1.0 [95% CrI, 0.61-1.60] groups when CMV incidence was compared. In the Rank probabilities table, the best order for lowering the CMV event was as high as dose of 450mg (71.1%). Incidence of leukopenia showed a significant difference, but there was no statistical significance in the low dose group 1.5 [95% CrI, 0.99-2.20] compared with the control group, but 4.3 times higher in the high dose group [95% CrI, 2.69-7.10], which was 2.9 times higher in the high dose group compared with low dose group [95% CrI, 1.88-4.67].

Conclusions: The use of valganciclovir did not show any difference in other side effects, but the use of low doses of leukopenia significantly reduced side effects. The incidence of CMV was not different among the three groups, but the tendency was also decreased at low dose.

FR-POI143
Incident Cancer After Kidney Transplantation in South Korea: A Nationwide-Population Based Study
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Background: Cancer is one of the most common cause of death with functioning graft in kidney transplantation (KT) patients. In this study, we aimed to investigate post-KT cancer incidence using a nationwide data compared with end-stage renal disease (ESRD) control and general population (GP).

Methods: We included incident KT recipients aged over 20 years without previous cancer history using a Nationwide Health Insurance Database of South Korea from January 1, 2007, to December 31, 2015. We analyzed the incidence rate (IR) per 1000 patient-year of cancer in KT recipients compared with ESRD and GP cohorts which were extracted after matching by age, sex, and inclusion year.

Results: A total of 10,203 KT recipients were analyzed with matched ESRD and GP controls. Their mean age was 45±10.7 years and 60.3% were men. Economic status of KT recipients was lower than GP but better than ESRD control. Combined diabetes or hypertension of KT recipients was similar to ESRD control but higher than GP. Incident cancer IR in KT recipients (8.63/1000 patient-year) was higher than that of GP (5.26/1000 patient-year), but lower than ESRD controls (12.27/1000 patient-year). In overall, KT recipients had 65.3% higher risk of incident cancer, whereas ESRD patients were at 2.4-fold higher risk of cancer development than GP. Among various cancer types, KT recipients showed higher risk of urinary tract cancer (HR 3.01, 95% CI 1.64-5.62), non-Hodgkin lymphoma (HR 3.97, 95% CI 3.1-4.79), and skin cancer (HR 43.1, 95% CI 1.46-12.83), whereas ESRD patients revealed higher risk of urinary tract cancer, and leukemia compared with GP. We can show a similar trend of cancer IR according cancer type within 5 years after KT, but after then, only stomach cancer IR in KT patients (0.68/1000 patient-year), was higher than that of GP (0.25/1000 patient-year).

Conclusions: In this study, we found that KT recipients had higher risk of incident cancer than GP, although this did not exceed that of ESRD patients. It is suggested that KT recipients should be monitored on the occurrence of urinary tract cancer, skin cancer and non-Hodgkin lymphoma more meticulously than GP, especially, within 5 years after KT. Gastroscopy should be recommended for all KT recipients regardless of the post KT duration.

FR-POI144
Graft Survival and Characteristics of Kidney Transplant Recipients with Renal Cell Carcinoma
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Background: The risk of acquiring renal cell carcinoma (RCC) is the greatest among all solid tumors in kidney transplant recipients (KTRs). While most RCCs are caught in the localized stage incidentally, leading to low cancer-specific mortality, there is limited information on how to properly screen for RCC in KTRs based on risk stratification, and how RCC impacts graft survival down the line.

Methods: We analyzed risk factors and determined patient and graft survival of all KTRs with RCC in both native and grafted kidneys compared to those without RCC in our institution between 01/01/1994 and 12/31/2014. Risk factors analyzed were race, age, mean time on dialysis prior to transplantation, causes of ESRD, re-transplant, type of graft, and type of induction agent.

Results: 48 cases of RCC were found among the 4,837 KTR’s performed at our institution. The mean interval from transplant to RCC was 8.0±6.3 years. Glomerulonephritis was the most common cause of ESRD in KTRs with RCC at our institution (n=17), but this was not found to be a significant risk factor for acquiring RCC (p=0.54 in univariate analysis, p=0.42 in multivariate analysis). None of the risk factors analyzed were associated with a statistically significant higher risk for RCC. Graft survival at 10 years was significantly lower in KTRs with RCC compared to those without (Figure 1, p<0.001). However, the trend toward shorter 10 year patient survival did not reach statistical significance (p=0.13).

Conclusions: Although no factor was identified in our sample population that specifically was associated with increased risk for RCC in KTRs, KTRs with RCC were found to have significantly lower graft survival. Identifying specific risk factors in patients with graft failure following RCC can lead to better screening, treatment, and immunosuppression strategies to bolster graft survival in KTRs with RCC.
FR-PO1145

Immunosuppression Management in Kidney Transplant Recipients with Malignancy/Mortality and Renal Graft Outcome

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Background: Kidney transplant recipients (KTR) are at high risk of cancer compared to general population. Prognosis is poor and the data of how to manage immunosuppression (IS) after cancer diagnosis is scarce. We aims to assess the impact of IS dose reduction on graft survival and mortality outcome in KTR diagnosed with cancer.

Methods: We retrospectively reviewed and collected the data of KTR with cancer diagnosis after kidney transplant. Early stage non-melanoma skin cancer was excluded. We divided our study population in 2 groups, IS reduction and no reduction. Study outcomes were mortality and graft failure. Follow-up time was 10 years. Data were calculated as percentages for categorical variables and mean or median for continuous variables. Patient survival and graft survival were analyzed using Kaplan-Meier survival curves with log-rank test. Competing risk analysis was used for graft failure outcome and Cox proportional hazards was used for mortality analysis.

Results: There were 110 patients in total. The mean age at cancer diagnosis was 62.2 years. IS was changed in 74%. Solid organ tumor was 79.1%. Mortality rate was 46.4% with median survival time of 1.8 years after cancer diagnosis. Graft failure rate was 16.4%. Median graft survival was 2.97 years. Kaplan-Meier curves showed that IS dose reduction was associated with higher mortality risk and graft failure. However, from multivariable models, history of chemotherapy was the only factor associated with increased mortality (image1). Creatinine at cancer diagnosis and history of rejection were significant predictors of graft failure (image2).

Conclusions: Reduction of IS after cancer diagnosis was not significantly associated with patient mortality, nor with increased risk of kidney allograft failure. The study has been conducted by reviewing medical records of kidney transplant recipients who had been followed by the transplant team at Keck Hospital of USC in 2000 through 2019. The findings have been compared in 200 patients who had received a kidney transplant in two time periods; 100 patients each in 2000 through 2004 (group 1) and 2006 through 2009 (group 2) and had at least 10 years of follow-up.

Results: Subjects (83 female, 116 male) were 134 recipients of a kidney transplant from a deceased donor and 66 from a living donor. Mean age of patients at the time of the first kidney transplant was 48 (range 17-77) and 48 (range 23-75) in group 1 and group 2, Hispanic is the majority followed by Caucasian, Asian, African American; 56, 22, 13, 3% in group 1 and 52, 19, 21, 7%, respectively in group 2. In group 1, 14 patients developed malignancy after kidney transplant, 8 within 10 years post-transplant. In group 2, 12 patients were diagnosed with malignancy; 11 within 10 years. In group 1, 32 patients died and in group 2, 25 patients died. Seven died with functioning graft in group 1 (22% of mortality) and 5 died with functioning graft in group 2 (20% of mortality). Types of cancers were variable; adenosquamous carcinoma of lung, GI and prostate, squamous cell carcinoma of the skin, lymphoma, and thyroid cancer. In group 2, HCC was in 4 among 12 reported malignancies. HCC was diagnosed in 3 recipients of combined liver and kidney transplant. In group 1, 15 patients received induction immunosuppression (OKT3, Thymoglobulin, Basiliximab, Daclizumab), while in group 2, 69 patients received Thymoglobulin or Basiliximab. Duration until the time of cancer diagnosis after transplant seems shortened considerably; median and mean time, 4 and 6.9 years in group 1 vs. 2.4 and 2.7 years in group 2, respectively.

Conclusions: In kidney transplant recipients who received a kidney transplant in 2000-2009, incidence of cancer seems decreased during 10 year follow-up and duration until the time of cancer diagnosis seems shortened, compared to those in 2000 through 2004, in the patient population studied.

FR-PO1147

Plasma Citrulline and Mycophenolate Mofetil-Induced Enterocyte Toxicity in Renal Transplant Recipients

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Background: Citrulline is a non-protein amino acid mainly produced by enterocytes of the small intestine which can be used as a biomarker of functional enterocyte mass. Plasma citrulline is reduced in diseases characterized by enterocyte damage. Diarrhea is a well-known side effect of Mycophenolate Mofetil (MMF), as a consequence of MMF induced gastrointestinal mucosal injury. To prevent complications from severe diarrhea, clinicians often lower MMF dosages or change to other immunosuppressive regimens. We aimed to investigate whether citrulline levels are associated with MMF use in a large cohort of stable renal transplant recipients (KTR).

Methods: Plasma citrulline concentrations were measured in 567 stable RTR with a ≥ 1 year functioning graft, from the TransplantLines Biobank and Cohort study (Clinicaltrials.gov NCT03272841). Citrulline was measured using a validated UHPLC-MS/MS method. MMF through levels were available in 234 RTR and were natural log transformed to obtain a normal distribution. Associations between MMF use, MMF through levels and plasma citrulline concentrations were analyzed using linear regression analyses.

Results: Mean age was 55.5±13.2 years and 392 RTR (69.1%) used MMF. Mean plasma citrulline concentration was 42.1±14.2 μmol/L. In univariable linear regression analyses, MMF use was inversely associated with plasma citrulline (β = -0.8, P<0.001). After adjustment for age, sex and eGFR, MMF use remained significantly associated with lower citrulline levels (β = -4.6, P<0.001). Moreover, among MMF users, through
levels were conversely associated with citrulline levels, independent of age, sex and eGFR (β=-2.8, P=0.02).

Conclusions: This study demonstrates that MMF use is associated with lower citrulline levels in RTR potentially related to MMF induced enterocyte toxicity, which may lower systemic citrulline levels. More research is warranted to validate whether citrulline can be used as biomarker of MMF induced enterocyte toxicity in RTR.

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FR-PO1148

Diagnostic Yield of Multiplex Polymerase Chain Reaction for Diagnosis of Acute Gastroenteritis in Renal Transplant Recipient: A Single-Center Study from India

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Background: Acute gastroenteritis is an unpreventable and harmful yet unavoidable complication in the renal transplant patient. Standard methods of staining and culture have poor sensitivity as well as require significant time for the reports. Stool Polymerase Chain Reaction is a quick, sensitive and hassle-free method which diagnose more than 20 organisms within 1 hour.

Methods: We retrospectively analyzed all renal transplant patients admitted between 2015 to 2018 with diarrhea. The sample was tested for conventional microbiological methods including stool routine for microscopy and culture. A stool sample was also sent for Multiplex PCR which was analyzed by Bio Fire FilmArray GI Panel which identifies 22 enteropathogens.

Results: 110 diarrheal events were recorded in 82 patients with 183 organisms isolated in all samples. 85% sample yielded a positive result. The conventional method yielded a positive result in only 32.3% as compared to stool PCR. Coinfections were common as 71.2% events were associated with ≥2 or more organisms. Norovirus (20%) was the most common organism isolated from stool followed by Giardia (17%) and Enteropathogenic E.Coli (16%). Giardia Lambia with Norovirus was the most common co-infection in 19% of patients.

Conclusions: Stool PCR significantly improves the diagnostic yield in diagnosing enteric pathogens. Stool PCR is especially sensitive in detecting multiple organisms. Norovirus is the most common enteropathogen. Giardia with Norovirus was the most common co-infection among post-transplant patient.

Frequency of Enteropathogens diagnosed by stool PCR

<table>
<thead>
<tr>
<th>Enteropathogen</th>
<th>No. of Positive cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus</td>
<td>17 (20%)</td>
</tr>
<tr>
<td>Giardia</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Enteropathogenic E.Coli</td>
<td>25 (29%)</td>
</tr>
<tr>
<td>Cryptosporidosis</td>
<td>21 (25%)</td>
</tr>
<tr>
<td>Salmonella Enteritidis</td>
<td>20 (23%)</td>
</tr>
<tr>
<td>Others</td>
<td>44 (34%)</td>
</tr>
</tbody>
</table>

FR-PO1149

Incident Dementia in Kidney Transplantation Recipients: A Nationwide Population-Based Cohort Study in Korea

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Background: Recent studies have shown that patients with end stage renal disease (ESRD) are at elevated risk of dementia. However, whether kidney transplantation lower the risk of dementia development or not remains unclear. In this study, we aimed to estimate the risk of incident dementia in KT recipients compared with ESRD patients and healthy controls (HCs).

Methods: From the Korean National Health Insurance Service database, we identified KT recipients aged ≥20 years without any history of dementia between 2007 and 2015. We also established two control cohorts without a history of dementia: 1) incident ESRD cohort and 2) a cohort of insured subjects without a history of kidney disease with frequency matched for age, sex, and inclusion year. All-cause dementia (F00-FO3), Alzheimer’s disease (AD, F00), and vascular dementia (VD, F01) were diagnosed on the code of the International Classification of Disease, 10th Revision.

Results: We followed 11,385 KT recipients, ESRD patients, HCs for 54,454, 46,260, and 56,020 patient-years, respectively (mean age: 45.7 years, 6754 male/4631 female). Over observation periods, 44, 231, and 44 dementias occurred in KT recipients, ESRD patients, and HCs. Age- and sex-adjusted dementia incidence rate was 0.264 per 1000 person-years in KT recipients and 0.095 per 1000 person-years in HCs. KT recipients showed lower risk of all types of dementia (hazard ratio [HR] 0.15; P < 0.001), AD (HR 0.11; P < 0.001), and VD (HR 0.20; P < 0.001) compared with ESRD patients even after adjustment. These findings were reproduced even when KT recipients were compared with HCs. The strongest predictors for dementia in KT recipients were older recipient age and sex and numbers of Charlson’s comorbidity index.

Conclusions: These findings suggest that KT recipients had a lower risk of incident dementia, AD, and VD than those of ESRD patients. Furthermore, their dementia development risk was lower than even HCs in spite of long-standing kidney disease and/or use of neurotoxic immunosuppressants.

FR-PO1150

Health-related Quality of Life Among Kidney Transplant Patients Using the PROMIS Global Health Scale

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Background: Survival after kidney transplant (KT) is increasing, turning attention to health-related quality of life (HRQOL). Brief but valid measures are needed to screen HRQOL among KT patients. We examined the 10-item PROMIS Global Health Scale (GHS) pre- and post-transplant among KT patients. We also examined GHS scores among a cohort of liver transplant (LT) patients for comparison.

Methods: Data were from KT and LT patients at a transplant center in the United States. PROMIS GHS was assessed pre-transplant (KT, n=189; LT, n=88) and 6 months post-transplant (KT, n=43; LT, n=16). We estimated global physical health (GPH) and global mental health (GHM) summary scores from the GHS. We compared KT and LT to the US general population normative mean value of 50. We then estimated associations between PROMIS GPH and GHM scores with clinician-rated functional status sourced from the Scientific Registry for Transplant Recipients.

Results: Among KT patients, the mean GPH and GHM scores at pre-transplant were 46.3 and 50.2, respectively, which increased to 51.1 and 54.1 at 6 months post-transplant. As expected, LT patients had lower physical and mental HRQOL than KT patients. Among LT patients, mean GPH and GHM scores at pre-transplant were 42.1 and 46.3, respectively, which increased to 44.7 and 50.1 at 6 months post-transplant. Pre-transplant differences in functional status were not statistically significant for KT patients. However, in comparison to LT patients with normal function, LT recipients unable to carry-on normal activities had significantly lower mean GPH (39.9 vs. 47.4, P<0.001) and GHM (44.5 vs. 50.3, P<0.01) scores.

Conclusions: The PROMIS GHS is a brief, clinically-feasible, and patient-centered approach to tracking changes in patients’ health over time for KT and LT patients. Inclusion of patient-reported outcomes like the GHS can enhance the standard health metrics collected for transplant patients.

FR-PO1151

A Modified Charlson Comorbidity Index (CCI) for Predicting Kidney Transplant Outcomes in the Elderly


Background: Contemporary kidney transplant recipients are older and tend to have significant comorbidities. However, the impact of comorbidities in elderly kidney recipients is unclear. This study used a modified Charlson comorbidity index (CCI) to compare the clinical features of elderly patients surviving ≤3 years versus those with post-transplant survival >3 years.

Methods: A prospective database was reviewed for patients aged ≥70 years undergoing deceased donor renal transplantation from 2007 – 2016. A modified CCI score was used designating 3 points for history of myocardial infarction and heart failure, diabetes (45%), heart disease (39%), and peripheral vascular disease (18%). Patients were stratified based on 3-year post-transplant survival (Table). Male gender, heart disease, and an unweighted and modified CCI scores were significantly greater among patients surviving ≤3 years post-transplant. Multivariable analysis identified the unweighted CCI and diabetes (OR= 1.00-1.69) as significant predictors of 3-year mortality, but not age, gender or time on waitlist. However,
after adjusting for age and gender, only the modified CCI was predictive (OR = 1.30, CI: 1.03-1.64).

Conclusions: A modified CCI is a simple and effective tool for predicting 3-year mortality following transplantation in elderly patients. This scoring system should be considered as an adjunct in determining transplant candidacy in this population.

FR-PO1152
A Cross-Sectional Prospective Study of High Serum Adipocyte Fatty Acid Binding Protein Level Associated with Low Handgrip Strength in Renal Transplant Recipients
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Background: Adipocyte fatty acid-binding protein (A-FABP) involved in lipid metabolism and metabolic responses and can accelerate cardiovascular disease. Low muscle strength is related to functional limitations and physical disability and is associated with all-cause mortality. The present study evaluated the relationship between fasting serum A-FABP level and handgrip strength (HGS) in renal transplant recipients.

Methods: Fasting blood samples were collected from 80 renal transplant recipients. HGS was measured using a Jamar Plus Digital Hand Dynamometer for assessment of muscle strength. Low muscle strength was defined as HGS less than 26 Kg for men and 18 Kg for women, according to the Asian Working Group for Sarcopenia (AWGS) criteria. Serum A-FABP levels were determined using a commercially available enzyme immunoassay.

Results: Thirty-one renal transplant recipients (38.8%) had low HGS, and they included a higher percentage of patients with diabetes (P = 0.025), serum triglyceride (P = 0.003), fasting glucose (P = 0.009), blood urea nitrogen (P = 0.003), creatinine (P = 0.005), and A-FABP level (P = 0.062), while lower estimated glomerular filtration rate (P = 0.008) compared with renal transplant recipients with normal HGS. After adjusting for factors significantly associated with low HGS in these patients by multivariate logistic regression analysis, serum A-FABP level (Odds ratio (OR): 1.037, 95% confidence interval (CI): 1.012–1.064, P = 0.004) was independently associated with low HGS in renal transplant recipients. The serum A-FABP level is also statistically significant in male renal transplant recipients (OR: 1.052, 95% CI: 1.000–1.107, P = 0.049) and female renal transplant recipients (OR: 1.132, 95% CI: 1.088–1.272, P = 0.037) after multivariate logistic regression analysis.

Conclusions: The serum fasting A-FABP level is positively associated with low HGS in renal transplant patients.

FR-PO1153
Impact of Delayed Graft Function (DGF) on Length of Stay After a Deceased Donor Kidney Transplant
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Background: The goal of the Medicare Diagnosis Related Group bundled payment system was to increase efficiency and decrease cost of hospital care. We examined trends over the past decade on the length of the index hospitalization (LOS) for deceased donor kidney transplant (DDKT) recipients and the impact of the increasing incidence of DGF.

Methods: We identified a cohort of 118,865 patients receiving a DDKT between 1/1/2009 and 12/31/2018, excluding those with LOS >180 days (0.3% of sample). We compared the LOS for patients with and without DGF (defined as the need for dialysis in the first 7 days post-transplant) and estimated the excess LOS attributable to DGF. Results: From 2009-2018, the incidence of DGF for DDKT rose from 23.9% to 28.3%. Median(IQR) LOS decreased from 8(6-13) to 6(5-10) days for DDKT with DGF but remained significantly higher than LOS for DDKT without DGF, which was unchanged at 5(4-7) days (p=0.001). Despite decreasing LOS for DDKT DGF patients with DGF accounted for an increasing share of the total LOS for all DDKT, from 32.9% in 2009 to 36.3% in 2018 and the excess LOS attributable to DGF rose by 13% from a total of 10,025 days in 2009 to 11,314 days in 2018. [Fig1]

Conclusions: Although the LOS in DDKT with DGF is decreasing, the increasing incidence of DGF has led to an absolute increase in the number of hospital days that are attributable to DGF after DDKT.

Funding: Commercial Support - Angion Biomedica Corp.

Figure 1. DCGF between study groups.

FR-PO1154
Histopathological Findings on Biopsy Among Kidney Transplant Recipients Needing Dialysis Within 2 Weeks Post-Transplant
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Background: The need for dialysis acutely after transplant is associated with an increased risk of graft loss. No studies have characterized post-transplant graft and mortality outcomes based on biopsy-proven causes of early need for dialysis, to our knowledge. Our study reports the incidence and outcomes of histopathological cause-specific need for dialysis within two weeks following kidney transplantation at our university.

Methods: We examined kidney transplant recipients transplanted at our center between 2000-2015 who required dialysis within the first two weeks of transplant and received a biopsy during this time. Subjects were categorized into one of five categories based on their biopsy results: acute rejection (AR), acute tubular necrosis (ATN), both acute rejection and ATN (Both), other findings including tubular injury (Other), and no findings on biopsy (None). Outcomes examined included baseline characteristics, graft failure, death-censored graft failure (DCGF), and death after biopsy.

Results: Of a total of 291 patients, 111(38.1%) had Other pathology, 86 (29.6%) had ATN, 67 (23%) had AR, 22 (7.6%) had Both, and 5 (1.7%) had None. Mean time to biopsy was 8 ± 2.83 days. Of those with a diagnosis of AR, the incidence of graft failure was 36.2 per 100 person-years within the first year post-biopsy, compared to 25.1 per 100 person-years for those with ATN, 18.9 per 100 person-years for those with Other pathology. A similar trend was seen for DCGF within the first year (32.4 for AR, 18.1 for ATN, and 12.6 for Other pathology). AR was associated with greater risk for DCGF compared to other categories, as illustrated in the K-M curve in Figure 1.

Conclusions: AR is associated with a greater risk for graft failure and DCGF than other causes of dialysis within the first two weeks post-transplant. Identification of cause of graft failure may help inform prognostic information.
FR-POI115

Delayed Graft Function (DGF) in Kidney Transplantation Patients: An Analysis of Disease Burden
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Background: Kidney transplantation patients with DGF are at greater risk of graft failure and mortality, as well as additional disease burden. Hospitals are sensitive to both short- and medium-term costs as they are reimbursed through a 90-day Diagnosis Related Group (DRG) code and must manage all related expenses within the bundled payment. This study aims to assess patient characteristics, Health Resource Use (HRU) and costs associated in post-transplant patients with and without DGF in the hospital setting.

Methods: A retrospective analysis of the Premier Hospital Database (PHD) was performed on adult kidney transplant patients from January 2014 to December 2018. Kidney transplant patients were identified via ICD9/10 procedure codes and charge codes. DGF status was defined as the presence of a dialysis charge code within 7 days following a transplant. Patient and admission characteristics, HRU and costs were calculated for patients with and without DGF.

Results: Of the 12,097 kidney transplant patients, 3,087 (25.5%) had DGF. The majority of transplants (79.2%) were performed at large 500+ bed facilities and in urban areas (95.5%); males represented 61.1% of all transplant patients with a slightly higher proportion (64.2%) in the DGF group. The primary insurer (67.9%) of all patients was Medicare. Black patients (36.5%) had a higher incidence DGF compared to other races. DGF patients were between median 55 vs 53 years, the incidence proportion of DGF increased from 22.6% to 26.7% from 2014 to 2018. Patients with DGF had longer mean and median hospital stays of 11.5 and 8 days, compared to 7.3 and 6 days (p<0.01) in non-DGF patients. A significantly higher proportion of DGF patients (56.4% vs 54.0%, p<0.01) were admitted to the ICU and had a longer length of stay (mean days: 4.8 vs 2.5, p<0.01). The mean total admission costs for the Medicare patients were higher in DGF patients ($113,628.9 vs $105,962.4, p<0.01). The same trend was observed for ICU costs during admission ($5,815.0 vs $3,901.4, p<0.01).

Conclusions: DGF leads to longer hospital stay, significantly higher admission costs and a higher percentage of patients being admitted to the ICU compared to patients without DGF.

Funding: Commercial Support - Angion BioMedica

FR-POI116

Potential Prognostic Value of Immediate Postoperative Proteinuria
Predicting Early Renal Outcome After Kidney Transplantation
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Background: Proteinuria in kidney transplant recipients (KTRs) is associated with poor patient and allograft survival. However, the relationship between urinary protein to creatinine ratio (uPCR) or urinary albumin to creatinine ratio (uACR) during the immediate postoperative period and renal outcome of KTRs is yet to be determined.

Methods: This single center retrospective cohort study included 474 KTRs who underwent kidney transplantation (KT) from January 2014 to December 2017 and followed up for a year. After excluding patients without urine PCR and ACR within 7 days after KT and those without serum creatinine at 1 year after KT, a total of 353 KTRs were finally analyzed: living donor KT in 186 KTRs and, deceased donor KT (DDKT) in 167 KTRs. Immediate postoperative uPCR and uACR were measured within postoperative day 7. The primary outcome was estimated glomerular filtration rate (eGFR) at 1 year after KT. The secondary outcome was the incidence of delayed graft function (DGF) in DDKT recipients.

Results: Patients with 50% higher eGFR (≥ 60 mL/min/1.73 m2) at 1 year after KT had lower uPCR (patients with a 60 mL/min/1.73 m2 vs. those with < 60 mL/min/1.73 m2, median 810 ug/mgCr [IQR 500 - 1780] vs. median 1220 ug/mgCr [IQR 632 – 3905]; p = 0.007) and lower uACR (median 342 ug/mgCr [IQR 165 - 976] vs. median 613 ug/mgCr [IQR 284 – 2562]; p = 0.002) during the immediate postoperative period than those with lower eGFR. DDKT recipients with uPCR > 3 mg/mgCr during the immediate postoperative period is associated with the higher incidence of DGF (DDKT recipients with uPCR > 3 mg/mgCr vs. those with < 3 mg/mgCr, 30% vs. 13% [odds ratio 2.87; p = 0.007], and lower eGFR before discharge (60 mL/min/1.73 m2 [IQR 41 – 84] vs 75 mL/min/1.73 m2 [56 – 92]; p = 0.001) than those with uPCR < 3 mg/mgCr.

Conclusions: Our results suggest immediate postoperative uPCR as a risk predictor of early renal outcome in KTRs.

FR-POI117

Preventable 30-Day Readmission After Kidney Transplantation: Classification System and Risk Association
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Background: Preventable readmissions post kidney transplantation (KT) may reflect cost inefficiencies and gaps in quality of care. There is no practical tool to identify preventable 30-day readmissions post KT, and it is not known whether socioeconomic status (SES) influences risk of preventable readmissions.

Methods: A single-center cohort of 756 adult first-time kidney-only transplant recipients from 2013-2017 was followed for 30 days post-discharge. We merged electronic health records with national databases to develop a classification system assignment of 30-day readmission (preventable vs. non-preventable) using All-Patient Refined Diagnosis Related Group and International Classification of Diseases, ninth and tenth revisions, Clinical Modification and assessed its performance and discrimination against clinical assignment (chart review). We used multivariable logistic regression to assess the independent association of patients’ SES and preventable readmissions.

Results: Patient median age was 57 years (IQR, 45-66); 51% were white, 45% black, and 4% Hispanic. The sensitivity and specificity of the classification system were 92% and 96%, respectively, with area under the receiver-operating-characteristic curve (AUC) 0.94 (95%CI 0.89-0.97). Residues within the lowest ZIP code level neighborhood household income had the highest odds of preventable readmissions (adjusted odds ratio [OR] 2.16; 95%CI: 1.25-3.72).

Conclusions: Our classification system had a comparable discriminating ability to the gold standard of chart review identifying preventable vs. non-preventable 30-day readmission; however, our new tool requires prospective validation. Low income recipients had greater risk of preventable readmission.

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Sensitivity: 91.78%; Specificity: 96.12%. Area under ROC: 0.9395

FR-POI118

Perioperative Antibiotics for Preventing Post-Surgical Site Infections in Solid Organ Transplant Recipients
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Background: No consensus exists on the role of antibiotics for preventing surgical site infections (SSIs) in solid organ transplant recipients (SOTRs). Objectives: To assess the benefits and harms of prophylactic antibiotics for preventing SSIs in SOTRs.

Methods: The Cochrane Kidney and Transplant Register was searched up to 8 Dec 2018. Studies were identified through searches of CENTRAL, MEDLINE, EMBASE, conference proceedings, International Clinical Trials Register (ICTR) Search Portal, and ClinicalTrials.gov. All randomized controlled trials (RCTs) and quasi RCTs in any language assessing prophylactic antibiotics for preventing SSIs in SOTRs at any time point after transplantation. Two authors independently determined study eligibility, assessed quality and extracted data. The primary outcome was SSI incidence. Secondary outcome effects estimates were obtained using a random-effects model and results were expressed as risk ratios (RR) and 95% confidence intervals (CI) for categorical variables, and mean differences (MD) or standardized mean differences (SMD) and 95% CI for continuous variables.

Results: This review included 9 eligible studies (803 participants). Six studies (416 participants) compared antibiotics versus no antibiotics and 3 studies (387 participants) compared extended duration antibiotics versus short duration antibiotics. Risk of bias was assessed as high for high for performance (9 studies), detection (9 studies), attrition (2 studies) and selective outcome reporting (1 study). Antibiotics had an uncertain effect on SSI incidence (RR 0.63, 95%CI:0.37-1.06; 6 studies; 416 participants, I2=61%, very low certainty evidence). Most RCTs occurred prior to 2000 (RR 2.17, 95%CI:0.84-5.66; 1 study, 188 participants), very low certainty evidence. Overall, 1 RCT in the last 2 decades (RR 0.30, 95%CI 0.15-0.60; 5 studies, 228 participants, I2=33%, very low certainty evidence).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Conclusions: There is very low certainty evidence to support perioperative antibiotics for preventing SSIs in SOTRs. Further high quality, adequately powered RCTs would better inform practice.

Funding: Other U.S. Government Support

FR-PO1159

Serum Phosphate Levels Modify the Impact of Intact PTH Levels on Renal Outcomes in Kidney Transplant Recipients

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Background: Mineral bone disorder (MBD) parameters including parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), calcium, phosphate (P), 1,25-dihydroxyvitamin D (1,25D), and 25-hydroxyvitamin D predict renal outcomes, while their associations with different MBD parameters are not fully understood, especially in kidney transplant recipients (KTRs). However, data evaluating those parameters simultaneously and interwoven relationships on renal outcomes are scarce.

Methods: In this single-center prospective cohort study, we included 263 KTRs with grafts functioning at least 1 year after transplantation. The renal outcome was a composite of estimated GFR (eGFR) halving and graft loss. We performed Cox regression analyses to assess associations of MBD parameters with the renal outcome. Results: Median eGFR was 38 ml/min/1.73m². The renal outcome occurred in 98 KTRs during a median follow-up of 10.7 years. In a multivariable Cox model, intact PTH (iPTH) and P (Pinteraction<0.1), however, high iPTH levels (69 pg/mL) were the only variable significantly associated with MACE+ at multivariate analysis (HR 1.60 per log scale; 95%CI 1.19-2.14, 1.60 per mg/dL; 1.14-2.23, 0.98 per pg/mL; 0.96-1.00, and 0.99 per log scale; 0.74-1.34, respectively). A competing risk analysis with death as a competing event yielded a similar result. After stratification into 4 groups by median values of iPTH and P (Pinteraction<0.1), however, high iPTH levels (69 pg/mL) were not associated with worse renal outcomes when serum P levels were less than median (3.2 mg/dL) (Figure). Only in KTRs not receiving oral active vitamin D, 1,25D levels predicted the renal outcome (Pinteraction<0.1). Conclusions: High iPTH, P, and low 1,25D levels predicted poor renal outcomes in KTRs. Given that PTH promotes phosphaturia and enhances 1a-hydroxylation activity in proximal tubules (PT), low P and high 1,25D levels may reflect viable PT function.

FR-PO1160

Bone Turnover Markers Are Associated with Hypocalcemia Immediately After Renal Transplantation

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Background: Bone and mineral disorders occur commonly after renal transplantation (RTx). Serum calcium levels decreased after RTx and gradually reach calcium homeostasis. Hypocalcemia immediately after RTx may influence QTc interval and myocardial contractility, thus it is a life-threatening phenomenon after RTx. Bone turnover markers (BTMs) are markers reflect the bone turnover stage and bone and mineral disorders. Whether BTMs can predict the occurrence of hypocalcemia after RTx has not been reported.

Methods: A total of 101 patients receiving ABO compatible living donor renal transplantation were assessed. General patient information, kidney function and calcium metabolism indexes were measured before transplantation. Calcium metabolism indexes included calcium, phosphorus, parathyroid hormone (PTH), 25-dihydroxyvitamin D (25(OH)D3) and BTMs. BTMs included procollagen type I N-terminal propeptide (PINP), N-terminal mid-molecule fragment osteocalcin (N-MID) and β-teleopeptide of type I collagen (β-CTX). The patients were divided into two groups dependent on post-transplantation calcium levels, non-hypocalcemia group and hypocalcemia group. The prediction value for hypocalcemia were evaluated by concordance index (c-index), akaike information criterion (AIC) and cayesian information criterion (BIC) methods.

Results: General patient information, kidney function and calcium metabolism indexes were compared between non-hypocalcemia group and hypocalcemia group. Age, dialysis type, serum calcium levels, PTH, 25(OH)D3 and BTM showed differences between non-hypocalcemia group and hypocalcemia group. Then correlation analysis showed that calcium levels after RTx were positively correlated with 25(OH)D3, PINP, N-MID and β-CTX amounts. Further utilizing multi-regression selected risk factors to establish basic model equation (AIC=126.85 and BIC=134.69; c-index 0.78).

Conclusions: Low levels of BTMs were associated with hypercalcemia after RTx. To predict the occurrence of hypocalcemia, β-CTX, one of BTMs, could improve the predictive ability.

FR-PO1161

Vitamin D Status in a Cohort of Renal Transplanted Patients: Factors Related to Impact on Rejection Occurrence and Long-term Graft Outcome

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Background: Immunomodulatory properties in renal transplant (RTx) have been hypothesized for vitamin D (VD). We evaluated retrospectively, in a cohort of renal transplanted patients (RTxp): a) VD status at t1 (T1) and T12 (T12) months after RTx; b) the factors related to VD status; c) the impact of VD status on rejection rate and long term graft outcome.

Methods: The study includes 438 (M=265, age 49[40-50]years), out of 670 patients (pts) transplanted between April 2004 and November 2017, where VD status were available both at T1 and T12. Included and not included pts did not differ in general features. VD status, based on 25OH-VD levels, was categorized as: insufficient (iVD) or sufficient (sVD), if 25OHD was ≥ or ≤ 30 ng/mL, respectively. Patients were followed-up for 653±39 months and evaluated for rejection rate, diagnosed on renal biopsy (RBx) performed for clinical indication, and for achieving combined major adverse clinical events (MACE: death or graft failure, considered as either return to dialysis or eGFR halving).

Results: A) 25OH-VD levels increased from 14[8-18] ng/mL at T1 to 17[10-23] ng/mL at T12 (p<0.0001), with iVD being present in 425 (97%) pts at T1 and in 380 (87%) pts at T12. VD status normalized spontaneously or after VD supplementation in 19 and 35 pts, respectively; 8 sVD pts at T1 were iVD at T12. B) 25OH-VD levels were negatively related with PTH levels both at T1 and T12, while they were positively related with Ca levels at T12. C) Rejection (REJ+) was diagnosed in 36 (36%) out of the 105 RTxp submitted to RBx. No difference was found in 25OH-VD levels between REJ+ and REJ- pts, both at T1 and T12. MACE occurred in 66 (15%) pts (MACE+). 25OH-VD levels at T12 were significantly lower in MACE+ pts and were the only variable significantly associated with MACE+ at multivariate analysis (OR=0.96, p=0.01).

Conclusions: With the limitations of the retrospective design and the relatively low number of pts, we found that iVD at T1 was highly prevalent in RTx patients both at T1 and T12; b) VD levels were inversely related with PTH levels; c) no association was found between VD status and REJ occurrence, while 25OH-VD levels at T12 were inversely and independently related to MACE+.

FR-PO1162

The Risk of Hypercalcemia After the Kidney Transplantation? Analysis of Cinacalcet Therapy with 10 Years of Follow-Up in a Single Center

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Background: The persistence of secondary hyperparathyroidism after kidney transplantation (KT) occasionally manifests itself by hypercalcemia and hyperphosphatemia. In patients with KT, Cinacalcet is an off label treatment for hypercalcemia related to hyperparathyroidism. The aim of our study is to evaluate which factors are predictive of hypercalcemia that requires the use of Cinacalcet.

Methods: We retrospectively examined all the patients who received a KT from 2008 to 2018. In each patient we evaluated demographic characteristics and the following parameters: creatinine, hemoglobin, albumin, Calcium, Phosphate, PTH, vitD25OH, and the linked therapies. T Student, Kruskal Wallis, and Pearson’s chi-square tests were used, as appropriate. The regression model was used to evaluate the predictive variables for the use of Cinacalcet.

Results: In a 10-year period 459 KT were performed. Only 9.2% of the patients needed Cinacalcet therapy. Table 1 shows the comparison of the characteristics of those
patients who needed CICCA test and those who did not. Dead donor transplantation (OR = 0.3 p = 0.023), number of KT received (OR 6.8 < 0.0001), PTH levels (OR 1.01 p < 0.001), and phosphate levels (OR 0.44 p < 0.01) were all independent predictors for CICCA use in multivariable analysis.

Conclusions: Our data show that dead donor transplantation, presence of previous KT, and both phosphate levels were critical to predict CICCA test. In these cases we suggest a more careful monitoring of the calcium levels.

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FR-PO1163
The Impact of Periodontitis on Recipient Outcomes After Kidney Transplantation
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Background: Periodontitis has a high prevalence in patients with chronic kidney disease and has been reported to increase systematic inflammations and cardiovascular risk. Although dental care is usually recommended prior to transplantation due to potential for serious infection, little is known about impact of periodontitis on transplant outcomes. The purpose of this study was to examine whether periodontitis before KT affects post-KT recipient outcomes.

Methods: This was a single center, retrospective study including KT recipients from April 2008 to October 2018. The panoramic radiographs at pre-KT work up were analyzed by a dentist with severity of periodontitis graded according to new classification system developed in 2017.

Results: One hundred and sixty-six recipients who received pre-KT dental examination were divided into 3 groups according to 1st, 2nd, 3rd and 4th-stage periodontitis; group1 (1st and 2nd stage), 28.9%, group2 (3rd stage), 35.8% and group3 (4th-stage, 22.6%) respectively. Seventy patients (46.4%) with periodontitis received treatments such as scaling or surgical extraction before KT. Advanced stage periodontitis patients were more likely to be older, obese, smoker and had higher prevalence of diabetes. However, pre-transplant immunological variables or immunosuppression were not different according to periodontitis grades. The mean follow-up period is 4.16 years. Advanced stage periodontitis without treatment was associated with significantly increased risk of CMV and BKV infection. However, rate of acute T cell mediated rejection was not different between groups at baseline and at 3 months showed that periodontitis score and CRP significantly came down at 3 months in intervention group as compared to non-intervention group.

Conclusions: These results suggest that pre-transplant periodontitis could be a manifestation of systematic inflammation and altered immune function in patients with end-stage renal disease. It may affect long-term post-transplant outcomes. Impact of periodontitis or its treatment on transplant outcomes needs to be further clarified.

FR-PO1164
Effect of a Good Oral and Dental Care on Inflammation and Oral Lesions in Renal Transplant Patients
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Background: Inflammation plays an important role in causing complications in CKD and transplant patients. C-reactive protein and pro-inflammatory cytokines could predict outcomes in transplant patient. Poor oral health results in inflammation and cytokine production. There is need to evaluate the benefit of good oral hygiene on renal transplant outcome.

Methods: A randomized controlled trial was carried out amongst CKD patients going for renal transplantation. All patients had dental and oral examination (Type III clinical examination as per American Dental Association specifications and WHO oral health proforma, 2013) Group I (Non intervention group) 50 patients. Group II (Intervention group) - 50 patients of chronic kidney disease going for transplantation. Group III (Control group) comprised of 50 healthy age, sex matched subjects. Intervention group followed regular tooth brushing, use of dental floss and mouth wash twice a day and counseling sessions for good oral and dental care for a period of 3 months after transplant. Non-intervention group continued usual oral and dental care. The oral and dental findings specially the periodontitis score was compared between groups I and II using t test. CRP (C- reactive protein) values were assayed at baseline and after 3 months.

Results: Comparison of CRP values between Interventional and non-interventional groups at baseline and at 3 months showed that periodontitis score and CRP significantly下降ed in intervention group as compared to non-intervention group. CRP values in the interventional and non-intervention groups were analyzed in relation to presence of donor specific antibodies (DSA) and HLAA mismatch scores in the two groups. Our data shows that after aggressive dental and mouth hygiene routine, intervention group patients showed significant decrease in CRP values as compared to the non intervention group. It almost reached close to values in normal controls.

Conclusions: The present study concludes that the oral hygiene of the patients with chronic kidney disease going for transplant is deteriorated. Good oral and dental care in transplant recipients can improve inflammation which could have beneficial effect on post transplant outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

FR-PO1165
Safety and Effectiveness of Ferric-Carboxymaltose in Kidney Transplant Patients
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Background: In kidney transplant patients (KTx), the post-transplant anemia (PTA) is associated with worst graft outcome and increased cardiovascular/all causes mortality. With common available iron treatments, iron deficiency (ID) is highly prevalent and moderate to severe anemia is one of the main causes of PTA. This prospective study evaluates the safety and effectiveness of ferric-carboxymaltose (FCM) in KTx patients with iron deficiency anemia (IDA) and no/low response to other previous iron treatment.

Methods: Consecutive, stable (tx age >1 y), CKD-3/5 stages, anemic (Hb <11g/dL) adult patients, iron deficiency (TSAT <20% and/or ferritin <100 ng/mL), previous iron intolerance or low-response, KTx were prospectively enrolled. Each patient was administered FCM, 500 mg, in standardized conditions at baseline, and eventually a second dose 500 mg dose one month later. Patients were evaluated for clinical conditions, iron status, anemia and renal function every month during a 6-months follow-up (irrespective of iron administration). Clinical and lab side-effects FCM related (nausea, vomiting, diarrhea, headache, fever, rush, erythema, itching, myalgia, bronchospasm, anaphylaxis) were monitored during the study.

Results: 32 KTx (M15-F17), Diabetes; 19%; Age; 55.8±11.7 years; BMI: 26.3±4.5 kg/m²; transplant age: 104±21, eGFR: 38.2±11.9 ml/min; SEMP:135±22, DBP:81±12 mmHg; ACEI/ARB:28.1%; previous iron: naïve, n=7 (reported intolerance during dialysis), os, n=20 (16 ongoing), i.v., n=4 (3 ongoing). At 34±4 days after FCM infusion, ferritin increased from 44±53 to 149±136 ng/mL (p<0.001), TSAT from 10±6 to 18±10% (p<0.001), Hb from 10.2±1.0 to 11.3±1.4 g/dl (p<0.01); at 160±71 days, ferritin was 93±110 ng/mL, TSAT 19±9% and Hb 12±0.17±1/7 g/dl (all p<0.05 vs Baseline and NS vs 34days). At baseline, 81% of pts on ESA were at a mean dose of 9.96±0.620; during the follow-up, pts on ESA reduced to 75% and 44% and ESA dose to 10.48±0.670 and 6.76±0.1220 µU/week, respectively. No changes of clinical parameters, renal function or electrolytes occurred; no side effect was detected.

Conclusions: In stable KTx patients with iron deficiency related anemia, the treatment with FCM is safe and effective, even in subjects resistant to previous iron treatment, allowing an optimal and stable correction of both iron deficiency or anemia, while reducing the ESA dose.

Funding: Private Foundation Support

FR-PO1166
Impact of Peritransplant Red Blood Cell Transfusion on Long-Term Renal Outcome After Kidney Transplantation
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Background: Patients undergoing kidney transplantation (KT) frequently receive red blood cell (RBC) transfusion perioperatively. Transfusion of blood products may induce allo sensitization in KT recipients. The effects of peri-transplant transfusion on graft survival were investigated using a nationwide database.

Methods: Data were collected from the National Healthcare Insurance Service database in Korea. 13,872 patients who received KT in Korea between 2007 and 2015 were analyzed. The outcome measures were graft failure rate at 5 years from KT and overall patient survival depending on the amount of RBC transfusion. Diabetes mellitus, hypertension, coronary artery disease, cerebrovascular disease, transplantation period, and Elixhauser comorbidity index were adjusted as covariates.

Results: The 5-year graft failure rates were 17% in the no transfusion group, 17% in 1-2 units group (OR 0.98 [95% CI 0.84 –1.16], 26% in 3-5 units group (OR 1.51 [95% CI 1.39 –1.81]) and 38% in 6 units or more group (OR 2.13 [95% CI 1.39 -3.27]) (P < 0.001, 3-5 units or 6 units or more vs no transfusion group). The 10-year survival rates were 97% in no transfusion group, 96% in 1-2 units group (OR 1.44 [95% CI 1.19-1.75]),
92% in 3-5 units group (OR 2.38 [95% CI 1.86-3.05]), and 67% in 6 units or more group (OR 10.78 [95% CI 8.47-13.71]) (P<0.001, 1-2 units, 3-5 units or 6 or more groups vs no transfusion group).

Conclusions: Peri-transplant RBC transfusions in KT recipients were independently associated with increased risk of renal allograft failure and death. Further studies are required to confirm the risk of allo sensitization following blood transfusion and to search for alternative ways to reduce sensitization with blood products.

FR-POI1167
Changes in Blood Pressure, Graft Function, and Proteinuria After Dialysis Arteriovenous Fistula Closure in Kidney Transplant Recipients Barbara Vajdic tramuz, Miha Arntl, Jadrinka Buturovic-Ponikvar. University Medical Centre Ljubljana, Ljubljana, Slovenia.

Background: The aim of our observational historic cohort study was to evaluate the impact of dialysis arteriovenous fistula (AVF) closure on systolic and diastolic blood pressure (SBP, DBP), graft function and proteinuria in kidney transplant recipients .

Methods: The study group included 111 kidney transplant recipients with an AVF closure after a median 34 months post-transplant. Controls included 53 recipients with a functioning AVF after a median 33 months of follow-up. Graft function was assessed by serum creatinine and estimated glomerular filtration rate (eGFR) using CKD-EPI formula, and proteinuria was assessed by spot urine protein/creatinine ratio. SBP and DBP was measured at each visit. We used linear mixed models to calculate the slope of serum creatinine, eGFR and proteinuria change versus time.

Results: Baseline mean SBP and DBP were comparable between groups (134±16 vs. 138±16 mmHg; P=0.150, and 79±10 vs. 77±13 mmHg; P=0.472). Following AVF closure, SBP increased (P=0.001), and DBP decreased (P=0.042). No change was observed in serum creatinine (P=0.122). The course of serum creatinine and proteinuria and 95% confidence intervals are shown in Figure 1. The mean eGFR slope improved before (0.024 mL/min/1.73m² per month) and deteriorated after AVF closure (-0.023 mL/min/1.73m² per month) (P=0.044).

Conclusions: The closure of a dialysis AVF may affect blood pressure and kidney graft function, but it does not impact proteinuria.

FR-POI1168
Kidney Recipients with Allograft Failure, Transition of Care (KRAFT): Practice Survey Tarek Alhamad,2 Michelle L. Lubetzky,1 Emmanuel Y. Edusei,14 Christopher D. Blosser,3 Neeraj Singh,2 Beatrice P. Conepacion,15 Leonardo V. Rielas,1 Guaurav Gupta,4 Krista L. Lentine,2 Miklos M. Mohan,5 Ekanada,8 John J. Akopyan,8 B. Adly,14 Alexander C. Wiseman,7 Martha Pavlikas,15 Ronald Parsons,16 Kenneth J. Woodsdie,7 James C. Rice,16 Edward S. Kraus,15 Darshana Dhadania,14 1Division of Nephrology and Hypertension, New York, NY; 2Washington University in St. Louis, St. Louis, MO; 3LSU Health Sciences Center, Shreveport, LA; 4University of California, San Francisco, San Francisco, CA; 5University of Washington, Seattle, WA; 6Northwestern University, Chicago, IL; 7University of Colorado at Denver and Health Sciences Center, Denver, CO; 8Virginia Commonwealth University Health System, Richmond, VA; 9University of Tennessee Health Science Center, Memphis, TN; 10Saint Louis University, St. Louis, MO; 11University of California, Irvine School of Medicine, Irvine, CA; 12Bingham and Women’s Hospital, Harvard Medical School, Boston, MA; 13Vanderbilt University Medical Center, Nashville, TN; 14Weill Cornell Medicine, New York, NY; 15Beth Israel Deaconess Medical Center, Boston, MA; 16Emory University School of Medicine, Atlanta, GA; 17University of Michigan, Ann Arbor, MI; 18University of San Diego, San Diego, CA; 19Johns Hopkins University, Baltimore, MD.

Background: Sensitization after failed allograft in the setting of withdrawal of immunosuppression makes re-transplantation increasingly difficult. We sought to understand how different centers and clinical care providers approach withdrawal of immunosuppression in a failing kidney allograft through a survey of US kidney transplant centers.

Methods: After approval from IRB and the AST Education Committee, a survey about practices related to withdrawal of immunosuppression was distributed electronically to members of the AST members between Nov 2018 and May 2019.

Results: There were 101 respondents with a response rate of 31%. Most survey respondents were Transplant Nephrologists (80.4%) at academic medical centers (90.2%). The most common approach to withdrawal of immunosuppression was withdrawal of the anti-metabolite first; with 64.2 % responding they would withdraw antimitobolite first, 24% with no unified protocol, and 9.4% responding they would stop CNI first. Most providers would stop immunosuppression over a time frame of 2-6 months (38.9%), although 24.1% responded they would keep a low dose of prednisone, and 20.4% had no unified protocol. Approach to tapering of immunosuppression did differ based upon whether or not practitioners felt the patient would be re-transplanted shortly. While most practitioners, 96.6% felt development of sensitization was of intermediate or most importance in the decision to taper immunosuppression there were many concerns of risk of infections, malignancy and patient age which were factors in the decision to taper or continue immunosuppression. Overall, 57.4% providers felt there was a need for standardized approach to taper immunosuppression in the failing allograft.

Conclusions: In a sample of US Kidney Transplant centers, we found a wide range of approaches to withdrawal of immunosuppression in a failed kidney transplant with no unified protocols in quarter of the respondents. Efforts to standardize clinical practice are warranted to tailor immunosuppression withdrawal according to the availability of a second kidney transplant and patient comorbidities.

FR-POI1169

Background: Kidney graft biopsies (KGB) are the gold standard for diagnosis of kidney graft dysfunction. Since Jan/2015 we have increased the KGB, reducing wait times and costs, due to the implementation of a ambulatory program (intra hospital surveillance -16 hrs), in charge of the fellows of the transplant nephrology program, supervised and guided by an interventional nephrologist.

Methods: Prospective, observational and descriptive study.

Results: 1091 KGB were made (jan/15-dec/18). Indications: protocol 463 (43.8%), de novo or increase of DSA 231 (21.2%), post-rejection control 149 (13.7%), graft dysfunction 146 (13.4%) and others 87 (7.9%). A total of 33 (3.0%) complications were reported; 5 (0.5%) were serious (persistent hematuria and hospitalization requirement). 11 (1%) were hematuria; 21 (1.9%) peri-graft hematomas. No infections, graft loss, or other procedures were required. In 1070 KGB (98.1%) the sample was adequate. Protocolized KGB at 3 and 12 mo post-KT and surveillance KGB for new pts from other centers carried out in 463 cases; 236 at 3 mo, 187 at 12 mo and 40 of newly admitted pts. Since not having clinical/laboratories alterations, the result of the KGB was abnormal in 58% of the total; 50% at 3 mo, 63% at 12 mo and 67% in new pts. Findings were: borderline alterations 158 (34%), humoral rejection 44 (9.5%), cellular rejection 24 (5%) and other alterations 36 (7.7%). In 161 (14%) pts we evaluated the relationship between the angle of incidence of the needle on the renal graft and the quality of sample procurement. The firing angle was 33.1±8.8 degrees, with a median of 12 (8-16 glom). There were no relation between angle of incidence and the quality of sample, or in the probability of

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO1170
Renal Transplant Complications in Patients with and without Gout
Masahiko Kawasaki,1 Jeffrey Kent,2 Megan Francis-Sedlak,3 Brian LaMoreaux,3 Robert J. Holt,4 Horizon Therapeutics plc, Lake Forest, IL

Background: Graft-related complications are among the most serious issues solid-organ transplant recipients and their healthcare teams face post-operatively. Gout is a known frequent co-morbidity in transplant patients. Whether renal transplant patients with gout suffer from higher rates of transplant-related complications, as compared to transplant patients without gout, has not been investigated. We analyzed a large US population database to determine the impact of transplant complication rate in patients having a renal transplant with and without gout.

Methods: A retrospective review of Humana Research Database claims (2007-2017) was undertaken to identify kidney transplant patients with ≥6 months in plan before and after transplant. Diagnostic gout codes (ICD-10) were used to categorize patients into gout and non-gout groups. Additionally patients were classified as having gout pre- or post-transplant based on first gout code occurrence. Transplant complications were determined using codes for complications of transplanted kidney, unspecified and other complications (ICD-10). The association between gout status and renal transplant complication rate in the overall cohort was 36.0%. Patients with gout had a higher complication rate (40.4%) than those without gout (34.6%, OR: 1.28, 95%CI: 1.136–1.443, p<0.001). The higher complication rate in gout patients was driven by those who developed gout post-transplant.

Table 1. Renal transplant-related complications

<table>
<thead>
<tr>
<th>Group/Sample</th>
<th>Number of Patients</th>
<th>Number with Complications</th>
<th>% with Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft and Transplant</td>
<td>1704</td>
<td>667</td>
<td>40.1%</td>
</tr>
<tr>
<td>Graft Pre-Transplant</td>
<td>939</td>
<td>504</td>
<td>53.4%</td>
</tr>
<tr>
<td>Graft Post-Transplant</td>
<td>765</td>
<td>163</td>
<td>21.5%</td>
</tr>
<tr>
<td>Non-Graft</td>
<td>228,005</td>
<td>39,103</td>
<td>17.1%</td>
</tr>
</tbody>
</table>

Conclusions: Further investigation is needed to determine if the presence, timing, and duration of gout in our population of renal transplant recipients is an independent predictor for return to dialysis.

Funding: Commercial Support - Horizon Therapeutics plc

FR-PO1172
Can Uric Acid Blood Levels in Renal Transplant Recipients Predict Allograft Outcome?
Ofer Isakov, Doron Schwartz, Tamar Hod, Souraski Medical Center, Tel Aviv, Israel.

Background: Hyperuricemia is common after renal transplantation, especially in those receiving calcineurin inhibitors (CNI). Increased uric acid (UA) levels were found predictive of kidney disease and end-stage renal disease in those with normal renal function and disease progression in individuals with kidney disease. Little, however, is known about the relationship between UA levels and allograft outcome.

Methods: We conducted a retrospective single-center analysis (N=368) in order to assess UA blood levels post-transplantation association with allograft outcome.

Results: Patients were divided into 2 groups based on the mean UA level measured between 1-12 months post-transplant. Those with mean UA level ≥7 and 6.5 mg/dL (N = 164) versus mean UA level< 7 and 6.5 mg/dL for men and women respectively (N=204) had lower GFR values at 1, 3 and 5 years posttransplant. In a multivariate analysis adjusted for age, gender, race, transplant type, mean CNI levels, presence of slow graft function (SGF) and baseline allograft function (GFR at 3 months posttransplant) the association of UA levels to allograft function were not significantly associated with differences in GFR at 1, 3 and 5 years posttransplant.

Conclusions: Hyperuricemia is a surrogate for a worse allograft function. After adjustment for baseline allograft function increased UA levels were not found to be an independent predictor of long-term allograft function despite the known association of hyperuricemia with progression of cardiovascular and allograft outcomes.

Baseline Characteristics of the High versus low UA groups

<table>
<thead>
<tr>
<th>Group</th>
<th>High UA (N=164)</th>
<th>Low UA (N=204)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.24 (17.76)</td>
<td>55.36 (12.99)</td>
<td>0.55</td>
</tr>
<tr>
<td>Male</td>
<td>68 (41.7%)</td>
<td>124 (60.6%)</td>
<td>0.08</td>
</tr>
<tr>
<td>White</td>
<td>90 (55.1%)</td>
<td>134 (65.7%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Black</td>
<td>10 (6.1%)</td>
<td>7 (3.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>LDL</td>
<td>70.4 (7.7)</td>
<td>78 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDO (mg/dL)</td>
<td>37 (4.9)</td>
<td>39 (7.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>SCr</td>
<td>37 (5.6)</td>
<td>38 (7.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>42 (18.9)</td>
<td>51 (18.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR (mL/min) (120)</td>
<td>43 (18.9)</td>
<td>50 (18.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Continuous variables are presented as means (and standard deviations), categorical variables are presented as number of patients (% of the entire group).
group. However, eGFR at baseline and 12 months in ACLF group was still significantly lower than that in non-ACLF group (53.6±20.1 and 62.3±22.2 ml/min/1.73m² in ACLF group and 65.4±26.2 and 70.5±22.6 ml/min/1.73m² in non-ACLF group) (Figure). The eGFR slope in non-ACLF group was decreasing (-2.58 ml/min/1.73m²/yr, 95%CI: -4.79 to -0.38); however, the eGFR slope in ACLF group did not have significant trajectory (0.93 ml/min/1.73m²/yr, 95%CI: -0.60 to 7.94) during observational period. These slopes were not statistically different between two groups (p=0.431).

**Conclusions:** The mid- and long-term eGFR in ACLF group would be corresponded to deteriorated eGFR before LT and would not recover to the same level of non-ACLF group.

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**FR-POI1175**

Long-Term Changes in Sleep Disordered Breathing in Renal Transplant Patients

Francesca Mallamaci, Rocco Tripepi, Grazzia D’Arrigo, Gaetana Porto, Carmela Marino, Maria cristina Sanguedolce, Giovanni Tripepi, Carmine Zoccali. IFC-CNR, Reggio Calabria, Italy.

**Background:** Sleep Disordered Breathing (SDB) triggers sympathetic over-activity, hypertension and cardiovascular (CV) events in the dialysis population. SDB improves after renal transplantation but long term changes in SDB in renal transplant patients have not been studied.

**Methods:** We studied long term changes in SDB in a series of 221 renal transplant patients (age: 46.9±11 years; M: 70.1%). Over a median follow up of 52.1 months (Interquartile range: 36.6-67.3 months) we performed 404 polysomnographic recordings (on average 2 studies per patient). Data analysis was performed by Generalized Estimating Equations (GEE).

**Results:** At baseline, the median value of the apnea-hypopnea index (AHI) was 1.8 episodes/h (Interquartile range (IQR) 0.6-5.0). One-hundred and sixty-six patients (75%) had a normal AHI (<5). Thirty-seven patients (17%) had mild to moderate SDB (AHI 5 to 14.9) and a minority (18 patients, 8%) had severe SDB (AHI >15). At baseline, AHI was directly related with age (rho=0.24, P=0.001), BMI (rho=0.27, P=0.001), fibrinogen (rho=0.16, P=0.027) and glucose (rho=0.14, P=0.035). The median values of minimum (MinSaO2) and average nocturnal O2 saturation were 98% and 95.6%. On longitudinal observation, the median AHI rose from 1.8 (IQR: 0.6-5.0) to 2.9 (IQR: 1.0-6.6) and to 3.6 (IQR: 1.7-10.4) at the second and the third longitudinal visit, respectively (P for trend=0.009) and the proportion of patients with mild to moderate and severe SDB rose to 22.7% and 20.5%, respectively. Longitudinal changes in MinSaO2 paralleled those in the AHI. In adjusted analyses BMI (P=0.001) and C-reactive protein (P=0.001) emerged as the sole independent longitudinal correlates of AHI and MinSaO2.

**Conclusions:** Sleep Disordered Breathing worsens over time in renal transplanted patients. The post-transplantation rise in BMI, a potentially modifiable risk factor, is an important factor underlying the risk for worsening in this population.

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**FR-POI1176**

Prevalence of Depression in Kidney Transplant Recipients: A Long-Term Population-Based Study

Semin Cho,1 Sehoon Park,2 Ji Eun Kim,1 Mi-yeon Yu,1 Seon Ha Baek,2 Hajeong Lee,2 Dong Ki Kim,1 Kwon Wook Joo,1 Yon Su Kim,1 Yong Chul Kim,1 1Seoul National University Hospital, Seoul, Republic of Korea; 2Seoul National University College of Medicine, Seoul, Republic of Korea; 3Hallym University Dongtan Sacred Heart Hospital, Hwasung-si, Republic of Korea.

**Background:** Depression is associated with impaired quality of life and increased morbidity and mortality in patients with end-stage renal disease (ESRD) and kidney transplant (KT) recipients. Few data is known about the prevalence of depression in KT recipients. In this study, we aimed to explore the prevalence of depression in KT recipients compared with ESRD patients and healthy controls (HCs) in a long-term population-based cohort.

**Methods:** We analyzed a Nationwide Health Insurance Database of South Korea and identified patients who received KT from the year of 2007 to 2015. KT recipients were selected and matched with ESRD patients and HCs considering age, sex, and inclusion year. KT and ESRD patients were further matched with diabetes and hypertension. The prevalence of depression in KT recipients was compared with ESRD patients and HCs, respectively.

**Results:** A total of 7,971 patients were analyzed in all three groups, respectively. Both KT recipients and ESRD patients were poorer, having more co-morbidities than matched HCs. KT recipients revealed markedly a lower prevalence of depression than in ESRD patients (IR, 66.1 vs 23.5 per 1000 patient-year; Hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.33-0.39), although they showed only slightly higher prevalence of depression than in HCs (IR, 19.4 vs 23.5; HR, 1.21; 95% CI, 1.09-1.35). Interestingly, after adjusting the comorbidity status with Charlson Comorbidity Index (CCI), KT recipients showed a lower risk of depression compared with HCs (adjusted HR 0.64; 95% CI, 0.54-0.75; P<0.001), whereas ESRD patients remained at higher risk of depression development than HCs (adjusted HR 1.80; 95% CI, 1.55-2.10; P<0.001). Among KT recipients, older age, female sex, lower socioeconomic status, and more co-morbidities represented by CCI score were associated with increased risk of depression.

**Conclusions:** KT recipients showed a markedly lower risk or depression than ESRD patients and even more than matched HCs after adjustment of co-morbidities. Our data suggest a broader role of KT than previously appreciated in terms of improving quality of life by reducing the risk of depression.

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**FR-POI1177**

The Potential for Improved Medication Adherence with a Complete Once Daily Immunosuppression Regimen in Kidney Transplant: Results of a Randomized Controlled Study

David J. Tabeg, Maria Aurora C. Posadas, Vinaya Rao, John McGillicuddy, Vinayak Rohan, Satish N. Nadig, Derek Dubay, James Fleming. Medical University of South Carolina, Charleston, SC.

**Background:** Medication non-adherence is common after transplant and a major contributor to rejection and graft loss. The objective of this study was to obtain preliminary

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**FR-POI1178**

Sex Differences in Multimorbidity Clusters in Kidney Transplant Patients: Data from a Multicentre Trial

Courtney J. Lightfoot, Thomas J. Wilkinson, Alice C. Smith, University of Leicester, Leicester, United Kingdom.

**Background:** Multimorbidity is a complex phenomenon which is highly prevalent in patients with chronic kidney disease (CKD). Comorbidities can create a ‘treatment burden’ and specific combinations of conditions may have greater effects on functional status, quality of life, and mortality than others. Before determining the impact of multiple chronic conditions on kidney transplant recipients, the patterns of multimorbidity disease need to be identified.

**Methods:** Data was derived from a cross-sectional multicentre survey study. Principal Components Analysis (PCA) (orthogonal (varimax) rotation with a minimum factor loading of 0.40) was used to identify multimorbidity clusters for both sexes. The number of components ('clusters') was determined by the Eigenvalue of >1 or visual interpretation of the scree plot.

**Results:** Data from 2240 transplant patients [age: 52.6 (13.6) years; males: 1289 (58%); white: 1503 (67%); total number of additional (to CKD) comorbidities: 1.35 (1.1); cadaver donor grafts: 1077 (48%); months with transplant: 71.0 (82.3)] were collected from 750 centres in 17 geographically diverse transplant centres. Five multimorbidity clusters were identified for males, and three for females, which are displayed in Figure 1. For males, one cluster included cardiopulmonary diseases; in females this cluster also included musculoskeletal conditions. In females, hypertension clustered with diabetes, whereas in males it was a standalone condition.

**Conclusions:** Patterns of comorbidities are different between male and female transplant patients, and include concordant (i.e. sharing common pathophysiological pathway with CKD; e.g. diabetes) and discordant conditions (i.e. not sharing common pathway with CKD (e.g. depression)). Recognition of multimorbidity clusters may help identify patients at risk of co-occurring diseases. This may favour a more patient-orientated management strategy to reduce treatment burden and improve quality of life. Further research is needed to enhance the understanding of the identified clusters to improve the management of multimorbidity kidney transplant recipients.

**Funding:** Private Foundation Support
Safety, tolerability and efficacy data of a complete once daily immunosuppression regimen of LCP-Tac (Envarsus XR), everolimus and pred, compared to LCP-Tac, mycophenolate BID and pred.

**Methods:** This was a randomized, controlled pilot study with the primary aim of assessing self-reported medication adherence and comparing this between a once and twice daily immunosuppressant regimen. At 3±2 months post-transplant, patients were randomized to receive LCP-Tac and everolimus once daily or LCP-Tac and mycophenolate BID (control arm) for 6-months.

**Results:** 354 were screened, 80 met eligibility, and 40 were randomized. The mean age was 51±14 years, 33% were female, 45% African-American, and 55% had a cPRA ≥ 20%. Baseline characteristics were similar between study arms. Tac exposure was lower in the intervention arm (left side of Figure). Self-reported high medication adherence was higher at baseline in the control group (80% vs. 45%, p=0.049), which equilibrated at study end (59% vs. 47%, p=0.525; right side of Figure). Medication side effect burden tended to be less severe in the intervention group, with both regimens being well tolerated. For QOL, role limitations improved in the entire study group similarly across arms while social functioning trended towards improving to a greater degree in the intervention arm (net change: +8.8 intervention arm, -4.1 control arm; p=0.0898). There were no acute rejections, graft loss or death in either arm during the study.

**Conclusions:** These results provide preliminary evidence of the safety, efficacy, tolerability and potential benefit of sustaining high medication adherence with a novel once daily immunosuppression regimen.

**Funding:** Commercial Support - Veloxis

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**FR-PO1179**

**Noncompliance: A Significant Contributor for Renal Allograft Loss**

Kartik Kalra, Srijan Sundukar, Dana R. Jorgensen, Rajil B. Mehta, Puneet Sood, Christine Wu, Chethan M. Puttarajappa, Nirav A. Shah, Sundaram Harihan.

**University of Pittsburgh Medical Center, Pittsburgh, PA.**

**Background:** United network for organ sharing (UNOS) implemented the new kidney allocation system (KAS) in 2014 to reduce inequity and improve life-years gained from kidney transplantation (KT). KAS allowed matching of high quality kidneys to younger recipients and allowed backdating of waitlist date to account for dialysis vintage. Additionally, transplant centers have aimed to increase access to KT by streamlining evaluation process and reducing barriers to wait listing. Potential unintended consequences of these policies may be selection of patients with higher disease burden and lower social support. We investigated this by examining causes of allograft loss within the first 5 years at our center.

**Methods:** Single center study of kidney transplant recipients between 2013 - 2017. Causes of death-censored allograft loss was examined using the following 7 categories: 1. Non Compliance (medication, follow up, blood work), 2. Donor Related (High KDPI), 3. Rejection (Acute/Chronic T- Cell and Antibody Mediated Rejection), 4. Recurrence of primary kidney disease, 5. Surgical/Technical, 6. Infection Related (BK Virus, Pyelonephritis), 7. Others. Differences in baseline characteristics for patients with and without noncompliance were examined.

**Results:** 18 of 63 (29%) graft losses were attributed to noncompliance. Noncompliance group had younger patients (mean age 38 y vs 53 y; p=0.0001) and higher proportion of African American race (47% vs 22%;p=0.055)

**Conclusions:** Early allograft loss due to noncompliance is high and is more common among African Americans and young patients. This might offset the potential benefits arising from the new KAS. This data should be used to further investigate specific reasons for non-adherence that can be targeted for intervention.

**Funding:** Commercial Support - Dialysis Clinic Inc

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**FR-PO1178**

**Can Pretransplant Psychosocial Factors Predict Racial Difference in Post-Transplant Adherence?**

Yue-Harn Na,1 Igor Livitinovich,1 Christopher G. Ford,1 Yiliang Zhu,1 Mary amanda Dew,2 Chethan M. Puttarajappa,2 Ron Shapiro,2 Mark L. Unruh,1 Larissa Myaskovsky.1 1University of New Mexico, Albuquerque, NM; 2University of Pittsburgh, Pittsburgh, PA; 3Recanati/Miller Transplantation Institute, New York, NY.

**Background:** The success of a kidney transplant (KT) relies on patients’ ability to adhere to a complex medical regimen and routine follow up post-transplant. Non-adherence is common post-transplant and is a leading cause of allograft loss. In this study, we aimed to identify non-medical factors at the time of initial KT evaluation that predicted racial difference in non-adherence post-transplant.

**Methods:** We performed a prospective cohort study of patients who underwent initial KT evaluation, received a KT and were interviewed at 6 months post-transplant. We collected data on baseline demographics, medical, cultural, psychosocial and transplant related factors. We quantified adherence to each medication within the first 6 months post KT (immunosuppressants and anti-hypertensives) with a Likert scale ranging from never to daily missing of medications and used the average of the individual scores as a continuous outcome variable. We then built multiple linear regression models using variables with effect estimates ≥0.2 and p-values <0.1 in bivariate analyses to identify factors that predicted adherence.

**Results:** 1152 patients were enrolled in the initial study, 149 patients underwent KT and had 6+ months follow up; 123(82.55%) were White, 84(56.38%) were male and 103(69.13%) were age ≥45; adherence scores ranged from 1-7 [mean(SD)=6.8(0.78)]. African American race predicted lower adherence, even after accounting for cultural, psychosocial and transplant factors. Age ≥ 45 and having public insurance predicted greater adherence(Table 1).

**Conclusions:** African American race was a significant risk factor for post-transplant non-adherence. Data from this study showed that cultural and psychosocial factors did not affect this association.
Clinical Outcomes of HLA-Identical Transplants in the Tacrolimus Era

Byron D. Bentall, Mark D. Stegall, Mayo Clinic, Rochester, MN.

Background: HLA identical living donor transplants (LDKT) have excellent graft survival. It remains unclear if causes of death/grant loss, histology or complications associated with tacrolimus-era immunosuppression are different when compared to non-HLA identical recipients.

Methods: We performed a nested case control study of HLA identical full sibling LDKT recipients (cases) and non-HLA identical LDKT recipients (controls) matched for age, sex and year of transplant from 1999 to 2018. Baseline characteristics, overall survival and death censored graft survival (DCGS), histology, and complications were compared.

Results: 184 recipients were in each cohort with similar baseline characteristics except for induction regimens: cases were more likely to receive anti-CD25 and alemtuzumab and less likely to receive thymoglobulin (p<0.01). Cases had longer median follow-up [7.6 (3.7-11.9) vs 5.7 (2.8-10.1) years, p=0.01], better overall survival (81% vs. 71%, p<0.001) and better DCGS (94% vs. 77%, p<0.001). Protocol biopsies at 1, 2, 5, and 10 years showed more tubulitis, peritubular capillaritis and glomerulitis in controls. Acute cellular rejection, chronic antibody-mediated rejection, and BK nephropathy were more common in controls. Causes of DCGS and death were similar. Rates of leukopenia, proteinuria, and urinary tract infections were similar.

Time to DCGS from alloimmune injury was shorter in controls (p=0.01); all events in controls (n=3) occurred in the absence of immunosuppression (two were non-adherent and one had PTLD). Rates of leukopenia, proteinuria, and urinary tract infections were similar.

Conclusions: HLA identical LDKT recipients had better patient survival and DCGS when compared to a non-HLA identical cohort. Causes of DCGS and death were similar. Time to DCGS from alloimmune injury was shorter in controls. Controls had higher rates of both cellular and antibody-mediated injury and BK nephropathy. These results suggest a potential role for reducing immunosuppression in HLA identical sibling LDKT.

Demographics and Results

FR-PO1180

Impact of 1-Year Post-Transplant Tacrolimus Trough Levels on Long-Term Renal and Cardiovascular Outcomes in Stable Kidney Transplant Recipients

Hee-Yeon Jung,1,2 Ji-Young Choi,1,2 Jang-Hee Cho,1,2 Sun-Hee Park,1,2 Yong-Lim Kim,1,2 Chan-Duck Kim,1,2 Kyungpook National University Hospital, Daegu, Republic of Korea; 3School of Medicine, Kyungpook National University, Daegu, Republic of Korea.

Background: This study aimed to investigate the impact of 1-year post-transplant tacrolimus (TAC) trough levels on renal and cardiovascular outcomes in stable kidney transplant recipients (KTRs).

Methods: KTRs receiving TAC and mycophenolate-based immunosuppression who have never experienced renal or cardiovascular events within 1-year post-transplant were included from a multicenter observational cohort study. Renal outcome was defined as a composite of biopsy-proven acute rejection, interstitial fibrosis and tubular atrophy, and death censored graft loss. Cardiovascular outcome was defined as a composite of de novo cardiomegaly, left ventricular hypertrophy, and cardiovascular events.

Results: A total of 603 eligible KTRs were divided into low-level (LL) and high-level (HL) TAC based on the median TAC level at 1-year post-transplant of 5.99 ng/mL (range 1.3-14.3). During the mean follow-up of 38.2 ± 13.0 months, 27 and 166 episodes of renal and cardiovascular outcomes occurred, respectively. Multivariate Cox regression analysis, LL-TAC and HL-TAC were not independent risk factors for renal and cardiovascular outcomes, respectively. Instead, decreased donor KT (adjusted hazard ratio [AHR], 2.52; 95% confidence interval [CI], 1.10-6.01; P = 0.037) and male (AHR, 1.62; 95% CI, 1.06-2.47; P = 0.025) were independent risk factors for renal and cardiovascular outcomes, respectively. No significant differences in estimated glomerular filtration rate at 2- and 3-year post-transplant were observed between two groups.

Conclusions: TAC trough levels after 1-year post-transplant were not directly related to long-term renal and cardiovascular events in stable KTRs. There might be no need to insist higher TAC trough levels after 1-year post-transplant in KTRs with stable post-transplant clinical course.

FR-PO1182

Induction Therapies in the Tacrolimus-Based Immunosuppression Era: A Meta-Analysis

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Background: Induction therapy with rabbit Anti-thymocyte Globulin (rATG) and IL-2 Receptor Antagonist (IL-2RA) resulted in marked reduction of acute allograft rejection rate. However, the relative value of these agents in the era tacrolimus-based maintenance immunosuppression remains uncertain.

Methods: A systematic review of Pubmed, Medline, Embase and Cochrane databases was conducted to identify outcomes in terms of graft and patient survival, rejection, infection and malignancy rates in renal transplant recipients (RTRs) (Figure 1). Based on received induction therapy, RTRs were divided into 2 groups (IL-2-RA versus rATG). All subjects were on tacrolimus (TAC) based immunosuppression. The meta-analysis included 6 randomized case-control studies with total of 1017 subjects and follow-up period ranged from 12 months to 36 months. Random effects model (REM) was used to identify risk difference. Confidence interval excluding the value 1 was used as evidence for statistically significant risk difference. Heterogeneity was assessed using Der Simonian analysis (P value<0.1).

Results: The REM showed no significant differences in acute rejection rates, graft survival and patient survival between IL-2A and rATG induction therapies with confidence interval range of 0.99 to 1.00 (Figure 2). All subjects were on tacrolimus-based immunosuppression. The meta-analysis included 6 randomized case-control studies with total of 1017 subjects and follow-up period ranged from 12 months to 36 months. Random effects model (REM) was used to identify risk difference. Confidence interval excluding the value 1 was used as evidence for statistically significant risk difference. Heterogeneity was assessed using Der Simonian analysis (P value<0.1).

Conclusions: The results of this meta-analysis suggest that both IL-2-RA and rATG induction therapies have similar efficacy in the era of tacrolimus-based induction therapies.
FR-POI1184

Renal Transplant Patients Under Calcineurin Inhibitor Therapy Rapidly Acquire an Aberrant Lysosomal Lesion in Proximal Tubular Cells

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Background: Calcineurin inhibitor therapy has changed the field of (renal) transplantation by considerably prolonging graft survival. Yet, all immunosuppressive calcineurin inhibitors are nephrotoxic that eventually contribute to scarring of the renal allograft. In renal biopsies, many histopathological features have been considered indicative of CNI nontoxicity, i.e. stripped fibrosis, vascular hyalinosis, isometric tubular vacuolization, glomerulosclerosis, cellular infiltration and tubular atrophy; however, all are rather aspecific and can be secondary to many other causes. During the course of evaluating the specificity of a recently discovered proximal epithelial lysosomal lesion (i.e. multiple enlarged (>1.2µm) dysmorphic lysosomes containing electron dense non-membrane bound aggregates) in patients with Chronic Interstitial Nephropathy in Agricultural Communities (CINAC), we observed this lesion in renal transplant patients treated with cyclosporine or tacrolimus. Here, we test the hypothesis whether this lysosomal lesion is acquired during CNI therapy.

Methods: A retrospective transmission electron microscopic analysis was performed to evaluate the presence of the typical lysosomal lesion on the following biopsies from renal transplant patients: 20 deceased donor implantation biopsies; 5 living donor implantation biopsies. For another 10 additional deceased donor renal allograft recipients, we evaluated implantation as well as protocol biopsies taken after 6 and 12 months of CNI treatment that started immediately after transplantation. Also included were 24 indication biopsies of CNI treated renal transplants.

Results: Of the total set of implantation biopsies (n=35), 2 (6%) were positive for the above described lysosomal phenotype on EM, whereas in the protocol and indication biopsies prevalence of the lesion was considerably higher ranging between 56% (protocol) and 80% (indication) of cases.

Conclusions: CNI therapy is associated with the fairly rapid appearance of a particular proximal tubular lysosomal phenotype observable on EM, that was not (or rarely) present at implantation. Whether this lesion is related to CNI toxicity and indicative for the outcome for the graft and/or patient survival after renal transplantation has to be investigated in a prospective trial.

Funding: Government Support - Non-U.S.

FR-POI1185

Prevalence of CYP3A Haplotype and Its Relation to Calcineurin Inhibitors Toxicity in Patients with Renal Transplantation Greater Than A Year in Western Mexico

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Background: ESRD is a public worldwide health problem and kidney transplantation is the RRT of choice. Immunosuppressive treatment with tacrolimus has significantly improved short-term graft survival. It has a narrow therapeutic index and a pharmacokinetic variability that may predispose to nephrotoxicity. Polymorphisms of cyP450 (CYP3A4 and CYP3A5) have been related to variability in tacrolimus metabolism.

Methods: Retrospective study in 338 patients with renal transplant over a year being cared in our hospital, in treatment with tacrolimus, January 2017 - January 2018. Genotyping of the variants CYP3A5*3, CYP3A5*1, CYP3A4*1, and CYP3A4*1b was performed and frequency of nephrotoxicity and blood tacrolimus levels were associated with each of the genotypes.

Results: The most frequent polymorphisms were CYP3A5*3/*3 in 53% and CYP3A4*1/*1 in 84%. The most frequent haplotype was CYP3A5*3/*3 + CYP3A4*1/*1 in 50.59%, followed by CYP3A4*1/*3 + CYP3A4*1/*1. Figure 1 shows the behavior of the CYP3A polymorphisms. CYP3A4*1b/*1b and CYP3A4*1/*1 required the highest tacrolimus weight dose and had the lowest blood tacrolimus levels, statistically different from CYP3A4*1/*1 and CYP3A5*3/*3, respectively. The comparison between different haplotypes showed a significant difference only in the weight dose, not in the tacrolimus blood levels. There was no significant statistical difference in CNI toxicity.

Conclusions: In the western Mexican population, CYP3A4*1/*1 and CYP3A5*3/*3 are the most prevalent polymorphisms, with a slow metabolizer profile. Recipients with CYP3A4*1b/*1b or CYP3A5*1/*1 polymorphisms require higher tacrolimus dosage and show a tendency to have higher rates of CNI toxicity despite having low tacrolimus blood levels.
FR-PO1186

Safety and Efficacy of LCP-Tacrolimus (LCPT) in Hispanic De Novo Kidney Transplant Recipients (KTR)

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Background: Safety and efficacy of once daily, LCPT have been established among various subgroups of KTR, however outcomes in Hispanic patients have yet to be analyzed. The purpose of this analysis was to investigate treatment failure and safety outcomes in Hispanic de novo KTR on LCPT or twice daily, immediate-release tacrolimus (IR-TAC).

Methods: A post hoc, subgroup analysis of patients identifying as Hispanic/Latino from a phase III randomized controlled trial was conducted. Patients were dosed at 0.17 mg/kg/day LCPT and 0.1 mg/kg/day IR-TAC on day 1, with target tacrolimus trough concentrations of 6-11ng/mL for the first month, then 4-11ng/mL. Treatment failure was defined as a composite of biopsy-proven rejection (BPAR), graft loss, death, and loss-to-follow up. Concomitant immunosuppressants included basiliximab induction, mycophenolate, and steroids.

Results: Seventy-four LCPT and 79 IR-TAC patients were included in the analysis. Demographics were similar between the two groups. Overall, fewer treatment failures occurred in Hispanic LCPT recipients compared to those on IR-TAC at 12 months (12.2% vs. 25.3%, p<0.004). BPAR largely accounted for the difference in efficacy (Table 1). Mean tacrolimus trough levels were higher with LCPT during the first 2 weeks post-transplant and similar thereafter. Renal function remained stable from 1 month to 12 months for LCPT patients, however the incidence of NODAT at 12 months in at-risk patients was 18.8% in LCPT patients and 3.8% in IR-TAC patients (p=0.057). Remaining adverse events and opportunistic infections were similar between groups.

Conclusions: Hispanic de novo KTR on LCPT experienced fewer treatment failures at 12 months, however a trend towards increased NODAT was noted. These findings may support the approved, lower recommended initial dose (0.14 mg/kg) in this population.

Funding: Commercial Support - Veloxis Pharmaceuticals

FR-PO1187

Weight-Based Dosing for Tacrolimus: A Single-Center Experience

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Background: Tacrolimus (FK) remains the mainstay of immunosuppression for kidney transplant (KT) recipients. A therapeutic trough (TT) is maintained by dose adjustments within an acceptable narrow range. Lowest TtS are associated with acute rejection (AR) episodes. In order to address a wide variability in the initial prescribed dose, as well as issues with delayed time to TT, we implemented weight-based dosing (WBD) for FK in our center. Herein we present the results following this change.

Methods: For WBD, patients received FK at 0.1mg/kg/day on first post operation day (POD), with dose adjustments thereafter per standard protocol, for target TTs of 8-11ng/mL. Patients who underwent KT in the 6 months pre and post implementation of WBD were included in the analysis. We looked at baseline demographics, as well as donor and recipient characteristics. Rates of AR (per Banff 2017 criteria) at 90 days, serum creatinine (SCr) at 30 days, time to TT, and delayed graft function (DGF) were reviewed. Multiorgan transplants, except kidney-pancreas were excluded.

Results: Following KT, 70 patients in the WBD cohort, and 68 patients in the cohort prior to the implementation [non WBD (nWBD) would] be included. AR was observed in 7/65 of the WBD group, and in 3/56 of the nWBD group; p=0.281. On POD 3, the median FK TT was 8.5ng/mL in the WBD, versus 5.9ng/mL in the nWBD (figure 1). To avoid confounding, 35 live donor KT recipients were excluded from DGF analysis. In patients with deceased donor KT (DDKT), DGF rate was significantly higher in nWBD versus WBD group (19/41 [46.3%] vs 9/42 [21.4%], respectively; p=0.05). No difference in median SCr was noted.

Conclusions: FK levels are expected to reach a steady state after 3-4 doses. The WBD group achieved TTS earlier than the nWBD group. Significantly higher DGF rate was noted in the nWBD group, with similar rates of rejection in both groups. Further large-scale studies are needed to examine the role of WBD on DGF, AR and its effect on graft function, as well as costs in the immediate post-transplant period.

FR-PO1189

Outcomes of Kidney Allograft Function in a Patient with Thrombotic Microangiopathy Switched to Co-Stimulation Blocking Agent (Belatacept)

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Background: Thrombotic microangiopathy (TMA) is a severe complication of kidney transplantation. TMA may occur de novo or as recurrent disease post transplantation. De novo disease is usually associated with immunosuppressive drugs [calcineurin inhibitors (CNI’s) and sirolimus] or can be seen as a part of endothelial damage that accompanies antibody-mediated rejection (AMR). Treatment for de novo TMA is limited to plasma exchange and change in immunosuppression. Belatacept a co-stimulation blocking agent

Table 1. Efficacy and Renal Function

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCPT (n=20)</th>
<th>IR-TAC (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (n%)</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>AR (n%)</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>BPAR (n%)</td>
<td>1.5 (2/132)</td>
<td>6.5 (10/153)</td>
<td>0.09</td>
</tr>
<tr>
<td>Treatment Failure (n%)</td>
<td>0.5 (1/132)</td>
<td>0.0 (0/153)</td>
<td>1.00</td>
</tr>
<tr>
<td>General linear model fixed effect p-values for renal function over 12 months. Treatment: p=0.04; Day: p=0.006</td>
<td>Treatment: p=0.001</td>
<td>Day: p=0.000</td>
<td></td>
</tr>
</tbody>
</table>
is considered least nephrotoxic, and may provide an immunosuppression option in patients with TMA.

Methods: A retrospective review of prospectively collected data was conducted on kidney transplant from 2013 to 2019, 45 kidney transplant patients were switched from CNI’s to a Belatacept due to concerns of TMA. Seventy percent of the patients had kidney biopsy proven changes of TMA. Continuous variables are being reported as mean with SD, A paired t-test was used and P value of <0.05 was considered to be significant.

Results: Majority of patients were Hispanic with age 54±11.9, 55% were females. Post belatacept switch follow up on these patients was 29.8±15 months. Significant improvement in pre and post switch serum creatinine (p=0.0001) and urine protein/creatinine (0.006) was observed (Graph). Fourteen patients had detectable DSA at the time of switch, out of these 4 patients were still positive at last follow up, where as 2 new patients developed DSAs. Four (8%) patients developed acute cellular rejection, and one (2%) patient had AMR.

Conclusions: Belatacept appears to be useful alternative immunosuppressive agent in kidney transplant patients with TMA without increasing the risk of rejection. Switching maintenance immunosuppression to Belatacept will likely result in significant improvement in renal outcome.

FR-PO1190
Surveillance Biopsy-Driven Steroid Withdrawal
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Background: Steroids withdrawal (SW) is the most frequently used IS minimizing-strategy, but it increases the risk of AR. We reasoned that surveillance biopsy (SB) could help individualized selection of patients with low risk of AR after SW. We implemented a systematic SB-driven SW protocol since 2007. We present a critical appraisal of the safety, efficiency and utility of this procedure.

Methods: Mono-centric analysis of all KTx performed from 2007 to 2015 and followed until March 2019. SB was performed at a prednisolone dose of 5 mg. SW was only allowed in kidney transplant (KT) with no sign of rejection (including borderline). Combining the two possible interventions (SB and SW) and adherence to the clinical protocol, we defined 6 groups as depicted in the study flow-chart. The safety and efficiency analysis are purely descriptive. The primary end-point for the utility analysis is the prevalence of late (occurring after the intervention) AR and the secondary is time-to-event analysis (Cox model) of a combination of graft lost or eGFR decline>30% from 1 to 3 years post-KT.

Results: The complication rate after SB was 2.5%; 1.8% requiring non- or minimally-invasive intervention and 0.3% necessitating an embolization. No graft lost or procedure-related death was encountered. Out of the 481 KTx analyzed, 169 (35%) were withdrawn from steroids after SB and 97 (20%) showed some degree of SCAR. Rate of late AR were distributed as follow: [SW pp] 6%, [No SW vp] 8%, [No SW pp] 14% and [SW vp] 22% (Chi-2 for trend 0.008). Breakdown of the population according to pre-specified groups was associated to the secondary end-point in both total (p=0.0002) and death-censored (p=0.019) in univariate analysis with [SW pp] being among the best survival groups.

Conclusions: SB-driven SW was safe and associated with good long term outcome.

FR-PO1191
Center-Level Variation in the Association of Clinical Factors with Use of an Early Steroid Withdrawal Regimen in Kidney Transplant Recipients
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Background: Early steroid withdrawal (ESW) may confer net benefit to low-risk kidney transplant (KT) recipients. However, there is limited evidence on what clinical factors constitute the “low-risk” status that favors ESW, possibly resulting in heterogeneous, and even contradicting, practices across KT centers. Quantifying this heterogeneity using real-world data is also crucial for making unbiased inferences on ESW. We aimed to characterize the center-level variation in how clinical factors influence the selection of ESW.

Methods: Using SRTR data, we studied 210,133 KT recipients in 2002-2017, after excluding who did not receive tacrolimus and mycophenolate for maintenance immunosuppression (n=47,756). ESW was defined as withdrawal of steroid by the time of discharge from KT admission. We quantified the center-level variation in the associations of 74 variables with ESW, via the standard deviation (SD) of the random slope terms in multilevel logistic models.

Results: We identified 10 variables with greater variation (Figure). Factors such as recipient hypertension and pulsatile perfusion were associated with ESW in opposing directions at different centers. For example, the center-specific odds ratio (OR) of ESW for recipient hypertension was < 0.8 at 110 (39.6%) centers, but >1.25 at 63 (22.7%) centers. On the other hand, factors such as increased PRA and longer cold ischemic time were associated with lower odds of ESW at most centers, but to substantially varying degrees. For example, while high PRA (80-100 vs 0-9) was associated with lower odds of ESW in the entire population (OR=0.500.58), this association was particularly stronger at some centers [eg, OR<0.2 at 29 (10.4%) centers].

Conclusions: Our findings suggest a substantial discordance among KT centers on what clinical factors indicate ESW and how important each factor is.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The Graft and Patient Survival Rate According to Ethnicity in US Kidney Transplant Recipients

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**Background:** African American (AA) kidney transplant recipients experience disproportionately high rates of graft loss. The aim of this analysis was to use a UNOS data set that contains detailed baseline and longitudinal clinical data to establish and quantify the impact of the current overall graft loss definition on suppressing the true disparity magnitude in US AA kidney transplant outcomes.

**Methods:** Longitudinal cohort study of kidney transplant recipients using a data set created by United Network for Organ Sharing (UNOS), including 266,128 (African American 70,215, Non-African American 195,913) transplant patient between 1987 and December 2016. Multivariable analysis was conducted using 2-stage joint modeling of random and fixed effects of longitudinal data (linear mixed model) with time to event outcomes (Cox regression).

**Results:** 195,913 non-African American (AA) (73.6%) were compared with 70,215 AA (26.4%) recipients. 10-year graft survival of AA in all era is lower than that of non-AA (31% in deceased kidney transplants (DKT) AA recipient and 42% in living kidney transplantation (LKT) non-AA recipient). 10-year patient survival of AA with functioning graft in all era is similar that of non-AA. Multivariate Cox regression of factors associated with patient survival with functioning graft are acute rejection within 6 months, DM, hypertension and etc. Pre-transplant recipient BMI in AA show the trend as a protective factor in patient survival with functioning graft although not significantly in statistics.

**Conclusions:** African American kidney transplant recipients experience a substantial disparity in graft loss, but not patient death with functioning graft.

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**FR-PO1192**

**The Impact of First Kidney Transplant Type on the Outcomes of a Subsequent Transplant**

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**Background:** Many patients with kidney failure will require more than one kidney transplant during their lifetime. It will be useful to know the impact of the type of living vs. deceased donor first transplant on the outcomes of a subsequent transplant as well as cumulative graft survivals between first (G1) and second (G2) especially in patients with limited living donor options.

**Methods:** Using OPTN/UNOS database, we identified patients who underwent a second kidney transplantation between 1996 and 2016. Patients were then stratified into 4 groups based on the sequence of the transplant type as follows: living donor (LD) first, LD second (n=4402); deceased donor (DD) first, LD second (n=2460); LD first, DD second (n=5723); DD first, DD second (n=11411). Using a Cox model, graft outcomes were compared for the second transplant (G2) in all 4 transplant sequences. Subsequently a cumulative combined allograft failure risk (G1 + G2) was also calculated.

**Results:** Survival plots for G2 are shown in figure 1. Adjusted graft failure risks for DD first, DD second compared for the second transplant (G2) in all 4 transplant sequences. Subsequently a cumulative combined allograft failure risk (G1 + G2) was also calculated.

**Conclusions:** We observed reduced cumulative graft failure risk associated with DD followed by LD sequence compared to LD followed by DD sequence. This interesting observation could be related to the disproportionately negative impact of second DD transplant on overall outcomes.
Graft Failure by Donor Type Sequence

<table>
<thead>
<tr>
<th>1st-2nd</th>
<th>3rd Failure</th>
<th>21-52 Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD-LD</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>DD-DD</td>
<td>1.25 (1.13, 1.39)</td>
<td>1.43 (1.36, 1.58)</td>
</tr>
<tr>
<td>DD-DD</td>
<td>1.64 (1.51, 1.78)</td>
<td>2.06 (1.94, 2.28)</td>
</tr>
<tr>
<td>DD-DD</td>
<td>1.81 (1.70, 2.00)</td>
<td>2.54 (2.36, 2.73)</td>
</tr>
</tbody>
</table>

FR-PO1196
Pre-Transplant Dialysis Modality and Long-Term Patient and Kidney Allograft Outcome: A 15-Year Retrospective Cohort Study
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Background: Among factors determining long-term kidney allograft outcome, pre-transplant renal replacement therapy (RRT) is the most easily modifiable. The study aim was to calculate, respectively, and analyzing the impact of RRT modality on patient and graft survival. Studies on allograft function are scarce and lack sufficient size, follow-up time or generalizability.

Methods: We retrospectively studied patient and allograft survival as well as allograft function. We used Cox proportional hazards regression in case mix, transplant data, and fully (transplant data plus preemptive therapy) adjusted models.

Results: Unadjusted (Kaplan-Meier) primary outcomes demonstrated superior 5-, 10-, and 15-year patient and death-censored graft survival in PD vs. HD patients (p=0.001 and p=0.016, respectively). Adjusted Cox regression revealed 35.6% lower hazards of death (p=0.038), whereas hazards for death-censored graft loss were similar (p=0.204). Secondary outcomes of allograft function showed significantly lower 1-, 3-, and 5-year serum creatinine in PD vs. HD groups (p=0.007, p=0.048, and p=0.012, respectively). Living donation benefit for allograft function was most pronounced in groups ‘no RRT’ and ‘PD’. Although not statistically significant, functional allograft decline measured by estimated glomerular filtration rate (eGFR) slope was lowest in PD patients. Recipients on pre-transplant PD with living donation grafts even demonstrated eGFR gain during post-transplant years 1-5.

Conclusions: Allograft recipients on pre-transplant PD vs. HD demonstrated superior all-cause and similar graft survival. Allograft function was better in PD vs. HD patients, although the trajectory of functional decline was similar.

Funding: Private Foundation Support

FR-PO1197
CKD Progression Rate from Stage 4 to 5 is Faster in Kidney Allograft Recipients
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Background: In kidney transplant recipients (KTR), average glomerular filtration rate (GFR) is around 55-70 ml/min in early period after transplantation. Although, chronic kidney disease progression (CKD) rates have been extensively studied in non-transplanted CKD patients, there are limited comparative studies in KTR. In this study, we aimed to evaluate whether CKD progression from stage 4 to 5 is different in KTR than those of CKD patients.

Methods: The study included 76 stable CKD patients and 34 stable RTR (24 living donor, 10 deceased donor) with stage 4 CKD who reached stage 5 during their follow-up between May 2017 and December 2018 in our hospital. Patients with graft loss due to early acute rejection, early graft loss due to surgical complications, immunosuppressive non-compliant patients were excluded in KTR. In control, patients with rapidly progressive glomerulonephritis, acute kidney injury on chronic were excluded. CKD stage was determined according to Kidney/Disease Outcomes Quality Initiative staging system. The progression rate from stage 4 (GFR 4 CKD to 2) was calculated retrospectively and compared through Kaplan-Meier analysis between groups. Also, clinical features which could contribute to disease progression were assessed and Cox regression analysis was performed for adjustment.

Results: The KTR were under triple immunosuppressive treatment including prednisolone, mycophenolate mofetil (azathioprine) and tacrolimus (cyclosporine). The average follow-up were 89±77 months in KTR. Median progression time in RTR patients was significantly shorter than CKD patients 18 (95% CI: 13.5-22.6) vs 38 (95% CI: 33.25-42.75) months, p=0.012. GFR levels were 28.2 m/l/min and 29.5 ml/min in KTR and CKD patients on stage 4, respectively. At the end GFR levels were 7.43 ml/min and
7.4 m/minute in KTR and CKD groups on stage 5. Male patients had shorter progression time than women [25% [95% CI, 22.1-27.8] vs 42 [95% CI, 37.2-46.7] months, p < 0.01]. After Cox regression analysis, gender (p = 0.016) and transplant status (p = 0.015) remained their significance.

**Conclusions:** Progression time from stage 4 to 5 is shorter in KTR than native CKD patients. Gender and age also can contribute disease progression.

FR-POI198

**Reporting and Handling of Missing Outcome Data in Systemic Reviews of Kidney Transplant Studies**

Pooja Budhiraja,1 Mohamad A. Kalot,1 Abdallah El alayli,1 Ahmad B. Dimassi,2 Anna Ilbhe,1 Reem Mustafa,1 University of Kansas, Kansas city, KS; 2Lebanese American University Medical Center, Beirut, Lebanon.

**Background:** Missing outcome data (MOD) can be absent not at random but due to side effects or in effectivity of interventions and can have implications on the validity, reproducibility and generalizability of the results. Hence, before concluding the effectiveness of the intervention in clinical setting it is important for the systematic reviews (SRs) to collect information about MOD and perform appropriate analysis to assess the robustness of the results.

**Methods:** We conducted a methodological survey of reporting and handling of MOD in SRs published in past 5 years. We included meta-analyses of randomized controlled trials performed in adult kidney transplant recipients that provided pooled estimate of an intervention and at least one dichotomous outcome. We used a standardized pilot tested forms with detailed instructions for each step of the review process. Title, abstract, full text screening and data abstraction all are done in duplicates. We studied how SRs collected, reported and handled MOD in the primary analysis.

**Results:** Seventy-one SRs (14 Cochrane and 57 Non-Cochrane reviews) met the inclusion criteria. Drugs were the most common intervention studied (84%) and average follow up was 12 months. Intention to Treat (ITT) or modified ITT was reported in 50% Cochrane and 9% non-Cochrane reviews. Ninety one percent of SRs did not collect information for number or reasons for participants with MOD. Only 5% handled and justified the analytical method(s) used to handle MOD. Furthermore, only 4% performed sensitivity analysis to account for MOD and considered the uncertainty associated with imputing outcomes in the analysis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for evaluation of the confidence in estimates of effect was used in 21% of the SRs.

**Conclusions:** Missing outcome data can introduce bias due to systematic differences between the observed and unobserved data, which can compromise the certainty in the results. SRs in kidney transplant recipients do not adequately report, handle or discuss the risk of bias associated with the MOD before concluding the results.

FR-POI199

**Clinical Trials in Nephrology: An Updated Systematic Review of ClinicalTrials.gov**

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**Background:** Previous published reviews have highlighted low rates and poor quality of clinical trials in nephrology compared to other specialties. In this review, we assessed temporal trends in the quantity and quality of nephrology trials.

**Methods:** We conducted a systematic review among nephrology trials registered on ClinicalTrials.gov from inception to November 2018. Two independent reviewers assessed temporal trends in the quantity and quality of nephrology trials.

**Results:** A database of 288,515 registered interventional trials was restricted to studies that included one of 154 nephrology terms. We screened 512 studies and included 4943 in the analysis. Figure 1 summarizes the number of registered nephrology trials over time. Trials were grouped into 3 Eras [Table 1]. Compared to Era 1, Era 3 had more trials (28.2% increase). Between Era 2 and Era 3, there was a decrease in transplant trials, there was an increase in living donor recipient and in glomerular disease trials.

**Conclusions:** There has been an increase in the number of nephrology trials conducted over time with some improvement in quality and an increase in trials for devices, behavioral interventions, and rare kidney diseases.

**Table 1**

<table>
<thead>
<tr>
<th>Era</th>
<th>Trials (Number of PP)</th>
<th>% Increase</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Era 1</td>
<td>1142 (1092)</td>
<td>1142 (1092)</td>
<td>0.001</td>
</tr>
<tr>
<td>Era 2</td>
<td>2027 (2174)</td>
<td>2027 (2174)</td>
<td>0.001</td>
</tr>
<tr>
<td>Era 3</td>
<td>1094 (1103)</td>
<td>1094 (1103)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Figure 1.** Number of registered nephrology trials on ClinicalTrials.gov from inception to November 2018.

FR-POI200

**Plasmapheresis Reduces Mycophenolic Acid Concentration: A Study of Full AUC<sub>0-12</sub>**

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**Background:** Mycophenolic acid (MPA), which is a crucial immunosuppressive drug, and plasmapheresis, which is an effective immune reduction method, are simultaneously used for the management of various immune-related diseases, including kidney transplantation. While plasmapheresis has been proven for removing many substances from the blood, its evidence on MPA levels remains unestablished.

**Methods:** A cross-sectional study was conducted in kidney transplantation recipients who were taking a twice-daily oral dose of mycophenolate mofetil (MMF, Cellcept®) and undergoing plasmapheresis at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, during January 2018 and January 2019. The MPA levels were measured by enzymatic method (Roche diagnostic®) at 0, 1/2, 1, 2, 3, 4, 6 h and, 12 hours for AUC<sub>0-12</sub> calculation on the day with and the day without plasmapheresis sessions. Plasmapheresis was started within 4 hours after the oral morning dose of MMF. Our primary outcome was the difference of AUC<sub>0-12</sub> between the day with and without plasmapheresis.

**Results:** Forty complete AUC measurements included 20 measurements on the plasmapheresis day and the other 20 measurements on the day without plasmapheresis of six kidney transplant patients. The mean age of patients was 56.2 ± 20.7 years. All patients had received MMF 1,000 mg/day for at least 72 hours before undergoing 3.5 ± 2plasmapheresis sessions. Mean AUC on the day with plasmapheresis was lower than the day without plasmapheresis sessions (28.22 ± 8.21 vs 36.79 ± 10.29 mg x hour/L, p = 0.001) and the percentage of AUC reduction was 19.49 ± 24.83 %. This was mainly the result of a decrease in AUC<sub>0-4</sub> of MPA (23.96 ± 28.12% reduction).

**Conclusions:** Plasmapheresis significantly reduces the level of full AUC<sub>0-12</sub> of MPA. The present study is the first to measure the full AUC<sub>0-12</sub> in MPA-treated patients undergoing plasmapheresis. Our study suggests that a supplementary dose of MPA in patients undergoing plasmapheresis is necessary.

**Funding:** Private Foundation Support

AUCO-12 on PP and non-PP day

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day without PP</th>
<th>PP day</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCO-12</td>
<td>36.79 ±10.29</td>
<td>28.22 ±8.21</td>
<td>p=0.001</td>
</tr>
<tr>
<td>AUCO-12 reduction (%)</td>
<td>23.96 ±28.12%</td>
<td>19.49 ±24.83 %</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Number of registered nephrology trials on ClinicalTrials.gov from inception to November 2018.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

758
FR-PO1201
Outcome Implications of Benzodiazepine and Opioid Co-Prescription in Kidney Transplant Recipients: A Pharmacoepidemiologic Analysis
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Background: Recent studies identify coprescription of benzodiazepines and opioids as a risk factor for adverse outcomes in the general population, but relationships have not been described among kidney transplant (KTx) recipients.

Methods: We examined a novel linkages of national registry data with records from a pharmaceutical claims warehouse (2008 to 2017) to characterize benzodiazepine and opioid use in the year after KTx and associations (adjusted hazard ratio, 95% CI) with death >1 to 5 years post-KTx.

Results: Among 103,969 KTx recipients 15% filled benzodiazepines in the year after transplant: 6.3% long-acting, 7.5% short-acting, 1.8% both. Considered alone, benzodiazepine use in the first year posttransplant was associated with increased (P=0.05) mortality >1 to 5 years after KTx: aHR long-acting, 1.25 (1.12, 1.40); aHR short-acting, 1.44 (1.27, 1.65); aHR both, 1.64 (1.42, 1.91). Opioid use was higher in those who also filled benzodiazepines, especially both long- and short-acting (Fig A). Use of both medications was more common among recipients who were white, unemployed, and received prior KTx. There was also graded association of higher level opioid use with mortality that appeared additive with benzodiazepine coprescription (Fig B). Patients who filled both classes of benzodiazepines and high-level opioids had 2.6-times mortality risk, compared to no use.

Conclusions: Benzodiazepines use is correlated with opioid fills after KTx, and coprescription of long- and high-level opioids had 2.6-times mortality risk, compared to no use. Opioid Use by Benzodiazepine Use, and Associated Outcomes

FR-PO1202
Correcting Anemia and Native Vitamin D Supplementation in Kidney Transplant Recipients: A Randomized Clinical Trial
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Background: Higher levels of hemoglobin (Hb) and serum 25(OH)D have been described among kidney transplant (KTx) recipients. As a risk factor for adverse outcomes in the general population, but relationships have not been described among kidney transplant (KTx) recipients.

Methods: We used validated data from TRANSFORM trial (NCT01950819), a RCT that compared KTR to receive everolimus with low-exposure CNI or mycophenolic acid (MPA) with standard-exposure CNI. We applied the iBox Clinical Trial Simulation Tool to fast track the development and approval of pharmaceutical agents.

Results: A total of 1855 patients (930 with everolimus and 925 with MPA) reached the 1 year after transplant primary endpoint. Mean eGFR was 55.9 ± 19.7 mL/min/1.73 m² with everolimus vs 62.6 ± 19.7 mL/min/1.73 m² with everolimus <0.001. The rate of BPAR was of 2.5% with everolimus vs 3.6% with MPA. The rate of DSA was 13.7% with everolimus vs 15.9% with MPA. These immunological, functional, and histological parameters were entered into the iBox, which translated to an overall patient graft survival at 3, 5 and 10 years after randomization of 94.2% vs 94.7%, 91.2% vs 92.0% and 83.8% vs 84.9% in the everolimus and MPA arms respectively (95%CI -3.1% to 0.2% below the non-inferiority margin of 10%) Figure. The iBox system confirms the non-inferiority of everolimus vs MPA 10 years after patient’s randomization in the RCT. Given the unmet need for surrogate endpoint for clinical trials, this study shows the potential of a clinical trial simulation tool to fast track the development and approval of pharmaceutical agents.

Conclusions: The iBox system confirms the non-inferiority of everolimus vs MPA 10 years after patient’s randomization in the RCT. Given the unmet need for surrogate endpoint for clinical trials, this study shows the potential of a clinical trial simulation tool to fast track the development and approval of pharmaceutical agents.
FR-PO1204

Association Between Post-Transplant Opioid Use and Immunosuppressant Therapy Adherence Among Renal Transplant Recipients

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Background: Little is known about the effect of post-renal transplant opioid use on adherence to immunosuppressant therapy (IST).

Methods: Longitudinal data were analyzed from a retrospective cohort study examining US veterans undergoing renal transplant from October 1, 2007 through March 31, 2015. Opioid prescriptions dosages were collected and divided based on annual morphine milligram equivalent (AMME) within a year of transplant. Proportion of days covered of at least 80% indicated adherence to tacrolimus. We used logistic regression analyses to examine the association between post-transplant opioid use and adherence to IST.

Results: Compared to renal transplant recipients (RTRs) without opioid usage, RTRs with opioid usage had lower probability of being adherent to tacrolimus in unadjusted and multivariable adjusted models (model 2-5) [Figure]. In the adjusted Model 5, RTRs with AMME opioid dose of 1-30 [OR (95% CI): 0.17 (0.05-0.56)], 31-60 [OR (95% CI): 0.21 (0.06-0.74)], and >60 [OR (95% CI): 0.18 (0.05-0.61)] had lower probability of tacrolimus nonadherence compared to RTRs without opioid usage.

Conclusions: RTRs who use prescription opioids during the first year posttransplant are less likely to be adherent to tacrolimus. Future studies are needed to better understand underlying causes of the association between opioid use and tacrolimus nonadherence.

Funding: NIDDK Support

FR-PO1205

Trends in Causes of Death in Australian and New Zealand Kidney Transplant Recipients: A Registry Analysis by Era and Time Post Transplant

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Background: Donor and recipient characteristics in kidney transplantation (KT) have changed dramatically since the 1980s. Along with an increase in marginal donors and older recipients, incremental improvements have ensued in immunosuppression, surgical techniques and cardiovascular (CV) disease management. A contemporary assessment of the risks and determinants of deaths in KT recipients is required to better inform our patients.

Methods: Using the ANZDATA registry, we included all kidney-only transplant recipients between 1980 to 2017. We censored patients at graft loss or date of last follow-up. We calculated crude death rates by dividing the number of deaths by the total patient-years at risk. Adjusted death rates per 5-year intervals were compared using a piecewise exponential model, stratified by time period post-transplant.

Results: 22,078 incident KT recipients accumulated 183,964 person-years of follow-up. The adjusted all-cause death rate was 2% per annum, remaining stable since 2005. Compared with 1995-1999, KT recipients in 2015-2017 were older (mean age 47 vs. 41) and had more comorbidities (CVD 25% vs. 13%, diabetes 24% vs. 10%). Since 1980, there has been a significant reduction in CV and infection-related deaths at all periods post-transplant (Figure). Recipients in the current era had a 56% reduction in CV deaths (adjusted HR=0.44, 95%CI 0.36-0.52) and 53% reduction in infection-related deaths (adjusted HR=0.47, 95%CI 0.36-0.61), compared with recipients in 2000-2004. Short-term cancer-deaths have remained stable over time, with a marginal fall in long-term cancer-deaths since 2005.

Conclusions: The risk of death after KT has reduced significantly since the 1980s, driven by a reduction in CV death at all time points and a decline in infection-related deaths. Contrary to previous studies, cancer-deaths have remained stable over time after adjusting for time post-transplant.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO1206
Improvement in Long-Term Graft Survival of Post-1-Year Survivor Kidney Transplant Recipients in the United States
Catherine Wu, Abbas Rana, John A. Goss, Samaya J. Anumudu, Bhamidipati V. Murthy. Baylor College of Medicine, Houston, TX.

Background: Advancements in prevention and treatment of acute rejection of kidney transplants significantly improved the short-term allograft survival. However, these successes have not been translated to long term outcomes of kidney transplants. We re-evaluated long-term graft survival for recipients whose survived one year after kidney transplantation such that the short-term adverse outcomes do not cloud the long term outcomes.

Methods: We retrospectively analyzed 219,645 recipients from 1995 to 2017 using data from the United Network for Organ Sharing. Patients undergoing re-transplants, multiorgan transplants, and recipients <18 years age at transplantation were excluded. Patients who died within 1 year of transplantation were excluded. Multivariable Cox regression was employed to estimate graft survival.

Results: Compared with patients transplanted during the period 1996-2000, on multivariate analysis, the hazard ratio (HR) for graft loss for 2001-2005 was 0.88, 2006-2010 was 0.73, and 2011-2016 was 0.63. The HR for graft loss for males was 1.12, age >60 years (vs 18-40) was 1.39, Blacks (vs Whites) was 1.34, BMI >30 (vs 18.6-25) was 1.13, dialysis prior to transplant (vs pre-emptive) was 1.40, diabetes was 1.52, and deceased donor (vs living donor) was 1.38. Compared with patients with PRA 0-79%, the HR for graft loss for PRA 80-89% was 1.15, and for 90-100% was 1.22. Compared to donor age 18-29 years, HR with donors 30-39 yrs was 1.10, 40-50 years was 1.26, and >50 years was 1.50. All these were statistically significant with p<0.0001.

Conclusions: Long-term graft survival among kidney transplant recipients in the US has improved steadily over time. While advances in maintenance immunosuppression, and prevention and treatment of antibody-mediated rejection may have contributed, further research is needed to better understand other causes behind this improvement in kidney graft survival over the past 30 years.

FR-PO1207
Outcomes of Deceased Donor Kidney Transplant Recipients Based on Age and Kidney Donor Profile Index
Josh Bodnar,1 Aniruddha Srivastava,1 Sandesh Parajuli,1,2 Brad C. Astor,1 Brenda L. Muth.1,3 1University of Wisconsin School of Medicine and Public Health, Madison, WI; 2UW Health, Madison, WI.

Background: The Kidney Donor Profile Index (KDPI) is a score used to estimate the overall quality of a deceased-donor kidney prior to transplant. This study sought to determine the outcomes of receiving KDPI >85% Kidneys relative to KDPI ≤85% kidneys based on graft survival and patient survival at 2 different age groups.

Methods: This was an observational study of all deceased-donor kidney transplant recipients ≥40 years of age at the time of transplant between 2011 and 2015 at our University hospital (n=837). Patients were divided into two groups, group 1 included patients between 40 and 59 years of age at the time of transplant (n=176) who received a KDPI >85% (n=15) or KDPI ≤85% (n=161). Group 2 included patients ≥60 years of age (n=121) who received a KDPI >85% (n=11) or KDPI ≤85% (n=110).

Results: Most of the baseline characteristics were similar across groups. Around 25-27% of ESRD was due to Diabetes (DM) in both groups, Recipients were on dialysis for a longer time in group 1 compared to group 2. In the univariate analysis, KDPI >85% compared to ≤85% was associated with increased risk of graft failure and patient death in both groups. After adjustment in multivariate analysis, in group 1, DM was associated with increased risk of graft failure and patient death in both groups. In group 2 post transplant, rejection rate (RR) and delayed graft function (DDF) rate in the elderly who received high KDPI deceased donor kidneys. Data was analyzed using SPSS. GFR is calculated using MDRD.

Results: Among 154 patients who received kidney transplantation at our institute, 52 (33.8%) patients were elderly and 34.6% of them received high KDPI kidneys. The Kidney Donor Profile Index (KDPI) higher than 85 for obese patients requires selective use of weight management strategies. RYGB and SG improved survival for CKD patients with Class III obesity, but not for patients with Class I and II obesity. As such aggressive weight loss interventions should be reserved for patients with Class III obesity, while more conservative methods should be offered to those with Class I and II obesity.
Characteristics of our cohort were represented in table 1. The elderly who received high KDPI kidneys have similar rate of DGF, RR and GFR 1 year post transplant compared to the rest of the cohort (50.0% vs 48.6%, 11.1% vs 18.9%, 47 vs 58 ml/min/1.73m², all p>0.05). Elderly patients had significantly higher cold ischemic time (CIT) compared to the rest of the cohort (32.4±9.7 vs 27.2±12.5h).

Conclusions: Elderly patients at our institute who received high KDPI kidneys have similar rate of DGF, RR and GFR 1-year post transplant compared to the rest of the cohort. Compared to the national rate, elderly high KDPI recipients in our study have prolonged CIT (32.4±9.7 vs 17.0±8.7) and higher DGF (50% vs 23.8%) but comparable rejection rate (9.5% vs 11.1%) and GFR 1-year post transplant was 47 vs 58 ml/min/1.73m².

FR-PO1210
Single Cell RNA-Seq profiling of renal endothelial cells in experimental diabetic nephropathy model reveals transcriptomic changes in separate endothelial subpopulations
Alex X. Zhou,1 Pernille B. Laerkregaard Hansen,2 Christer Betsholtz,3 Marie Jeansson,4 Lixin He,9 Martin Uhrbom,1 Jianping Liu,1 Anna Granqvist,5 Pernilla Tonelius,6 Åstrazeneca Gothenburg, Malmö, Sweden; 1Imed CVMD, Malmö, Sweden; 2Uppsala University, Uppsala, Sweden; 3Karolinska Institutet, Huddinge, Sweden; 4Åstrazeneca, Malmö, Sweden; 5Åstrazeneca R&D Gothenburg, Sweden, Malmö, Sweden.

Background: Endothelial dysfunction and vascular rarefaction are hallmarks of chronic kidney disease, while little is known about the transcriptomic changes of renal endothelial cells (ECs) during disease progression. Moreover, kidney contains heterogeneous EC subpopulations that are structurally and functionally distinguishable. This study aims to determine and compare transcriptome profiles in separate renal EC subpopulations between healthy mice and mice of diabetic nephropathy (DN) using single cell RNA-seq (scRNA-Seq).

Methods: Kidneys of BTBR lean and ob/ob mice at 6, 11 and 20 weeks of age were enzymatically dissociated with Liberase9,10. After incubation with Pecam1 antibody and Calcine-AM, Pecam1- and Calcine-AM-positive single live cells were FACs sorted into 384 well plates. Single EC cDNA library was generated by Smart-seq2 technique and the sequencing was performed on Illumina HiSeq 3000. Unsupervised clustering of EC subpopulations was performed with Pagoda analysis.

Results: BTBR ob/ob mice develop vascular rarefaction with age. Compared to the lean mice, the proportion of renal single live ECs in the ob/ob mice showed no difference at 6 weeks of age, a 25% reduction at 11 weeks of age, and a 32% reduction at 20 weeks of age (P<0.01). The current Pagoda analysis on the 11-week-old lean and ob/ob mice revealed two EC subpopulations and 142 genes with significantly altered expression in ob/ob mice. Among differentially expressed genes (DEGs), certain redox genes were ubiquitously regulated. However, majority of the DEGs were altered in distinct EC subpopulations, likely owing to either the different sample sizes or the heterogeneity on gene expression/regulation in various EC subpopulations. The data of 6- and 20-week-old BTBR mice is under analysis to explore the time course of the transcriptomic changes.

Conclusions: The full length scRNA-seq on FACs sorted renal ECs provides a feasible approach to a high-resolution transcriptomic profiling of heterogeneous EC populations in kidney and importantly the heterogeneous transcriptomic changes in an experimental DN model.

Funding: Commercial Support - AstraZeneca R&D Gothenburg

SA-PO001
ASN Communities: A Growing Thriving Online Educational Asset
Roger A. Roddy,1 Susan Willner.2 Rush University Medical Center, Chicago, IL; 1American Society of Nephrology, Washington, DC.

Background: Doctors are turning to social media (SoMe) and internet-based venues to teach, improve patient care, and to bolster knowledge. In 2016, the American Society of Nephrology launched “ASN Communities” (“Comms”) an online collaboration platform designed to provide ASN members with a dynamic international peer to peer venue to discuss challenging clinical cases, as well as other professional education activities. The clinically oriented Comms include: Open Forum, Patient Care Q&A, AKI, Kidney Transplantation, Onco-Nephrology and Nephrologists Transforming Dialysis Safety. Other Communities include Public Policy and Public Health, Renal Educators, Women’s Health and Research, Basic Science Research, Career Advancement, Fellows Connect, and Renal Educators.

Methods: ASN members are automatically enrolled in the Open Forum Comm while the other Comms require a one-click join process. Members can opt to receive email alerts for each Comm in which they are a member. ASN Comms combines the best of all SoMe platforms into a professional, iterative, educational experience for the mundane to the most complex questions of health care workers around the world, and by design not limited to academia. Each Comm has “Community Leaders” (topic experts that help lead the discussions) who are chosen by the ASN’s Media and Communication Committee which also oversees the activities of all Comms.

Results: ASN members from throughout the world regularly leverage the expertise and knowledge of the greater community as evidenced by 25% of logsins and 30% of posts originating from outside of the U.S. To date there have been 3,902 Discussions generating 27,871 replies (see Figure) from 180 countries and over 4,800 cities, with 330,149 logins representing 13,300 ASN Members. Each month approximately 3,000 ASN members access Comms. Comms are accessible on any computer as well as smartphones via a dedicated Comms app and on Twitter at @ASNCommmunities.

Conclusions: ASN Communities should serve as a template for other medical subspecialties interested in the education and growth of their members.

SA-PO002
Survey-Based Evaluation of Home Dialysis Education During Nephrology Fellowship in United States
Nupur Gupta,1 Elizabeth Taber-Hight,1 Brent W. Miller,2 Indiana University, Indianapolis, IN; 1Indiana University School of Medicine, Carmel, IN.

Background: Home Dialysis seems to be an underutilized modality for many reasons, one of which includes physician unfamiliarity with the practical aspects in both Peritoneal Dialysis (PD) and Home Hemodialysis (HHHD). Previous surveys have suggested suboptimal exposure and confidence amongst fellows. The goal was to identify gaps in knowledge and evaluate possible areas of improvement in Home Dialysis.

Methods: A 23 question survey on education during fellowship training was developed and distributed at 3 Home Dialysis University Symposia in 2019. Survey assessed core competencies, clinical experience and overall preparedness of Home based renal therapies amongst graduating fellows.

Results: 76 out of 250(30%) graduating fellows completed the survey. Nearly all the respondents (98.7%) desired more teaching focused on both Home Therapies. Assessing the core competencies of PD, majority (55.6%) of them were “somewhat confident” and 26.2 % selected “no confidence”. A larger portion of respondents (31.8%) felt “Not at all confident” regarding HHHD key competencies. Most of the participants believed fewer than national average (< 10%) patient population were on Home Therapies in their Academic practice. A large number of fellows (71.7%) reported that patients followed in Home Continuity clinic were on PD but fewer on HHHD. Approximately half the fellows have opportunity of continuity clinic with Faculty mentorship.

Conclusions: Nephrology fellows felt significantly more prepared for PD than HHHD but moderate overall preparedness. Implementation of well-structured curriculum integrated with robust clinical experience would improve preparation of Home Therapies with preparedness of fellows.
SA-PO003

Comparing Author Gender and Publications in Two Medical Subspecialties

Niralee Patel, Yuwen Wen, Nidhi Naik, Benjamin O. Adegbite, Steven G. Coca, Girish N. Nadkarni, Lili Chan. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: A gender gap exists in scientific publications, with women being underrepresented. We assessed the proportion of oral presentations that are subsequently published in peer-reviewed journals and their impact factor (IF) by gender in nephrology (49% female fellow trainees) and rheumatology (60% female fellow trainees).

Methods: We reviewed oral abstracts presented at American Society of Nephrology (ASN) Kidney Weeks 2011-2013 and American College of Rheumatology (ACR) annual conferences 2011-2013. Proportions of gender combinations for first and last author (Female-Female (FF), Female-Male (FM), Male-Female (MF), and Male-Male (MM)) were compared utilizing Chi² and IFs using ANOVA.

Results: Of 1,262 ASN oral abstracts, 39% had female first authors and 21% had female last authors. MF had the lowest proportion (59%) of abstracts published compared to FF, FM, and MM authors (74 vs. 73 vs. 73%, p=0.005) (Figure 1A). MM papers were published in journals with higher IF (Figure 1B). In contrast, of 1,191 ACR oral abstracts, females comprised 52% of first authors and 41% of last authors. There were no significant differences seen in the combinations of authorship (FF 68%, FM 73%, MF 67%, vs. MM 72% p=0.35) (Figure 1A). MM papers were published in journals with higher IF (Figure 1C).

Conclusions: Author gender differences seen in the proportion of oral abstracts that were later published were inconsistent between nephrology and rheumatology. However, MM abstracts were published in higher impact journals in both fields. Whether these findings hold true in other medical subspecialties with varying proportions of female trainees should be further explored.

SA-PO004

Kidney Disease Screening and Awareness Program Is an Effective Model to Expand the Recruitment Pipeline by Capturing Undergraduates for Nephrology

Rui Song, Rebecca P. Chen, Min Zhuo, Sirine Bellou, Andrew Cho, Jiahua Li, Li-Li Hsiao. Kidney Disease Screening and Awareness Program (KDSAP) Clinical Research Team 1Beth Israel Deaconess Medical Center, Boston, MA; 2University of California, Los Angeles, San Diego, CA; 3Brigham & Women’s Hospital, Brookline, MA; 4Brigham and Women’s Hospital, Chestnut Hill, MA; 5Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 6Harvard University, Cambridge, MA.

Background: Physician shortage in nephrology is causing an impending workforce crisis. The Kidney Disease Screening and Awareness Program (KDSAP) is a national student-led organization targeting college students via community health screening and mentorship. This longitudinal study aims to assess the impact of KDSAP on career choice of its alumni in nephrology.

Methods: KDSAP alumni were defined as college graduates from 2009 to April 2019, who have attended at least one KDSAP health screening or KDSAP academic event. There are 124 alumni who met the criteria and with valid contact information. An online survey evaluating demographics, career choice impact, perspectives on nephrology was sent by email. To gain in-depth knowledge of KDSAP’s impact, one-on-one interviews were conducted with those who are currently practicing medicine; and focus group discussions were conducted with medical students and health-related graduate students. This study was conducted via a mixed-method study approach.

Results: Our study enrolled 112 alumni who completed the survey. Among them, 75 (67%) reported “very” or “extremely” invested in KDSAP activities. The community screening is the most meaningful (97%) and influential (69%) to their career choices. Out of 112 respondents, 94 (84%) are in the field of medicine in various stages, including 3 nephrologists. While 40 (36%) consider doing kidney-related research or patient care, impressively 8 (24%) of those attending medical school (n=34) consider Nephrology as their career choice. Our results also revealed favorable perceptions of Nephrology among KDSAP alumni: Nephrology is exciting compared to other specialties (79%), Nephrologists are important to community health (97%), Nephrology is a rewarding field for a career option (88%) and considering a kidney-related profession for the further career (31%). Qualitative analysis (n=9) revealed four main categories in the impact of KDSAP on alumni: career choice, mentorship, career development, and community health services.

Conclusions: In fighting the Nephrology workforce crisis, KDSAP is an effective model to expand the recruitment pipeline by capturing undergraduates entering the field of Nephrology.

Funding: Other NIH Support - Sundy Fund

SA-PO005

What Do Internal Medicine Residents Consider When Choosing Careers? An Exploratory Q Sort Study with a Focus on Nephrology Interest

John K. Roberts, Charles Hargrett, Myles Wolf. Duke University, Durham, NC.

Background: Interest in nephrology among internal medicine (IM) residents has been low in recent years. A better understanding of contemporary attitudes about career choice decisions in IM residents could help nephrology recruiting efforts. Therefore, we used a Q sort survey to better understand IM resident attitudes surrounding career choice decisions in the modern era.

Methods: We invited IM residents (post-graduate year 2/3) at an academic medical center to take a Q sort survey in the late fall of the training year. Residents prioritized 50 statements that reflected issues affecting career choice: scope of practice, patient care, procedural care, consultant care, general care, family responsibilities, debt, remuneration, length of training, interest in physiology, and lifestyle concerns. To find statistically significant perspectives, we performed by-person factor analysis using the Centroid method. At the conclusion of the Q sort, we collected the residents’ top three career interests.

Results: Out of 47 sorts, we identified four viewpoints that accounted for 43% of the variance in the sample. Figure 1 shows the viewpoints. Across all four groups, all agreed that positive interactions with a faculty role model and control over future practice are important for career decisions. Among residents considering nephrology, two loaded onto the Academic Proceduralist viewpoint, five loaded onto the Lifestyle-Family viewpoint, and one loaded onto the Lifestyle-Salary group.

Conclusions: The Q-sort survey identified the dominant career choice viewpoints of contemporary IM residents. Two of the viewpoints were centered on lifestyle considerations: one focused on family responsibilities and the other focused on remuneration, educational debt, and burnout. To make nephrology more attractive to the current generation, changes to the profession are needed. Interventions that support an attractive lifestyle, control of practice, while accommodating to family responsibilities and educational debt may impact interest more than other factors.

Funding: Private Foundation Support
SA-PO006
A Unique Hybrid Nephrology Training-Hospitalist Medicine Track: The University of Kentucky Experience
Faris Khasawneh,1 Jon C. Webb,2 B. Peter E. Sawaya,3 University of Kentucky, Lexington, KY; 1University of Kentucky Medical Center, Lexington, KY.

Background: There has been a declining interest in nephrology training as evidenced by a decline in the number of applicants and increased number of unfilled positions through the Match. On the other hand, hospitalists are a growing group of physicians with some gaining interest in nephrology. However, salary disparity has been an obstacle to translate this interest into pursuing nephrology training. The creation of a hybrid program combining nephrology training and hospitalist work is a possible pathway that would be of value to Nephrology programs and interested hospitalists.

Methods: In 2016, the nephrology program at the university of Kentucky embarked in a systematic creation of a hybrid program combining nephrology training and hospitalist practice. A curriculum expanding over 4 years with alternating 6-month blocks was developed. The salary of the candidates alternates between PGY-4 or 5 remuneration and those of a full time hospitalist faculty. The curriculum was approved by the university graduate medical education (GME) and by the ACGME. ABIM recognizes this fellowship under the “interrupted” training track. A major obstacle is the alignment of the offices of human resources, hospital administration and GME. An effective communication system is necessary to signal the switching between the different status. A geographic separation where the training is in one hospital, while the faculty hospitalist practice is in another proved to be a practical mechanism to circumvent potential confusion. Once the program is approved, advertisement in prominent hospitalists journals was necessary.

Results: After 1 month of advertisement in two hospitalists journals at a cost of $2,500, we identified 9 interested candidates after the match. We offered the position to two. The average yearly salary for the hospitalist-fellow trainee is $138,250/year. Moonlighting is allowed as a supplementation to their salary, provided that it does not interfere with the duty hours regulation. Currently, the two hybrid trainees have completed two years in this program with 1 year of accredited training toward nephrology. Their feedback has been very positive.

Conclusions: Nephrology Fellowship-hospitalist track appears to be a valid approach to ameliorate the negative impact of declining interest in nephrology fellowship on the manpower and overall training programs.

SA-PO007
The Nephrology Immersion Classroom: Using Digital Videos to Boost Knowledge in Nephrology
John K. Roberts, Myles Wolf. Duke University, Durham, NC.

Background: Improving residents’ nephrology knowledge is one way to stimulate interest and self-efficacy in nephrology. Newer methods of resident education should be sought to better personalize the learning process and meet resident needs. One way to foster self-directed, asynchronous learning is through digital chalk talk videos. We hypothesized that adding a nephrology video curriculum to a nephrology rotation would improve medical knowledge in internal medicine residents.

Methods: Internal medicine residents (post-graduate year 2/3+1) on the nephrology consult rotation were invited to participate in the study. In both a control and intervention year (access to the videos), we surveyed and tested residents’ knowledge using 15 case-based multiple-choice questionnaires (MCQs) before and after their nephrology rotation. We created a library of 32 short, digital blackboard videos that covered high-yield topics in nephrology. We hosted the video curriculum on Google Classroom, so that access could be restricted to study participants and they could view content using the Google Classroom smartphone app. In the post-rotation survey, we measured satisfaction and usability of the nephrology classroom.

Results: 39 residents completed the nephrology rotation in the control group and 26 (66%) participated in the study. In the intervention group, 33 residents completed the nephrology rotation. 25 (75%) enrolled in the Google classroom, and 30 (80%) participated in the study. Performance on nephrology MCQs improved between the pre and post-tests in both years, but the difference was not statistically significant. During the study period, videos were viewed on average 5.6 times and the classroom was considered very easy to use. Other usability metrics suggest high levels of satisfaction with the video curriculum.

Conclusions: Adding a digital chalk talk curriculum did not improve short-term medical knowledge, but hosting videos on a mobile classroom platform resulted in modest usage with high resident satisfaction. Efforts to boost video views may improve both short and long term learning outcomes.

Funding: Private Foundation Support

Nephrology Medical Knowledge in Control and Intervention Years

<table>
<thead>
<tr>
<th>Study Condition</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Pre-Test</td>
<td>Pre-Test</td>
</tr>
<tr>
<td>N</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Mean MCQ Score</td>
<td>Pre-Test</td>
<td>Pre-Test</td>
</tr>
<tr>
<td>N</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Mean Number of Correct Responses (%)</td>
<td>Pre-Test</td>
<td>Pre-Test</td>
</tr>
<tr>
<td>N</td>
<td>18 (100%)</td>
<td>19 (85.7%)</td>
</tr>
</tbody>
</table>

Interim analysis, full data will be available by Oct 2019

SA-PO008
Internal Medicine Residents’ Perception of the Nephrology Specialty
Georges Nakhoul,1 Ali Mehdi,2 Jonathan J. Talerico,3 Andrei Brateanu,1 Amit Diwakar,2 Remy Daou,2 John R. Sedor,2 John F. O'Toole,2 Joseph V. Nally,2 S. beth Bierer,2 1Cleveland Clinic Foundation, Cleveland, OH; 2Cleveland Clinic, Mayfield Hts, OH; 3Glickman Urological and Kidney Institute, Cleveland, OH; 4Saint Joseph University, Beirut, Lebanon.

Background: Interest in nephrology as a specialty has been declining among US medical graduates. As a result, more than half of the fellowship programs remain unfilled. To better understand this phenomenon, we intended to qualitatively explore the nephrology perceptions among Internal Medicine (IM) residents and to identify factors influencing their choice of a subspecialty career.

Methods: A qualitative study was designed using the grounded theory methodology. Ten semi-structured interviews were conducted with randomly selected internal medicine residents (Postgraduate Year (PGY) 1 and 2) and 2 post- PGY residents. The questions were guided by the Professional Identity (PI) Formation Framework, which captures key elements of the socialization processes contributing to the development of the PI. Interviews were recorded and transcribed verbatim. Coding was performed by 2 independent reviewers who met to reach consensus on emerging themes. Data saturation was reached after the 8th interview. Decision to stop interviewing was made after the 10th interview.

Results: Several recurring themes emerged in our analysis (Table 1). The negative factor that recurred most commonly was the lack of exposure to nephrology rotations both in the clinical and pre-clinical years. This was mentioned by 9 out of 10 residents. Other frequently recurring themes were: patient population (mentioned by 5/10 residents), lack of innovation in the field (4/10) and inability to make a difference (4/10). Factors by influence residents’ decision included: breadth (5/10) and complexity of pathology (7/10) and perception of nephrology as a highly intellectual specialty (7/10).

Conclusions: Lack of exposure to nephrology rotations in preclinical and clinical years appears to be the most important factor dissuading residents from pursuing a career in nephrology.

Funding: Private Foundation Support

SA-PO009
Factors Influencing Residents Career Decision-Making
Georges Nakhoul,1 Ali Mehdi,2 Jonathan J. Talerico,3 Andrei Brateanu,1 Amit Diwakar,2 Remy Daou,2 John R. Sedor,2 Joseph V. Nally,2 John F. O'Toole,2 S. beth Bierer,2 1Cleveland Clinic Foundation, Cleveland, OH; 2Cleveland Clinic, Mayfield Hts, OH; 3Glickman Urological and Kidney Institute, Cleveland, OH; 4Saint Joseph University, Beirut, Lebanon.

Background: Interest in nephrology as a specialty has been declining among US medical graduates and more than half of the nephrology fellowship programs remain unfilled. To better understand this phenomenon, we aimed to identify factors influencing residents’ choice of a “subspecialty career”.

Methods: A qualitative study was designed using the grounded theory methodology. Ten semi-structured interviews were conducted with randomly selected internal medicine residents (Postgraduate Year (PGY) 1 and 2) and 2 post- PGY residents. The questions were guided by the Professional Identity (PI) Formation Framework, which captures key elements of the socialization processes contributing to the development of the PI. The residents’ answers were recorded and transcribed verbatim. Coding was performed by 2 independent reviewers who met to reach consensus on emerging themes. Data saturation was reached after the 8th interview. Decision to stop interviewing was made after the 10th interview.

Results: Several recurring themes emerged in our analysis and were classified into three general categories: personal attributes (personality, family tradition, experiences and values), social factors (Mentors, transformative events, exposure, quality of instruction, performance and autonomy) and specialty-specific factors (Field, lifestyle and job-related

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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SA-PO010

Jennifer B. Plotkin,1 Eric Jia Yi Xu,2 Derek M. Fine,2 Daphne H. Knicely,2 John Sperati,2 Stephen M. Sozio,3 Department of Medicine, UCLA, Los Angeles, CA; 4Division of Nephrology, Johns Hopkins University, Baltimore, MD.

Background: Johns Hopkins was early to adopt an in-house nephrology fellowship night float to improve work-life balance. The aim of our study was to elucidate attitudes about night float to guide fellowship structuring.

Methods: We conducted a mixed-methods study. We surveyed current fellows, program alumni, and current faculty and conducted a focus group of current fellows. Surveys were developed through literature review, queried on a 5-point Likert scale, and analyzed with unpaired t and ANOVA tests. The focus group transcript was iteratively analyzed by two independent reviewers to identify major themes.

Results: Survey response rates were 14 (100%) fellows, 32 (91%) alumni and 17 (94%) faculty. All groups felt quality of patient care was good to excellent with no significant differences among groups (mean (SD) range 4.12 (0.70) - 4.57 (0.65), p<0.12), but we found a statistically significantly more positive view on autonomy rated by fellows compared to faculty (4.57 (0.51) vs. 4.12 (0.33), p=0.006). Exploring the impact on the day team experience, fellows indicated a statistically significant improvement across domains (range 4.21 (0.80) - 4.64 (0.63), p<0.001 compared to neutral effect). Focus group themes included wellness, professional development, patient care, continuity of care, and structural components. Says one fellow, “…my bias is that every program would switch to a night float system if they could.” All groups were satisfied with night float with 4.71 (0.47), 4.18 (0.81) and 4.03 (0.86) for fellows, faculty, and alumni respectively; fellows were more enthusiastic (p=0.028). Overall, all three groups preferred night float; fellows did so unanimously.

Conclusions: Night float was well-liked by fellows and improved the experience of the daytime fellow. Alumni and faculty were also positive about night float; however, they were less enthusiastic than fellows possibly because alumni and faculty have concerns about career preparation. Implementation of night float at other nephrology programs should be considered.

SA-PO011

Non-Tunneled Hemodialysis Catheter Placement Experience and Perception of Graduating US Adult Nephrology Fellows
Hitesh H. Shah,1 Fatima Sheikh,2 Kenar D. Jhaveri,2 Zuckar School of Medicine at Hofstra/Northwell, Great Neck, NY; 3Northwell Health Sys, Great Neck, NY; 4Northwell, New Hyde Park, NY.

Background: Nephrology fellows are required to acquire skills and demonstrate competency in the placement of non-tunneled hemodialysis catheter (NT-HDC) during fellowship. To gain a greater insight in the NT-HDC placement experience and perception of US adult nephrology fellows, we carried out a national survey.

Methods: An on-line survey was created and sent to US adult nephrology fellows in May 2018. Data was further analyzed for fellows graduating in 2018.

Results: 254 fellows responded to our survey (31.4% response rate), 128 (50.4%) were graduating in 2018. Most NT-HDCs were placed in the hospital and 17.3% reported having a dedicated rotation for NT-HDC placement. 33.9% received simulation based training, 14.2% received bedside training, 20.5% received both simulation and bedside training, while 29.1% did not receive any formal training in NT-HDC placement. 45.3% did not receive any formal didactic session on NT-HDC placement during fellowship. Of the 128 graduating nephrology fellows (G-NFs), 27.3% had not placed any femoral NT-HDC during fellowship while 25.8% had placed ≥3 and 27.3% had placed ≥10. While 35.1% of G-NFs had placed ≥10 internal jugular NT-HDCs during fellowship, 21% had placed ≥3 and 23.4% had not placed none. 14.8% of G-NFs had not placed any NT-HDC. 41.4% of G-NFs needed to place at least 5 NT-HDCs before independently performing this procedure during fellowship, while 11.7% required ≥10. While 64.8% of the G-NFs reported having received adequate training in NT-HDC placement, only 37.5% planned to place NT-HDCs after graduation. Majority (57%) of G-NFs felt that nephrologists should not place NT-HDC in clinical practice. Reasons cited for those who had inadequate or no training in NT-HDC placement included: lack of opportunities to place NT-HDCs (53.9%), lack of formal training (41.4%), lack of nephrology faculty interest (42.97%) and expertise (32.8%).

Conclusions: While majority reported adequate training in NT-HDC placement, a significant percentage of graduating fellows had not placed either a femoral or internal jugular NT-HDC or both during fellowship. Majority received simulation based training, however a significant percentage did not receive any didactic session or formal training in NT-HDC placement during fellowship. Fellowship programs should take measures to ensure that all fellows receive adequate training in NT-HDC placement.

SA-PO002

A Program of Renal Biopsy Training Using Low-Cost Realistic Models
Guilherme P. Santa Catharina, Igor Smolentzov, Roberto Zatz, Lecticia Jorge. Univ of Sao Paulo, Sao Paulo, Brazil.

Background: Renal biopsy is a necessary procedure in Nephrology practice, but adequate training is necessary to minimize its inherent risks.

Methods: We developed a method for the training of residents and professional nephrologists in percutaneous renal biopsy, utilizing homemade simulators that imitate a lumbar torso and contain a dummy kidney made of colored forensic gelatin. The “kidneys” exhibit realistic physical appearance, consistency and ultrasound properties, yielding equally real looking fragments when “biopsied”. The models were manufactured locally with a cost of less than 20 USD.

Results: Two workshops were carried out involving 61 nephrologists and Nephrology residents. The procedure consisted of the presentation of archived glomerulopathy cases, followed by an explanation of the biopsy procedure, after which hands-on ultrasound guided training of “kidney” fragments (Figure), available to all participants, was performed. Afterwards, the possible complications, and the measures to avoid or limit them, were discussed. As a final step, the “results” were presented and discussed in the form of digitized renal slides corresponding to each case studied, along with the response to treatment and outcomes. When invited to evaluate the course, 98% of the respondents declared that they would recommend the course to others, whereas 100% considered the workshop “excellent” or “very good”, and 92% assigned these same attributes to the hands-on training procedure. This method is currently being applied in the training of Nephrology Residents in our Division.

Conclusions: The use of these inexpensive dummies is a useful and well-received tool that can improve the efficiency of training in renal biopsy and increase the safety of the procedure.

Funding: Government Support - Non-U.S.
Willfulness of nephrologists to allow patients to be approached for research kidney biopsies. Results are reported as mean (SD) on a 1 through 5 scale (higher number suggests higher likelihood)

<table>
<thead>
<tr>
<th>Item</th>
<th>Primary care clinic (n=17)</th>
<th>Primary research (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserve a portion of an upcoming care day</td>
<td>4.7 (0.8)</td>
<td>4.7 (0.29)</td>
<td>0.74</td>
</tr>
<tr>
<td>Perform extra pass to obtain a research core</td>
<td>3.3 (1.4)</td>
<td>3.3 (1.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>ASK with clinical approval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected ALN from solid Rx vs. ATN from hypertension</td>
<td>2.9 (1.2)</td>
<td>3.6 (0.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Suspected CTS vs. after-postScript cardiac catheterization</td>
<td>2.9 (1.2)</td>
<td>3.2 (0.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>Suspected ATN vs. ALN post cardiac surgery</td>
<td>2.9 (1.3)</td>
<td>3.4 (0.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>ASK without clinical indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical diagnosis of ALN from solid Rx</td>
<td>2.1 (0.8)</td>
<td>3.1 (1.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Suspected CIN post cardiac catheterization</td>
<td>2.1 (1.0)</td>
<td>2.6 (1.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Suspected ATN post cardiac surgery</td>
<td>1.9 (0.8)</td>
<td>2.6 (0.9)</td>
<td>0.09</td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non proteinuric CKD stage 5</td>
<td>2.4 (1.1)</td>
<td>3.2 (0.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>CKD stage 1 susceptible to be due to diabetes</td>
<td>2.5 (1.2)</td>
<td>3.3 (1.2)</td>
<td>0.01</td>
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<tr>
<td>Average score</td>
<td>2.5 (1.6)</td>
<td>3.5 (0.6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

SA-PO014

Association of Nephrology Inpatient Service Size on Medication Safety Recommendations
Huwen Chen,1 Syeda B. Ahmad,1 James R. Johnston,1 Ranil N. DeSilva.2
1University of Pittsburgh Medical Center, Pittsburgh, PA; 2University of Pittsburgh, Pittsburgh, PA; 3University of Pittsburgh School of Medicine, Pittsburgh, PA.

Method: Retrospective chart review of general nephrology consults placed from Jan 1st 2018 to Dec 31st 2018. Daily service size and physician work schedules were reviewed with distribution analyzed. High patient census defined as greater than 40 (top 10%), low patient census defined as less than 26 (bottom 10%). Four types of renal related medications were assessed: electrolyte related, antibiotics related, nephrotoxic agents and central nervous system related. Medication errors were expressed as percentage and compared using independent sample t-test.

Results: 11.2% of the medication errors were experienced by our patients during the high census vs 19.4% during the low census days. P = 0.025. Potential confounders include: higher census days were more prevalent in the winter months, and more experienced fellows and house staff worked during the winter months. Also there was low awareness of nephrologists responsibility to commend of renal dosed medication as standard consult recommendations amongst nephrology fellows.

Conclusions: The number of overloaded medication errors did not differ based on renal service size. However, patients experienced greater than 10% of the medication errors in 2018. A pharmacist might be needed in the nephrology consult service to reduce the errors of renally excerted medication experienced by our patients. Awareness of nephrologists’ role in medication safety recommendation shall be heightened by nephrology training programs.

SA-PO013

Exploring Nephrologists’ Attitudes Towards Kidney Biopsies for Research
Afolarin A. Amodu,1 Gearoid M. McMahon,2 Ragnar Palsson,3 Suraj Sarvode Mothi,1 Sushrut S. Walkar1 (Brigham and Women’s/ Massachusetts General Hospital, Boston, MA; 2Brigham and Women’s Hospital, Brookline, MA; 3Harvard, Belmont, MA; 4Brigham and Women’s, Boston, MA; 5Harvard Medical School, Boston, MA).

Method: We sent an IRB-approved, anonymous, online survey to 98 nephrologists at three Boston academic hospitals. Participants were asked about their clinical experience, their perception of the risk of kidney biopsies, and the likelihood that they would support biopsies being obtained from their patients for research purposes. We scored responses using a Likert Scale (1 = “absolutely not”; 5 = “definitely yes”). We compared scores using independent sample t-test.

Results: Response rate was 58%. The Table shows mean scores according to whether nephrologists were primarily clinicians (n=12) or clinician-researchers (n=43). There were no differences between the respondents’ assessment of renal biopsy risk when comparing researchers vs. clinicians or stratifying by years of experience or number of nephrology consultations. However, there were statistically significant differences when comparing researchers vs. clinicians when considering the likelihood that they would support biopsies.

Conclusions: Substantial variability exists among nephrologists regarding the indications for kidney biopsy and their comfort with kidney biopsies for research purposes.

Funding: Other NIH Support - T32
09:00, though a second mode arose between 15:00 and 16:00 (Figure 2). The frequency of consultation was not different between the 4 consult services. Limitations include subjectivity and interrater variability in RFC categorization, and inability to capture consult requests that were not submitted electronically.

**Conclusions:** We identified the timing and type of consults requested over a 12-month period. Our hope is to identify consultation patterns that place workload strain on the available nephrology staff. From that, we seek to undertake quality improvement initiatives to alter these patterns in order to maximize the quality of care rendered by our limited workforce.

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**SA-PO016**

The Impact of the Electronic Medical Record (EMR) on Nephrology Fellowship Training

Christina M. Yuan,1 Dustin J. Little,1 Rajeev Raghavan,2 Robert Nee.1

1Nephrology Education Research and Development Consortium (NERDC)

2Walter Reed National Military Medical Center, Laurel, MD; 3Baylor College of Medicine, Houston, TX; 4AstraZeneca, Gaithersburg, MD.

**Background:** A potential unintended consequence of EMR use is the impact on physician training. We surveyed U.S. Nephrology fellows to assess perceived burdens and benefits of the EMR on fellow education.

**Methods:** Using the ACGME 2018-2019 public list of nephrology programs, we contacted 148 program directors (PDs) by email requesting completion of an anonymous on-line survey on EMR impact on fellow education. PDs were asked to forward an anonymous survey link to their clinical fellows, and indicate to how many they forwarded the link. Surveys were open for 2 months, with reminders sent to PDs every 2 weeks.

**Results:** PD response rate was 34% (51/148 programs). 22% (33 PDs) forwarded the link to their fellows (n=216; 26% of U.S. nephrology fellows). Median fellows/program was 6 (range 2-280). 72 fellows (33%) responded. 39 were 1st year; 33 were 2nd/3rd year fellows. 42% indicated that their institution’s EMR functionality was “slowed, disrupted, or completely lost” monthly or more. 51% of fellows agreed/strongly agreed that the EMR contributed positively to their education. The 3 most frequently cited positive effects were: access to EMR from home/mobile device (81%); efficient laboratory result communication (74%); and almost all were first or second year fellows. Over 75% reported no or limited (1-2 times) teaching in how to define CC, identify who would benefit from CC, and use a values-based communication framework for treatment decisions for CC or time-limited trial (TLT). Using a 5-point Likert scale, most fellows felt ‘not very’ or ‘somewhat’ prepared to use a communication framework for treatment decisions for CC or TLT. Almost all fellows who completed the curriculum (46 at time of submission) felt ‘very’ and ‘extremely’ prepared to do the following: define conservative care; identify patients who will do poorly on dialysis; how to respond when a patient is emotional; and how to incorporate values-based communication framework for CC and TLT. Almost all fellows were ‘very’ to ‘extremely’ satisfied with the curriculum.

**Conclusions:** Fellows report little to no preparedness in CC or how to discuss CC with patients. An online conservative care curriculum led to increased perceived preparedness in core CC skills. Future research can track CC curriculum impact on patient outcomes and treatment decisions.

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**SA-PO017**

Evaluation of an Online Conservative Care Curriculum for Nephrology Fellows

Jane O. Schell,1 Alexandra E. Bursic,1 Emily Chan,1 Robert A. Cohen.2

1University of Pittsburgh Medical Center, Pittsburgh, PA; 2Beth Israel Deaconess Medical Center, Boston, MA.

**Background:** Older patients with advanced kidney disease experience increased mortality and morbidity despite life prolonging treatments such as dialysis. Conservative care (CC) without dialysis may provide better symptom management and quality of life. Yet nephrologists rarely offer CC, and most patients initiate dialysis without knowing about CC as a treatment option. We developed an online CC curriculum for nephrology fellows to increase knowledge and preparedness in CC skills.

**Methods:** ACGME accredited nephrology programs were invited to participate in the curriculum and designate a nephrology educator to serve as local champion of the curriculum. Participating programs received the multimodal curriculum including: 1) four online content modules; 2) online communication skills demonstrations; 3) worksheet activities; and 4) a post-curriculum session at each participating program facilitated by local champion to augment the online learning. Using REDCap data management, pre- and post- surveys measured fellow experience, preparedness, and knowledge in CC before and after undergoing the curriculum.

**Results:** Nineteen nephrology programs participated in the online CC curriculum. 150 of 176 participating fellows (85%) completed the CC pre-survey. Fifty-nine (49%) of fellows were female and almost all were first or second year fellows. Over 75% reported no or limited (1-2 times) teaching in how to define CC, identify who would benefit from CC, and use a values-based communication framework for treatment decisions for CC or TLT. Almost all fellows who completed the curriculum (46 at time of submission) felt ‘very’ and ‘extremely’ prepared to do the following: define conservative care; identify patients who will do poorly on dialysis; how to respond when a patient is emotional; and how to incorporate values-based communication framework for CC and TLT. Almost all fellows were ‘very’ to ‘extremely’ satisfied with the curriculum.

**Conclusions:** Fellows report little to no preparedness in CC or how to discuss CC with patients. An online conservative care curriculum led to increased perceived preparedness in core CC skills. Future research can track CC curriculum impact on patient outcomes and treatment decisions.

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**SA-PO018**

Teaching Renal Physiology and Pathophysiology to Second- and Third-Year Medical Students by Combining Lecturing and Hands-on Computer Simulation

Roberto Zatz,1 Luis C. Arcon, Antonio C. Seguro, Rosa M. Moyes, Giovana C. Boer, Patricia Z. Tempski. Univ de Sao Paulo, Sao Paulo, Brazil.

**Background:** Teaching of Renal Physiology and Pathophysiology (RPP) is one of the most challenging tasks in medical training, given the complexity of concepts and the number of interacting variables.

**Methods:** We devised a method to teach RPP to second and third-year medical students, consisting of one-hour lectures, followed by one-hour hands-on computer simulation during which students utilize mathematical models that we developed in Visual Basic® and Delphi®, presented through a friendly graphic interface (example in figure). Complex events such as glomerular ultrafiltration and acid-base disorders are simulated by changing variables through ordinary tools such as scrolling bars and sliding arrows. In a final step, students undergo a quick exam consisting of multiple-choice tests, which are discussed afterwards. At the end of each class, students are invited to fill in a self evaluation form about their perception as to whether preestablished learning outcomes were achieved.

**Results:** Evaluation made by third-year students in 2018/19 showed a high degree of perceived learning, with 79.1% reporting complete, and 18.5% partial, goal fulfillment in subjects such as Dehydration, Acute Kidney Injury, Chronic Kidney Disease and Acid-Base Disorders. In a more objective evaluation, 92 students who attended computer simulation scored 7.8±0.2 SE (on a 0−10 scale) in a test involving the pathophysiology of Edema and Hypertension, as compared to 7.1±0.1 obtained by 87 who just watched the presentation of a computer model (p=0.05).

**Conclusions:** These observations indicate that computer technology associated with classical methods can strongly improve the teaching of RPP, and confirm the concept that hands-on activity can be a more efficient learning method than passive transmission of knowledge.

**Funding:** Government Support - Non-U.S.
Acid-base equilibrium: dynamic Davenport nomogram.

SA-PO019
Application of a Virtual Patient (VP) Program in a Medical School Nephrology Curriculum
Georges Nakhol,1 Jonathan J. Taliereco,2 Shreya Louis,3 Raoul Wadhwa,3 Cecile M. Foshee,3 S. beth Bierer,3 Neil Mehta,4 Michael Lioudis,3 Joseph V. Nally.3 1Cleveland Clinic Foundation, Cleveland, OH; 2Glickman Urological and Kidney Institute, Cleveland, OH; 3Cleveland Clinic, Cleveland Heights, OH; 4Cleveland Clinic Lerner College of Medicine, Cleveland, OH.

Background: Immersive simulations have been shown to motivate students and promote learning in a fun and safe environment. Body Interact (BI) is among the most successful VP programs and has been used as a teaching adjunct by medical schools in the United States and Europe.

Methods: We identified 2 nephrology cases that would be appropriate for virtual simulation. We solicited the help of experts in order to build them in a VP platform. The VP cases were piloted then used during class in groups of 8 students accompanied by 1 teaching faculty. The VP allows direct interaction with the students including history gathering, physical examination, testing and live reaction to proposed treatments. At the end of each class, students were asked to fill a survey/feedback form that consisted of a 4-point Likert scale questionnaire rating student agreement [(SA) strongly agree, (A) agree, (D) Disagree and (SD) Strongly Disagree]. The questionnaire focused on 6 parameters: program interface, user engagement, perceived educational value, likability, need for improvement and interest in dissemination.

Results: All 32 CCLCM students used the VP platform for the 2 designed cases. The survey response rate was 73%. Ninety two percent of answers related to the program interface fell into positive categories (55% A and 37% SA). 90% of answers related to user engagement fell into positive categories (50% A and 40% SA). 85% of answers related to educational value fell into positive categories (55% A and 30% SA). 90% of answers related to the likability/need for improvement fell into positive categories (61% A and 29% SA) and 90% of answers related to the interest in dissemination fell into positive categories (60% A and 30% SA). Despite generally favorable feedback by the students, 68% thought that the program could be improved. Most of the desired improvements related to the speed of the program and to the presence of technical glitches on library computers.

Conclusions: We successfully incorporated a VP platform into the nephrology educational curriculum. The BI program was well received and was found to be a useful educational adjunct. Our experience taught us that the use of gaming engines may require considerable computer processing power and this will need to be taken into account in future virtual endeavors.

SA-PO020
The Renal Biopsy Trainer: A Cheaper and More Practical Approach to Procedure Simulation
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Background: Current kidney biopsy simulators are scarcely available, expensive and hard to maintain. We developed a Renal Biopsy Trainer (RBT) based on 3D printing technology. This RBT is a life-size recreation of the abdominal cavity, kidney and lumbar region with use of 3D volume visualization of CT images of the abdomen. From the CT the kidney was reconstructed and ported into a CAD program and to create a mold. Silicone molds of the various anatomical structures (e.g. cortex, medulla, calices) were printed so that these structures can be visually distinguished upon inspection.

Results: We created a life-size RBT at a cost of $20. It allows more than 20 passes. The replacement parts (lower pole of the kidney) cost less than $10. The RBT is ultrasound compatible and allows real-time performance of the kidney biopsy. The varied density of each layer allows the operator to “feel” when penetrating the cortex. The color coded sections of the kidney permits immediate feedback about the section from which the biopsy was obtained.

Conclusions: In contrast to commercially available simulators, which are prohibitively expensive, and their use is limited to only a few large medical education centers with a high cost of operation. The RBT is a practical and cheap introductory tool to teach both the anatomy of the kidney and the performance of a renal biopsy with all its intricacies. It can be easily located in the trainees’ room for practicing frequently and gaining confidence in performing this critical procedure in Nephrology training.

SA-PO021
NephroPro v2: A New Smartphone App for Medical Students and Residents
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Background: There has been a marked decline in applicants to US Nephrology programs. According to some studies, one-third of the medical residents would have considered Nephrology as a career path if topics would have been explained in a manner that facilitated improved understanding.

Methods: We formed a committee of IM residents and Nephrology faculty at Saint Louis University and the University of Pittsburgh Medical Center with the aim to design an educational tool that would help trainees to engage in nephrology. A list of high yield topics was created and ranked. Selection criteria included relevance for medical education and complexity. We then generated short case-scenarios based on real-world problems. Questions were added to help solidify the educational points.

Results: We created NephroPro, an interactive app that includes medical scenarios designed around high yield knowledge useful for inpatient rounds, and shelf examinations. In the exploration of the case, students touch on relevant aspects of renal physiology/pathophysiology. An immediate feedback system helps to efficiently educate users on diagnostic tests/management. Each case has a set of 5 questions. Correct/incorrect alternatives are followed by a short explanation, summary tables/graphics. NephroPro was developed in partnership with professional developers and is available through Android/iPhone with no registration fee. The maintenance cost of the app is very low. New cases can be upload via our software (Mobincube). This app is not financially supported by any private or public institution.

Conclusions: NephroPro offers an innovative teaching tool to learn Nephrology. By expanding its use in the medical community, NephroPro could serve to generate a dynamic and fun environment to promote renal education.
SA-PO022
Role Play Simulation to Improve Empathy in Nephrology Trainees
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Background: Empathy enables one to identify with another’s situation, thoughts, or condition. Empathizing with patients is believed to enhance patient satisfaction & treatment adherence. Simulation is increasingly used to teach empathy to health professionals. Using a randomized controlled trial design we assessed whether role play simulation improves empathy in nephrology trainees (NT).

Methods: All NT at the University of Toronto were eligible to participate. Participants were randomized to either Intervention or Control. The intervention comprised participation in medication intake (7-day dosette with QID placebo pills) & a clinical encounter (either ½ day outpatient clinic (MCCK) or a mock dialysis visit. Both involved clinical assessment by a physician, dietician, social worker & pharmacist. Control group was not exposed to any interventions. Empathy was assessed using the questionnaire for empathy (Jefferson Scale of Empathy for Health Professionals – JSE) at baseline (JSEa), within 24h of interventions (JSEb), & again at 3 months (JSEc). A difference in empathy scores was analyzed, between JSEA & JSEb, and JSEa & JSEc, using the paired t-test.

Results: All 36 NT were approached, 29 consented & randomized (Intervention n=16; Control n=13). Participants were mostly male (69%) & aged 31-40 yrs. In the Intervention group, 16 completed all JSE questionnaires & medication intake, 5 completed a dialysis session, & 5 completed MCCK session. Incomplete questionnaires were given by 2 Control group NT. At baseline, no differences were found between Intervention & Control groups (JSEa 108 ± 14 & 113 ± 8 respectively, NS). An increase in empathy was seen in the intervention group, but not the control group (JSEb 117 ± 113, P=0.03, Fig 1). A trend to persistent improved scores was seen (115 ± 113, P=0.09 at JSEc).

Conclusions: This small study suggests that role play simulation can increase empathy in NT at least over the short term. Larger studies, with longer time period follow up are required.

SA-PO023
NephSim: An Innovative, Mobile-Friendly Nephrology Education Tool
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Background: The evolving landscape of technology in medicine has created the need for new approaches to medical education in nephrology. Free open-access medical education (FOAMed) tools provide educational growth at no cost to the user. NephSim is a FOAMed tool that teaches pathophysiology and diagnostic approach to interactive nephrology cases through history and physical, diagnostic tests, and pathology. Cases provide real-time, iterative feedback and allow users to learn from mistakes. Tutorials and infographics illustrate nephrology concepts. NephSim, recipient of the 2018 ASN Innovation in Kidney Education Award, was created as an innovative tool for educators and trainees.

Methods: Built in WordPress, new content is published on NephSim.com every 2-4 weeks and can be accessed using mobile devices or computers. HIPAA compliant, peer reviewed content is distributed via social media and an email subscriber list. To evaluate the scope, effectiveness, and reach of NephSim, we assessed the website demographics and experience. Usage via WordPress analytics and administered an anonymous survey to evaluate user feedback. To evaluate the scope, effectiveness, and reach of NephSim, we assessed the website demographics and experience. Usage via WordPress analytics and administered an anonymous survey to evaluate user feedback.

Results: To date, 31 cases have been published on NephSim (29% glomerular, 23% acid-base/electrolyte, 19% dialysis, 19% AKI/other, 6% transplant). 94,000 pageviews represent 100 countries. 17% (76445) of email subscribers completed the survey. Most users were between 31-45 years (52%). 32% of users were nephrology fellows, 25% nephrology attendings, 9% internal medicine residents, and 14% medical students. The majority of users agreed or somewhat agreed that they use NephSim for individual learning, teaching, or to teach others (75%). 96% agreed or somewhat agreed that NephSim was easy to use. Nearly all users either agreed or somewhat agreed that they enjoyed using NephSim (96%) and planned to continue using it in the future (99%). Anecdotally, NephSim has been used by educators to guide case-based lectures, teach medical students on nephrology electives, and foster independent learning for trainees at all levels.

Conclusions: NephSim has successfully deployed a mobile-friendly, case-based approach to teaching nephrology. In just 1 year, usage continues to grow with global participation. Feedback has been positive. We aim to incorporate NephSim in medical school, internal medicine, and nephrology training program curricula while diversifying content and contributors.

SA-PO024
CME Effectively Improves the Clinical Performance of Nephrologists, Nurses, and Nurse Practitioners Related to Comprehensive, Chronic Hyperkalemia Management
Amy Larkin,1 David R. Anderson,2 George Boutsalis.3

Background: Chronic hyperkalemia requires comprehensive management. We sought to determine if online continuing medical education (CME) could improve the clinical performance of nephrologists and nurses/nurse practitioners related to chronic management of hyperkalemia.

Methods: The CME activity was a 15-minute interactive case study with patient-physician vignettes featuring a patient with uncontrolled T2D, HF, and CKD for whom chronic hyperkalemia management was required. A repeated pairs pre/post-assessment study design was used and chi-square test (P <.05 is considered significant) assessed the difference in clinical performance of each activity. Cramer’s V was used to calculate the effect size (0.06-0.15 is a noticeable effect, 0.16-0.26 considerable, and >0.26 extensive). The activity launched September 21, 2018 and data were collected through November 30, 2018. Results: In total, 88 nephrologists and 1,504 nurses were included in the study. Upon presentation with acute hyperkalemia, more than 50% of nephrologists (P <.001; V=.442) and nurses (P <.001; V=.364) improved at recommending a low-potassium diet in addition to dose reduction of a potassium-lowering drug One month later, upon recognition of chronic potassium elevation, 36% of nephrologists (P <.001; V=.357) and 29% of nurses (P <.001; V=.214) improved at adding a potassium binding agent Three months post potassium binder initiation, patient returns with normal serum potassium levels, 42% of nephrologists (P <.001; V=.388) and 36% of nurses (P <.001; V=.370) improved at managing continued elevated blood pressure, 32% of nephrologists and 44% of nurses reported increased confidence in adding a potassium binding agent in a patients taking multiple drugs that can induce hyperkalemia Continued educational gaps: 36% of nephrologists and 53% of nurses failed to effectively manage the patients’ blood pressure 23% of nephrologists and 39% of nurses failed to initiate a potassium binding agent when indicated.

Conclusions: This study demonstrates the success of online, CME-accredited, interactive case study with patient-physician vignettes on significantly improving clinical performance of nephrologists and nurses related to chronic management of hyperkalemia. Continued gaps were identified for future educational targets.

Funding: Commercial Support - independent educational grant from AstraZeneca

SA-PO025
Online Quizzes Based on Nephrology Social Media Coverage: A Novel Enduring Educational Material
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Background: The ACGME defines an enduring educational material as one that can be repeatedly utilized for learning purposes. Social media education, however, poses a challenge in creating enduring materials. Learning from tweets is difficult because of a large number of tweets posted rapidly and poor Twitter search engine. A quiz employs active learning which helps develop critical thinking and enhances interest in knowledge acquisition. The ISNeducation team created online quizzes to package scientific tweets into a readily useable enduring educational material. This is a pilot study to evaluate them as a tool to disseminate knowledge and improve social media learning.

Methods: Each monthly quiz is untimed MCQ based learning activity, consisting of 10-20 questions. Questions are derived from the most informative tweets on a concept covered in a recent nephrology conference. Answers, scores, and global ranking are revealed in real-time. Each question also has an explanation with a link to the original supportive evidence-based tweet. Learner details and scores are recorded. The quizzes can be freely shared via a link on Twitter, Facebook, WhatsApp and the top scorers for each quiz are acknowledged at the end of the month.

Six quizzes were analyzed on the following topics: Glomerular diseases, AKI, Potassium disorders, Advances in membranous nephropathy, SGLT2 inhibitors, and WCN. Continued gaps were identified for future educational targets.

Funding: Commercial Support - independent educational grant from AstraZeneca
is a gender imbalance and the percentage of invitations that females receive from their male counterparts to join various online discussions, particularly during #KidneyWk remains low. Indeed cross-gender invitations (either M-F and F-M) are low and can promote “educational islands” where knowledge of female perspectives are not adequately represented. Having gender diversity in #SoMe would not only mean a high number of female educators tweeting, but an equal exchange of ideas between females and males.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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SA-PO030
Nephrology Fellow Performance on a Formative Peritoneal Dialysis Objective Structured Clinical Examination

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Background: Less than 10% of prevalent ESRD patients are treated with peritoneal dialysis (PD), and nephrology fellows may not have sufficient PD exposure to be comfortable with the procedure. We previously developed and initially validated a formative OSCE for assessing managing patients with PD-associated peritonitis (based on the International Society for Peritoneal Dialysis practice guideline). We now report the preliminary results of formative testing.

Methods: The OSCE test committee set the passing threshold at 16/22 points (Ebel’s method), with median relevance essential/important for all questions (content validity index 91%). Validators (16 board-certified practicing nephrologists) had a mean score of 19 (SD 2) points, with 94% passing. Cronbach’s alpha was 0.70. Score agreement between validators was very good (Kappa = 0.85). The OSCE is being prospectively administered by 19 U.S. nephrology fellowship programs. Fellows are anonymous, and have 1 hour to take the test (using local institutional order sets at the program director’s discretion).

Results: 9 programs have submitted OSCE results. 48 fellows were tested (25 1st year and 23 2nd year). Mean time to take the test was 34 (SD 8) minutes. Mean score was 17 (SD 3), with 71% passing. 19% correctly indicated the 3 diagnostic criteria for peritonitis (vs. 44% of validators); 72% recognized peritonitis-associated ultrafiltration failure (vs. 100% of validators); and 22% correctly prescribed a 21 day course of antibiotics for gram negative peritonitis (vs. 67% of validators). Sometime next year we propose the OSCE to included a didactic session on PD-associated peritonitis management.

Conclusions: The OSCE is an opportunity for program directors to assess local curriculum effectiveness, and for fellows to ascertain their familiarity with PD-associated peritonitis management practice guidelines. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or the US Government.

SA-PO031
A Novel Smartphone-Based Self-Management System for Hemodialysis Patients

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Background: Dialysis patients are commonly disengaged from hemodialysis their care. Evidence suggests that the care of patients with advanced CKD and ESRD does not optimize patient engagement. Lack of self-participation in dialysis care may worsen clinical outcomes and exacerbate and warns the need to educate and engage patients. In particular, patient engagement is essential to achieve optimal fluid balance and avoid excessive fluid intake. Increasing patient active participation in their dialysis care through a digital health application can potentially improve the clinical outcomes and patient satisfaction. Mobile app use among healthcare professionals is still limited. Smartphone apps are deemed “useful tools at the point of care and in mobile clinical communication,” as well as in remote patient monitoring and self-management of disease.” Utilization of digital health application in hemodialysis patients has not been explored yet. There is a lack of readily available and validated mobile apps for the HD population.

Methods: We performed 200 interviews with hemodialysis patients. Dedoose software was used for coding and conducting this qualitative research. Smartphone app (herein referred to as Kidney Tracker) was developed through feedback loops.

Results: The smartphone dialysis application proposed (Kidney Tracker) offers four main functions. The first function of the smartphone dialysis application is the dialysis tracking function. Data from the patient’s dialysis treatments is uniquely encrypted and can be migrated to the fluid tracking function. The second function of the smartphone dialysis application, the fluid, and activity-tracking page, features intuitive fluid tracking that streamlines the tracking process. The third function of the smartphone dialysis application, the game functionality, offers engaging challenges that use game-design concepts to keep the patient engaged. The fourth function of the dialysis application is the direct patient to care provider contact function.

Conclusions: This is an innovative project that specifically targets HD patients and resulted in developing a smartphone app for use in this patient population. This digital health technology can be a very helpful tool in the dialysis setting.

SA-PO032
Establishing Inpatient Dialysis Education Program Using an iPad

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Background: It is well known that providing chronic kidney disease education to patients will result in better planning for dialysis. However, there are patients who are admitted to hospitals with advanced kidney disease and require dialysis either during hospitalization or shortly after discharge. Many of these patients are started on hemodialysis (HD) rather than home dialysis despite dialysis modalities such as peritoneal dialysis (PD) and home hemodialysis (iHHD) offering better quality of life. To address this gap, we established a quality improvement initiative to educate hospitalized patients near dialysis about kidney disease and dialysis modalities. The primary aim is to improve the patient understanding of dialysis and chronic kidney disease. Secondary aim is to refine educational material and determine what dialysis modality patients chose in long term and if there is an increase in number of peritoneal dialysis patients.

Methods: Enrollment criteria was patients admitted to UPMC Magee-Women’s and Presbyterian-Monongie hospitals who are advanced CKD (stage 4/5) and planning to start dialysis on their admission or within several weeks of discharge as identified by nephrologist. The dialysis education was provided on iPad by a physician. Patient response to dialysis education was recorded using survey.

Results: The project was initiated in January 2019 with enrollment of 10 patients. The average age was 57.5 years and 70% female with 70% of patients having previously seen a nephrologist. The average time required for education was 45 minutes. Patient reported post education understanding of dialysis and kidney disease as 4.6 (scale of 1 to 5). Post education, 50% of patients were leaning towards home PD, 25% to in-center HD and 25% to in-center peritoneal dialysis. Secondary aim is to determine if there is an increase in number of peritoneal dialysis patients.

Conclusions: Our preliminary results show that providing education increases awareness of home dialysis modalities with 50% choosing to do so. Interestingly, majority of our patients had previously seen a nephrologist but had required re-education highlighting that CKD patients require significant re-education of their disease process. The patient response is overall positive (rating 4.6 out of 5). Results of a follow up survey to patients who did and did not receive education are pending and will help in determining the secondary aim. For future improvement, we aim to incorporate tele-health nurse and patient advocate as educators.

SA-PO033
Effect of an Audiovisual Educational Program on Nutritional Knowledge and Adherence to Dietary Treatment in CKD Patients Undergoing Hemodialysis

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Background: Multiple complications of advanced chronic kidney disease require specialized treatment and nutritional education. In Mexico, there are no formal education programs in hemodialysis (HD) that allow improving in that patient group’s knowledge. The aim of this study was to assess the effect of an audiovisual nutritional education program on the nutriological knowledge and adherence to dietary treatment in patients of different hemodialysis units.

Methods: Three videos, with dietary phosphorus, potassium and sodium topics, were created and projected during the HD sessions of all shifts during 9 weeks. Nutritional knowledge was measured with a questionnaire and adherence to diet was evaluated with a 3-day food record, before and after the educational intervention. Level of knowledge was measured according to the percentage of correct answers, being bad with <60%, regular between 60 and 79.9% and good > 80%.

Results: One hundred and thirty eight patients from both units were included. Average age was 38.9 ± 14.3 years. Nutritional knowledge changed significantly after the intervention from 30.4% to 66% for the bad level, from 57.2% to 30.4% for the regular level, while the level of adequate knowledge increased from 12.4% to 63%. Increase of knowledge was greater in potassium topic followed by phosphorus. After the intervention, the percentage of correct answers for sodium, potassium and phosphorus knowledge
were significantly higher; 75.5 ± 17 vs 87.6 ± 9.0 (p <0.001), 57.3 ± 20.4 vs 78.3 ± 12.8 (p = 0.001) and 64.4 ± 18.3 vs 81.9 ± 15.7 (p < 0.001). A significant correlation was found between educational level, dialysis vintage and nutritional knowledge; r = -0.41, p < 0.05 and r = -0.43, p < 0.05, respectively. Regardless of the increase in nutritional knowledge, no improvement in adherence to the dietary plan was found (Fig 1).

The audiovisual educational program had a positive impact on the nutritional knowledge of the patients, however nutritional education alone did not improve adherence to diet

SA-PO034
Respectful Engagement of Indigenous Peoples in a Pan-Canadian Kidney Research Network
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Background: Kidney disease has a disproportionate impact on the health of Indigenous communities in Canada. A national strategy to improve kidney health must include meaningful, culturally appropriate engagement with Indigenous peoples. Can-SOLVE CKD Network is a Pan-Canadian patient-oriented kidney research initiative that is working to improve the health of all Canadians and bring Indigenous ways of knowing into health research.

Methods: As part of the Can-SOLVE CKD Network, Indigenous patients, caregivers, researchers, and community leaders created an Indigenous Peoples’ Engagement and Research Council (IPERC). IPERC supports collaboration grounded in traditional values and partnerships with Indigenous peoples and communities. IPERC guides Can-SOLVE CKD research projects in respectful engagement of Indigenous communities. The network has a shared learning pathway, Wabishki Bichiko Skaanj (“White Horse” in Anishinabek), helping researchers and patient partners build respectful partnerships with Indigenous peoples in health research. Participants are encouraged to look, listen, learn, and lead their way along the pathway by examining racial identities, privileges, and biases, as well as participating in interactive learning exercises, facilitated online modules and webinars.

The Wabishki Bichiko Skaanj learning pathway includes a focus on Indigenous Elders in research. This training aims to create a culturally safe space for researchers, patients, and Elders to come together to gain understanding of a holistic context for scientific observations.

Results: Can-SOLVE CKD and IPERC has created a culturally safe space for Indigenous individuals to participate in all aspects of patient-oriented kidney research. Wabishki Bichiko Skaanj represents a novel learning platform for Indigenous cultural safety in Canadian health research. By enhancing knowledge, self-awareness and strengthening cultural competency, this learning pathway is enabling all partners in health research to close the gaps in kidney health outcomes between Indigenous and non-Indigenous communities.

Conclusions: The Can-SOLVE CKD Network offers a model for respectful engagement of Indigenous communities in health research. By adopting Indigenous ways and fostering cultural competency, kidney health outcomes and overall wellness for and with Indigenous peoples across Canada will be enhanced.

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SA-PO035
Patient and Caregiver Views on the Definitions and Impact of Terms Used to Describe Kidney Health
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Background: The terminology for kidney health is inconsistent, inaccessible, and may be conceptualized differently between patients and health professionals. These problems can impair the quality of communication, care and patient outcomes. As part of the Kidney Disease: Improving Global Outcomes (KDIGO) Nomenclature Initiative, we aimed to describe patient perspectives on the definitions and impact of terms for kidney health.

Methods: 54 patients and 13 caregivers from the United States, United Kingdom and Australia participated in 10 focus groups to discuss terms and concepts used for kidney health (e.g. kidney, renal, CKD, end-stage kidney disease, kidney failure, and descriptors and measures for kidney function i.e. CKD stages). Transcripts were analyzed thematically.

Results: We identified four themes: frustrated by ambiguity (with subthemes of: confused by medicalized language, lacking relevance to personal circumstances, baffled by precision in meaning, uncertainty of what can be controlled, opposed to obsolete terms); making sense of the prognostic enigma (conceptualizing level of kidney function, characterizing function based on symptoms and life impact, predicting progression and need for intervention); provoking and exacerbating undue trauma (fear of the unknown, denoting impending death, losing hope in having no treatment options, premature labeling and assumptions, judgment and failure of personhood); and mobilizing self-management (need to accept the harsh reality, prompting and motivating behavior change, learning medical terms for self-advocacy). (Fig 1)

Conclusions: The obscurity and imprecision of terms in CKD can be unduly distressing and traumatic for patients. Consistent and meaningful patient-centered terminology may improve patient autonomy, satisfaction and outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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SA-PO036
Computational Fluid Dynamics Modeling (CFD) of Wall Strain in a Murine Glomerular Capillary Segment
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Background: Mechanical forces such as pressure and stress in the glomerular capillary tuft have been proposed to mediate hyperfiltration and podocyte injury and detachment, leading to irreversible glomerular disease. However, the actual forces imposed by blood flow in the tuft are incompletely defined. Simple tube models poorly capture the complex anatomy of the tuft. We undertook to model fluid flow through an actual capillary tuft to understand the feasibility of applying CFD to glomerular physiology.

Methods: Mouse kidneys were cut into 1 mm cubes and fixed with glutaraldehyde and prepared for electron microscopy with osmium. Tissue was mounted onto an aluminum cryo pin using cyaanoacrylate and all block surfaces trimmed. A gold coating was applied to the block to create a conductive surface. The block was placed in the Quanta 250 FEG/Hitachi 3-view system and a 4 x 41 field of view was imaged at an approximate pixel size of 10 nm and section thickness of 50 nm. MIMICS (Materialise, Ann Arbor, MI) image reconstruction software was used to create a 3D surface representation of the capillary segment. The flow through the capillary segment was then modeled using ANSYS-Fluent (ANSYS, Canonsburg, PA) software. Steady-state, laminar flow conditions were modeled and a pressure differential across the section was applied to provide the desired velocities within the capillary lumen. Estimates of desired fluid velocity in the capillary were drawn from 2-photon intravital microscopy experiments.

Results: The CFD solution predicted that blood flow shear stress, fluid streamlines, and wall strain along the glomerular capillary segment.

Conclusions: End-to-end estimation of physical forces at the glomerular capillary wall is possible by computational modeling of flow through structures imaged via serial block section EM. Further work is needed to capture unsteady flow and the influence of blood cells on local wall strain.

Funding: Clinical Revenue Support
and stored at -20°C. MatrigelMA was added to PA mixes designed to produce gels with expected stiffnesses of 4.5 kPa or 40 kPa. The elastic modulus was measured using an Electroforce 3100 mechanical analyzer.

**Results:** Gel stiffnesses were not significantly altered by the addition of up to 100 ug/ml of MatrigelMA. Immunoistochemical staining for laminin was highly uniform within and between gels. RTPEC/TER1 cells were found to attach exceptionally well when seeded on both soft and stiff gels containing 100-1000 ng/ml MatrigelMA. However, the cells tended to become round and detach from the soft gels after 6-8 days in culture, but persisted for several weeks on stiffer gels.

**Conclusions:** Extracellular basement membrane (Matrigel) was functionalized with methacrylic groups to facilitate crosslinking to polyacrylamide. The addition of 100 ng/ml to PA gels resulted in surfaces with the expected stiffnesses that promoted excellent attachment of RTPEC/TER1 cells. However, cells tend to detach from the softer gels. We are continuing to determine if this results from degradation of matrix or if this is due to a cellular response to soft matrix.

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SA-PO037

**Prolonged In Vivo Perfusion of a Re-Endothelialized Human-Scale Tissue Engineered Kidney Graft**

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**Background:** Advances are desperately needed to increase the supply of transplantable kidneys for the 100,000 patients on the waiting list. Whole organ engineering is one approach that holds tremendous promise and to date, the most successful approach utilizes perfusion decellularization to provide the ideal kidney extracellular matrix scaffold that maintains the organ’s native vasculature and architecture, and allows recellularization with human cells. A critical component and the focus of the current study is to demonstrate the ability to functionally revascularize clinically relevant whole kidney matrix with human endothelial cells and provide sustained in vivo perfusion following orthotopic implantation.

**Methods:** Kidneys recovered from adult pigs were decellularized via detergent perfusion through the vasculature. The porcine matrix was seeded with human umbilical vein endothelial cells (HUVECs) and cultured using a custom perfusion recellularization bioreactor until sufficient cellular coverage of the vasculature was obtained. Functional testing of the renal vascular bed was performed using an ex vivo porcine blood flow model. Re-endothelialized kidney grafts were transplanted orthotopically in a pig model and evaluated with angiography at days 3, 7, 10, and 14 days before explantation.

**Results:** A minimum glucose consumption rate of 20 mg/hr was determined to represent sufficient endothelialization to sustain continuous blood flow (>100 mL/min) ex vivo, and was predictive of early patency in orthotopic transplants. At 7 days after transplantation in pigs, 83.3% (n=5/6) pigs of grafts in surviving animals maintained renal perfusion during follow-up angiography. One kidney graft remained patent through post-operative day 14.

**Conclusions:** As 14 days is the longest reported continuous perfusion of a revascularized kidney graft to date, these results lay the foundation for the long-term success of human-scale recellularized kidney grafts and move the field closer to increasing the supply of transplantable kidneys.

**Funding:** Private Foundation Support

SA-PO038

**Tunable Stiffness Polyacrylamide Hydrogels with Functionalized Matrigel for Renal Tissue Culture**

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**Background:** Tunable stiffness polyacrylamide (PA) based hydrogels are commonly used for mechanotransduction studies. PA gels must be functionalyzed with protein for cell attachment. This is commonly accomplished using sulfo-SANPAH or acryl acid NHS ester to bind protein to the gel surface. However, these methods do not produce reliably uniform surface protein concentrations. In order to produce PA gels with highly reproducible surfaces, we modified methods used for producing methacrylated gelatin (GelMA), to produce methacrylated Matrigel. The “MatrigelMA” can be added into the polymerization mix prior to casting gels, where it is covalently linked to the gel network.

**Methods:** 5 ml of Matrigel (10 mg/ml) with phenol red, was mixed with 5 ml of ice cold 50mM HEPES pH 8.5 while stirring at 4°C. 25 ul of methacryl anhydride was added dropwise. 1N Sodium hydroxide was added as needed to maintain an alkaline pH. After 30 minutes, this was repeated with an additional 25 ul of methacryl anhydride. The reaction was continued overnight, then the mix was dialyzed against sterile deionized water for 5 days at 4°C, with daily changes of water. The resulting solution was aliquoted and stored at -20°C. MatrigelMA was added to PA mixes designed to produce gels with

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

SA-PO039

**A High-Throughput Oxygen Biosensing Platform for a Microfluidic In Vitro Kidney Models**

Samuel H. Kann,1,2 Hesham Azizgolshahi,2 Jonathan Coppeta,2 Xin Zhang,1 Else M. Vedula,2 Joseph L. Charest,2 Boston University, Boston, MA; 1Draper Laboratory, Cambridge, MA.

**Background:** Oxygen concentration and dynamics directly influence renal cell function in vivo. For example, low oxygen tension plays a significant role in both acute and chronic kidney disease. In addition, decreased cellular oxygen consumption in the kidney has been linked to mitochondrial and metabolic dysfunction. Therefore, monitoring oxygen levels within in vitro kidney models will enable more physiologically accurate oxygen conditions for the models and allow assessment of metabolic function for normal tissue or metabolic changes due to toxic insults, disease states, or therapy administration. Current microfluidic in vitro kidney models control flow to generate tissue with kidney-specific functions, however, such systems lack high-throughput oxygen sensing capability.

**Methods:** We integrated optical luminescence based oxygen sensors into a high-throughput microfluidic in vitro kidney model platform (PREDICT-96), previously developed at Draper, for real-time and non-destructive monitoring of dissolved oxygen in the tissue microenvironment. PREDICT-96 supports renal co-cultures under flow in a 96 tissue replicate device. The oxygen sensor probes, deposited in each microfluidic channel, are excited by red-light transmitted via a fiber optic cable resulting in near infrared emission with an oxygen dependent phase-shift. The O2 measurement system was adapted to a standard microscope stage. High-throughput readings are accomplished by programming the stage to align the optic fiber with each sensor probe and to cycle through all 96 devices.

**Results:** Oxygen consumption rates for co-cultured human renal proximal tubule epithelial (RPTEC) and human microvascular endothelial cells under flow and static conditions were quantified. A COMSOL-based computational model indicates the ability to regulate oxygen concentration via controlling flow of the PREDICT-96 pumps. In this way, oxygen levels will be characterized for varying in vitro model parameters, resulting in both physiologically accurate renal co-culture conditions of normal tissue and hypoxic or ischemic injury tissue.

**Conclusions:** The PREDICT-96 oxygen biosensing platform will enhance in vitro renal tissue function and provide a high-throughput respirometric platform for studying renal metabolic dynamics in response to nephrotic drugs or disease progression.

**Funding:** Other U.S. Government Support, Commercial Support - Draper Laboratory, Boston University

SA-PO040

**Screening of Drugs for Nephrotoxicity Using a Microfluidic Proximal Tubule on-a-Chip**

Leslie Donoghue,1 Palaniappan Sethu. University of Alabama at Birmingham, Birmingham, AL.

**Background:** Off target effects of pharmaceutical drugs account for approximately 20% of all patients diagnosed with acute renal failure. To avoid such scenarios and prevent drugs that have nephrotoxic effects from advancing past pre-clinical testing to late-stage clinical trials, it may be necessary to evaluate drug induced nephrotoxicity early during the drug discovery cycle to ensure safety and minimize costs associated with drug failure in late-stage clinical trials.

**Methods:** We engineered a scaffold that enables co-culture of human proximal tubule epithelial cells (RTPECs) with renal microvascular endothelial cells (MVECs) on either side of a porous polycarbonate membrane which enables cell-cell and soluble factor communication and facilitate reabsorption. The surface was coated with Collagen IV for cell attachment and approximately 1x10^6 cells of each RPTECs and MVECs were seeded on each side of the membrane. The device was then integrated into a microfluidic flow loop assembly to match physiological and biomechanical conditions associated with tubular flow and resorption to accurately recreate the proximal tubule.

**Results:** We evaluated the cells integrated within a flow loop to determine the effects of flow shear associated with tubular flow. Our results indicate that the cells can be grown to confluence and can be maintained in culture under fluid flow at physiological levels of shear (approximately 0.1 dynes/cm²). We used immunofluorescence to determine cellularity using phallidin for actin skeleton, LIVE/DEAD® for cell viability, and communication and facilitate reabsorption. The surface was coated with Collagen IV for cell attachment and approximately 1x10^6 cells of each RPTECs and MVECs were seeded on each side of the membrane. The device was then integrated into a microfluidic flow loop assembly to match physiological and biomechanical conditions associated with tubular flow and resorption to accurately recreate the proximal tubule.

**Results:** We evaluated the cells integrated within a flow loop to determine the effects of flow shear associated with tubular flow. Our results indicate that the cells can be grown to confluence and can be maintained in culture under fluid flow at physiological levels of shear (approximately 0.1 dynes/cm²). We used immunofluorescence to determine cellularity using phallidin for actin skeleton, LIVE/DEAD® for cell viability, and

**Funding:** Other NIH Support - NIBIB, Private Foundation Support
Conclusions: In this project, we were able to recreate the architecture of the proximal tubule using the bilayer scaffold within the microfluidic flow loop to reproduce the fluid flow associated with both tubular flow and resorption ensuring a physiologically accurate model of the tubule. This model was evaluated for cell viability, resorption and establishment of barrier function to further validate the physiological function. Finally, we expect to be able to reproduce effects of drugs known to have low, intermediate and high levels of toxicity using our model and will confirm that this model can be used for preclinical evaluation of new drugs.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO041

Culturing of Murine Podocytes via a 3D Suspension Culture System Using the Microcarrier

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Background: Cell culture in two dimensions has been well established in the worldwide for the past decades. However, the culture of cells in two dimensions is unable to representative of real cell environments, lack of predictivity to anatomy or physiology in vivo. Creating a third dimension for cell culture is clearly a better way of representing physiological relevant than 2D culture.

Methods: Murine podocytes were determined that stirred suspension bioreactors utilizing Cytodex-3 microcarrier beads represent a viable platform for the differentiation of podocytes. 1 gram microcarrier beads were loaded, an inoculation ratio of 2 x 10^7 cells per 1 gram beads, and discontinuous agitation in a medium with 10% serum resulted in high cell attachment efficiencies.

Results: At the end of incubation, the expression levels of nephrin and synaptopodin were examined after various microcarriers beads culture time periods. Compared to static tissue culture dishes, a bioreactor-based bioprocess requires fewer handling steps, lower operating cost of culture consumable, less differentiation time needed when compared to 2D culture.

Conclusions: stirred suspension bioreactors incorporating microcarrier technology represent a viable and more efficient platform than tissue culture flasks for the generation of differentiated podocytes in culture.

Funding: Government Support - Non-U.S.

SA-PO042

Protocol to Make Renal Tubuloids from Human Kidneys

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Background: Kidney organoids derived from human induced pluripotent stem (hiPS) cells can be used to simulate a response to drugs in human kidneys. We have developed an alternative way to make more homogeneous epithelial-like structures from kidney tissue derived from multiple patients over a short period of time.

Methods: Human primary epithelial cell cultures were obtained from the non-tumor kidney tissue removed from patients with renal cell carcinoma. Human renal cortex was diced and then digested with collagenase. Tubuloids were seeded on matrigel-coated plates with serum-free media containing epidermal growth factor. After passage, primary cells and immortalized LLC-PK1 cells, for comparison, were cultured on ultra-low attachment plates for several days. Then cells were transferred into media containing matrigel, hepatocyte growth factor, fibroblast growth factor-2 and 5% fetal bovine serum.

Results: Primary human renal tubular epithelial cells (hRTECs) tubuloids were generated from dissected patients’ kidneys using epithelial growth factor, serum-free media and matrigel. We have generated a library of hRTECs derived from 15 patients. hRTECs showed phenotypes reflecting age and renal function of each original patient, especially in growth rate and in β2XAX expression, a marker for DNA damage response. We also generated tubuloids using a 3D culture technique both with hRTECs and with LLC-PK1 cells. Tubuloids had polarized expression of cell surface markers, LTL, KIM-1 (apical) and Na-K-ATPase (basolateral).

Conclusions: We succeeded in making renal tubuloids using hRTECs derived from multiple patients. This strategy is potentially an excellent way to simulate pathological conditions and response of epithelial cells to toxins and therapeutic agents in a personalized fashion.

Funding: NIDDK Support
SA-PO045

Machine Learning and Glomerular Remodeling


Background: Glomerular hypertrophy is an early biomarker of ongoing renal disease and informs glomerulosclerosis and proteinuria. Using machine learning we trained a computer to first identify glomeruli and then measure glomerular dimensions.

Methods: The training set comprised 100 images (varying magnification) of hematoxylin-eosin (H-E) or periodic acid Schiff (PAS)-stained kidney tissue sourced from published literature. An open-source git-hub implementation of the mask region-convolutional neural network was used to generate a model and Keras HDF5 data used to identify, count, and measure areas of glomeruli present in the renal tissue on a Raspberry Pi 3 server. The test set comprised images (40X and 10X, n=16) of stained kidney tissue from rats sacrificed 14 days after puromycin aminonucleoside (167 mg/kg, intraperitoneal, n=3) administration, and a sham cohort of animals (n=3). Kidney sections comprising the test set had been stained with H-E or hematoxylin alone.

Results: The Raspberry Pi 3 machine was able to correctly identify glomeruli (A) while excluding non-glomerular structures in all test cases. Having correctly identified glomeruli, the machine was able to measure (B) glomerular area using a precalibrated tool. Results: While our decoded (simulated) glomeruli images lack detail, exploration of the image code space shows smooth interpolation between holdout images, verifying the continuity of the encoded data distribution. Figure 1 shows simulated samples between class I and IV DN glomeruli generated by our VAE. Despite having only 54 staged biopsies, an RNN model using our image codes for biopsy level DN class prediction predicts <1 class off with a mean square error of 0.971 and linear weighted Cohen’s kappa of 0.402 with 10-fold cross validation.

Conclusions: Further refinement of the VAE architecture is needed to produce sharp images, but current image codes are predictive of Tervaert DN class using supervised regression modeling. In the future, this promises powerful ways to incorporate unlabeled biological data to augment machine learning training sets of medical images.

Funding: NIDDK Support

SA-PO047

Analyzing the Influence of Glomerulus Structural Features Using Minimum Spanning Trees

Samuel P. Border,1 Kuang-Yu Jen,2 Sanjay Jain,3 Agnes B. Fogo,4 John E. Tomaszewski,1 Pinaki Sarder,1 SUNY Buffalo, Buffalo, NY; 2University of California, Davis, Sacramento, CA; 3Washington University School of Medicine, St. Louis, MO; 4Vanderbilt University Medical Center, Nashville, TN.

Background: Patients with Type 1 or Type 2 Diabetes mellitus are at an increased risk for extensive vascular dysfunction which leads to Diabetic Nephropathy (DN) in close to 40% of cases. Structural changes within the glomerulus resulting from the diabetic phenotype are used to classify glomeruli into different stages of DN. Using Minimum Spanning Trees (MST’s) we are able to quantitatively define these structural abnormalities and assess their contribution to DN stage of that glomerulus. We employed Bayesian Networks (BN) to visualize and assess the relationships between different MST features and the glomerulus’s DN stage.

Methods: We used stain deconvolution to isolate nuclear regions in 799 H&E stained glomerulus images. The centroids of glomerular nuclei were used as nodes to create a MST in Matlab. Features calculated from these MST’s quantified expansion, cellularity, and sclerosis. Using these features, a BN was generated in R using the Hill-Climbing structure learning method. The resulting network was thresholded so that only the most significant relationships were included.

Results: Graph features calculated from the glomerular MST had a significant influence on the DN Stage. From this network, we are able to generate conditional probability distributions for each of the feature values that can be used to predict the DN classification.

Conclusions: By analyzing glomeruli using MST’s we can improve robust measures of nuclear distribution and derive further information as to what biological factors contribute to DN progression. Incorporation of BN and other probabilistic graphical models in medicine allows for more informed diagnosis and research.

Funding: NIDDK Support

SA-PO046

Unsupervised Modeling of Glomeruli for Diabetic Nephropathy Staging in Renal Biopsies

Brendon Lomick,1 Brandon Ginley,1 Kuang-Yu Jen,2 Sanjay Jain,3 Pinaki Sarder.1 SUNY Buffalo, Buffalo, NY; 2University of California, Davis, Sacramento, CA; 3Washington University School of Medicine, St. Louis, MO.

Background: As biological science pushes for computational analysis, the success of deep learning has obliged its adoption. However, biological datasets are different from the well-annotated standardized data used to develop such algorithms. Due to availability of unlabeled biological data, we have tested a variational autoencoder (VAE) for unsupervised modeling of glomeruli images (without labels). We show that encoded features allow interpolation between image states and are predictive of biopsy-level Tervaert classing of diabetic nephropathy (DN).

Methods: A VAE was trained using 87k 256x256 PAS and H&E stained glomeruli images, segmented from whole-slide kidney biopsies. The VAE encodes the images into a code of 200 numbers able to be decoded back to the input image. This technique automatically clusters similar images together in the code space. To show the relevance of our trained VAE, we model Tervaert DN class for expert staged human biopsies using the image codes as sequential input for a recurrent neural network (RNN). Namely a network model which predicts DN class from sequential reading of glomeruli codes, similar to how experts read biopsies.

Results: While our decoded (simulated) glomeruli images lack detail, exploration of the image code space shows smooth interpolation between holdout images, verifying the continuity of the encoded data distribution. Figure 1 shows simulated samples between class I and IV DN glomeruli generated by our VAE. Despite having only 54 staged biopsies, an RNN model using our image codes for biopsy level DN class prediction predicts <1 class off with a mean square error of 0.971 and linear weighted Cohen’s kappa of 0.402 with 10-fold cross validation.

Conclusions: Further refinement of the VAE architecture is needed to produce sharp images, but current image codes are predictive of Tervaert DN class using supervised regression modeling. In the future, this promises powerful ways to incorporate unlabeled biological data to augment machine learning training sets of medical images.

Funding: NIDDK Support
Contribution of Glomerular Phenotype to Digital Classification of Diabetic Nephropathy
Brandon Ginley,1 Brendon Lutnick,1 Kuang-Yu Jen,2 Agnes B. Fogo,3 Sanjay Jain,4 Avi Z. Rosenberg,3 Vighnesh Walavalkar,4 John E. Tomaszewski,1 Giovanni maria Rossi,1 Pinaki Sarder,1 SUNY Buffalo, Buffalo, NY; University of California, Davis, Sacramento, CA. Vanderbilt University Medical Center, Nashville, TN; Washington University School of Medicine, St. Louis, MO; Johns Hopkins University, Baltimore, MD; UC San Francisco Medical Center, San Francisco, CA.

Background: Diabetic nephropathy (DN) is a leading cause of kidney disease; renal pathologists assess its pathology via visual interpretation of biopsied tissue in the form of a digitized whole slide image (WSI). Inter-rater agreement increases with consensus classifications like the Tervaert approach, but reproducibility could still be improved. Computing can unify interpretation of image structure. We engineered a complete start-to-finish glomerular detection and classification pipeline for digitized biopsies of DN. Further, we investigated the glomerular phenotypes and features that it relies on to make decisions.

Methods: We studied 54 patients. Glomeruli were detected from WSIs using our previously published method for WSI segmentation. Glomerular structure was condensed to a three-component system that facilitates detection in widely varying phenotypes. Handcrafted features (n = 232) were used to quantify glomerular structures. Glomerular features from a single biopsy were fed as a sequence to a recurrent neural network (RNN) which yields a continuous number representing Tervaert class. Glomeruli and features were dropped from the network one-by-one; the resultant shift in predicted class was used as a proxy to investigate how much each glomerulus and feature contributed to the overall output. We trained our method by taking one renal pathologist as ground truth, and used as a proxy to investigate how much each glomerulus and feature contributed to the overall output. We trained our method by taking one renal pathologist as ground truth, and compared its performance against two other renal pathologists.

Results: Digital classification agreed with the ground truth of two renal pathologists with ω = 0.68, 95% confidence interval (CI) [0.5, 0.86]. The other two renal pathologists agreed with the first with ω = 0.0002. Therefore, we explored how each feature contributed to the overall output. We trained our method by taking one renal pathologist as ground truth, and compared its performance against two other renal pathologists.

Conclusions: Our digital classification reaches agreement similar to renal pathologists and makes decisions intuitively. Digital quantification of renal tissue can enhance clinical workflow by improving precision used to describe disease state.

Funding: NIDDK Support

SA-PO048
Neutrophil Extracellular Trap (NET) Quantification in Lupus Nephritis Potentiates NETs as a Prognostic Biomarker
Brigama A. Santo,1 Brandon Ginley,1 Brendon Lutnick,1 Sanjay Jain,1 Braham Segal,4 John E. Tomaszewski,1 Pinaki Sarder,1 SUNY Buffalo, Buffalo, NY; University of California, Davis, Sacramento, CA; Roswell Park Comprehensive Cancer Center, Buffalo, NY.

Background: Lupus Nephritis (LN) is a major risk factor for morbidity and mortality in Systemic Lupus Erythematosus (SLE), with 10% of patients developing ESRD. LN classification, which involves pathologist visual scoring of active and chronic lesions in renal biopsies, is limited due to lesion complexity. NETs have been implicated in SLE as immunogenic structures which contribute to lesion manifestation. Glomerular NET density may function as a predictive biomarker in LN, defining active to chronic lesion transition. We have developed a whole slide image (WSI) NET segmentation pipeline which enables computation of NET glomerular density in renal biopsies.

Methods: LN biopsies (n = 21) were labeled according to accepted immunofluorescence (IF) NET staining protocols, post-stained with H&E, and imaged. Our WSI NET segmentation pipeline, as well as a convolutional neural network for glomerular boundary segmentation, were applied. NET regions were identified and lesions were hand annotated in glomerular images.

Results: A two-sample t-test confirmed that glomerular NET density, for all active and chronic lesion affected glomeruli, is significantly different with p = 0.0002. Therefore, NET glomerular density co-occurrence with active lesion manifestation is statistically significant.

Conclusions: Our pipeline enables evaluation of glomerular NET density as a prognostic biomarker of LN progression, which could improve the clinical interpretation and treatment of LN in SLE. This pipeline may be used to compute NET density in other diseases featuring NET effected tissues, thus potentiating NET density as a universal prognostic biomarker. In addition, NET quantification will enable implementation of supervised classification for classifying NET structures in histology WSIs.

Funding: NIDDK Support

SA-PO050
Measuring Nephron Endowment by Positron Emission Tomography
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Background: Nephron loss is a primary feature of kidney disease. Recent MRI tools using cationic ferritin (CF) offer a unique view of nephron mass in the intact kidney in vivo. We propose a novel contrast agent (RadioCF) based on CF for positron emission tomography (PET). Because RadioCF is detected in trace (<100 ug) doses in humans, RadioCF-PET may enable rapid translation of nephron endowment as a clinical marker.

Methods: Cationic ferritin was filled with Cu-64 created by cyclotron. Radiochemical purity was assessed by radio-TELC. 24 mice were anesthetized and administered intravenous injections of radioCF (n = 8), radioNF (uncationized native ferritin, n = 8), or Cu-64 alone (n = 8). Mice were injected with 50-80 µCi of radioCF. In four animals of each cohort, a single 3D image series was acquired post-injection.

Results: RadioCF accumulated specifically in the cortical glomeruli, while radioNF and Cu-64 did not. Binding of radioCF was confirmed by phosphorimaging. RadioCF and Cu-64 did not bind. Dynamic imaging and time-course from renal cortex showed continuous radioCF accumulation in cortex over 90 minutes compared to radioNF or Cu-64. Selective accumulation of RadioCF in cortex was confirmed by biodistribution.

Conclusions: RadioCF is a new, translatable molecular imaging tool. Because it binds selectively to the glomerulus, RadioCF accumulation should directly reflect the number of perfused nephrons.
SA-PO051
Renal PET/CT-Rubidium-82 (Rb-82) Is a Precise and Reliable Method for Determination of Renal Blood Flow (RBF)
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Background: Changes in RBF may play a pathophysiological role in hypertension and kidney disease; however, RBF determination in humans has proven difficult. In a previous study, we demonstrated that RHF estimation based on PET/CT and Rb-82 is feasible and established that RBF can be determined based on a single PET/CT-Rb-82 scan, thereby minimizing radiation exposure associated with the method. We also found an intra-assay coefficient of variation of approximately 5.5% for both kidneys which indicates that the method is precise. The aim of this study is to test the reliability of renal PET/CT-Rb-82 for RBF estimation.

Methods: Ten healthy subjects underwent three dynamic PET/CT-Rb-82 scans spread over two days. Rb-82 was given as bolus injections. On day 1, a single 8 min dynamic scan was performed. On day 2, an 8 min dynamic scan was performed before and after RBF was stimulated by a two-hour long infusion of an amino acid solution. Time activity curves of arterial activity and renal uptake were recorded, and a 3-tissue compartment model was used for Rb-82 renal clearance estimation using PMOD® software. The clearance constant K1 in the model represents RBF. The day-to-day variation was calculated as the difference between the unstimulated K1-values on day 1 and day 2. K1-values determined before and after RBF stimulation on day 2 were compared.

Results: The mean unstimulated K1 value was 1.80 ± 0.17 ml/min/g for the right kidney and 1.78 ± 0.19 ml/min/g for the left kidney. The mean stimulated K1 value was 1.97 ± 0.17 ml/min/g for the right kidney and 1.95 ± 0.19 ml/min/g for the left kidney. There was no significant difference between the right and the left kidney for either the unstimulated or the stimulated K1 values. The day-to-day variation was 5.2% for the right kidney and 5.3% for the left kidney. For both kidneys, K1-values determined after RBF stimulation were significantly higher than K1-values determined before stimulation.

Conclusions: The approximate 5% day-to-day variation was acceptably low. For both kidneys, a significant increase in RBF was detected after application of a well-documented RBF stimulus. In conclusion, our preliminary results indicate that renal PET/CT-Rb-82 is a precise and reliable method for RBF determination.

Funding: Government Support - Non-U.S.

SA-PO052
Diffusion-Weighted Magnetic Resonance Imaging (DWI) Correlates with Renal Injury in Patients with Renovascular Disease (RVD)
Christopher M. Ferguson,1 Alfonso Eirin,2 Abdellrhman Abumawaad,3 Kai Jiang,4 Ahmad F. Hedayat,1 Amir Lerman,1 Stephen C. Textor,2 Lilach O. Lerman,1 Mayo Clinic College of Medicine, Rochester, MN; Mayo Clinic, Rochester, MN; 3University of Mississippi Medical Center, Jackson, MS.

Background: There is pressing need to identify novel markers that can predict response to therapy in patients with RVD. DWI is a useful tool for the assessment of renal microstructure and DWI-derived apparent diffusion coefficient (ADC) reflects unobstructed water diffusion. We hypothesized that lower values of ADC (index of fibrosis) can be used as an index of renal injury and response to therapy.

Methods: ADC of renal hypoxia (R2*, blood oxygen level dependent-MRI) were measured before and after ASL performed in 20 patients (23 stenotic kidneys) with hemodynamically significant RVD under constant sodium intake. Patients were treated with medical therapy (n=9) or medical therapy plus renal revascularization (n=11; n=14 kidneys). Serum creatinine (Scr), eGFR (CKD-EPI), blood pressure (BP), and systemic levels of pro-inflammatory marker tumor necrosis factor (TNF-α) were measured at each time-point. Baseline ADC values were correlated with change in renal hypoxia and systolic BP (SBP), as well as TNF-α levels at 3 months.

Results: BP and Scr decreased and eGFR increased 3 months after therapy (Table), but renal hypoxia and TNF-α levels remained unchanged. Overall, ADC values increased 3 months after therapy (Fig. A), although not in medical therapy or renal revascularization considered separately. Baseline ADC values modestly and inversely correlated with changes in hypoxia and SBP, and with TNF-α levels at 3 months (Fig. B), but not with levels or changes in renal function.

Conclusions: Lower levels of ADC may potentially reflect kidney injury, but do not predict changes in renal injury after therapy over 3 months in patients with RVD. Future studies need to identify indices of renal recovery potential.

Funding: NIDDK Support, Other NIH Support - NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NIHBB): HL123160

SA-PO053
Detection of Acute Change in Renal Perfusion Using Arterial Spin Labeling MRI
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Background: Magnetic resonance imaging (MRI) with arterial spin labeling (ASL) is a noninvasive promising approach to measure renal blood flow without the use of contrast dyes. The purpose of this study was to evaluate change in renal perfusion following a physiological stress (Experiment 1), by ASL kidney perfusion measurements. We also compared the renal perfusion in 3 different study populations (healthy controls, C, patients with hypertension (HT) and chronic renal failure (CRF)) - Experiment 2).

Methods: MRI with ASL was performed with a 1.5 Tesla MRI (Magnetom Aera, Siemens Healthineers, Erlangen, Germany) using a FAIR True-FISP sequence. Cortical, medullary, and whole kidney parenchymal perfusion were determined separately. After initial MRI measurement in C and HT, the measurement was repeated after both feet were covered with 1 degree C ice packs, which trigger a systemic sympathetic activation leading to vasoconstriction (cold pressor test).

Results: The group of C subjects (11 males, aged 35.2 ± 12 years) was compared to HT (11 males, aged 39.2 ± 10.3 years) and CRF patients (8 males, 2 females, aged 68.3 ± 7.8 years). The renal perfusion of both kidneys in HT (309.5 ± 17.3 mL/100 g/min) and CRF patients (200.4 ± 29.0 mL/100 g/min) were significantly lower compared to C subjects (338.7 ± 30.0 mL/100 g/min, C vs. HT adjusted p=0.004, C vs. CRF- age and gender adjusted p<0.004). Renal perfusion was also significantly different between patients with HT and patients with CRF (age- and gender-adjusted p=0.047). In the first experiment blood pressure and heart rate increased significantly in response to the sympathetic trigger. Significant reduction in renal cortical perfusion also has been found. A trend has been noticed in the whole renal perfusion.

Conclusions: With Experiment 1, we could demonstrate that acute changes in renal blood flow could be detected using ASL-MRI. Experiment 2 documented that this technology is able to detect differences in renal perfusion between healthy subjects and diseased subjects by needing only few subjects per group. This offers an advantage in conducting clinical trials in humans compared to other technologies.

<table>
<thead>
<tr>
<th>Table 1: Characteristics of study patients</th>
<th>A: Immunohistochemical analysis in patients with RVD at baseline and 3 months after therapy B: ADC values correlated inversely with delta R2*, delta SBP, and TNAI values at 3 months.</th>
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<tbody>
<tr>
<td><strong>Baseline ADC</strong></td>
<td><strong>3 months after therapy</strong></td>
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<tr>
<td><strong>ADC (mL/min/g)</strong></td>
<td><strong>ADC (mL/min/g)</strong></td>
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<tr>
<td><strong>Whole kidney perfusion</strong></td>
<td><strong>Whole kidney perfusion</strong></td>
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<tr>
<td>324.1 ± 28.2</td>
<td>315.1 ± 27.8</td>
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<td><strong>Cortical perfusion</strong></td>
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<td>364.3 ± 41.5</td>
<td>370.3 ± 38.5</td>
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<td><strong>Medullary perfusion</strong></td>
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<td>301.1 ± 32.4</td>
<td>297.5 ± 32.1</td>
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Fluid Dynamics Analysis by CT Imaging Technique of Hollow Fiber Dialyzer with Medium Cut-Off Membrane

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Background: Inadequate removal of molecules between 5and50kDa, due to their restriction in diffusibility, may cause long-term complication in chronic hemodialysis patients. Medium Cut-off(MCO) is a new class of membranes with enhanced sieving properties and negligible albumin loss, thanks to its high molecular weight(MW) retention onset and MW cut-off value lower than albumin MW. MCO membrane used in HD allows to perform expanded hemodialysis (HDx), a technique based on high internal filtration(IF). Our previous study quantified the IF of Theranova dialyzer leveraging a nuclear imaging technique. In order to characterize the local distribution of the IF, an in vitro study assessing the fluid dynamics inside Theranova dialyzer was conducted through CT imaging technique.

Methods: Dialyzer Theranova400(Baxter, Deerfield, USA) was placed in vertical position in the CT gantry. Blood and dialysate compartments were analyzed separately. Dye solution was circulated through blood compartment at 300ml/min and through dialysate one at 500ml/min. Longitudinal sections, 0.5cm thick, were recorded for 60seconds.

Results: In blood compartment, dye solution immediately after its entrance in the dialyzer demonstrates homogeneous progression, while different velocity profiles were observed among the fibers proceeding to the outlet port(Fig a). In dialysate compartment, dye solution is distributed in the periphery first(Fig d), then seeps in the fibers bundle and reaches the complete compartment filling.

Conclusions: The homogeneous dye profile immediately after its entrance in blood compartment demonstrated a good design of the inlet port; the optimal dye distribution in the periphery first (Fig d), then seeps in the fibers bundle and reaches the complete compartment filling. Different velocity profiles were observed among the fibers proceeding to the outlet port, allowing to perform expanded hemodialysis (HDx), a technique based on high internal filtration(IF).

Poster, Saturday

SA-PO054

Feasibility and Effectiveness of 6-Week Planter Electrical Stimulation Therapy During Routine Hemodialysis Sessions to Improve Gait and Balance: A Randomized Controlled Trial

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Background: Poor gait and balance are serious problems for people with diabetes undergoing hemodialysis (HD). These patients visit their clinic three times weekly to receive HD which provides an optimal opportunity for intervention. This study aims to examine the feasibility and effectiveness of plantar electrical stimulation therapy (PEST) during routine HD sessions to improve gait and balance.

Methods: Twenty-six participants with diabetes receiving HD were recruited and randomized into an intervention group (IG: n=13, age=59.5±10.4 years, BMI=29.7±6.0kg/m², female=39%) or a control group (CG: n=13, age=63.2±6.1 years, BMI=30.9±6.0kg/m², female=54%). The IG received 1-hour PEST during routine HD process (3 sessions/week) for 12 weeks. The CG was provided with an identical but non-functional device for the same period. Participants were blinded to the group allocation. Gait and balance were examined at baseline, midline (6-week), and conclusion of the program. This study however focused on changes in gait and balance at 6-week.

Results: All participants in the IG tolerated the PEST and completed all sessions of the therapy indicating the feasibility. None of the gait or balance parameter showed noticeable differences in the CG group (p>0.050). However, improvement trends were observed in the IG with the largest effect observed in double support for gait parameters (13% improvement, Cohen’s effect size d=0.66) and eyes-open center of mass sway for balance parameters (27% improvement, d=0.31).

Conclusions: This pilot study provides earlier results on the feasibility and effectiveness of PEST during routine hemodialysis. The study is still ongoing and is expected to recruit 100 eligible participants for sufficient power. If results can hold in a larger sample size, it may recommend the use of routine plantar electrical stimulation therapy to improve mobility and potentially prevent falls in this highly vulnerable population, who are highly prevalent with frailty, depression, and falls caused by decline in motor function associated with hemodialysis.

Funding: Government Support - Non-U.S.

SA-PO056

Size and Charge Effects of Nanoparticles for Renal Targeting in Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by renal cyst formation and leads to ESRD. Tolcavaptan, the only FDA approved treatment for ADPKD, has low bioavailability and results in non-specific uptake and liver toxicity. Our group has recently developed a novel nanoparticle system based on peptide amphiphile micelles (PAM) with the kidney-targeting peptide, (KKEEE)3K (K3) (Wischnjow, 2016 and Wang, 2018). To improve the nanoparticle targeting efficiency, we incorporated and tested a variety of peptide sequences: (EEKKK)3E (E3), (KKEEE)2K (K2), (EEKKK),E (E2), (KKEEE),E (K1), and (EEKKK),E (E1). K2, E2, K1, and E1 are shorter amino acid sequences that result in smaller nanoparticles to cross the filtration barrier easily and E3, E2, and E1 are positively-charged sequences to allow for binding to the negatively-charged glomerular basement membrane.

Methods: All peptides were synthesized on an automated peptide synthesizer, conjugated to DSPE-PEG2000, and purified and characterized by HPLC and mass spectrometry. Size and charge of nanoparticles were measured by dynamic light scattering and zeta potential. The in vivo renal targeting ability of Cy7-labeled nanoparticles was assessed by tail vein injection of kidney-targeting PAMs, non-targeting PAMs, or PBS in C57BL/6 mice models. Organs were excised and imaged for Cy7 and the fluorescence signal was quantified using the AMI imaging system.

Results: K3 micelles had the largest diameter of 15.4 nm with a negative charge of -17.04 mV, while E1 had the smallest size of 10.6 nm with a near-neutral charge of 0.1 mV. Ex vivo imaging results demonstrated all micelles accumulated in the kidneys to a greater extent than other organs, and K3 and E3 demonstrated the highest uptake indicating the feasibility. None of the gait or balance parameter showed noticeable differences in the CG group (p>0.050). However, improvement trends were observed in the IG with the largest effect observed in double support for gait parameters (13% improvement, Cohen’s effect size d=0.66) and eyes-open center of mass sway for balance parameters (27% improvement, d=0.31).

Conclusions: Our approach demonstrated that our library of kidney-targeting PAMs can accumulate in the kidney. Future studies will further optimize charge and size to understand nanoparticle structure-function relationships in the context of kidney uptake.

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SA-PO057

Next-Generation Renal Replacement Therapies (RRT): How Do Patients Weigh the Risks and Benefits?

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Background: Device developers are increasingly asking patients for input on product developments, and the FDA now uses patients’ risk/benefit preferences in approving new devices. Implantable/wearable devices under development may revolutionize patient lives by providing more frequent/prolonged RRT, releasing them from in-center/home dialysis (ICHFD). Our objective was to determine key risk/benefit considerations that would drive ERSD patient choices.

Methods: We developed a choice-based conjoint discrete choice instrument (CDBC) and validated by computer 498 ERSD patients. The CDBC1 consists of 9 attributes of risk and benefit derived from literature reviews, patient/clinician interviews, and pilot testing. Attributes include risk of: serious infection, death within 5 years, permanent rejection, surgical requirements, diet restrictions, flexibility in mobility (no ICHFD), follow-up requirements, pill burden, and fatigue reduction. We used a random, full profile, balanced overlap design from Sawtooth Software with 12 choice pairs and 2 fixed tasks to test validity. We used a mixed effects regression with attribute levels as independent predictor variables and choice decisions as dependent variables.

Results: In univariate and multivariate analyses, all variables were significantly important to choice preferences except follow-up requirements. For each 1% increase in risk of death within 5 years, preference utility across factors decreased by 2.2, while for each 1% increase in infection, utility decreased by 1.4. Avoiding a 1% risk of infection or death was 1 and 1.5 times preferred over no ICHFD, respectively. Pill burden and diet restrictions were less important.

Conclusions: ERSD patients had a strong aversion to even a 1% increase in death within 5 years, infection risk or permanent device rejection, but were willing to trade-off these risks for the benefit of moving to complete mobility. These results will inform device developers on acceptable benefit-risk thresholds for next generation RRT.

Funding: Other NIH Support - NIBIB, Private Foundation Support

SA-PO058

Diagnosticator: A Time-Sparing Web-Based Tool for Easy Clinical Annotation of Genetic Data

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Background: Genetic testing is increasingly used in clinical medicine and has been shown to impact clinical care in Nephrology. The American College of Medical Genetics and Genomics (ACMG) has provided standardized guidelines for clinical interpretation of variants, but the large quantity of data generated from genome-wide testing pose a challenge for seamless clinical interpretation of results. We developed a web-based tool that allows users to upload genetic data, analyze them with customizable filters and easily navigate results.

Methods: The analysis algorithm prioritizes results based on customizable parameters: allele frequency from several publicly available databases (GnomAD, ExAC, IVS and 1000Genome), prior reports of disease association (Clinvar and HGDMD) and proximity with hot-spot regions, functional and pathogenicity prediction (VEP, pLI, SIFT, PolyPhen, REVEL, dbSNFP, dbsCNV), and ACMG interpretation. Both Dominant and Reccessive models are analyzed based on the OMIM-known (or selected) disease inheritance mode for each gene. The final results are presented as an easily interacting and customizable patient-, geneist- or gene-centered interface. Aggregated variant information is presented on a single page, facilitating decision-making about its pathogenicity. Once accepted/rejected, the variant is flagged, to avoid needless re-interpretation of the same variant on other patients or by other users. Moreover, the platform offers a feature that will alert users about a change in status of variants based on interpretation from available databases or other users in the group.

Results: We tested our algorithm on a cohort of 331 patients with nephropathy with known and validated genetic results (Groopman et al. NEJM, 2019) and we could replicate all of the significant findings (n: 343). The average time required for upload and generation of candidate genes was only 277. Moreover, causative variants were properly attributed to the top 10 candidates in 97.8% of the time, significantly speed up annotation. Diagnosticator also flagged 87 new possibly pathogenic variants that we are currently validating.

Conclusions: In summary, we developed an easy to use interface for prioritization and annotation sequencing results, which facilitates clinical interpretation of results and keeps users updated about their findings.

SA-PO059

Outcomes of Using Telemedicine to Provide Nephrology Care in Rural Hospitals

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Background: Telemedicine has recently permeated into the nephrology space allowing patients in rural underserved areas to be treated in their local hospitals without transfer to larger healthcare systems miles away. We report our two year experience providing telenephrology consult services to both ERSD and non-ESRD patients in rural hospitals.

Methods: A retrospective, descriptive study of patients receiving tele-nephrology consultation and chronic dialysis services between September 2017 and May 2019 in three South Georgia (GA) rural hospitals. Consultations were requested by the on-site physicians and were performed by Emory University Tele-nephrologists based in Atlanta, GA by reviewing the patient’s hospital electronic medical record (EMR) and performing a real-time history and physical exam with audio-video technology and Littman electronic stethoscope. Nephrologists documented treatment plan in the hospital’s EMR on each follow-up visit and provided orders for dialysis when indicated using portable dialysis machines that captured electronic data on each HD session.

Results: In three rural hospitals we provided care to 128 unique patients (pts) with a total of 525 patient encounters. Average age for ERSD pts -59 and for non-ESRD-66. 60% of the consults were in dialysis patients with congestive heart failure being the major admitting diagnosis in 42%, while 88% of ERSD pts were discharged to home. For the non-ESRD consults: 24.6% were acute kidney injury who had 71% renal recovery at discharge and 56.5% were electrolyte disorders mainly hypernatremia. 34% of all renal consult patients were treated in the ICU with 8.3% requiring pressor support. See Table for other outcomes including length of stay (LOS), mortality rate, and discharge status (DC) for both the ERSD and non-ESRD patients.

Conclusions: Both ERSD and non-ESRD patients in rural hospitals who received nephrology care via telemedicine were effectively managed in their local hospitals, had low mortality rates, and had similar LOS to larger healthcare systems. Telemedicine is an innovative and feasible option to provide specialty care in rural hospitals.

Clinical Outcomes of Rural Hospital Patients Managed by Telemephrology Services

SA-PO060

Identification of Very Early Response Genes and Sex-Dependent Response Genes for Ischemia-Reperfusion Injury in Human Transplant Patients

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Background: Ischemia-reperfusion injury (IRI) is highly implicated in various kidney conditions leading to acute (AKI) and chronic kidney disease (CKD). IRI during renal transplantation often initiates responses that can result in poor outcome and the loss of a transplant graft. It is important to identify: very early response programs that can be utilized to better characterize the pathobiology and identify therapeutic targets to minimize the injury. Furthermore, it has been shown that sex influences susceptibility to kidney IRI. However, such early response programs for IRI and sex-dependent response programs are poorly understood with most of our knowledge derived from animal studies or tissue analyses after longer times post-ischemia in the transplant population.

Methods: Twenty paired biopsies from the cortical region of the human kidney were obtained before and after ischemia-reperfusion during living donor transplantation, with minimal cold ischemia time (1-2 hours) compared to other studies. Glomeruli were

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Underline represents presenting author.

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SA-PO061

Circular RNA Expression Profiles in Cisplatin-Induced AKI in Mice

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Background: Cisplatin is an effective chemotherapeutic agent whose nephrotoxicity is a serious clinical problem. However, the molecular mechanisms underlying cisplatin-induced acute kidney injury (Cis-AKI) remain unknown. Circular RNAs (cRNAs), a novel class of noncoding RNAs, have been reported to be involved in a variety of diseases. However, the roles of cRNAs in AKI are poorly understood.

Methods: In this study, an AKI model was established in cisplatin-treated mice, and the expression of cRNAs was profiled by next-generation sequencing. The differential expression profiles of cRNAs were obtained by qRT-PCR. Bioinformatics analysis was conducted to predict the functions.

Results: In total, 368 cRNAs were detected to be differentially expressed in response to cisplatin treatment. The qRT-PCR analysis showed that the expression of six selected cRNAs was consistent with that determined by RNA sequencing. The GO and KEGG pathway analyses indicated that the parental genes of the differentially expressed cRNAs were predominantly implicated in the cell part and organelle, cellular process, metabolic process and cancer pathways.

Conclusions: Our study yielded a comprehensive expression profile of differentially expressed cRNAs associated with AKI, indicating the possible involvement of these dysregulated cRNAs in the pathophysiology of cisplatin-induced nephrotoxicity.

Funding: Government Support - Non-U.S.

SA-PO062

Mitochondrial Fission and Apoptosis-Related CircRNA Plays an Important Role in Ischemia-Reperfusion-Induced AKI by Sponging mir-652-3p

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Background: Circular RNAs (cRNAs) can serve as sponges of microRNAs (miRs) to participate in the pathogenesis of various diseases. A study reported that mitochondrial fission, a mitochondrial mitochondrial RNA (miR) with an important role in the death of myocardial apoptosis by sponging mir-652-3p to regulate mitochondrial fission process 1 (MTF1P1) pathway. However, the role of MTFAR in acute kidney injury (AKI) remains unclear. We aim to investigate whether MTFAR is involved in ischemia and reperfusion (IR) induced AKI and its corresponding mechanisms.

Methods: Male Balb/c mice were subjected to 35 mins of bilateral renal ischemia and then reperfusion. We evaluated AKI by examining blood urea nitrogen (BUN), renal tubular necrosis scores on PAS and positive apoptosis on TUNEL staining in kidneys. We measured the levels of MTFAR, mir-652-3p, and Mtp1. We analyzed the match seeds between MTFAR and mir-652-3p as well as miR-652-3p and Mtp1 with TargetScan and miRanda.

Results: We found that kidney function declined with elevated BUN levels, increased renal tubular necrosis scores on PAS and positive apoptosis on TUNEL staining in kidneys 48h after IR in mice compared to the sham control mice. BUN elevate 14 folds and Tpfx elevated about 5-folds in IR mice compared to sham mice. Renal mitochondrial damage biomarkers including OPA1, PGIC-1a, TFMAR statistically decreased in IR group compared with the levels of their miRNAs and proteins. Importantly, renal MTFAR was downregulated, mir-652-3p was upregulated, and Mtp1 was downregulated in IR-induced mice compared to the sham mice. Firstly, we found perfect match seeds between MTFAR and mir-652-3p as well as between mir-652-3p and Mtp1 on TargetScan and miRanda analysis.

Conclusions: Our findings suggested that MTFAR played an important role in IR-induced AKI. The mechanism might be that MTFAR regulates renal mitochondrial fissions by sponging mir-652-3p and consequently increasing MTPF1. Regulating MTFAR-mir-652-3p-MTPF1 pathway may open a novel therapeutic avenue for AKI.

Funding: Government Support - Non-U.S.

SA-PO063

Sex Transcriptomic Signatures in Pig Kidneys After Ischemia-Reperfusion Injury and Recovery

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Background: Renal ischemia/reperfusion injury (IRI) is a major cause of acute kidney injury (AKI). Men are more prone to AKI and to CKD than women and it is accepted that androgens have a role in these processes. The mechanisms involved in injury/regeneration and the impact of gender remain to be fully elucidated. We propose that the identification of differentially expressed genes in male and female pigs kidneys in basal, after injury and upon renal function might unravel gender and pathways useful to understand the different outcomes observed in men and women.

Methods: IRI was performed in single-kidney female and male pigs by clamping the renal artery for 30 minutes. Pre-ischemic, ischemic and post-ischemic kidney tissues (one week later) were collected for microarray assays. Pathway enrichment analysis and visualization of -omics data was done by GSEA, cytoscape and enrichment map. Systems biology-based mathematical models were also conducted to identify injury/recovery pathways and networks modulated in a sex-dependent manner.

Results: The numbers of genes differentially expressed in males versus females (adj P value 0.25) were 100 in pre-ischemic conditions, 858 at 5 min post-ischemia and 2 at one week post-ischemia, indicating that although males were exhibiting differences in gene expression in basal situation and after injury, the general pattern of expression was similar to that of the females after one-week post-injury. Enriched pathways containing genes from basal, one-week post-injury and one-week after reperfusion were further evaluated in males after-one-week post-injury, but activated in basal situation and injury included, among others, immune cell regulation, ion transport, transmembrane, steroid hormone response, type intergene interleukins and intrinsic and extrinsic apoptosis. Contrarily, males after one-week have activated responses to grow factors such as the TGF-beta family members and extracellular matrix organization and collagen formation. Anaxomics systems biology patented technology has also pointed to STAT-1 and STAT-3 as crucial effectors of androgen mediated injury in kidney.

Conclusions: The targets identified in female and male pig samples together with the existing bioinformatic analysis approaches or methods shall provide with novel mechanistic insights into the role of sex hormones in the kidney injury and regeneration processes.

Funding: Government Support - Non-U.S.

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SA-PO065

**Neuro-Immune Cross-Talk in Pathophysiology of AKI**

Sanjeev Puri, Veena Puri, Ajrapija Gupta. Panjab University, Chandigarh, India.

**Background:** Acute kidney injury is a heterogeneous syndrome characterized by inflammation, decrease in glomerular filtration rate, vascular modulation, oliguria and swing in nervous system. Its progression is mediated by cytokines production, neuro-molecular interactions and infiltration of immune cells into kidneys and other organs including brain. Lead molecule, TNF-α aids in the recruitment & activation of immune response. The neuropeptide calcitonin gene-related peptide (CGRP) has been significantly observed in pain pathways, hemodynamic and nerve signal modulation in AKI. The interdependent modulation of immune molecules and neuropeptide during AKI further point to the progression of pain pathways that still remains unexplored in AKI.

**Methods:** A systems biology approach was used to find neuro-inflammatory molecules of AKI by employing in-silico retrieval of AKI genes and investigation of their role in mouse model. The neuro-inflammatory genes in AKI and the respective signaling pathways were searched by PANTHER, GENOMATIX and Target Explorer. Common interactors between TNF and CGRP were expedited by STRING and CYTOSCAPE. The AKI was induced in male Balb/c mice through an intraperitoneal injection of folic acid (250 mg/kg). Kidneys and brains were harvested and expression of CGRP and TNF-α, TRPV1, PTGER4 and CGRP receptor genes were analyzed by quantitative real-time PCR analysis. Immuno-histology of kidney and brain and Serum ELISA were employed to study the CGRP and TNF protein expression. The changes in BBB were evaluated by Evan’s blue estimation.

**Results:** The in-silico search retrieved a list of 49 genes which participate in neuro-immune axis of AKI. KEGG pathway analysis revealed that most of these communicators converge through the calcium signalling pathways. With progression of injury mRNA expression of CGRP and other gene expression was also increased. The protein expression was also reflected by immuno-histology in kidney and brain. The serum CGRP and TNF were also modulated in similar fashion as estimated by ELISA. The changes in the cell architecture of brain and the changes in BBB evidence the kidney cross talk with brain.

**Conclusions:** The study unveils the route of the communication between CGRP and TNF on neuro-immune axis. Most of the mediators signal through calcium mediated pathways leading to pain and pointing towards one of the pilot routes between them.

**Funding:** Government Support - Non-U.S.

SA-PO066

**Kidney-Targeting Nanoplatform for the Specific Delivery of Triptolide to Treat Renal Ischemia-Reperfusion Injury**

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**Background:** Tripletolide (TP) has been proved with a therapeutic effect on a few kinds of kidney diseases. However, its clinical application is limited due to high toxicity and low specificity. Herein, we report a novel kidney-targeting, safe nanoplatform for the specific delivery of TP.

**Methods:** TP was wrapped in a kind of meso-scale nanoparticles (MNsPs) with promising kidney-targeting ability to synthesize the nano-polymer MNPs-TP. TP and then it was administrated to mice through tail vein to evaluate its toxicity to organs and immune system. The targets of MNPs-TP and its mechanism were explored by organ imaging, Transwell and other experimental methods. Finally, a mouse model of renal ischemia-reperfusion injury (IRI) was applied to explore the protective effects and mechanism of different concentrations of TP and MNPs-TP on renal tubules.

**Results:** The toxicity test showed serious pathological changes in liver and the proteinuria index (CD41-CD11b) decreased in TP group, suggesting immune function was damaged. However, MNPs-TP showed no obvious toxic effect on organs and immune system. The pharmacokinetic experiments showed that free TP had no specificity in the distribution in various organs, while the MNPs-TP showed longer metabolic cycle and clear kidney targeting. Transwell experiments showed that renal tubular epithelial cells could ingest MNPs-TP from the basal medium and transport it to the apical side, suggesting that the uptake of MNPs-TP is related to their endocytosis and exocytosis. After administration of TP at the dose of 0.1mg/kg body weight to the IRI mice, the renal function assessed by BUN and SCr was alleviated. The lower score of renal tubular injury, and the down expression of kidney injury molecule1), Lcn2 (encoding neutrophil gelatinase-associated lipocalin), and cytokeratins. Gene ontology analyses identified unique cell-type specific signaling such as oxidative stress responses in the KIM1-expressing proximal tubular segment. The interdependent system. The kidney-targeting MNPs may provide a promising drug delivery platform of reperfusion injury (IRI) model in comparison with TP. Furthermore, MNPs-TP conjugate presented much lower hepatotoxicity and no adverse effect on the immune and genital system compared with kidney-targeting MNPs may provide a promising drug delivery platform of hydrophobic drugs for treatment of renal diseases.

**Funding:** Government Support - Non-U.S.

SA-PO067

**Transcriptomic Mapping of Early Cellular Responses to Renal Ischemia-Reperfusion at Single-Cell Resolution**

Shintaro Ide, Yoshihiiko Kobayashi, Sarah A. Strassner, Anisha Watve, Purushothama rao Tata, Tomokazu Souma. Duke University, Durham, NC.

**Background:** Therapeutic options for treating acute kidney injury (AKI) and the subsequent development of chronic kidney disease (CKD) are limited. The lack of a clear molecular understanding of its pathogenesis and renal reparative pathways contributes to this scarcity of targeted therapeutics. Recent technological advancements in single-cell RNA sequencing have revolutionized our understanding of complex and dynamic tissues such as the kidney. However, optimization is still required to successfully apply this technology to rodent AKI models. Understanding cellular events in AKI at single-cell resolution will guide us to develop new therapeutic strategies.

**Methods:** We have optimized the kidney digestion protocol to achieve high viability (~95%) and very few doubtel formations to avoid flow-cytometry-based cell isolation. We used our unilateral ischemia-reperfusion injury (uIRI) mouse model, which causes severe renal atrophy at 21 days after IRI. Droplet-based single-cell RNA-seq libraries were created and sequenced from a total of 10,000 cells from both injured (IRI) and contralateral kidneys (CLK) using a Drop-Seq platform. Single-cell transcriptome profiles were clustered and annotated based on the expression patterns of known marker genes.

**Results:** Our isRNA analyses identified at least 25 clusters in our combined dataset of IRI and CLK. We captured podocytes in 1.97% of total cells, which is close to the published single-nucleus RNA-seq dataset (2.4%, Wu et al., JASN 2019). There was clear separation among epithelial cells between IRI and CLK kidneys. We successfully mapped the known expression pattern of epithelial injury marker genes such as Hac1 (encoding kidney injury molecule), Lcn2 (encoding neutrophil gelatinase-associated lipocalin), and cytokeratins. Gene ontology analyses identified unique cell-type specific signaling such as oxidative stress responses in the KIM1-expressing proximal tubular segment. Finally, we have developed an optimized platform for generating and analyzing the single-cell transcriptome of mouse kidneys which underwent IRI. Future studies using this platform will inform us as to how the cell-type specific and shared gene signatures change during the course of the disease and guide us to identify novel therapeutic approaches for AKI and its transition to CKD.

**Funding:** Commercial Support - Duke university

SA-PO068

**Whole-Genome Chromatin Immunoprecipitaiton Sequencing Identifies a Role of CtBP2 in Renal Cell Dysfunction and AKI**

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**Background:** Acute kidney injury (AKI) is a clinical syndrome characterized by rapid decline in renal function that results in 2 million deaths annually worldwide and pays for billions of dollars in US healthcare costs. In a pathophysiologic manner, renal tubular cell dysfunction and cell death is the hallmark and the underlying cause of AKI. However, the transcriptional regulators that control alteration in epithelial cell gene expression that triggers renal tubular cell dysfunction and death remain underexplored. The application of deep transcriptional sequencing has provided the new insights of AKI. Here we have examined the role of transcription regulator C-terminal binding protein 2 (CtBP2) in the pathogenesis of AKI through global profiling.

**Methods:** The mRNA and protein expression of CtBP2 were determined in multiple AKI-associated mouse models, namely rhabdomyolysis, ischemia reperfusion injury, and cisplatin nephrotoxicity. To define the role of CtBP2 in vivo, a pharmacological inhibitor (MTSOB) and CtBP2-specific siRNA knockdown (hydrodynamic intravenous injection) were examined in ischemia- and cisplatin- associated AKI. Finally, to directly determine the molecular targets of CtBP2, we carried out chromatin immunoprecipitation followed by sequencing (ChIP-Seq) in rhabdomyolysis-induced AKI and associated changes of the target gene expression of CtBP2 in multiple AKI-associated mouse models with RNA-sequencing (RNA-Seq) data.

**Results:** During the early phase of rhabdomyolysis, ischemia, and cisplatin induced AKI, there is a remarkable increase in CtBP2 protein expression in renal epithelial cells. Functional in vivo studies showed that inhibition of CtBP2 function significantly improves renal impairment in ischemia and cisplatin-associated kidney injury. Global analysis of CtBP2 in rhabdomyolysis-induced AKI revealed that it drives DNA damage, cell cycle, cell proliferation/differentiation pathway, and carbohydrate/lipid metabolism. These target genes of CtBP2 were validated by RNA-Seq and qPCR analysis in all three AKI-associated murine kidneys.

**Conclusions:** Here we first have identified broad roles for CtBP2 as a transcriptional repressor during acute kidney injury. We propose that development of CtBP2 targeting small molecules could provide a therapeutic strategy for the treatment of AKI.

**Funding:** Private Foundation Support
**SA-PO069**

Erythropoietin-Derived HBSP Binding to Tubular Epithelia In Vitro Reduces Apoptosis and Synergistically Protects Kidneys with Caspase-3 siRNA Against 2-Week Ischemia-Reperfusion Injury in the Mouse

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**Background:** Ischemia-reperfusion injury (IRI) induced acute kidney injury has high morbidity and mortality, but no specific treatment. Renoprotection by caspase-3 siRNA (C3siRNA), erythropoietin (EPO) derived peptide HBSP, or cyclic HBSP or C3siRNA, has been previously demonstrated against IRI at 24 or 48 h. HBSP only recognizes tissue specific membrane receptors, protective heterodimer receptor (EPOR/β) and highly expresses in early IRI kidneys. This study further explored the synergistic long-term effect and mechanism of these agents administered at the onset of injury.

**Methods:** Bilateral renal occlusion and sham operation of renal pedicles for 30 min were performed on adult male C57BL/6 mice, followed by reperfusion for 2 w, with or without the treatment of HBSP + C3siRNA/negative control siRNA (NCsiRNA, n=5-9). Twenty-four nmol/kg BW of HBSP was administrated at the onset of occlusion and 15 min after reperfusion, while 30 nmol/kg BW of C3siRNA or NCsiRNA was injected via tail vein 2 h before surgery. Moreover, the localization of fluorescent iodinated labeled HBSP (HBSP-IR) at 25 µm was detected at 1 h post incubation with TCMK-1 cells (mouse kidney tubular epithelial cell line, TECs) ± H2O2 at 200 µM post 24 h. Apoptosis was assessed when HBSP was added with TECs in the presence of 5, 10, 20 or 40 µM H2O2, was added together with H2O2, or for 24 h.

**Results:** The typical impairment of renal structure and function was observed in the IRI kidneys, with increased apoptotic cells. However, this injury was reversed by HBSP or C3siRNA, which decreased serum creatinine, tubulointerstitial damage and apoptosis. Furthermore, HBSP treatment not only preserved renal structure and function but rescued apoptotic cells in both agents co-administered groups. The protective effect was potent in small expressing HBSP and NCsiRNA injected kidneys.

**Conclusions:** HBSP binds to TECs and induces anti-apoptosis. HBSP administration at the early stage of injury has long-term and synergistic effects with C3siRNA on renal IRI. These data indicate that HBSP might be a guide for cell-specific delivery of siRNA, if both are conjugated, targeting caspase-3 in specific cells highly-expressed EPOR/β in IRI kidneys.

**SA-PO070**

Phenotype of Ksp-Cadherin Deficient Mice: Enhanced Recovery from AKI

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**Background:** We have generated a mouse line that is deficient in Ksp-cadherin (Ksp-null), a member of the cadherin superfamily of cell adhesion molecules that is primarily expressed on the basolateral membrane of renal tubular epithelial cells (Thomson et al. ASN 2019). To further elucidate the phenotype of this null-mutation, we exposed Ksp-null and wild-type (WT) mice to an aristolochic acid toxic nephropathy (AAN) and unilateral ischemia reperfusion injury (UIRI). To further explore the effect of Gsa on cell regeneration, we next knocked down Gsa in cultured human HK-2 cells using a specific small interfering RNA.

**Methods:** We generated a distal tubule epithelial-specific Gsa deletion (Gsa flox/flox Ksp-Cre) mouse to demonstrate the essential role of Gsa in renal tubular epithelial cell regeneration in two AKI models: acute aristolochic acid toxic nephropathy (AAN) and unilateral ischemia reperfusion injury (UIRI). To further explore the effect of Gsa on cell regeneration, we next knocked down Gsa in cultured human HK-2 cells using a specific small interfering RNA.

**Results:** Gsa flox/flox Ksp-Cre mouse developed more severe renal impairment including higher levels of serum creatinine and massive tubular necrosis after AAN and URII. Gsa inactivation dramatically impaired renal tubular epithelial cell regeneration and blocked proliferating tubular cells in G1/S transition due to the reduction in the number of BrdU-positive cells and the depression of cyclin-dependent kinase 2 (CDK2)/cyclin E activities. In vitro, treatment of renal tubular epithelial cells with Gsa-targeting small interfering RNA inhibited tubular epithelial cells proliferation by preventing cell cycle progression from G1 to S phase. Down-regulation of Gsa inhibited the activity of CDK2/cyclin E and inhibited the Gsa-ERK signaling pathway before and after aristolochic acid stimulates HK-2 cells.

**Conclusions:** Gsa is required for tubular epithelial cell regeneration in the kidney repair stage after AKI. Loss of Gsa could dramatically impair the regeneration of renal tubular epithelial cells by blocking Raf-MEK-ERK pathway.

**SA-PO071**

GSK3-Beta Inhibits Tubular Regeneration in AKI by a FoxM1-Dependent Mechanism

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**Background:** Acute kidney injury (AKI) is characterized by injury to the renal epithelium. Although renal tubules are capable of regeneration, inadequate repair and fibrosis can lead to chronic kidney disease. FoxM1 is a forkhead box family member that regulates the cell cycle machinery, division, survival and oxidative stress. FoxM1 is also a substrate for glycogen synthase kinase 3beta (GSK3-beta), a known inhibitor of renal tubular regeneration in AKI. The current study tested the hypothesis that GSK3-beta suppresses tubular repair after AKI by inhibiting FoxM1.

**Methods:** To determine the role of FoxM1 in tubular repair, the effect of FoxM1 inhibition was examined in renal ischemia/reperfusion (IR) induced AKI in C57BL/6J mice and HK2 proximal tubular cells in vitro.

**Results:** Renal FoxM1 expression increased after 1 IR induced AKI in mice and was arrested by increased FoxM1 inhibition. Treatment with Thiostrepton, a FoxM1 inhibitor reduced renal tubular cell proliferation and kidney tubular repair. To test if GSK3-beta regulates FoxM1, the effect of FoxM1 inhibitor on tubule-specific GSK3-beta knockout mouse was determined. In Gsk3-beta knockout mice, FoxM1 expression, cell proliferation and tubular repair were significantly high, leading to improved renal function. Significant increase in p21, a cell cycle inhibitor and reduction in pro-fibrotic factors were found in cells and kidneys where Gsk3-beta was inhibited. Thiostrepton treatment abolished the improved tubular repair in Gsk3-beta knockout mice.

**Conclusions:** These studies demonstrate GSK3-beta, an important factor for renal tubular regeneration following AKI, and that GSK3-beta suppresses tubular repair by inhibiting FoxM1.

**Funding:** NIDDK Support, Private Foundation Support
Dok-4 to the membrane by a myristoylation signal rescued the cooperative inhibition of Rac by Dok-4 and Chn2.

Conclusions: The Rac-GAP Chn2 is a novel pY-dependent Dok-4 partner and effector expressed in the injured kidney. Dok-4 facilitates inhibition of Rac1 by promoting recruitment of Chn2 at the membrane. This cooperative inhibition of Rac1 may regulate key downstream events in renal IRI, including proliferation, migration, and tubular repair.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO076

Induction of Hnf-1β Transcription Factor Protects Against Epithelial Hypoxia During Renal Ischemia-Reperfusion Injury

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Background: Ischemia-reperfusion injury is the crucial cause of acute kidney injury (AKI) in clinical settings. Proximal tubular cells are highly sensitive to ischemic injury and the following repair capability. Hnf-1β transcription factor drives the normal nephrogenesis and epithelial homeostasis. In the present study, we investigated the role of Hnf-1β regulation against hypoxic damage of proximal tubular cells in renal ischemia-reperfusion injury.

Methods: Renal ischemia-reperfusion was induced by bilateral clamping renal pedicles, the clamps were released for reperfusion. Kidney function was measured by BUN and serum creatinine, pathological damage was evaluated by HE and TUNEL stain. In vitro, cells were treated with hypoxia (1% oxygen) to represent ischemic condition, to test the effect of Hnf-1β, the editing-proficient Cas9 cell line was generated before hypoxia. Expression of the editing-proficient cell line was validated by western blot and Hoechst dye. To explore the further effect of GJB1, the down-regulated stable cell line was created, and the expression was tested by realtime PCR. ChIP analysis was used to confirm the binding of NF-κB and Hnf-1β.

Results: Western blot, we identified expression of Hnf-1β are significantly increased in kidney after 30 minutes of bilateral renal ischemia and reperfusion 12h, while the HIC staining showed the signal mainly in cortex. In vitro, hypoxia can also induce Hnf-1β in rat kidney epithelial cells (RPTC) as early as 4h and lasted to 12h. Interestingly, hypoxia was associated with Hnf-1β knockdown and tubular cells with exacerbated apoptosis induced by hypoxic condition and caspase activity, whereas overexpression of Hnf-1β revealed more resistant to apoptotic responses in hypoxic cells. We further indicated these protective effects of Hnf-1β were mediated by NF-κB, which were confirmed by ChIP analysis, and its specific inactivator TPCA-1. Moreover, we also show that gap junction gene GJB1 could serve as downstream target of Hnf-1β as evidenced of inhibition of GJB1 rescued Hnf-1β anti-apoptotic effect.

Conclusions: The study indicates the protective role of Hnf-1β against ischemic/hypoxic conditions in kidney. Hnf-1β performs anti-apoptotic factor mediated by NF-κB, and the renal protective effect may carry out via regulating its downstream gene GJB1.

SA-PO077

Inhibition of Ataxia-Telangiectasia Mutated Exacerabates AKI by Activating p53 Signaling

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Background: The DNA damage response (DDR) after kidney injury induces cell cycle arrest in renal tubular epithelial cells. Cell cycle-arrested tubular epithelia secrete pro-fibrotic cytokines, thereby promoting interstitial fibrosis in a paracrine manner. Phosphorylation of ataxa-telangiectasia mutated (ATM) is the initial step in DDR and subsequent cell cycle arrest. ATM inhibitors are emerging cancer drug candidates; however, the effects of ATM inhibition on the injured kidney have not been explored.

Methods: We administered KU55933, a selective ATM inhibitor, to cisplatin-treated mice and UUO mouse model. In order to specifically investigate the underlying mechanisms in tubular epithelia, we isolated the proximal tubular epithelia by FACs from bregenic SLC34a1-CreERt2; R26tdTomato proximal tubular-specific reporter mice.

Results: ATM inhibition did not ameliorate but rather exacerbated cisplatin-induced DNA damage and tubular injury, thereby increasing mortality. Numerous tubules with demad tubular basement membrane where the tubular epithelia had completely detached were observed in the kidneys of mice that received KU55933 and cisplatin. Analysis of isolated tubular epithelial cells revealed that KU55933 upregulated p53 and subsequent pro-apoptotic signaling, such as PUMA and Bax expression, in tubular epithelia of cisplatin-treated mice, leading to marked mitochondrial injury and apoptosis. In addition, ATM inhibition did not increase the nuclear expression of Mdm2, homologue 1 in tubular epithelia of cisplatin-treated mice, suggesting that DNA mismatch repair after tubular injury was not sufficient to prevent cisplatin-induced tubular injury. Lastly, we investigated the effect of ATM inhibition on UUO kidney and found that KU55933 did not ameliorate the kidney fibrosis.

Conclusions: Our study suggested that ATM inhibition does not increase DNA repair after cisplatin-induced DNA damage and exacerbates tubular injury through the upregulation of p53-dependent pro-apoptotic signaling. Acute kidney injury must be carefully monitored when ATM inhibitors become available in clinical practice in the future.
**SA-PO078**

PTIP Deletion in Renal Proximal Tubules May Cause Epigenetic Change and Prevent Recovery After AKI

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*Background:* Pax-lp gene encodes a PTIP nuclear protein that is expressed in most cells and is implicated in a variety of nuclear processes, including DNA repair, and transcription activation. Consequent to acute kidney injury (AKI), surviving proximal tubule cells re-enter mitosis and will form cysts if disease associated genes are mutated. Thus, epigenetic information that maintain a stable phenotype must be reset during regeneration. PTIP is part of an MII3/4 histone H3K4 methyltransferase complex that is essential for development. To test whether such epigenetic imprints are dependent on histone H3K4 methylation, we generated a mouse model with deletion of PTIP (PTIP-/-) in the terminally differentiated renal proximal tubular cells.

*Methods:* We used Cre-loxP system, standard genetic and biochemical techniques to generate and study the deletion of PTIP- specifically in renal proximal tubular cells. Also mice received the 2mg/kg Pepck-cre. Age were matched and injected i.p with a single dose of folic acid.

*Results:* The kidneys of mice carrying the PTIP- appeared normal with little evidence of loss of kidney function or other abnormalities. Upon AKI, such mice failed to regenerate damaged tubules leading to scarring and interstitial fibrosis. The inability to re-enter mitosis was likely due to a failure to re-enter mitosis and reactiveate regulatory genes such as S0x9, PTIP- reduced histone H3K4M3 in uninjured kidneys but had no effect on H3K4M2. A transient decrease in trimethylation was also observed in controls after AKI but returned to normal after repair. Strikingly, cell lineage tracing revealed that surviving PTIP mutant cells could alter their phenotype and lose epithelial markers. These data demonstrate PTIP is needed for regenerating proximal tubules and to maintain or reestablish the cellular phenotype.

*Conclusions:* The process of regeneration must require changes in gene expression of surviving epithelial cells, which may involve the reactivation of genes controlling development and proliferation. Despite PTIP-, mice had no gross morphological phenotypes, suggesting that PTIP- at this stage of differentiation had little apparent effect on kidney function. However, when such mice were subjected to AKI, the ability to repair and repopulate damaged tissue was severely compromised.

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**SA-PO079**

HDAC3 Contributes to Necrotic Tubular Damage in Ischemic AKI

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*Background:* Histone deacetylases (HDAC) are group of enzymes that remove acetyl groups from lysine residues of histone and nonhistone proteins. The action of histone deacetylation condenses chromatin and DNA structure, resulting in the repression of gene transcription and expression. We reported that HDAC inhibitors attenuate apoptosis of renal proximal tubular cells during cisplatin treatment. This study was designed to determine the specific role of HDAC3 in acute kidney injury (AKI).

*Methods:* In vivo, we generated proximal tubule-specific HDAC3 knockout (PT-HDAC3-ko) mice, which were subjected to 30min of ischemia with 4hrs of reperfusion. We injected the mice with 75mg/kg PTBA (a specific pharmacological inhibitor of HDAC3). Serum sample was collected to check blood urea nitrogen (BUN) and serum creatinine. Kidney tissue was collected for histology, immunohistochemistry and immunoblot analysis. In vitro, rat proximal tubular cells (RPTC) were treated with azide for 4.5hrs following ischemia reperfusion to induce necrotic cell death to examine the effects of RGFP966. Necrosis was indicated by propidium iodide staining and LDH release. In addition, the effect of HDAC3 knockdown was examined.

*Results:* HDAC3 was localized in the nucleus and cytoplasm of proximal tubular cells in kidneys. After ischemic AKI, HDAC3 was induced. Compared to wild-type mice, PT-HDAC3-ko mice showed less ischemic AKI as indicated by less necrotic damage in proximal tubules and improved renal function with lower levels of BUN and serum creatinine. Consistently, RGFP966 protected against ischemic AKI in mice. In immunoblot analysis, acetylation of histone H3, H2B and H4 was better preserved in kidney tissues of PT-HDAC3-ko mice. In RPTC cells, HDAC3 was induced during azide treatment and significantly increased during subsequent recovery. Both RGFP966 and HDAC3 knockdown suppressed HDAC3 induction and preserved the acetylation of histone H3, H2B and H4, while both RGFP966 and HDAC3 knockdown suppressed necrosis following azide treatment.

*Conclusions:* HDAC3 is induced during ischemic AKI and plays an important role in necrotic damage in proximal tubules. Specific blockade of HDAC3 may have therapeutic potential in AKI.

*Funding:* NIDDK, Support, Veterans Affairs Support

**SA-PO080**

Hdac8 Knockout Results in Amelioration of AKI in Zebrafish

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*Background:* Despite the prevalence of AKI, the need for therapeutics is currently unmet. One candidate for a small molecule therapeutic is 4-(phenylthio) butanoic acid (PTBA), which previously showed increased RTEC productive repair and functional recovery by enhancing deacetylation and decreasing injury in both murine and zebrafish models of AKI. Here, we show that histone deacetylase 8 (HDAC8) is potential target which interacts with cell cycle regulators, such as SMC3 and p53, to acetylate and modulate cell cycle activity. We further investigate the role of Hdac8 in affecting the cell cycle using a larval zebrafish model of AKI.

*Methods:* Cellular thermal shift assay (CETSA) was used to evaluate the target engagement of PTBA with HDACs. hdac8 sa14948/- and hdac8 sa14948/+ mutant zebrafish were injected with gentamicin to induce AKI and observed for post-injury survival from 1-7dpi. Cells harvested from whole larvae were stained with propidium iodide and analyzed with flow cytometry for variation in the cell cycle phase. Using cell cycle specific antibodies, DNA content of larval pronephros were stained for S and G2/M phases at various timepoints following AKI.

*Results:* PTBA was shown to stabilize HDAC8 at higher temperatures compared to control, consistent with PTBA binding to HDAC8. hdac8 sa14948/- fish showed significantly increased survival when compared with wildtype and hdac8 sa14948++. Analysis of whole larvae cell cycle showed increased G1/S population with injury at 1dpi. Immunohistochemistry showed increased Edu during an early injury timepoint (1dpi) while showing delayed G2/M entrance in a later injury timepoint (4dpi).

*Conclusions:* Absence of Hdac8 in larval zebrafish model of AKI improved survival. The data is correlated with increased G1/S cell cycle phase during times of injury, as well as delayed entrance to G2/M. Here, we demonstrate the role of Hdac8 in increasing repair by delaying proliferation after injury. Furthermore, we have identified PTBA as an HDAC8 inhibitor. Taken together these data suggest a potential mechanism to induce productive repair after an AKI event.

*Funding:* NIDDK Support, Other U.S. Government Support

**SA-PO081**

Removal of Apoptotic Cells During AKI

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*Background:* The incidence of acute kidney injury (AKI) is increasing worldwide, however, effective treatment for AKI remains elusive and no approved pharmaceutical agents exist. Tubular cell apoptosis has been shown to be present in preclinical models and also in some clinical samples from patients with AKI. The human body removes over 200 billion cells every day, and it is clear that the body has evolved an efficient manner to deal with apoptosis, termed autophagy, which occurs in nearly every major organ (Morioka et al., Nature 2018). Clearance machinery can often become overwhelmed by massive induction of apoptosis as occurs with ischemia reperfusion injury (IRI). While it has been shown that defective clearance leads to exacerbation of AKI, whether promoting efficiency leads to amelioration of AKI has not been explored.

*Methods:* In order to delineate whether apoptotic cell clearance could be boosted for beneficial effects during AKI, we established a way to boost apoptotic cell clearance by modulating the protein structure of the death inducing factor, thereby changing it from a phosphatidylserine (PtdSer) receptor, BA11. Previous studies have shown that while BA11 interacts PdSer via its extracellular region, BA11 also binds via its cytoplasmic tail to ELMO1 and in turn, a second protein Dock180, which together serve as a guanine nucleotide exchange factor complex for the GTPase Rac1. Activation of Rac1 induces a conformational change of the actin filament to initiate the uptake of target cells. We generated a chimeric version of BA11 where we deleted the natural ELMO1 binding site and directly fused ELMO1 to the BA11 cytoplasmic tail (denoted BELMO). Strongly boosted apoptotic cell engulfment. This chimeric receptor still behaved faithfully as it was dependent on PdSer recognition, and an intact ELMO1 that can engage the downstream Dock180 and Rac1 signaling machinery. We have also generated transgenic mouse expressing BELMO receptor. We demonstrate that BELMO expression in tubular cells provided the opportunity for targeting cell clearance in AKI therapy. In addition, BELMO transgenic mice allow us to explore the effect of boosting apoptotic cell clearance on variety of other disease models involving accumulation of dead cells.

**SA-PO082**

Quantifying Autophagic Flux in Kidney Tissue with Super-Resolution Structured Illumination Microscopy Imaging

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*Background:* Autophagy, a key homeostatic catabolic pathway in eukaryotic cells, is linked to pathological conditions in most organs as well as cancer and aging. In the kidney, autophagy has been shown to modulate both acute and chronic injury. Despite the importance of autophagy for many diseases, it is difficult to measure autophagic flux, i.e. clearance of autophagosomes by the lysosome. Autophagy is usually evaluated by presence of autophagosomes, LC3 II levels or EM but not autophagic flux. We combined the RFP-GFP-LC3 reporter mice with super-resolution structured illumination microscopy to measure autophagic flux at an individual autophagosome level in response to kidney ischemia.

*Methods:* Kidneys of RFP-GFP-LC3 reporter mice were injured by unilateral ischemic reperfusion injury. The GFP of the reporter is sensitive to low pH, quenching the fluorescent signal upon autophagosome/lysosome fusion, leaving only RFP signal. At 48 hours after injury, mice were sacrificed and an imaging z-stack was acquired at 6-8um and mounted on silanized coverslips. Immunofluorescence staining was done using...
SA-PO085

Deciphering the Molecular Mechanisms Underlying Nephroprotection by Hypoxia-Signalling: A Comparative Analysis of Prolyl Hydroxylase Inhibition and Hypoxic Preconditioning

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Background: Kidney injury (AKI) is one of the most common kidney diseases leading to increased morbidity and mortality. However, preventive or therapeutic strategies in the clinical setting are still missing. In animal models, AKI can be effectively prevented by preconditioning strategies – e.g. activating hypoxia signalling – that increase cellular stress resistance. Since translation of this approach by exposure to hypoxia (HP) is not feasible in clinical set up, pharmacological strategies would be a favourable alternative. Therefore, inhibition of prolyl-hydroxylases (PHD) and consecutive activation of hypoxia inducible factors (HIF) is an attractive strategy. Our aim was to confirm the protection by HP and PHDi in renal ischemia-reperfusion injury (IRI) and to characterize shared molecular pathways between both strategies.

Methods: Male 14-week-old C57Bl6 wildtype mice were either treated with a PHD-inhibitor or by incremental exposure to hypoxia on three following days aiming for a similar induction of the HIF-target gene EPO to increase the comparability of both approaches. Afterwards all mice underwent a right nephrectomy and 40 min of contralateral renal IRI. In the following they were characterized functionally (e.g. by creatinine), histologically and by a transcriptomic and proteomic analysis of the right and left kidneys to unravel the molecular key players.

Results: Hypoxia and PHD-inhibition significantly ameliorated AKI 24 h after reperfusion. Histological analysis confirmed the protective effect of both strategies. The omics-analyses of the right kidneys revealed only little influence of HP and PHD before damage. After damage, kidneys from HP and PHDi treated animals differed strongly from controls. There was only a limited overlap between both approaches which will allow for narrowing down the pathways and genes causally involved in organ protection.

Conclusions: Here, we confirmed the protective effect of HP and PHDi and performed the first comparative molecular phenotyping of kidneys treated with these strategies. Future studies will answer the question whether the genes and pathways identified can be modulated to prevent AKI.

Funding: Commercial Support - Bayer AG

SA-PO086

Identification of Small Molecule Inducers of Heme Oxygenase-1 (HO-1) in Renal Epithelial Cells

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Background: Acute kidney injury (AKI) is a major public health concern that is associated with increased morbidity and mortality in hospitalized patients. Furthermore, AKI is one of the leading causes of care for the end-stage renal disease (ESRD) patient, and the number of treatments is growing rapidly. While several promising biomarkers are emerging to aid in the early identification of AKI, no new therapies have succeeded in clinical trials. Currently, the only FDA approved treatment for AKI is dialysis. Recent studies from our laboratory and others have demonstrated the beneficial effects of HO-1, an enzyme that catalyzes heme breakdown into biliverdin, carbon monoxide and iron, in animal models of AKI.

Methods: We designed an assay suitable for high throughput screening to assist in the identification of novel small molecule targets that both induce HO-1 and have desirable pharmacokinetic characteristics. We used a stable HEK293 cell line containing multiple copies of the human HO-1 promoter and a unique 220 bp enhancer sequence in a luciferase reporter vector to screen a library of >150,000 compounds.

Results: We identified 2240 candidate compounds in the initial screen. Based on chemical structure, we pared these down to 800. Compounds exhibiting E<sub>0.5</sub> ≥ 70% of 5µM hemin and E<sub>0.10</sub> < 10M were assayed for endogenous HO-1 expression in HEK293 cells. The screen was repeated on a library of >4,000 FDA approved compounds and several additional candidates were identified, including brodaluridine, an antiprotozoal drug. At low nanomolar concentrations (1-5nM), brodaluridine markedly high expression of HO-1 mRNA, protein and enzyme activity. Using RNA seq, the transcription factor,
Nrf2 was identified as a target for broxaldine induced HO-1 expression, which significantly protected from tubular cell death (PAS and cleaved caspase 3 staining) and enhanced renal function and accompanied exogenous CHP pre-treatment prevented kidney function and accompanied changes in plasma creatinine (P=0.02), tubular damage (P=0.04), and tubular cell death (P=0.01; P<0.05; P<0.05; P=0.04) compared to rats receiving control IgG. However, effect of anti-HMGBl ab was only observed in males; treatment with anti-HMGBl did not alter plasma creatinine (P<0.1; P=0.003), tubular damage (P=0.09; P=0.003), and tube death (P=0.07; P=0.003). The expression of proinflammatory cytokines such as IFN-γ was significantly increased in the high dose treatment did not show favorable effects on hypoxic HK-2 cells.

Conclusions: In conclusion, greater levels of HMGBl in males compared to females results in enhanced pro-inflammatory signaling and exacerbation of IR injury-induced.

Funding: Other NIH Support - NHLBI

SA-PO090
Cyclo(His-Pro) Prevents Against Oxidative Stress-Induced Renal Apoptosis and Fibrosis Through Activating the Nrf2-Mediated Pathway

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Background: Apoptosis is a key feature of the pathogenicity associated with glomerular and tubulo-interstitial injury of acute kidney injury (AKI) and chronic kidney disease (CKD). Cyclo(His-Pro) (CHP) is an endogenous cyclic dippeptide that exerts cellular protective effects against oxidative damages. Here, we show that treatment with exogenous (recombinant) CHP prevented renal structural and functional injury triggered by experimental ischemia-reperfusion injury (IRI) model in mice as well as 5/6 nephrectomy (Nx) model in rat.

Methods: In this study, to investigate the effect of CHP on AKI, we used IRI mice model. Exogenous CHP was employed in vitro models with cultured human tubular epithelial cells (TECs). In addition, 5/6 nephrectomy rat model and TGF-β1 and hydrogen peroxide (H2O2)-induced apoptosis models with cultured human podocytes were employed.

Results: Exogenous CHP pre-treatment prevented kidney function and accompanied by significant reduction in ischemia-induced tubular cell death, apoptosis, and inflammatory cell infiltration on renal IRI model. In vitro stimulation of TECs with hypoxia, CHP-mediated renal protection was associated with reduced IL-11, IL-18, reactive oxygen species (ROS) and the proportion of dead cells. Compared with control-treated 5/6 Nx rats, CHP-treated 5/6 Nx rats also restored kidney function and decreased proteinuria and pathologically decreased glomerulosclerosis, tubulo-interstitial fibrosis in the remnant kidney of 5/6 nephrectomized rat. The administration of exogenous CHP significantly reduced not only ROS production via TGF-β2-dependent pathway, but also the resultant oxidative stress induced by H2O2 in cultured human podocytes. Microarray analysis highlights a cascade of specific gene expression patterns related to kidney injury, repair, and innate immunity. Notably, tubular epithelial cell and podocytes cell cycle arrest in G2/M mediate oxidative stress after injury.

Conclusions: This study has uncovered a major protective role of CHP in renal IRI and 5/6 nephrectomy through TECs and podocytes regeneration that could be potentiated as a therapeutic strategy.

SA-PO089
Greater High-Mobility Group Box 1 (HMGBl) in Male Spontaneously Hypertensive Rats (SHR) Enhances Renal Ischemia-Reperfusion (IR) Injury Compared with Females

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Background: Renal IR injury is a major cause of acute kidney injury, which carries a high mortality rate and increases the risk of later developing hypertension and CKD.

There are sex differences in renal IR injury, with males exhibiting greater injury following an ischemic insult than females. The mechanisms that are responsible for observed sex differences in IR injury are unknown. Recent studies have reported that increased HMGBl activity in male rats contributes to renal damage. The contribution of HMGBl to renal IR injury in females is unknown. We hypothesized that greater HMGBl in males promotes enhanced renal IR injury compared to females.

Methods: 13wk old male and female SHR were subjected to sham or 45-min warm bilateral ischemia followed by 24hr reperfusion. A separate set of SHR were pre-treated with control (IgG) or neutralizing anti-HMGBl antibody (300 µg/rat) 1hr prior to renal IR (n=4-6). Blood was collected for biochemical analysis; kidneys were harvested for histological and WB analysis.

Results: IR injury significantly increased renal HMGBl levels in both sexes compared to sham (P<0.001). Renal HMGBl levels were greater in males vs. females, although the effect of IR to increase HMGBl levels was comparable between the sexes (P=0.009, P=0.03). Treatment with anti-HMGBl ab prior to IR attenuated IR-induced increases in plasma creatinine (P=0.003), tubular damage (P=0.004), and tubular cell death (P=0.004) compared to rats receiving control IgG. However, effect of anti-HMGBl ab was only observed in males; treatment with anti-HMGBl did not alter plasma creatinine (P<0.001; P=0.003), tubular damage (P=0.09; P=0.003), and tubular cell death (P=0.07; P=0.003) following IR in females. In addition, HMGBl neutralization attenuated IR-induced activation of pro-inflammatory signaling molecules downstream of HMGBl only in male SHR, including decreased renal Toll-like receptor (TLR) 4 phosphorylation (P=0.08; P=0.003). IL-1β mRNA expression (P=0.08; P=0.04) and plasma TNFα (P=0.06; P<0.03).

Conclusions: In conclusion, greater levels of HMGBl in males compared to females results in enhanced pro-inflammatory signaling and exacerbation of IR-induced injury.

Funding: Other NIH Support - NHLBI
To examine the intra-renal localization of T-MSCs, T-MSCs were labeled with PKH-26

Tubular Injury via ALOX12-12HETE-GPR31 Signaling

Overexpression of MIOX Accentuates Gentamycin-Induced Acute Nephrotoxicity in Mouse

Interleukin (IL)-34 is reported to mediate macrophage (Mo) proliferation and to be associated with kidney disease progression. However, the physiological properties of IL-34 on tubular epithelial cell (TEC) injury remain unclear. Thus, we investigated the effect of IL-34 on TEC damage caused by cisplatin nephrotoxicity (CP-N).

Methods: 7-week-old male C57BL/6 (B6) mice (n=16) were fasted for 8 hours and then induced CP-N by intraperitoneal injection (IP) of CP (25 mg/kg) on day 0. Groups of animals were given either anti mouse IL-34 antibody (CP+anti-IL-34 Ab) 400 mg/kg, n=8) or vehicle (CP+V, n=8) daily by IP from day -1 to day 2. Three age-matched male B6 mice were used as normal control (NC). All mice were sacrificed on day 3. In addition, mouse renal proximal TECs (mMREpiC) were cultured to analyze the inhibitory effects of IL-34 on cisplatin nephrotoxicity.

Results: Compared to the NC, CP+V mice exhibited marked acute kidney injury (AKI) and upregulated expression of IL-34 and its receptors, C-FMS and PTP-ζ. Compared to the vehicle treatment, anti-IL-34 Ab treatment significantly suppressed the protein levels of IL-34 and its receptors in CP-N mice; it also significantly improved serum Cr levels, ameliorated the numbers of casts/HPE, and suppressed the increased numbers of F4/80, TUNEL+ cells, and caspase-3+ cells in CP-N mice. The renal transcript levels of Kim-1, MIP-1α, CCL-2, TNF-α, and Bax were significantly lower in the CP+anti-IL-34 Ab mice than in the CP+V mice. Furthermore, CP+anti-IL-34 Ab mice showed significantly less renal infiltration of CD11b+F4/80+TNF-α+ cells. In vitro, stimulation with CP induced the expression of IL-34 and its receptors in MREpipC. Treatment with anti-IL-34 Ab significantly suppressed CP-induced caspase-3 and Bax expression with degradation of ERK1/2 phosphorylation in the damaged MREpipC.

Conclusions: These results indicated that IL-34 secreted from damaged TEC binds to its receptors and aggravates CP-N. Treatment with anti-IL-34 Ab directly prevented the upregulation of IL-34 and its receptors in CP-N mice, leading to amelioration of renal proximal tubular cell apoptosis and acute kidney injury via an E-cadherin dependent mechanism and suggest that combined application of 3-DZNeP with cisplatin is a novel chemotherapeutic strategy that enhances the anti-tumor effect of cisplatin and reduces its nephrotoxicity.

Funding: Government Support - Non-U.S.

SA-PO094
Renoprotective Effect of IL-34 Inhibition on Cisplatin-Induced Nephrotoxicity in Mouse

Interleukin (IL)-34 is reported to mediate macrophage (Mo) proliferation and to be associated with kidney disease progression. However, the physiological properties of IL-34 on tubular epithelial cell (TEC) injury remain unclear. Thus, we investigated the effect of IL-34 on TEC damage caused by cisplatin nephrotoxicity (CP-N).

Methods: 7-week-old male C57BL/6 (B6) mice (n=16) were fasted for 8 hours and then induced CP-N by intraperitoneal injection (IP) of CP (25 mg/kg) on day 0. Groups of animals were given either anti mouse IL-34 antibody (CP+anti-IL-34 Ab) 400 mg/kg, n=8) or vehicle (CP+V, n=8) daily by IP from day -1 to day 2. Three age-matched male B6 mice were used as normal control (NC). All mice were sacrificed on day 3. In addition, mouse renal proximal TECs (mMREpiC) were cultured to analyze the inhibitory effects of IL-34 on cisplatin-induced TEC apoptosis. Cells were stimulated with CP (2 µg/mL), then treated with or without anti-IL-34 Ab (1000 pg/mL).

Results: Compared to the NC, CP+V mice exhibited marked acute kidney injury (AKI) and upregulated expression of IL-34 and its receptors, C-FMS and PTP-ζ. Compared to the vehicle treatment, anti-IL-34 Ab treatment significantly suppressed the protein levels of IL-34 and its receptors in CP-N mice; it also significantly improved serum Cr levels, ameliorated the numbers of casts/HPE, and suppressed the increased numbers of F4/80, TUNEL+ cells, and caspase-3+ cells in CP-N mice. The renal transcript levels of Kim-1, MIP-1α, CCL-2, TNF-α, and Bax were significantly lower in the CP+anti-IL-34 Ab mice than in the CP+V mice. Furthermore, CP+anti-IL-34 Ab mice showed significantly less renal infiltration of CD11b+F4/80+TNF-α+ cells. In vitro, stimulation with CP induced the expression of IL-34 and its receptors in MREpipC. Treatment with anti-IL-34 Ab significantly suppressed CP-induced caspase-3 and Bax expression with degradation of ERK1/2 phosphorylation in the damaged MREpipC.

Conclusions: These results indicated that IL-34 secreted from damaged TEC binds to its receptors and aggravates CP-N. Treatment with anti-IL-34 Ab directly prevented the upregulation of IL-34 and its receptors in CP-N mice, leading to amelioration of renal proximal tubular cell apoptosis and acute kidney injury via an E-cadherin dependent mechanism and suggest that combined application of 3-DZNeP with cisplatin is a novel chemotherapeutic strategy that enhances the anti-tumor effect of cisplatin and reduces its nephrotoxicity.

Funding: Government Support - Non-U.S.
SA-PO095

McCP Promotes Cisplatin-Induced AKI Through Epigenetic Regulation of Irf8

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Background: Emerging evidence suggests that epigenetic regulation like DNA methylation plays an important part in the process of acute kidney injury (AKI), but the mechanism remains largely elusive. Methyl-CpG binding protein 2 (MeCP2) is an epigenetic regulator which binds to methylated cytosines and functions as a gene transcriptional inhibitor or activator. The role of McCP2 was examined most notably in brain development, while the involvement of McCP2 in renal disease remains unknown.

Methods: Twenty male C57 mice were randomly grouped into control, cisplatin-1d, cisplatin-2d, and cisplatin-4d according to the time of exposure after cisplatin intraperitoneal injection. HK-2 cells were exposed to cisplatin at 20µM for variable incubation time. HK-2 cells were transfected by siRNA to knockdown McCP2 expression. Apoptosis was detected with the TUNEL method. Chromatin immunoprecipitation assay (ChIP) was used to analyze the binding of McCP2 to the interferon regulatory factor 8 (Irf8) gene.

Results: We found consistent expression of McCP2 in renal cortical tubules of SD rat, WKY rat, and C57 mouse. Compared with the sham group, cisplatin-treated mice kidney showed significant upregulation of McCP2 in proximal tubules in both protein and mRNA level, accompanied by severe renal histology changes and the upregulation of NGAL and KIM-1. In vitro, McCP2 was also induced in cultured proximal tubular cells by cisplatin treatment. Interestingly, knocking down McCP2 alleviated caspase-3-dependent tubular cell apoptosis, but did not affect autophagy induced by cisplatin. In addition, a pro-apoptotic gene interferon regulatory factor 8 (Irf8) was found upregulated in tubular cells by cisplatin in vivo and in vitro. Importantly, we demonstrated that McCP2 upregulated Irf8 expression by directly binding to its gene.

Conclusions: Elevation of expression of McCP2 was found in cisplatin-treated renal proximal tubules in vivo and in vitro. McCP2 promoted cisplatin-induced renal tubular damage by facilitating apoptotic process and inhibiting autophagy activity. The epigenetic regulation of pro-apoptotic gene Irf8 by McCP2 may be the possible mechanism implicated in the pathophysiological process of cisplatin-induced AKI.

Funding: Government Support - Non-U.S.

SA-PO096

The mRNA Editing via Apobec-1 Is Necessary to Repair Kidneys from Cisplatin (CP)-Induced Renal Injury

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Background: Cisplatin (CP) induces AKI as the proximal tubules (PT) undergo regulated necrosis. Repair is almost complete following such a single dose. Repeated doses of CP, however, leads to unresolved injury and progresses to chronic kidney disease (CKD). Interruption of the renal transcriptome throughout the process of AKI to CKD may provide insight into the mechanism of AKI and CKD.

Methods: We have reported that preconditioning renal tubular cells with A-769662, a specific pharmacologic activator of AMPK, increased the survival of these cells when subjected to hypoxic stress. We have also shown that preconditioning mice A-769662 ameliorates the severity of ischemic AKI in mice in vitro. In these studies we examined the role of AMPK and the Kruppel-like transcription factor-4 (KLFL4) in determining the fate of human umbilical epithelial cells (HUEVECs) exposed to cisplatin.

Results: We have reported that preconditioning renal tubular cells with A-769662, a specific pharmacologic activator of AMPK, increased the survival of these cells when subjected to hypoxic stress. We have also shown that preconditioning mice A-769662 ameliorates the severity of ischemic AKI in mice in vitro. In these studies we examined the role of AMPK and the Kruppel-like transcription factor-4 (KLFL4) in determining the fate of human umbilical epithelial cells (HUEVECs) exposed to cisplatin.

Conclusions: The phosphorylation (activity) of AMPK was determined by immunoblotting and expressed as % of total AMPK. The expression of KLFL4 was knocked down (by ~85%) using a specific siRNA (“KD cells”). “Control cells” were transfected with a scrambled siRNA. The response of HUEVECs to cisplatin-induced injury was determined by first pretreating the cells with either A-769662 (250µM) or its vehicle for 24h, followed by incubation with either cisplatin (100µM) or its vehicle for an additional 18h. Then cell survival was determined by flow cytometry and expressed as % of vehicle-treated cells.

Funding: Other NIH Support - NCI

SA-PO097

Proteome Studies of Cisplatinated DNA Binding Proteins Identifies RtcB, a Novel RNA Ligase, as an Essential Regulator of Epithelial Cell Death and DNA Damage Response

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Background: Cisplatin is one of the most widely used and effective anti-cancer drugs. The therapeutic efficacy and side-effects of cisplatin are largely dependent on its ability to cause DNA damage in both normal and cancer cells. However, the molecular mechanisms involved in cisplatin-mediated DNA damage response and repair remains incompletely understood. In order to uncover novel proteins involved in the cisplatin-associated DNA damage response, we carried out immunoprecipitation of cisplatin-DNA adducts followed by mass spectrometric analysis of associated proteins. These studies revealed that RNA ligase RtcB is associated with cisplatinated DNA under in vitro and in vivo conditions.

Methods: In order to identify novel proteins associated with cisplatin-mediated DNA damage response, we used a cisplatin-DNA adduct antibody to pull down chromatin-associated proteins in murine kidneys after cisplatin treatment. Mass spectrometric analysis was then carried out to identify the proteins associated with cisplatinated-DNA. In vivo and in vitro siRNA approaches were then used to decipher the functional relevance of identified proteins in cisplatin-mediated renal epithelial cell death and DNA damage signaling. Western blot and immunofluorescence experiments were carried out in epithelial cells and renal tissues to measure the extent of DNA damage as well as the activation of DNA damage response.

Results: Initial pulldown studies followed by mass spectrometric analysis identified RtcB as a previously unknown sensor of cisplatin-associated DNA damage. Functional studies in murine renal epithelial cells showed that RtcB knockdown impairs DNA repair, increases DNA damage response and sensitizes cells to cisplatin-mediated cell death. In vivo siRNA-mediated RtcB knockdown resulted in augmented AKI and higher renal epithelial cell death. While RtcB is known to play a role in RNA splicing and unfolded protein response, our work has identified RtcB as a novel player involved in the DNA damage response and repair.

Conclusions: Together, these results suggest an important role for RtcB in the therapeutic efficacy and toxicities associated with the anti-cancer drug cisplatin.

Funding: Other NIH Support - NCI

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Underline represents presenting author.

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SA-PO099

Activation of Renal AMP-Activated Protein Kinase (AMPK) Is an Adaptive Response to Sepsis/Inflammation That Can Be Pharmacologically Harnessed to Improve Survival

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Background: To determine the role of renal AMPK activation and inhibition in the renal proximal tubular cell (PTC) metabolic response to sepsis, and to investigate the effects of AMPK signaling on sepsis-induced TEC injury, clinical status and survival.

Methods: Animals: Twelve-week-old C57BL/6 (n=6-10/group) mice were randomized to vehicle, 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) or control (CC), and were subjected to cecal ligation and puncture (CLP). Outcome: Survival at 7 days. Cells: Human kidney 2 (HK2) cells were cultured in serum-containing medium containing 21% O2 and were assigned to control, AICAR and CC, and then exposed to inflammatory mix (IM=LPS+HMGB1). Using a Seahorse metabolic analyzer, we measured oxygen consumption rate (OCR) as a surrogate of OXPHOS (mitochondrial respiration) and extracellular acidification rate (ECAR) as a surrogate of glycolysis at 24 hours. Spontaneous respiratory capacity defined as the capacity of the cell to increase ATP production in conditions of increased energetic demands was measured by comparing OCR at baseline and after uncoupling mito-median.

Results: Pharmacologic activation of AMPK with AICAR before or after sepsis improves mice survival at 7 days (AICAR+CLP vs CLP; 70% vs 19%; p<0.05), and inhibition with CC before sepsis increases mortality at 7 days (CC+CLP vs CLP; 100% vs 81%; p<0.05). Cells exposed to IM and CC showed a decrease in OCR and spare respiratory capacity by 24% and 93% respectively when compared to IM (Figure 1B, C), and the limited recovery of glycolysis upon blockade of the mitochondrial electron transport chain (Figure 1D).

Conclusions: Enhancement of AMPK with AICAR increases survival, whereas inhibition with CC decreases survival. AMPK inhibition limited the capacity of tubular epithelial cells to recruit OXPHOS and glycolysis, thereby limiting metabolic flexibility. These findings suggest that TEC metabolic response to sepsis is an adaptive mechanism and that maintenance of metabolic flexibility may be key to survival from sepsis.

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SA-PO100

Alpha-7 Nicotinic Receptor Agonist GTS-21 Ameliorates Contrast-Induced Nephropathy in Rats

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Background: Despite the extensive use of contrast agents in medicine, no proven pharmacological therapies exist to prevent contrast-induced nephropathy (CIN), which causes renal damage by renal vasoconstriction, medullary hypoxia, oxidative stress and direct tubular toxicity of the contrast agent. In an experimental CIN model, we aimed to evaluate the possible therapeutic effects of GTS-21, a selective alpha-7 nicotinic receptor agonist with anti-apoptotic, anti-inflammatory and anti-oxidative properties.

Methods: In male Sprague-Dawley rats, CIN was induced by intravenous injection of iohexol (10 mg/kg), L-NAME (10 mg/kg), a high-osmolar contrast agent (Urografin 76%, 6 mg/kg) and then GTS-21 (21 mg/kg) 24 h earlier. Kidney, blood and plasma samples were obtained for the determination of cytokine expression (RT-PCR), oxidative stress parameters and histopathological analysis. Data were analyzed using ANOVA and Student’s t-test.

Results: When compared to control, GTS-21 treatment significantly increased urinary creatinine and BUN levels in the contrast group were elevated (p<0.05), while these measurements in GTS-21-contrast group were not different than controls. Increased histopathological damage score in contrast group (p<0.01) with respect to both control groups was significantly decreased in GTS-21-contrast group (p<0.001). Elevated malondialdehyde level in control group (p<0.001) was partially lowered by GTS-21 treatment, while antioxidant glutathione level was increased (p<0.05). In both contrast groups, an increase in IL-6 expression and a reduction in TGF-β expression were observed (p<0.05), but GTS-21 treatment decreased TGF-β expression by 0.05 and slightly depressed IL-6 expression.

Conclusions: GTS-21 improves renal dysfunction and provides a significant protection against contrast nephropathy via anti-oxidant and anti-inflammatory mechanisms.

Funding: NIDDK Support

SA-PO101

Molecular Pathways Driving Omeprazole Nephrotoxicity

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Background: Omeprazole, a proton pump inhibitor used to treat peptic ulcer and gastrointestinal reflux disease, has been associated to chronic kidney disease and acute interstitial nephritis. However, whether omeprazole is toxic to renal cells is unknown. Omeprazole has a lethal effect over some cancer cells, and cell death is a key process in kidney disease.

Methods: Thus, we evaluated the potential lethal effect of omeprazole over cultured tubular proximal cells.

Results: Omeprazole induces dose-dependent cell death in human and murine proximal tubular cell lines and in human primary proximal tubular cell cultures. Increased cell death was observed at the high doses used in cancer cell studies and also at lower concentrations similar to those in peptic ulcer patient serum. Cell death induced by omeprazole has features of necrosis such as annexin V+/7-AAD staining and irregular chromatin condensation. Weak activation of caspase-3 was observed but inhibitors of caspases (carbonylbenzoxyl-valyl-alanyl-asparyl-[3-Methyl]-fluoromethylketone, zVAD), necroptosis (necrostatin-1) or ferroptosis (ferrostatin-1) did not prevent omeprazole-induced death. However, omeprazole induced a dose-dependent and early increase in ROS production as assessed by CM-H2DCFDA staining and flow cytometry. ROS production increased in mitochondria, as assessed by MitoSOX staining, and by NADPH activity role, determined by lucigenin assay. Moreover, the antioxidant molecule N-Acetylcysteine (NAC) partially prevented omeprazole-induced ROS production and cell death as assessed by flow cytometry and by annexin V+/7-AAD staining. Omeprazole also induced lysosomal stress, evidenced by an increase in lysosomal pH and this was also prevented by NAC. Autophagy activation was also observed but blockade of autophagosome formation by 3-methyladenine did not decrease omeprazole-induced death. An adaptive increase in the expression of the antipapoptotic protein Bcl2 failed to protect the cells. In mice, parental omeprazole increased tubular cell death and the expression of NGAL, a marker of renal injury.

Conclusions: In conclusion, omeprazole nephrotoxicity may be related to induction of oxidative stress and renal tubular cell death, supporting the biological plausibility for the epidemiological association of chronic proton pump inhibitor use to kidney disease.

Funding: NIDDK Support

SA-PO102

Mechanistic Modelling of the Linkage Between Proximal Tubule Cell Sublethal Injury and Tubular Sodium Reabsorption Impairment


Background: Renal epithelial cell injury, a prominent feature of drug-induced acute kidney injury (AKI), is characterized by loss of brush border and cellular polarity of proximal tubular cells (PTCs). The key alterations caused by sublethal injury involve impaired energetics and associated disruptions in cytoskeletal structure and sodium transporters activity. A mechanistic model relating AKI mediated cellular injury with renal tubular dysfunction is needed to address the complexity of renal physiology.

Methods: We developed a model of sublethal PTC’s injury and sodium reabsorption impairment within the framework of RENAsym, a quantitative systems toxicology (QST) model of drug-induced AKI under development. The mathematical model represents major components of renal sublethal injury in a system of equations accounting for ATP decline, microfilament redistribution, and Na+/K+ ATPase activity reduction. The model equations were parameterized with an experimental study in which induced sublethal injury in rats, by selectively inhibiting cortical ATP production using maleic acid, was investigated and the effect of dose-dependent ATP decrement on apical F-actin networks and tubular sodium reabsorption was measured [1].

Results: Microfilament disruption was quantified with ATP decrement and then related to translocation-based loss of Na+/K+-ATPase, while a decline in the molecular activity of a sodium pump was directly related to ATP decrement. The model recapitulated the link between ATP decrement and sodium reabsorption impairment through the intermediate pathway of microfilament redistribution and Na+/K+ ATPase activity reduction. Simulations of varying ATP decrement reveals a sharp decline in sodium reabsorption as the relative ATP decrement exceeds 40%, in accord with observations [1].

Conclusions: A mechanistic model of subcellular injury is developed to link cellular ATP decrement and tubular sodium transport impairment. The model serves as a bridge between cellular toxicity and renal tubular functional impairment, allowing mechanistic prediction of AKI induced renal hemodynamics.

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Underline represents presenting author.
SA-PO103

Evaluating the Nephrotoxicity of Exemplar Compounds Using a Mechanistic Model of Drug-Induced AKI

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Background: Drug-induced nephrotoxicity is a common source of acute kidney injury (AKI) and brings clinical complexities. Drugs cause nephrotoxicity by various mechanisms, including mitochondrial dysfunction and oxidative stress. Predicting the AKI potential and toxicity mechanisms of drugs remains a challenge. We utilized a quantitative systems toxicology (QST) model to evaluate the nephrotoxicity and underlying mechanisms of two positive (cisplatin, gentamicin) and one negative (acetaminophen) control exemplar compounds.

Methods: We employed RENAsym, a QST model of drug-induced AKI that is currently under development, to evaluate the toxicity and injury mechanisms of the exemplar compounds. RENAsym represents aspects of renal proximal tubule cells (PTCs) including cell life cycle, bioenergetics, drug-induced cell death pathways, and biomarker (otGST) responses. In vitro data from literature were utilized to parameterize the oxidative stress production and clearance of the compounds. To determine the effects of drugs on mitochondrial dysfunction, electron transport chain (ETC) inhibition mechanism was parameterized using literature in vitro data.

Results: Drug nephrotoxicity was predicted by performing simulations using a virtual human model. In the simulations, a single dose of 533 mg/m² cisplatin resulted in 17% decline of PTC viability in 2 days. The simulations also showed a significant rise in urine αGST, a biomarker that marks PTC death. Similarly, a single dose of 3 mg/kg gentamicin showed 40% cell viability decline and high αGST elevations in 1 day. In contrast, no cell viability loss or αGST elevations were observed after multiple doses of 1 g QID (a maximum recommended dose for human) acetaminophen for over a week. In terms of injury mechanisms, simulations showed oxidative stress as the dominant mechanism for both cisplatin and gentamicin-induced toxicities.

Conclusions: Simulations predicted toxicity for two positive control compounds and no toxic response to the negative control compound, in qualitative agreement with the expected behaviors. RENAsym shows promise in providing a unique tool for drug-induced AKI prediction.

Funding: NIDDK Support

SA-PO104

Intravital Imaging of Single Collecting Ducts Micro-Perfused with Uropathogenic Escherichia coli Demonstrates Phagocytosis by Intercalated Cells

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Background: Renal epithelial cells have a different lineage and historically were considered to have different functions than myeloid derived macrophages. However some epithelial cells, such as renal intercalated cells have been recently demonstrated to have distinct immune functions.

Methods: VATPaseH1-cre transgenic mice were crossed to tdTomato-loxp homozygous mice which results in red fluorescence of intercalated cells. Under isoflurane anesthesia a kidney was surgically exposed and a single collecting duct was cannulated with UPEC could be confirmed by visualization GFP expressing bacteria flowing through intercalated cells renal epithelial cells. Phagocytosis was confirmed by visualization GFP expressing bacteria flowing through intercalated cells.

Results: Single collecting ducts could be cannulated (Figure 1A). Micro-perfusion with UPEC could be confirmed by visualization GFP expressing bacteria flowing through a tubular structure (Figure 1B). Bacteria were internalized selectively in red fluorescent expressing intercalated cells (Figure 1C-D). Ecoli coated bioparticles were also selectively internalized by intercalated indicating an intercalated cell activated process not just bacterial invasion.

Conclusions: We demonstrate that micro-perfusion of single collecting ducts can be accomplished in vivo and imaged using intravital microscopy. Renal intercalated cells phagocytize bacteria similar to myeloid immune cells such as macrophages even though intercalated cells are renal epithelial cells.

Funding: NIDDK Support

SA-PO105

In Vitro and Ex Vivo Exploration of the Expression of MicroRNAs to Assess the Progression of AKI

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Background: MicroRNAs are endogenous short, non-protein coding RNAs that post-transcriptionally/translationally control protein expression by binding to target mRNA. There is increasing interest in miRNAs in disease research because of their ability to coordinate the regulation of protein expression by influencing multiple signalling pathways. Some miRNAs have previously been shown to be responsive to AKI, suggesting they may be mediators of the damage and repair processes and potential markers. To build on this work, we have sought to determine miRNA expression in AKI using a combination of in vitro and ex vivo models.

Methods: We first sought to categorise the urinary expression of selected miRNAs to determine their biological importance in AKI. Recognising the challenges of recovering low abundance transcripts in urine, we sought to firstly validate our experimental approach. We found that RNA recovery was similar in urine before centrifugation and after centrifugation. We further compared the RNA recovery rates between normal sample and exosome enriched samples, demonstrating that whilst exosome enrichment did not increase the overall yield of miRNAs, it did result in improved amplification profiles. Having demonstrated experimental validity, miRNA was assessed in urine samples obtained from patients with KDIGO Stage 2 and 3 and samples from non-AKI donors. Expression of miR-30a-5p, miR-192, miR-101-3p was reduced in KDIGO 3 and KDIGO 2 compared to healthy control samples.

Results: Having shown that these miRNAs are differentially regulated in AKI ex vivo, we next sought to categorise in vitro. For these investigations, HK2 tubule epithelial cells were cultured with 10 µM/m, 1 mg/ml and 0.1 mg/ml of LPS for 2, 4, 6, 12 and 24 hours. Results: MicroRNAs that are downregulated in vivo are also downregulated in vitro.

Conclusions: These investigations demonstrated LPS dysregulation of these target miRNAs in a time and concentration dependent manner. These data suggest these mediators respond to tubule injury and thus may be useful as early markers of AKI, as well as contributing to the changes in transcription which underpin the initiation, progression and outcome of AKI. Further investigations will focus on delineating the functional importance of MiRNAs as molecular drivers of AKI.

SA-PO106

Administration of miR-486-5p Protects Against Kidney Ischemic Injury and Alters the Transcriptome in Male and Female Mice

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Background: Ischemia-reperfusion is a common cause of acute kidney injury (AKI), and no treatments exist to restore function. We showed that cord blood endothelial colony forming cells (ECFCs) release exosomes (enriched in miR-486-5p) that are protective against ischemic AKI in male mice. This response involves inhibition of phosphatase and tensin homolog (PTEN), a target of miR-486-5p and Aki activation. Here, we studied effects of direct administration of miR-486-5p to mice with AKI, and defined sex differences.

Methods: Kidney injury was induced in mice by 30-minute bilateral renal vascular clamping followed by reperfusion and sacrifice at 24 or 48 hrs. ECFC exosomes, miR-486-5p mimics (in cationic lipid) or scrambled miR were injected i.v. at the start of reperfusion. Kidney endothelial cells and proximal tubules were isolated for transcriptomic analyses.

Results: Male and female mice treated with miR-486-5p mimic at the time of reperfusion had increased miR-486-5p levels in kidney endothelial cells and proximal tubules, liver and spleen (P<0.01, n=8), but not in lung, heart or brain. In male or female mice with kidney ischemia-reperfusion, miR-486-5p mimic or exosomes significantly
decreased serum Cr and urea, histologic injury, apoptosis, and neutrophil infiltration (n=6). Delivery of miR-486-5p reduced kidney PTEN protein expression, and increased Akt phosphorylation (P<0.05, n=6). Female mice were resistant to kidney injury compared to males, by all parameters (P<0.05 vs male), showed fewer differentially expressed genes compared to males, and had less gene variation with treatments. Kidney ischemia induced higher numbers of differentially expressed genes in tubules compared to endothelial cells. In male mice treated with miR-486-5p mimic, the expression of most tubular genes that were significantly changed with ischemia-reperfusion alone returned to levels close to sham.

Conclusions: Systemic delivery of miR-486-5p to male and female mice with AKI increases miR-486-5p levels in kidney endothelial cells and proximal tubules, and prevents ischemic injury. Female mice are resistant to AKI compared to males, and exhibit fewer differentially expressed genes. Changes in the kidney transcriptome with miR-486-5p may define pathways relevant to prevention of AKI in humans.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO107
Association of Altered Urinary miR-141 and miR-192 Expression with AKI Outcome
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Background: Acute Kidney Injury (AKI) is characterised by a sudden decline in kidney function and affects over 20% of US hospitalisations, resulting in a greater than 4-fold increased mortality. The mechanisms underlying AKI recovery versus non-recovery remain poorly understood, and current biomarkers have limited capacity to predict outcome. Several factors limit the development of new therapies. Here we evaluated the potential of urinary microRNAs (miRNAs) as biomarkers in patients with severe AKI.

Methods: Daily consecutive urine samples were collected from 30 patients with AKI stage III by KDIGO criteria. 377 miRNAs were profiled by RT-qPCR screening in pooled samples from recovery (n=6) and non-recovery (n=5) groups, with validation using individual assays. MiRNAs exhibiting altered expression in the urine of patients subsequently recovering vs. non-recovering kidney function were evaluated in vivo using individual assays. MiRNAs exhibiting altered expression in the urine of patients subsequently recovering vs. non-recovering renal function were evaluated in vitro (ischemia reperfusion injury (IRI) in the rat) and in vitro (proximal tubular epithelial cells (PTEC) exposed to hypoxia or oxidative stress) models by RNA sequencing and RT-qPCR. To identify miRNA targets, selected miRNAs were manipulated using transfection-based gain- and loss-of-function approaches in vitro.

Results: An extensive pattern of miRNA changes was observed, notably decreased miR-141 and increased miR-192 expression that predicted non-recovery. Alterations in miRNA expression were validated and linked to changes in our rat IRI model and in PTC miRNA expression in vivo. Network analysis of predicted miRNA targets converged on protein tyrosine phosphatase type G (PTPRG) and dysregulated PTPRG expression was confirmed in vivo.

Conclusions: These data identify quantifiable urinary miRNAs that predict outcome following AKI, and link these miRNAs to potential mechanisms of injury and recovery following AKI.

SA-PO108
miR-214 Promotes Mitochondrial Fragmentation and Cellular Apoptosis by Targeting MFN2 in ATP-Depleted Renal Proximal Tubular Cells
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Background: Mitochondria injury is a pathological factor for AKI by promoting cell apoptosis. microRNAs have been reported to play important regulatory roles in AKI. However, microRNA associated with mitochondrial injuries are poorly understood.

Methods: Azide-induced ATP-depletion model to study AKI in renal proximal tubular cells (RPTCs) in vitro. The miRNA expressions of miR-214 were detected by RT-qPCR. The protein levels of MFN2, p-actin and cleaved-caspase3 were determined by western blot, then analysis by image J. The mitochondria morphology was detected by confocal microscopy.

Results: We found that miR-214 level was upregulated after azide treatment and reperfusion in RPTCs, while MFN2 protein level was reduced. Overexpression of miR-214 by transfection decreased MFN2 protein level. The inhibition of miR-214 by anti-miR-214 LNA reduced the decrease in MFN2 and induced by AZT depletion, and the percentage of RPTCs with fragmented mitochondria were decreased as well. The number of apoptotic cells and the increase in cleaved-caspase 3 expression induced by azide treatment in RPTCs were reduced by anti-miR-214 LNA transfection. On the contrary, overexpression of miR-214 increased apoptosis and cleaved-caspase 3 expression in ATP-depleted RPTCs.

Conclusions: These results suggest that miR-214 upregulation promotes mitochondrial fragmentation and cellular apoptosis by downregulating MFN2 expression and inhibition of miR-214 ameliorates mitochondrial fragmentation and reduces cellular apoptosis by upregulating MFN expression in ATP-depleted RPTCs. Targeting miR-214 could show potentially therapeutic effect in AKI.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO109
Endothelial-Derived miR-17–92 Protects Against Renal Ischemia-Reperfusion Injury
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Background: Acute kidney injury (AKI), resulting from renal ischemia reperfusion injury (IRI) among others, is an independent predictor of morbidity and mortality, and is identified as in many as 50% of ICU patients. Damage to the renal microvasculature is a hallmark of renal IRI. miR-17–92 encodes 6 polycistronic microRNAs that show potent pro-angiogenic capacity by targeting anti-angiogenic factors. The function of miR-17–92 in renal microvasculature after renal IRI remains unknown. We hypothesized that endothelial-specific miR-17–92 mediates endothelial repair and kidney recovery after renal IRI.

Methods: Endothelial-specific miR-17–92 knockout (miR-17–92−/−) transgenic mice were generated and a renal IRI model was performed. Mice were monitored for the development of AKI using serum chemistries, histology, and markers of renal tubular injury. The renal vasculature and infiltrating macrophages post-injury were evaluated using multiple markers.

Results: We demonstrate that miR-17, miR-18a, miR-19h and miR-20a in the miR-17–92 cluster are up-regulated in CD11b+ renal endothelial cells following renal IRI. Loss of miR-17–92 in endothelial cells does not affect renal vascular development and renal function in adult mice. Following renal IRI, miR-17−92−/− mice had worse renal dysfunction and epithelial damage, and exhibited up-regulation of the injury marker NGAL in proximal tubules compared to the controls. miR-17–92−/− kidneys had decreased Endomucin-positive renal microvasculature post renal IRI. miR-17–92−/− kidneys upregulated the potent anti-angiogenic factor Thrombospondin-I (TSP1) in a subset of Endomucin-positive renal microvasculature. miR-17–92−/− kidneys also had increased F4/80-positive infiltrating macrophages post renal IRI along with up-regulation of multiple macrophage markers in its kidneys.

Conclusions: These data suggest that miR-17–92 in renal endothelial cells confers protection from damage in the renal microvasculature during renal IRI mediated by targeting an anti-angiogenic factor TSP1. This, in turn, mitigates hypoxia damage in tubular epithelial cells and down-regulates inflammatory activation following injury.

Funding: NIDDK Support, Private Foundation Support

SA-PO110
Proteomics Reveals the Principle of Transition from AKI to CKD
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Background: Chronic kidney disease (CKD) compromises renal function and occurs as a potential long-term outcome in response to acute kidney injury (AKI). Currently, lack of mechanistic understanding prevents the progression from AKI to CKD. As we enter the ‘big data’ era, multiple OMICS analyses provide a platform not only assist the field to further understand kidney disease transition, but also significantly enhance the possibility to translate novel findings from basic research into the clinic. The present study aims to systematically analyze the proteomes profiles from the onset of kidney injury to end stage renal disease and identify dynamic network biomarkers during disease progression.

Methods: We constructed renal ischemia reperfusion injury (IRI) mouse model for time series courses. Quantitative proteomics (isobaric peptide tags for relative and absolute quantification, iTRAQ) was applied in revealing the proteomes profiles in kidney tissues. Dynamic network biomarker (DNB) analysis was performed to clearly identify the critical state or tipping point during the transition of kidney disease.

Results: We identified 6146 proteins in the disease kidneys. Pearson correlation analysis indicated that the transitional process from AKI to CKD could be divided into 4 periods in mice, initiate phase (0-12h), switching phase (1d), repair phase (3-5d), and steady phase (7-10d). Among these periods, two time points (4h and 3d) were critical in determining the prognosis of kidney disease. We then analyzed time-series protein expression data with the DNB method, and identified NCBP1 as a core DNB member. At a network level, the biological role of NCBP1 is prominent in kidney repair and regeneration.

Conclusions: Establishing disease monitoring system at appropriate time points will be greatly beneficial in understanding the pathogenesis of kidney disease transition.

Funding: NIDDK Support
SA-PO111
Proteomic Analysis of the Tubulointerstitial Characteristics in Acute Tubular Necrosis
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Background: Acute tubular necrosis (ATN) is the most common form of acute kidney injury (AKI) in the hospital setting. Urine proteomic analyses have been extensively performed in AKI, but the kidney proteome has largely been unexplored. Here, we performed unbiased proteomics on the tubulointerstitium (TI) from kidney biopsies with ATN to identify kidney specific proteomic signatures that characterize ATN.

Methods: Mass spectrometry was performed on ATN kidney biopsy tissue from 8 ATN and 8 living transplant donor kidney biopsy controls (LTx). The TI was isolated and total protein was extracted and submitted for HPLC-MS/MS analysis using the Orbitrap Elite. Label free quantification followed by global normalization of spectral count data was performed. Proteins identified in ATN were compared to LTx. Statistical significance was considered if 2-fold change and P<0.01.

Results: All patients had biopsy proven ATN. The average serum creatinine in ATN was 5.7mg/dl (SD: ±2.7). Overall, 86 proteins were upregulated and 44 downregulated in ATN compared to LTx. The top upregulated markers included extracellular matrix (ECM) proteins implicated in AKI to CKD transition, ER stress proteins, and wound repair proteins (Figure 1). Meanwhile, transport, metabolism, and mitochondrial markers were suppressed. Pathway analysis revealed activation of remodeling of epithelial adheren junctions, acute phase response signaling, and coagulation and suppression of metabolic pathways.

Conclusions: Kidney proteomic evaluation demonstrates overexpression of ECM proteins in ATN that previously have been implicated in CKD progression and may reflect AKI to CKD transition. These markers could serve as novel therapeutic targets to arrest injury early and prevent progression to chronic kidney disease.

Funding: NIDDK Support

SA-PO112
Long-Term Outcomes in Mouse Models of Ischemia-Reperfusion-Induced AKI
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Background: AKI is a risk factor for CKD, but no therapies have improved outcomes. Therapies that are effective in models that mimic features in patients, and evaluate long-term outcomes, are more likely to be predictive of success in the clinic. Here, we evaluated susceptibility to CKD after unilateral ischemia reperfusion injury (URIRI) with a delayed contralateral nephrectomy (DN-IRIR) in mice. We define the conditions to induce renal dysfunction and fibrosis without increased mortality, and evaluate effect of mouse strains, sexes, and pre-existing diabetes.

Methods: Studies were performed in different strains and sexes of mice, and in mice with streptozotocin (STZ)-induced diabetes mellitus (DM). DN-IRIR with different renal pedicle clamp times was performed along with contralateral nephrectomy (Nx) 8 days after injury to identify conditions associated with reduced GFR 4 weeks after injury. After optimizing IRIR clamp time, we evaluated renal function with serial BUN, creatinine and transdermal GFR. Renal fibrosis: QPCR for fibrosis markers, picrosirius red (PSR) quantification. Peritubular capillary density (PTCD) by quantifying CD31 positive blood vessels. Fibrosis was assessed with trichrome and picrosirius red stain. Collagen and vascular endothelial growth factor (VEGF) levels were also assessed.

Results: SRU was capable of the accurate identification of microvessels with a resolution of 32 microns. Using SRU, a clear reduction in vascular density was identified in the IRI kidneys compared to control. SRU measurements correlated favorably with traditional CD31 immunohistochemical staining (R=0.8). This was accompanied by a reduction in renal blood volume and kidney size. As expected, there was an increase in renal fibrosis that appeared to peak at 21 days. VEGF levels were also decreased after IRI. Conclusion: SRU was capable of identifying the decrease in microvascular density after IRI in mice at late timepoints after injury. This correlated favorably with traditional immunohistochemistry and could be a method to monitor the progression of kidney disease after AKI.

Funding: NIDDK Support, Private Foundation Support

SA-PO113
Super-Resolution Ultrasound to Monitor Microvascular Rarefaction After AKI in Mice
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Background: Acute kidney injury is associated with an increased incidence of chronic kidney disease. One mechanism to explain this is the loss of vascular density in the kidney post-AKI, leading to chronic hypoxia. Current techniques to evaluate the vasculature are limited by a lack of resolution, technique causing harm to the subject, or inability to perform in live subjects. Super-resolution ultrasound (SRU) is an emerging technology to achieve high spatial resolution to identify microvessels in live animals.

Methods: C57BL/6 mice were subjected to unilateral ischemia-reperfusion injury (IRI) surgery. At 21 and 42 days after injury, mice were injected with clinical ultrasound contrast agent (Definity) and both the injured and contralateral control kidneys were evaluated in vivo under anesthesia. Using B-mode imaging the kidneys were imaged in the maximal longitudinal plane. Imaging data from 900 effective frames were acquired using multi-angle ultrasound plane wave imaging at an effective frame rate of 250 Hz. Off-line signal processing was performed in MATLAB with radio-frequency data processed through beamforming, motion compensation, singular value decomposition filter, Richardson-Lucy deconvolution, and frame summation. After imaging, mice were euthanized, kidneys were recovered and subjected to immunohistochemistry to identify CD31 positive blood vessels. Fibrosis was assessed with trichrome and picrosirius red stain. Collagen and vascular endothelial growth factor (VEGF) levels were also assessed.

Results: These data define renal pedicle clamp times for the DN-IRIR model in different mouse strains, sexes, and pre-existing diabetes. This provides insight into the potential role of capillary rarefaction as being the key driver to CKD progression, rather than renal fibrosis.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Transplanted Senescent Renal Tubular-Like Cells Induce Renal Microvascular Injury

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Background: Cellular senescence is characterized by a senescence-associated secretory phenotype (SASP), which reinforces senescence and exerts noxious effects on adjacent cells. Recent studies suggest that transplanting small numbers of senescent cells suffices to provoke tissue inflammation. Several models of kidney disease show increased prevalence of senescent renal cells. We hypothesized that senescent cells can directly augment renal injury.

Methods: Cellular senescence was induced in primary tubular-like cells acquired from pig kidneys by 100 Gy of cesium radiation, and 3 weeks later cells were characterized for senescence and SASP markers. Control (CON) or senescent (SEN) renal tubular-like cells were pre-labeled and injected intra-orta to C57BL/6J mice. Four weeks later renal oxygenation was studied using magnetic resonance imaging, and by plasma creatinine level. Renal markers of SASP, fibrosis, and microvascular density were evaluated.

Results: Per flow cytometry, 80-99% renal tubular-like cells were senescent after irradiation. They showed increased mRNA of senescence and SASP markers, SA-β-gal staining, and cytokines levels secreted in conditioned-medium. Four weeks after injection, cells were detected engrafted in the kidneys with no evidence for rejection. Plasma creatinine and renal tissue hypoxia tended to increase in SEN compared to CON. SEN kidneys were more fibrotic, with fewer CD31+ endothelial cells, and showed upregulation of IL-6 gene expression.

Conclusions: Senescent renal tubular-like cells directly induce renal inflammation, fibrosis, microvascular loss, and hypoxia. These observations suggest a role for cellular senescence in the pathogenesis of kidney injury, and support development of senolytic therapy.

Funding: NIDDK Support

SA-POI15

IKKα Aggravates Renal Fibrosis by Positively Regulating the Wnt/β-Catenin Pathway

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Background: Acute kidney injury (AKI) with maladaptive repair is a major contribution to renal fibrosis characterized by tubulointerstitial fibrosis. Previously, we have revealed that IKKα was involved in inhibiting inflammation and kidney regeneration.

Methods: By mating IKKα−/− mice with Kap-Cre transgenic mice, mice with IKKα gene specifically ablated in arterial tubular cells were created. After dorsal incision, the left renal pedicle was clamped with a micro vascular clamp for 45 min, while the sham-operated mice underwent the same treatment except clamping renal pedicle. We added TGF-β1 to the culture medium to establish the cell fibrosis model in human tubular epithelial cells.

Results: The expression of IKKα was up-regulated in kidney tubular epithelium in mice models of unilateral ureteral obstruction and ischemic reperfusion injury. In addition, immunohistochemical staining showed IKKα renal expression positively correlated with the kidney fibrosis in chronic kidney diseases (CKD) patients. Furthermore, we generated a knockout mouse model with IKKα gene specifically deleted in renal tubules. These knockout mice were phenotypically normal at birth and had no significant defects in kidney morphology and function. Compared with controls, Kap-IKKα−/− mice showed Wnt/β-catenin activation, serum creatinine and attenuated interstitial fibrosis at 14 days after ischemic reperfusion injury. In vitro, IKKα blocked the interaction of GSK-3β with β-catenin in TGF-β1-stimulated human tubular epithelial cells resulting in β-catenin nuclear translocation. Additionally, blocking IKKα by siRNA specifically suppressed β-catenin activation and profibrotic gene expression such as fibronectin and α-smooth muscle actin.

Conclusions: IKKα aggravates renal fibrogenesis by amplifying regulation of the Wnt/β-catenin signaling pathway which may provide a potential anti-fibrosis therapy target for chronic kidney diseases.

SA-POI17

β-Catenin/FoxO Promotes Epithelial Healing in Kidney Injury

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Background: Transforming growth factor (TGF-β) is known to promote healing after tissue injury, but also drives a maladaptive fibrotic response that leads to fibrosis and organ failure. β-catenin/TGF-β is central to TGF-β’s profibrotic signaling pathways. β-catenin also binds to FoxO in competition with TCF and promotes survival under oxidative stress. We propose that targeting TGF-β signaling by using an inhibitor of β-catenin/TCF will promote β-catenin/FoxO which results in physiological healing with epithelial rather than mesenchymal cells.

Methods: Scratch assay was used as an in vitro model of healing in murine proximal tubule-like epithelial C1.1 cells treated with TGF-β1 (3ng/ml) with or without β-catenin/ TCF inhibitor ICG-001 (5µM). CRISPR/Cas9 was used to knock out FoxO1. Wound closure was measured as the percentage area of wound closure at 48 h (%). In vivo kidney injury healing was evaluated in murine unilateral ischemia reperfusion injury (IRI) mice by Gomori trichrome staining. Epithelial (E-cadherin) or mesenchymal (α-SMA) healing was examined by immunofluorescence staining and measured as percentage area of positive staining (%). β-catenin/FoxO or β-catenin/TCF interactions were examined by proximity ligation assay (PLA).

Results: The combined treatment of TGF-β1 and ICG-001 in C1.1 cells and UIR caused increased β-catenin/FoxO interaction as demonstrated by PLA. The combined treatment inhibited TGF-β-induced α-SMA expression and showed dominant E-cadherin expression to a greater extent than seen with TGF-β alone; α-SMA, 52±% vs 40±%, P<0.01 in vitro, and 18±% vs 42±%, P<0.01 in vivo; E-cadherin, 29±% vs 2±%, P<0.05 in vitro, and 22±% vs 11±%, P<0.05 in vivo. FoxO1 KO in C1.1 cells showed significant reduction in the closure of wound gap compared to WT cells (75±% vs 95±%, P<0.05). FoxO1 KO C1.1 cells slowed wound closure under combined treatment compared to that of WT cells (70±% vs 98±%, P<0.01) which could be explained by absence of β-catenin/FoxO in FoxO1 KO C1.1 cells. In UIR mice, combined treatment with rhTGF-β1 and ICG-001 significantly attenuated kidney fibrosis compared with TGF-β1 alone (42±% vs 73±%, P<0.01).

Conclusions: These results indicate that β-catenin/FoxO may serve as a therapeutic target to prevent pathological fibrotic healing and fibrosis in the treatment of kidney diseases.

SA-POI18

Endothelial Nitric Oxide Synthase/Nitric Oxide Pathway Underlies the Mechanisms of AKI to CKD Transition via Prolonged Activation of the Wnt/β-Catenin Pathway

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Background: Acute kidney injury (AKI) is not always reversible, but often promotes to chronic kidney disease (CKD), known as “AKI to CKD transition.” Aging and disease conditions such as hypertension and diabetes are recognized as risk factors for AKI to CKD transition. These conditions are also closely associated with endothelial dysfunction (ED). Therefore, we hypothesized that AKI to CKD transition is promoted by ED characterized by overexpression of eNOS/Nitric Oxide (NO) and cGMP/PKG pathway.

Methods: Wild-type mice (C57BL/6J: WT) and eNOS deficient mice (eNOSKO) were used. WT and eNOSKO mice were divided into 4 groups: WT-sham, WT-IRI, eNOSKO-sham and eNOSKO-IRI. Mice were sacrificed on day 28 (D28) after ischemic reperfusion injury (IRI-28) and sham-IRI (D28). To evaluate the potential of GSK activation on the AKI to CKD transition, eNOSKO-IRI mice treated with PDE5 inhibitor (PDE5i, Sildenafil citrate, 5mg/kg/day, drinking water) from day 7 (D7) to day 28 (D28) after IRI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Acute kidney damages of IRI were fully recovered in WT-IRI-D28 group. However, tubulointerstitial injuries, tubular cell damage, interstitial fibrosis and infiltration of inflammatory cells remained in eNOSKO-IRI-D28 group. These results indicate that deficient eNOS/NO/sGC/PKG signaling pathway promotes AKI to CKD transition after IRI. Next, the kidney damages in the early phase, day 1 and day 7, after IRI were examined in all groups. Histological examinations of kidney tissues failed to detect any differences in both groups at day 1 and day 7. However, RNA-seq analysis revealed significant increased expressions of Wnt/β-catenin-related genes and M2 macrophage (MΦ) related genes in eNOSKO-IRI-D7 group compared with WT-IRI-D7 group. In addition infiltration of M2 MΦ, evaluated by flow cytometric analysis, were increased in eNOSKO-IRI-D7 but not WT-IRI-D7. Furthermore, PDE5 treatment significantly ameliorated the kidney injury compared with non-treated group.

Conclusions: Over 13% of the world’s population have chronic kidney disease (CKD). Severe acute kidney injury can lead to chronic kidney disease (CKD) through maladaptive repair of proximal tubular cells (PTC) and cyclic arrest in the G2/M transition. Recently, we identified an atypical cyclin, cyclin G1 (CG1), as a key mediator of G2/M arrest, maladaptive repair and fibrosis; however, the underlying mechanism how CG1 regulates G2/M arrest and fibrosis remains to be resolved. The aim of the current study is to ascertain whether CG1-induced dedifferentiation drives PTC profibrotic signaling and kidney fibrosis.

Methods: Protocol 1; 8-week-old male BL6/B6 (WT) and CG1 knockout mice (CG1KO) received unilateral ureteral obstruction (UUO). Kidneys were taken at day 9 and fibrosis was assessed by picrosirius red staining and polarized microscopy. PTC dedifferentiation was defined by upregulated kidney injury molecule (KIM-1) and staining and PCR for differentiation/dedifferentiation marker expression. Protocol 2; Primary PTCs isolated from WT and CG1KO mice were treated with aristolochic acid (AA) and gene expression was analyzed by PCR and western blot.

Results: In response to UUO, kidney fibrosis was dramatically reduced in CG1KO compared with WT. Upregulation of KIM-1 in WT-UUO was ameliorated in CG1KO and markers of differentiation were preserved at both protein and mRNA levels in CG1KO. Compatible with our animal data, connective tissue growth factor (CTGF) and fibronectin were upregulated by AA treatment in WT PTC and attenuated in CG1KO PTC. Further, AA-induced cell enlargement was restored by deletion of CG1. Na-K-ATPase and AQP1 mRNA were also maintained in CG1KO PTC. Importantly, inhibition of dedifferentiation reduced levels of G2/M arrested cells, marked by phosphorylated Histone 3 (pH3), in CG1KO-UUO kidneys compared to WT-UUO.

Conclusions: Cyclin G1 drives a maladaptive dedifferentiation of proximal tubular cells after kidney injury, resulting in increased secretion of profibrotic cytokines and promotion of renal fibrosis. Cyclin G1-induced dedifferentiation facilitates G2/M arrest and subsequent maladaptive responses. As cyclin G1 is only expressed in chronically injured cells, it represents a potential therapeutic target for prevention of kidney fibrosis.

SA-PO119
Cyclin G1-Mediated Dedifferentiation of Proximal Tubular Cells Drives Fibrosis
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Background: Over 13% of the world’s population have chronic kidney disease (CKD). Acute kidney injury (AKI) is a devastating condition with high morbidity and mortality. The pathologic features of AKI are characterized by tubular injury, infiltration of inflammation cells and vascular integrity impairment. Prxvate kinase is the last rate-limiting enzyme in the glycolysis pathway. We have previously shown that Pyruvate kinase M2 (PKM2) plays an important role in regulating the glycolytic recombination of fibroblasts in chronic kidney disease. But the role of PKM2 in fibroblasts in the pathogenesis of AKI is unknown.

Methods: Lentivirus was used to down-regulate PKM2 expression in NRK-49F cells, and then analyzed the expression of the key enzymes of glycolysis and the ability of cell proliferation. In vivo, we generated fibroblast specific PKM2 knockout mice (Fibroblast-PKM2/-) by crossingbreeding PKM2-flox mice with S00A4-Cre mice. Then we compared renal function, expression of urinary KIM-1 and NGAL, pathological damage and renal tubular cell apoptosis between Fibroblast-PKM2/- mice and control mice after ischemia-reperfusion injury (IRI) or folic acid (FA) injection. Rneo-protective factors secreted by fibroblasts such as HGF and EPO were determined by RT-PCR and Elisa. Co-culture of NRK-52E cells and NRK-49F cells under oxygen deprivation condition was used to investigate the interaction between fibroblasts and renal tubular cells.

Results: Down-regulation of PKM2 can reduce glycolysis level and decrease the ability of proliferation of NRK-49F cells. Compared with control mice, Fibroblast-PKM2/- mice had less fibroblast activation, more kidney injury indicated by increased BUN, KIM-1 and NGAL levels and more apoptosis of tubular epithelial cells after AKI induced by I/R or FA injury. Furthermore, Fibroblast-PKM2/- mice secreted lower renal protective factors such as HGF and EPO. Additionally, Fibroblast-PKM2/- mice showed suppressed of HGF-cmet signaling and decreased expression of p-ERK and p-bad. Co-culture experiment in oxygen deprivation condition revealed that down-regulation of PKM2 in NRK-49Fcells could decrease the expression of HGF and EPO in NRK-49F cells and inhibit fibroblast activation, and increase apoptosis in NRK-52E cells.

Conclusions: Collectively, these results suggest that PKM2 mediated fibroblasts activation plays a critical role in the pathogenesis of AKI.

Funding: Government Support - Non-U.S.

SA-PO121
Pyruvate Kinase M2 Mediates Fibroblasts Activation Alleviates AKI
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Background: Acute kidney injury (AKI) is a devastating condition with high morbidity and mortality. The pathologic features of AKI are characterized by tubular injury, infiltration of inflammation cells and vascular integrity impairment. Pyruvate kinase is the last rate-limiting enzyme in the glycolysis pathway. We have previously shown that Pyruvate kinase M2 (PKM2) plays an important role in regulating the glycolytic recombination of fibroblasts in chronic kidney disease. But the role of PKM2 in fibroblasts in the pathogenesis of AKI is unknown.

Methods: Lentivirus was used to down-regulate PKM2 expression in NRK-49F cells, and then analyzed the expression of the key enzymes of glycolysis and the ability of cell proliferation. In vivo, we generated fibroblast specific PKM2 knockout mice (Fibroblast-PKM2/-) by crossingbreeding PKM2-flox mice with S00A4-Cre mice. Then we compared renal function, expression of urinary KIM-1 and NGAL, pathological damage and renal tubular cell apoptosis between Fibroblast-PKM2/- mice and control mice after ischemia-reperfusion injury (IRI) or folic acid (FA) injection. Rneo-protective factors secreted by fibroblasts such as HGF and EPO were determined by RT-PCR and Elisa. Co-culture of NRK-52E cells and NRK-49F cells under oxygen deprivation condition was used to investigate the interaction between fibroblasts and renal tubular cells.

Results: Down-regulation of PKM2 can reduce glycolysis level and decrease the ability of proliferation of NRK-49F cells. Compared with control mice, Fibroblast-PKM2/- mice had less fibroblast activation, more kidney injury indicated by increased BUN, KIM-1 and NGAL levels and more apoptosis of tubular epithelial cells after AKI induced by I/R or FA injury. Furthermore, Fibroblast-PKM2/- mice secreted lower renal protective factors such as HGF and EPO. Additionally, Fibroblast-PKM2/- mice showed suppressed of HGF-cmet signaling and decreased expression of p-ERK and p-bad. Co-culture experiment in oxygen deprivation condition revealed that down-regulation of PKM2 in NRK-49Fcells could decrease the expression of HGF and EPO in NRK-49F cells and inhibit fibroblast activation, and increase apoptosis in NRK-52E cells.

Conclusions: Collectively, these results suggest that PKM2 mediated fibroblasts activation plays a critical role in the pathogenesis of AKI.

Funding: Government Support - Non-U.S.
parchyma after AKI. We hypothesized that altered citrate metabolism contributes to maladaptive tubular repair after AKI and progression of diabetic nephropathy.

Methods: We generated C57B6/ Akita mice expressing the human diaphanous toxin receptor (DTR) in the renal tubule in a non-obese diabetic background. Animals on a high-fat diet (HFD) were administered one dose of DT to induce tubular injury, and the kidneys were damaged as assessed at four months. In a citrate-ligated tubular injury model, LLC-PK1, kidney epithelial cells were exposed to high glucose or high palmitic acid concentrations, and analyzed for cell cycle arrest, DNA damage response, and alteration in citrate metabolism.

Results: DT-treated Akita mice on HFD developed overt proteinuria, severe tubulointerstitial fibrosis, severe glomerular sclerosis, interstitial inflammation, capillary rarefaction, and podocyte dropout, while the control littermates without tubular injury, or without diabetes, or without HFD did not. The Akita mice on HFD had impaired renal function without proteinuria. Histopathological analysis indicated PTC injury and apoptosis, even interstitial fibrosis and secondary cyst formation and kidney enlargement in long-term induced mice, which indicated AKI-CIK transition. Vpr overexpression in podocyte led to massive podocyte injury, proteinuria and secondary cyst formation. Dox-induced vpr-related cell-cycle arrest was associated to relate with AKI-CIK transition, which indicated vpr overexpression was responsible for those kidney lesions. P53 and PLK 1 activation were induced in vpr overexpression related G2/M arrest. Both inhibitors reduced P53 and PLK 1 level in vivo, and partially rescued tubular cell injury, proteinuria and AKI-CIK transition in vpr induced damaged mice.

Conclusions: Our study demonstrated that vpr played an important role in the pathogenesis of tubular epithelial cell and podocyte damage and subsequent AKI or AKI-CIK transition. P53 and PLK 1 inhibition are useful to relieve or rescue tubular cell injury, proteinuria and AKI-CIK transition in vpr induced damaged mice.

Funding: NIDDK Support, Veterans Affairs Support, Government Support - Non-U.S.

SA-PO125

ATG5-Mediated G2/M Arrest Through ATR-Chk1 Signaling Contributes to Renal Fibrosis After Injury Induced by Aristolochic Acid I

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Background: Recent studies have shown that autophagy is involved in the regulation of G2/M arrest and plays a renoprotective role after kidney injury. However, its role in aristolochic acid (AA)-induced unclariﬁed AKI transition CKD remains largely unclarified.

Methods: Here, we investigated whether autophagy-related gene 5 (ATG5) modulatation of Chk1 phosphate expression during AKI contributes to the progression to CKD. We tested this hypothesis by administration of aristolochic acid-1 (AA1) in vitro.

Results: (1) CCK-8 showed that the viability of HK-2 cells treated with different concentrations of AA1 (0, 2.5, 5, 10, 20, 40 µM) for 48 h decreased in a concentration-dependent manner. The cell viability decreased in a time-dependent manner when HK-2 were stimulated with 5 µM AA1 for different durations (0, 3, 6, 12, 24, 48 h). (2) Western blot showed that the expression level of LC3-II/I, DNA double-stranded damage marker hHAX and FN in concentration-dependent, time-dependent increase after AA1 stimulation. Phosphorylation level of Chk1(s345) and its upstream regulatory protein ATR(s48) showed parabolic trends at 48 h after AA1 stimulation. Chk1(s345) and ATR(s48) phosphorylation level increased in a time-dependent manner when AA1 stimulation concentration was 5 µM. (3) Flow cytometry: After AA1 treat of HK-2 cells for 48 h, the cell cycle G2/M arrest rate increased most at AA1 concentrations of 5 µM and 10 µM and the proportion of G2/M was 39.12±9.9% and 40.88±10.1% respectively; the difference was statistically significant compared with 0µM (8.09±1.5%) (p=0.05, 0.05). While stimulation with AA1 concentration of 5 µM for 48 hours. The proportion of G2/M arrest gradually increased with time, and it was 41.57±16.6%at 48h; the difference was statistically significant compared with 0h (6.94±4.7%) (p=0.05).

Conclusions: ATG5 mediated G2/M arrest through Chk1 mediates the progression of AA1-induced kidney injury. Further studies are required to determine the molecular mechanisms underlying this regulation system.
Results: In Grhl2−/− mice following FA injection, renal IL-18 and serum interferon-γ production were increased compared with the progression from AKI to TF. In addition, the serum TNF-α (1.019 vs 0.4917, p<0.05) and IL-6 (1.027 vs 0.511, p<0.05) in Grhl2−/− mice 21 days after IR. Through the use of both detection methods, we found that the IL-18 deficiency suppressed renal tubular damage, necroptosis, and fibrosis in AKI-CKD transition associated with renal fibrosis.

Conclusions: The data suggest that IL-18 deficiency suppresses renal tubular damage, necroptosis, and fibrosis in AKI-CKD transition associated with renal fibrosis.

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of YAP-MCP1 associated inflammation, whereas the higher-doses of Verteportin has increased mortality.

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**SA-PO131**

**15-Lipoxygenase Alters Inflammation, Metabolism, and Fibrosis in a Model of Renal Injury**

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**Background:** 15-Lipoxygenase (15-LO, ALOX15) is implicated in the pathogenesis of a growing number of inflammatory and fibrotic diseases such as asthma, heart failure, and stroke but its role in renal injury is unexplored. We sought to examine if manipulating 15-LO would influence renal inflammation and fibrosis using a rodent model of unilateral ureteral obstruction (UUO).

**Methods:** Wild Type (WT) mice (N=18), mice lacking 15-LO (Alox15−/−) (N=11), and mice with transgenic overexpression of 15-LO (N=9) were subjected to UUO and kidneys were collected at 3 and 10 days postoperatively for histology, qRT-PCR, hydroxyproline assessment, and metabolic and lipidomic analysis of over 200 unique compounds.

**Results:** At 3 days after UUO, as compared to WT controls, Alox15−/− mice had decreased mRNA levels of pro-inflammatory cytokines tumor necrosis factor alpha (TNFα) and fractalkine (CX3CL1) (0.84 vs 1.71 mean fold decrease, p<0.05, and 0.41 vs 1.04 mean fold decrease, p<0.01, respectively). Similar results were obtained 10 days after UUO (0.93 vs 1.39 mean fold decrease, p<0.01, and 2.79 vs 5.32 mean fold decrease, p<0.01, respectively). At 3 days after UUO, injured Alox15−/− mice had reduced levels of toxic reactive eosinocoids including 12(13)- and 9(10)-dihydroHOMES, 9- and 13-oxoODEs, and 5(S)-HETE compared with WT specimens. At 10 days after UUO, Alox15−/− mice had evidence of marked oxidative phosphorylation vs. WT mice, which demonstrated a shift towards glycolysis. Also at 10 days after UUO, there was a trend towards reduced fibrosis in Alox15−/− WT by Picrosirius red staining (p=0.09), but not by mRNA for transforming growth factor beta (TGF-β) and smooth muscle alpha actin (αSMA). Next, we determined if overexpressing 15-LO would promote inflammation and fibrosis 10 days after UUO. As compared with WT mice, 15-LO transgenic mice had increase message for TNFα (1.48 vs 1.69 mean fold increase, p=0.001), TGF-β (6.22 vs 2.35 mean fold increase, p=0.001), and αSMA (4.34 vs 2.52 mean fold increase, p=0.001). Fibrosis was significantly worse among the 15LOTG mice as compared to WT controls by Picrosirius red staining (7.52 vs 4.03 % fibrosis, p<0.05) and cortical hydroxyproline content (4.09 vs 1.99 mg/mg total protein, p=0.01).

**Conclusions:** 15-Lipoxygenase contributes to inflammation, metabolic changes, and fibrosis in mice undergoing UUO.

**Funding:** Veterans Affairs Support

**SA-PO132**

**Increased HIPK2 Expression in Tubular Epithelial Cells Aggravates Kidney Fibrosis**

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**Background:** Irrespective of etiology, kidney fibrosis is a final common pathogenic process for the progressive development of chronic kidney disease (CKD) to end-stage renal disease. Therefore, there is an urgent need to develop effective anti-fibrosis therapy for CKD.

**Methods:** We previously demonstrated that homeodomain interacting protein kinase 2 (HIPK2) is overexpressed in tubular epithelial cells in kidney fibrosis. However, the direct effects of HIPK2 in renal tubular epithelial cells in kidney fibrosis.

**Results:** Increased HIPK2 expression in tubular epithelial cells in kidney fibrosis.

**Conclusions:** Increased HIPK2 expression in tubular epithelial cells aggravates kidney fibrosis.

**Funding:** NIDDK Support

**SA-PO133**

**Urinary EGF and ICAM-1 Predict Glomerular Number Using Cationic Ferritin Enhanced-MRI in a Murine Model Folic Acid Nephropathy**

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**Background:** Chronic kidney disease (CKD) is difficult to detect in the earliest stages. Cationic ferritin enhanced-MRI (CFE-MRI) has been used to measure glomerular number in mice, however, the use of this technique in larger animals and humans has limitations. Therefore, urinary biomarkers are used as early and sensitive predictors of acute kidney injury (AKI), there is little data correlating urinary biomarkers to nephron number following AKI. We hypothesize that urinary biomarkers can predict microstructural changes detected by CFE-MRI in the transition from AKI to CKD.

**Methods:** To induce AKI, male mice were injected with intraperitoneal folic acid (125 mg/kg, n=3); controls received NaHCO3 (n=5). Urine was collected on day 4 after folic acid and at 12 wks following AKI. The mice received horse spleen cationic ferritin 12 wks after injury. Kidneys were imaged ex vivo using a 7T Bruker ClinScan MRI (3D T2*-weighted, TE=20, TR=80, 60 µm, 460x640). MRI-derived biomarkers included Nglomer and cluster size (volume where glomeruli were detectable but lacked tubules). Forty urinary biomarkers (inflammation and growth factors) were analyzed using Mouse Cytokine Arrays Q1000 (RayBiotech).

**Results:** By CFE-MRI, the CKD group had 28% fewer glomeruli (8008 ± 2880) as compared to the controls (11051 ± 818, p<0.04). In the CKD cohort, nearly 9% of the kidney had labeled glomeruli with a lack of surrounding tubules designated as “clusters” (CKD: 8.8±4.2% vs. controls: 2.3±0.59%, p<0.03). Urinary EGF was higher 4 days after injury (AKI:11538 vs controls: 5078 pg/ml, 0.0004) and ICAM-1 was lower at 12 weeks (CKD: 2621 vs controls: 6629 pg/ml, p=0.007). Four days after injury urinary EGF correlated to Nglomer at 12 weeks after injury (r=0.71, 0.02) and cluster size (r=0.78, p<0.008). At 12 wks after injury, urinary ICAM-1 correlated to Nglomer (r=0.76, p<0.01) and cluster size (r=0.80, p<0.005).

**Conclusions:** In this murine model of AKI transitioning to CKD, urinary EGF at the time of AKI correlate with both a lower Nglomer and larger cluster size. At CKD, 12 wks after injury, ICAM-1 correlates negatively with glomerular number and cluster size. Further work to define the pathophysiology of these biomarkers in AKI and CKD is needed, however this work highlights the utility of urinary biomarkers and CFE-MRI to noninvasively detect early nephron injury and track progression of CKD.

**Funding:** NIDDK Support

**SA-PO134**

**MiR-874/ADAM19 Mediates Macrophage Activation and Renal Fibrosis After AKI**

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**Background:** The pathogenesis of CKD following AKI is not fully investigated.

**Methods:** We established a mouse AC (AKI to CKD) model caused by ischemia/reperfusion (IR), and identified miR-874 downregulated in fibrotic kidneys of both AC model and UUO model by RNA-Seq. Then we used human patient samples as well as animal and cell models to investigate how miR-874 regulates renal fibrosis after IR injury.

**Results:** MiR-874 was reduced at different time point after IR and UUO. In vitro, miR-874 was downregulated in HK2 cells treated with TGF-β1. Moreover, miR-874 level of peripheral mononuclear cells was lower in IgA nephropathy (IgAN) patients with proliferative sclerosing glomerulonephritis than those in pathological stage M0/0STG(p=0.01). In vivo, transient transfection of miR-874 inhibitor in HK2 cells induced the increase of mesenchymal markers, and transfection of miR-874 mimic in HK2 cells treated with TGF-β1 could alleviate EMT compared with negative control. Overexpression of human miR-874 into AC and UO mice led to alleviated renal fibrosis with decreased expression level of Acta2, Col1a1, Fln, chemokines including CCL2/CCL5, and ADAM19, a target gene of miR-874 verified by luciferase microRNA target reporter assay. F4/80 staining was also junior in miR-874 mice compared with negative control. In vivo, transfection of miR-874 mimic in mouse macrophage cell line Raw264.7 stimulated with LPS downregulated the expression of CCL2/CCL5. Then we focused on the biological function of ADAM19 expression towards renal fibrosis. ADAM19 was induced in both UO mice and AC at different time point. Transfection of adenovirus carrying human ADAM19 into HK2 cells, ADAM19 could induce the increase of mesenchymal makers and inflammatory factors and decrease of epithelial makers. Overexpression of ADAM19 directly induced fibrotic changes in vivo.

**Conclusions:** Our results suggest miR-874/ADAM19 could mediate renal fibrosis through regulating renal tubular epithelial cell injury and macrophage activation.

**Funding:** NIDDK Support

**Underline represents presenting author.**

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO135
A Selective USP30 Inhibitor Attenuates Progressive Fibrosis in Ischemia-Induced CKD
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Background: Much literature evidence points towards an essential role of mitophagy and mitochondrial dysfunction in the early stages of renal injury progression. Ischemic-reperfusion injury (IRI) results in metabolic adaptation of Proximal Tubule Epithelial Cells (PTECs), a site of high mitochondrial turnover (1). Moreover, exacerbation of renal injury has been demonstrated following IRI in both KIM-1 KO and PARC2 KO mice (2). USP30 is a mitochondrial-associated deubiquitylating enzyme and reduces KIM1 in a PARC2-dependent manner (3). It is well known that renal interstitial fibrosis is triggered by renal congestion.

Methods: MTX008 was administered to C57BL/6 mice 15 mg/kg (p.o.) and compared to vehicle treatment from Day -1 through to Day +21. On Day 0, mice were anaesthetized, and their left renal pedicle clamped for 45 min, then released to induce IRI. Mice were monitored and urinary kidney injury biomarkers (KIM-1 and NGAL) were measured on Day +1 and +7. On Day +14 and Day +21 kidneys were harvested. Morphology, fibrosis and immune cell infiltration were assessed.

Results: Body weight was similar between groups and remained constant throughout the observation periods. MTX008 appeared to limit urinary kidney injury biomarkers, KIM1 and NGAL on Day +1. There were large interindividually variations and the differences did not reach significance. Macrophage infiltration was significantly reduced on Day +21. Masson trichome stain revealed significantly less tubular atrophy in MTX008 treated animals on Day +14 and Day +21. Fibronectin expression in the cortex was significantly reduced in MTX008 treated mice on Day +14 and +21.

Conclusions: MTX008, a novel selective small molecule inhibitor of USP30 has shown efficacy in a model of IR-induced CKD. Daily treatment has shown significant benefits towards attenuated tubular atrophy and reduced cortical fibrosis. Mission Therapeutics is investigating MTX008 in a variety of preclinical renal injury models with a view to developing this novel molecule towards the clinic.


Funding: Commercial Support - Mission Therapeutics Limited

SA-PO136
Tubulointerstitial Injury in Renal Congestion Was Suppressed by Inhibiting Platelet-Derived Growth Factor Pathway
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Background: Increased central venous pressure in congestive heart failure is responsible for renal dysfunction. We created a novel rat renal congestion model, resulting high renal interstitial hydrostatic pressure, tubulointerstitial injury and pericyte-myofibroblast transition (PMT). In this model, platelet-derived growth factor receptors (PDGFRs), PMT indicators, were also upregulated, especially in outer medulla. Thus we examined the effect of PDGFR inhibition for renal injury.

Methods: The inferior vena cava (IVC) between the renal veins was ligated by suture in male Sprague-Dawley rats to increase upstream IVC pressure and induce congestion in the left kidney only. Imatinib mesylate (20 mg/kg) or saline were injected intraperitoneally every other day from one day of the operation. Both control right kidney and congestive left kidney were obtained after 3 days of the surgery and were weighted. The expression of every day from one day of the operation. Both control right kidney and congestive left kidney were obtained after 3 days of the surgery and were weighted. The expression of KIM1 and NGAL on Day +1. There were large interindividually variations and the differences did not reach significance. Macrophage infiltration was significantly reduced on Day +21. Masson trichome stain revealed significantly less tubular atrophy in MTX008 treated animals on Day +14 and Day +21. Fibronectin expression in the cortex was significantly reduced in MTX008 treated mice on Day +14 and +21.

Conclusions: MTX008, a novel selective small molecule inhibitor of USP30 has shown efficay in a model of IR-induced CKD. Daily treatment has shown significant benefits towards attenuated tubular atrophy and reduced cortical fibrosis. Mission Therapeutics is investigating MTX008 in a variety of preclinical renal injury models with a view to developing this novel molecule towards the clinic.


Funding: Commercial Support - Mission Therapeutics Limited

SA-PO137
The Role of Akt1 in a Murine Model of AKI to CKD Progression
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Background: Acute kidney injury (AKI) is an underestimated, yet important risk factor for development of end-stage renal disease (CKD). However, underlying mechanisms of AKI to CKD progression are poorly understood. Akt has been reported to be involved in renal ischemic reperfusion injury (IRI). In this study, we investigated the role of Akt1, one of the three Akt isoforms, in murine model of IRI-induced AKI to CKD progression.

Methods: We subjected the wild type and Akt1−/− mice to renal IRI. Renal IRI was induced by clamping the left main renal pedicle after 30 min followed by reperfusion. After 6 weeks of IRI, the renal fibrosis was assessed by histologic grading and Masson’s-trichrome staining. Fibrosis/apoptosis markers and MAPKs were also assessed by western blot. Results: After 6 weeks after IRI, kidney in wild type mice showed the typical features of progressive CKD, including tubular atrophy and perivascular fibrosis. Kidney in Akt1−/− mice show less fibrosis and perivascular fibrosis. BUN, creatinine, albumin, and total protein levels were significantly increased in the Akt1−/− mice compared with the wild type mice. In addition, western blot analysis showed that Akt1−/− had attenuated expressions of fibrosis marker (collagen-I and -IV), MAPKs (ERK, JNK, and p38) and Vimentin compared with wild type mice. Western blot analysis and TUNEL assay showed that the apoptosis was attenuated in Akt1−/− mice compared with wild type mice.

Conclusions: Our findings demonstrate that Akt1 contributes to IRI-induced AKI to CKD progression, suggesting that inhibition of this signaling pathway may provide a therapeutic approach for preventing IRI-induced AKI to CKD progression.

SA-PO138
Cholesterol Lipid Rafts When Blocked Prevent Epithelial-Mesenchymal Transition in Cisplatin-Induced Renal Injury
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Background: Cisplatin is a potent cytostatic, but its nephrotoxicity is a major complicating factor that limits its use as an anticancer therapy. Some evidence has shown that epithelial-mesenchymal transition (EMT) contributes to the progression from acute renal failure to chronic renal failure. We have found that binding of cisplatin to renal dehydroepiandrosterone-ß inhibits transport and signalling of brush border lipid rafts in proximal tubule, thus providing protection.

Methods: In this study we investigated whether the protective effects of cisplatin are related to the prevention of the EMT-induced by cisplatin. Male Wistar rats were divided into 4 groups: control rats, cisplatin-control rats, cisplatin-injected rats, cisplatin-treated cisplatin-injected rats. Nephrotoxicity was assessed 5 days after cisplatin treatment, by measuring serum creatinine, blood urea nitrogen (BUN), glomerular filtration ratio (GFR), proteinuria and renal morphology. Some typical markers of EMT and cell-attachment were measured by western blot and immunohistochemical studies.

Results: Cisplatin-treated rats showed significant elevations in BUN, creatinine, and proteinuria and decreased the GFR when compared with control rats. Cisplatin rats also exhibited severe morphological changes such as vacuolization and hyaline cast in the tubular lumens. Cisplatin significantly prevented partial or totally these changes in renal function and ameliorated histological damage in cisplatin-treated animals. On the other hand, cisplatin increased transforming growth factor beta, connective tissue growth factor (inducers of EMT and profibrotic markers), and vimentin (mesenchymal cell marker) levels while decreased significantly b-catenin and zona occludens-1 levels, both proteins involved in cell adhesion. Cisplatin treatment reversed these changes.

Conclusions: This study provides evidence that the protection offered by cisplatin to acute renal failure-induced by cisplatin, is associated to the prevention of the EMT by decreasing the signaling pathways that cause it and avoiding the loss of cell junctions. EMT signals seem to be triggered during the renal injury-induced by cisplatin.

Funding: Government Support - Non-U.S.

SA-PO139
A Furosemide Excretion Stress Test (FEST) Predicts Mortality After Sepsis Independent of Vasopressin Administration

Background: The furosemide stress test (FST) has been shown to be a sensitive and specific predictor of progression to AKIN stage III in the ICU. FST measures the volume of urine produced after a furosemide bolus. Furosemide is actively excreted by the proximal tubules into the lumen where it inhibits NKCC2 in the thick ascending limb. Vasopressin has been used as a vasopressor in some hypotensive sepsis patients and can markedly reduce urine production. We hypothesize that furosemide excretion (FEST) will be a more direct measure of tubule health than diuresis (FST) and may be insensitive to the effects of vasopressin on urine volume. We developed a protocol for FST and FEST in mice and tested this hypothesis in a murine model of septic-AKI.

Methods: Sepsis was induced in male and female CD-1 mice by cecal ligation and puncture (CLP). A subgroup of mice received 0.00114 U/(kg.min) vasopressin i.p. to simulate vasopressor support. The FST/FEST started at 42 hours post-CLP. 1 mg/kg furosemide s.c. was given and urine collected for 12 hours. The mice were monitored until 7 days post-CLP. Furosemide concentration was determined by a reverse phase HPLC assay.

Results: From 139 mice (79±60), 55 survived to 42 hours and underwent FST/ FEST, the remaining 84 mice surviving to 7 days. Both FST and FEST predicted time of death (R2 = 0.26 and 0.74) and mortality [AUC ROC values of 0.92 for FST in males, 0.95 for FST in females, 0.87 for FST for males, and 1.00 for FST in females]. Optimal performance was 91% sensitivity and 82% specificity for FST and 90% 79% for FEST.
with cutoffs of 0.94 ml and 44%, respectively. In the subgroup receiving vasopressin, urine production was reduced by 0.6 ml (p = 0.03) without altering furosemide excretion (p = n.s.). Therefore, when we used the optimal cutoffs from septic mice not treated with vasopressin for vasopressin-treated septic mice, the specificity of FST was eliminated (0%, p < 0.01) but specificity of FEST was preserved.

**Conclusions:** FST and FEST perform similarly in predicting mortality in untreated animals. Only the furosemide excretion stress test also predicted time to death and was insensitive to vasopressin treatment. In order to use FST in conjunction with vasopressin, cutoff values must be adjusted, but such adjustment is not needed for FEST.

**Funding:** NIDDK Support

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**SA-PO140**

**Lysozyme-Induced AKI: A Case Series**

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**Background:** Only rare case reports exist describing increased serum lysozyme with acute kidney injury. This study represents the first case series to describe the clinical and laboratory findings associated with this disease.

**Methods:** 17 kidney biopsy samples displaying lysozyme-induced acute kidney injury and associated clinical histories were prospectively collected from 2012-2019. 40 additional kidney biopsies were utilized as controls to compare morphologic findings. Light microscopy, immunofluorescence, electron microscopy, thiolavlin T, Congo red, and lysozyme IHC were performed. Laser microdissection coupled with mass spectrometry was performed on our initial two patients.

**Results:** 82% of patients were male with an average age of 66 years. 94% presented with acute kidney injury and average serum creatinine of 2.95 mg/dL. All patients had proteinuria with an average protein/creatinine ratio of 2.2. Hematuria was present in 42%, however where available, all urine sediments were bland. Serum lysozyme results were available in 10 patients all showing elevated levels. Hematologic disease was present in 71% of patients with chronic myelomonocytic leukemia affecting 31%. Outcome data was limited but showed recovery to near baseline serum creatinine in 4/4 (13 months f/u) who were treated for their underlying disease. Progressive CKD/ESKD was seen in 3/3 (3 months f/u), who did not undergo treatment of their underlying disease. The most helpful histologic features in identifying this disease were the pattern and intensity of lysozyme staining. Congo red reactivity without birefringence, weak Thioflavin T staining, extent of proximal tubule protein resorption droplets, and refractile protein resorption droplets in proximal tubules. Laser microdissection of proximal tubules followed by mass spectrometry showed lysozyme as the most frequent protein hit identified and a >20 fold increase in lysozyme hits compared to controls.

**Conclusions:** Lysozyme-induced acute kidney injury occurs in the setting of increased serum lysozyme leading to increased lysozyme in the proximal tubules. It is most commonly seen in the context of hematologic malignancy. While subtle, a constellation of morphologic and immunohistochemical findings exist that allow for accurate diagnosis. In our limited outcome data, treatment of the patient’s underlying disease is critical for recovery of kidney function and favorable prognosis.

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**SA-PO141**

**Assessment of Renal Angina Index for the Prediction of Severe AKI in Critically Ill Adults**

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**Background:** Risk-stratification tools of incident AKI in critically ill adults are needed. The renal angina index (RAI) was developed and validated in the pediatric population. We evaluated the performance of the RAI for the prediction of severe AKI in critically ill adults.

**Methods:** A cohort of 12,084 patients admitted to the ICU at the University of Kentucky (2009-2017) was utilized. Inclusion criteria consisted of age ≥18, ICU stay ≥2 days, at least 2 serum creatinine (SCr) measures in the first 2 days of ICU stay and one at 3-7 days of stay. Exclusion criteria included ESKD, kidney transplant or baseline SCr >3.5 mg/dL. A summation of the integer scores of the following variables: age, sex, expected surgery inhibitors, baseline eGFR, albuminuria hypoalbuminemia, anemia, and hyponatremia.

**Results:** Mean (SD) age was 57.3 (16.5), 42% were women and 90% white. Mean (SD) SCR was 1.8 (1.2), with 18,984 patients admitted to the ICU. We identified observational studies reporting clinical characteristics and laboratory findings associated with this disease. While subtle, a constellation of morphologic and immunohistochemical findings exist that allow for accurate diagnosis. In our limited outcome data, treatment of the patient's underlying disease is critical for recovery of kidney function and favorable prognosis.

**Funding:** Government Support - Non-U.S.
AKI: Epidemiology, Risk Factors, Prevention - III

were: raw SPARK score, 1.0 (1.0-1.0, 0.603); class A, 1.1 (0.8-1.4, 0.286); class B, 1.1 (2.0-1.2, 0.005); class C, 1.0 (0.9-1.1, 0.785); class D, unable to calculate due to small sample size. Pair-wise comparison of AUCs revealed significant differences between SUA and SCR (Z=3.6, <0.0003), GFR (Z=4.1, <0.0003) and SPARK score (Z=3.8, <0.0001). SPARK score did not demonstrate significant differences with GFR (Z=0.7-0.6, 0.552) or SCR (Z=1.2, 0.229).

Conclusions: Our data suggests that the SPARK Index is not a good predictor of AKI in CS where SCR, eGFR and SUA outperform its discriminatory capabilities and require only a single, cost-effective laboratory test.

SA-PO144
Impact of Clinical Variables at Dialysis Initiation for AKI in the ICU on In-Hospital Mortality
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Background: Current research on timing of dialysis in critically ill AKI has focused on analyzing survival outcome with arbitrary definitions of “early” or “late” start. However, the competing effects of other variables such as clinical comorbidities, dialysis indication, or acuity of illness at dialysis start are unknown.

Methods: We analyzed new adult AKI patients initiated on renal replacement therapy (RRT) while in 5 intensive care units (ICU) from 1/1/2010 through 12/31/2015, to identify clinical variables associated with survival to hospital discharge.

Results: Of the 235 patients initiated on RRT in medical and surgical ICUs, the mean age was 61.8±14.3 yrs; 60% were male, 47% were Afro-American with a Charlson Comorbidity Score (CCS) of 5.5 ±2.1 and acuity scores of 29.6 ±7.6 (APACHE-II). 9.0 ±4.4 (SOFA) at dialysis start. The most common modality of RRT was continuous (67.2%). Logistic regression identified independent association of survival with low serum lactate, low SOFA scores, elevated serum creatinine at RRT initiation and hyperkalemia but not with CCS and time from KDIGO Stage 3 AKI to dialysis initiation (as a surrogate for timing). Those with lean serum lactate (≤0.5 mEq/L) at initiation also correlated inversely with survival beyond 48 hours. Stratifying patients by SOFA scores at RRT initiation (<10-low-risk, ≥10=high-risk) identified severity of volume overload or hyperkalemia (low-risk group) and RRT modality type or serum lactate (high-risk group) as being associated with survival. Receiver-Operator Characteristics (ROC) of biochemical variables at dialysis initiation showed that only serum lactate had a moderate c-statistic of 0.759 in discriminating survivors from non-survivors.

Conclusions: Data from critically ill AKI patients initiated on RRT in the ICU primarily showed acuity of illness at the start of RRT affecting survival. Since time from KDIGO Stage 3 AKI to dialysis initiation was not associated with survival, the validity of definitions such as “early” or “late” RRT initiation remains uncertain. Triaging clinical decision based on acuity scores may optimize clinical outcomes. Finally, the absence of any association between hospital survival and co-morbid scores has great implications for prognostication and palliative care.

SA-PO145
Simplified Acute Physiology Score II Predicts 4-Year Outcomes in Critically Ill Elderly Patients with AKI
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Background: Acute kidney injury (AKI) is a serious complication of critically ill elderly. Several severity scoring systems have been used to predict the prognosis. However, which severity score has the better predictive efficiency in elderly AKI is unknown.

Methods: Data of AKI elderly was extracted from Medical Information Mart for Intensive Care III database. Subjects were divided into three groups, according to 65-75 years, 75 - 85 years and ≥85 years. SAPS II, OASIS, MLODS, SIRS and SOFA were compared. The Kaplan-Meier and receiver operating characteristic (ROC) curves were formed to assess the prognostic values.

Results: Totally 10472 AKI elderly were enrolled. Older patients had higher death rates (Figure A) and shorter survival time (Figure B). SAPS II had the best prognostic value (P < 0.01, Figure C). The AUC of SAPS II (95% CI, 0.676 to 0.694) was significantly the highest (P < 0.01, Table). The cut-off value of SAPS II was 40. Patients with SAPS II ≤ 40 would have a better prognosis than those with SAPS II > 40 (Figure D).

Conclusions: SAPS II could better predict the long-term prognosis of elderly patients with AKI.

SA-PO146
Atrial Fibrillation Chronicity in Patients with AKI on Continuous Renal Replacement Therapy

Background: Atrial fibrillation (AF) has been reported in 44% of patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT), but the chronicity of AF remains unclear. We aim to assess the epidemiology and outcomes of AF among AKI patients receiving CRRT, including predictors of new-onset AF (NOAF) on CRRT.

Methods: This is a retrospective analysis of a cohort of patients admitted to the ICUs at a tertiary care hospital from 12/2006 through 11/2015 who had AKI and received CRRT. The primary outcome was mortality at three years, which was assessed using a Cox proportional hazard model. Secondary outcomes included in-hospital mortality. AF was ascertained by manually reviewing the chart. A random sample of 10% of cohort was independently reviewed by another investigator and agreement was reported using kappa coefficient.

Results: Out of 1,394 CRRT patients who had AKI, 582 patients did not have any arrhythmia. There were 419 (30%) patients who were known to have AF prior to starting CRRT. NOAF occurring while on CRRT developed in 193 (19%) patients. Another 160 patients (11.5%) developed NOAF during their index ICU admission prior to initiation of CRRT. Kappa was 0.95 (95% CI: 0.87-1.0, p<0.001). A known history of AF (HR: 1.19, 95%CI: 1.01-1.54, p=0.043) and bicarbonate (HR 0.95, 95%CI: 0.92-0.98, p=0.003) were associated with increased and decreased risk of NOAF on CRRT, respectively.

Conclusions: Incident NOAF in critically ill patients with AKI receiving CRRT is common and carries an unfavorable prognosis similar to patients with prevalent AF. Further studies are required to elucidate modifiable risk factors for NOAF occurring on CRRT and the mechanisms driving the observed association with adverse outcomes.

SA-PO147
Hypoalbuminemia Is Related with Short-Term and Long-Term Mortality in Patients Undergoing Continuous Renal Replacement Therapy
Jong joo Moon,1 Yaerim Kim,1 Kwon Wook Joo,1 Yon Su Kim,2 Seung Seok Han,2 1Seoul National University Hospital, Seoul, Republic of Korea; 2Seoul National University College of Medicine, Seoul, Republic of Korea.

Background: Hypoalbuminemia reflects several pathological conditions such as nutritional deficiency and chronic inflammation. However, its relationship with short-term and long-term mortality in patients undergoing continuous renal replacement therapy (CRRT) remains unresolved.

Methods: A total of 1,581 patients who underwent CRRT due to acute kidney injury between 2010 and 2016 were retrospectively reviewed. Patients were categorized by the tertiles of albumin levels at the time of starting CRRT. Odds ratio (OR) and hazard ratio (HR) for the risk of all-cause mortality were calculated before and after adjustment of multiple covariates.

Results: Mean albumin level was 2.7 ± 0.6 g/dL. During the median follow-up period of 14 days (maximum 4 years), 1,040 patients (65.8%) died. The 1st tertile had a higher risk of mortality than the 3rd tertile with an HR of 1.91 (1.63-2.21). Although the mortality rate was stratified by the timeframe, the 1st tertile had a higher risk than the 3rd tertile as following ORs: 3.0 (2.34-3.87) in 2-week mortality; 2.7 (2.12-3.52) in 1-month mortality; 2.7 (2.08-3.53) in 6-month mortality; and 2.8 (2.11-3.67) in 1-year mortality. The 1st tertile had a higher risk than the 3rd tertile as following ORs: 3.0 (2.34-3.87) in 2-week mortality; 2.7 (2.12-3.52) in 1-month mortality; 2.7 (2.08-3.53) in 6-month mortality; and 2.8 (2.11-3.67) in 1-year mortality. The 1st tertile had a higher risk than the 3rd tertile as following ORs: 3.0 (2.34-3.87) in 2-week mortality; 2.7 (2.12-3.52) in 1-month mortality; 2.7 (2.08-3.53) in 6-month mortality; and 2.8 (2.11-3.67) in 1-year mortality.

Conclusions: Hypoalbuminemia is associated with short-term and long-term mortality among patients undergoing continuous renal replacement therapy.
tertile group had also higher rates of intensive care unit- and in-hospital mortalities than the 3rd tertile group.

Conclusions: Because hypoalbuminemia is associated with short-term and long-term mortality after CRRT, serum albumin levels should be monitored during the period of CRRT.

SA-PO148
Using Standardised Monitoring of Physiological Parameters (National Early Warning Score) to Predict AKI
Alexandra Riding, Kate Berresford, Clare Morledge, Suresh Mathavakkanam, Andrew Findlay. Renal Medicine, East and North East Herts NHS Trust, Stevenage, United Kingdom.

Background: Acute kidney injury (AKI) affects approximately 16% of inpatients, particularly the elderly and confers an increased length of hospital stay, medical intervention and mortality (Holmes et al, CJASN, 2016 and Kerr et al, NDT, 2014). Risk factors are well established and yet we cannot reliably identify susceptible patients before abnormal serum creatinine results, though this forms the basis of national AKI e-alert systems. In 2012, The Royal College of Physicians endorsed a National Early Warning Score (NEWS) to identify deteriorating and acutely unwell patients. The score is based on the physiological parameters of respiratory rate, oxygen saturation, systolic blood pressure, pulse rate, conscious level and temperature, with higher scores triggering urgent or immediate medical escalation. The utility of clinical early warning scores in predicting AKI severity and patient outcome has been variable (Kovacs et al, BJS, 2016; Potter et al, JICS, 2017 and Faisal et al, Clin Med, 2018). We predicted that those with high NEWS (>4) might correlate to AKI stage and form a useful pathway to highlight and appropriately escalate this patient group.

Methods: Retrospective data were collected on hospitalized patients (Jan-March 2019), identified by elevated serum creatinine results (as per national AKI reporting guidance). Highest NEWS within 5 days of AKI alert was recorded. Data sources were patient records and computerized reporting systems.

Results: 140 patients were identified (complete data for 138). NEWS is shown according to AKI stage in the table. Higher NEWS (>4) was unaffected by AKI stage (p= 0.75, 2-way ANOVA).

Conclusions: Those with stage 2 and 3 AKI did not trigger significantly higher NEWS. Whilst NEWS remains an important discriminator in escalating acutely unwell patients, it did not predict AKI or its severity. Biomarkers of AKI are in development, but clinically relevant discriminators remain elusive. Further parameters are urgently required to refine AKI algorithms for clinical use.

NEWS according to AKI stage

<table>
<thead>
<tr>
<th>AKI stage</th>
<th>NEWS (patients)</th>
<th>NEWS &gt;4 (%)</th>
<th>NEWS 3-6 (%)</th>
<th>NEWS &lt;3 (%)</th>
</tr>
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<tbody>
<tr>
<td>1 (5)</td>
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<td>14 (22)</td>
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<tr>
<td>3 (26)</td>
<td>16 (45)</td>
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</table>

SA-PO149
The Development of AKI After Acute Nephrons Loss: An Unexpected Journey
Francesco Trevisani,1 Federico Di Marco,1 Giacomo Dell’Antonio,2 Antonello Pan,3 Alessandro Larcher,1 Umberto Capitano,1 Arianna Bettiga,1 Esteban Porrini,1 Andrea Salonia,1 Alberto Briganti,1 Francesco Montorsi,1 Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy;2 Azienda Ospedaliera G. Brotzu, Cagliari, Italy;3 Università degli Studi di Cagliari, IRCCS San Raffaele Scientific Institute, Milan, Italy;4 University Hospital of the Canary Island, La Laguna, Spain.

Background: Acute Kidney Injury (AKI) following radical nephrectomy (RN) is associated with an increased risk of morbidity and mortality. Up to 8% is impossible to understand the major predictor for AKI development.

Methods: We collected prospectively clinical data of a group of 195 patients who underwent RN for renal masses. To evaluate the risk of AKI after surgery, serum-creatinine (Scr) values were collected before surgery (0), 24h and 48h after the operation (1 and 2), and at dismissal (0). We calculated eGFR with the MDRD formula. According to RIFLE criteria, we defined the AKI onset with a ratio of Scr/Scr(0) higher than 1.5. A pathological evaluation using the Remuzzi Score was carried out on the healthy renal parenchima based on glomerular global sclerosis, tubular atrophy, interstitial fibrosis and arteriolar narrowing.

Results: In our study a strong significative correlation (p=0.001) was found with the basal eGFR at 0. In fact, the lower was the basal eGFR, the higher was the risk of AKI development. A lower variation of eGFR from 0 to tf was related with the presence of tubular atrophy (p=0.01) or interstitial fibrosis (p=0.05).

Conclusions: An eGFR higher than 70 ml/min could represent an unexpected predictive cutoff of AKI development after RN. There are two possible explanation: a better medical treatment of the CKD patients; a “non adequate compensatory function mechanism” after acute nephron loss. In fact, in healthy pts, the hyperfiltration mechanism is not yet well established (as in CKD pts) so that RN results in an unexpected trauma for the remnant kidney who will take time to restore the renal function.

SA-PO150
Factors Associated with AKI in Mexican Patients with Acute Coronary Syndromes
Diana Ramírez-Flores,1,2 Adriana Banda Lopez,1 Milagros M. Flores Fonseca,1 Rodolfo Parra-Michel,1 Victoria G. Maldonado Gomez,1 Benjamin Gomez-Navaarro,4 Nephrology and Transplant Unit HE, IMSS, Zapopan, Mexico;4 Centro Medico Nacional de Occidente, Guadalajara, Mexico;4 Universidad de Guadalajara, Guadalajara, Mexico;4 IMSS, HECMNO, Zapopan, Jalisco, Mexico;4 Instituto Mexicano del Seguro Social, Guadalajara, Mexico.

Background: AKI is a leading cause of morbidity and mortality in hospitalized patients with ACS. The aim of this study was to identify potential risk factors and patient characteristics associated in patients with ACS.

Methods: We analyze a single center retrospective review of 77 patients with ACS. The length of hospital stay and during the coronary unit was available for analyzed patients to diagnose AKI. Demographics, clinical and biochemical profiles, risk factors for AKI and RRT prescription was assessed and reported during diagnosis and discharge. Outcome measures were renal recovery, mortality and causes of death. Statistical analysis was done with SPSS version 26.0. The categorical variables were analyzed using chi-square test or Fisher’s exact probability test, as appropriate. The continuous variables were analyzed using the Student’s t test. A value of p< 0.05 was regarded as statistically significant.

Results: Mean age was 65.45 ± 10.84 years and 70% were male. AKI was diagnosed in 50% of ACS cases. The mortality rate was 31% due to cardiovascular complications. Pre-existing comorbidities and other factors found to have increased association with AKI presence were: CKD (p <0.0001), diabetes with complications (p=0.001), bacteremia (p=0.028), history of surgery complications (p=0.001), nephrotoxic use (p=0.004) and biochemical alterations as anemia, hyperbilirubinemia, hyperglycemia, hyperlactatemia, metabolic acidosis, and elevated cardiac biomarkers (p=0.005).

Conclusions: This study shows that AKI is a frequent complication of ACS and its association with predictive factors. Further studies are needed to establish early strategies aimed to prevent AKI or at reducing its severity might provide significant clinical benefit in patients with ACS.

Comparison of AKI presence in ACS patients

<table>
<thead>
<tr>
<th>AKI</th>
<th>N = 39</th>
<th>Non-AKI</th>
<th>N = 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.41 ± 11.22</td>
<td>65.45 ± 10.19</td>
<td>0.418</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>25.47 ± 3.37</td>
<td>25.90 ± 4.90</td>
<td>0.360</td>
</tr>
<tr>
<td>Physiological age (years)</td>
<td>20.56 ± 0.78</td>
<td>20.48 ± 0.65</td>
<td>0.601</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/L)</td>
<td>532.24 ± 732.07</td>
<td>742.28 ± 672.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin I (ng/ml)</td>
<td>1.79 ± 2.38</td>
<td>1.76 ± 2.35</td>
<td>0.461</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.20 ± 0.95</td>
<td>1.90 ± 0.31</td>
<td>&lt;0.001</td>
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</table>

Diagnosis was made using the RIFLE criteria, we defined the AKI onset with a ratio of Scr(0)/Scr(0) higher than 1.5. A pathological evaluation using the Remuzzi Score was carried out on the healthy renal parenchima based on glomerular global sclerosis, tubular atrophy, interstitial fibrosis and arteriolar narrowing.

Conclusions: Those with stage 2 and 3 AKI did not trigger significantly higher NEWS. Whilst NEWS remains an important discriminator in escalating acutely unwell patients, it did not predict AKI or its severity. Biomarkers of AKI are in development, but clinically relevant discriminators remain elusive. Further parameters are urgently required to refine AKI algorithms for clinical use.

Results: 140 patients were identified (complete data for 138). NEWS is shown according to AKI stage in the table. Higher NEWS (>4) was unaffected by AKI stage (p= 0.75, 2-way ANOVA).

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SA-PO151
Predicting Major Adverse Kidney Events in the First Year After AKI
Emily J. See,1 Kevan Polkinghome,2 David W. Johnson,3 Nigel D. Toussaint.4
1Austin Health, Melbourne, VIC, Australia; 2Monash Medical Centre and Monash University, Melbourne, VIC, Australia; 3Princess Alexandra Hospital, Greenslopes, QLD, Australia; 4The Royal Melbourne Hospital, Parkville, VIC, Australia.

Background: Acute kidney injury (AKI) is a common complication of hospital admission, and survivors are at increased future risk of major adverse kidney events (MAKE), including chronic kidney disease (CKD), end-stage kidney disease (ESKD) and death. High-risk patients may benefit from specialist follow-up; however, the factors associated with increased risk have not been reported.

Methods: We conducted a retrospective study of all adult patients admitted with AKI to a single centre between 1 January 2012 and 31 December 2016. Cox regression models were performed to examine the primary outcome, which was the development of a MAKE in the first year following hospital discharge. The secondary outcomes (CKD, ESKD, and death) were studied using Cox and competing risk regression analyses. Candidate predictor variables included patient demographics, comorbidities, and laboratory values available at the time of hospital discharge.

Results: Of 2,101 patients included in the study, 767 patients (37%) developed a MAKE within the first year. MAKE occurred more frequently in patients who were older (HR 1.02 95% CI 1.01-1.02) and in those with a history of chronic heart failure (HR 1.41 95% CI 1.19-1.67), liver disease (HR 1.68 95% CI 1.39-2.03), and either non-metastatic (HR 1.44 95% CI 1.14-1.82) or metastatic (HR 2.26 95% CI 1.80-2.83) malignancy. They were also more common in patients with a greater severity of AKI (stage 2 HR 1.38 95% CI 1.11-1.66; stage 3 HR 1.62 95% CI 1.31-2.01) and in those with a higher serum creatinine level at discharge (HR 1.01 95% CI 1.00-1.01). Female sex (SHR 1.54 95% CI 1.27-1.88) and hypertension (SHR 1.28 95% CI 1.04-1.58) were additional risk factors for the development of CKD.

Conclusions: A significant number of patients with AKI will develop a MAKE within the first year. Clinical variables available at the time of discharge could be used to stratify risk and identify patients who may benefit from specialist follow up.

SA-PO153
The Association Between Kinetic Estimated Glomerular Filtration Rate and Clinical Outcomes: A Systematic Review
Cairina E. Frank,1 Thomas Mavraganis,2,3 Ahsan Alam.1,3 McGill University Health Centre, Montreal, QC, Canada; 2Geneva University Hospital, Geneva, Switzerland; 3McGill University, Montrel, QC, Canada.

Background: Accurate assessment of kidney function is an essential aspect of clinical care. In acute kidney injury or renal function recovery, serum creatinine lags behind true kidney function, and GFR estimation using conventional formulae is problematic when serum creatinine is not at a steady state. The kinetic estimated glomerular filtration rate (KeGFR) was proposed as an alternative as it takes into account changing creatinine over a period of time. The objective of this systematic review was to examine the association between KeGFR and clinical outcomes.

Methods: We conducted a systematic review of studies examining the association between KeGFR and clinical outcomes. The databases searched were PubMed, EMBASE, CINAHL, Scopus and Web of Science, searching for articles in French and English and published from 2013 until 2019. Quality of each study was assessed using the Newcastle-Ottawa scale.

Results: Of 488 articles identified, there were 19 that met inclusion criteria (12 full articles, 7 supplements/abstracts). Ten articles examined the association between KeGFR and acute kidney injury (AKI). KeGFR was not only associated with AKI, but all but one study found that it better discriminated risk or injury in certain populations. KeGFR could also detect AKI earlier than other commonly used formulae. Four of the five studies that examined mortality found that KeGFR was associated with an increased risk of death and performed better than other biomarkers. KeGFR was also found to accurately predict delayed graft function (n=3) and discontinuation of renal replacement therapy (n=4). Two studies examining the use of KeGFR in therapeutic drug monitoring found it to be a poor predictor.

Conclusions: KeGFR has been shown to be an accurate method of predicting adverse outcomes including acute kidney injury, mortality and renal recovery, however, it appears to not be as effective when used for therapeutic drug monitoring. Prospective studies to validate its use in clinical practice are warranted.

SA-PO154
Severity of Sepsis-Associated Acute Kidney Disease and 90-Day Survival
Priyanka Priyanka,1 David Wilfert,2 Anat Shinarv,2 Wayne M. Dankner,3 John A. Kellum.1 The University of Pittsburgh, Pittsburgh, PA; 2Atox Bio, Ltd, Ness Ziona, Israel.

Background: Current evidence suggests that survival following sepsis with AKI (S-AKI) is strongly associated with recovery of renal function by hospital discharge. Acute Disease Quality Initiative (ADQI) consensus classifies persistent renal dysfunction for >7 days as acute kidney disease (AKD) with staging as per AKI using serum creatinine or dialysis. However, the relationship between AKD stage and the risks of death, chronic dialysis or persistent renal dysfunction over the following three months are unknown. Further, it is unknown if 14 or 28 day AKD status reflects 90 day status. Here, we examined the relationship between AKD at days 14, 28 and outcomes at 90 day in patients with S-AKI.

Methods: We conducted a retrospective cohort study of patients admitted to any of 16 hospitals with in the University of Pittsburgh Medical Center between October 2008 and May 2014. We included critically ill adult patients who had s-AKI (stage 2-3 as per KDIGO criteria occurring after sepsis). Sepsis was identified using Sevisus-3 criteria plus an ICD9 code. We staged AKD at day 14 and 28 from first max AKI stage. Our primary outcome was survival at 90 day. We also assessed rates of dialysis and persistent renal dysfunction (>150% of baseline creatinine) as well as the composite of all three—major adverse kidney events (MAKE) at 90 day.

Results: Of 121,817 patients, 10,999 met our definition of s-AKI. Median age was 67 (IQR, 56-79) years., 50.2% were male, estimated baseline glomerular filtration rate was 70.12 (IQR, 47.19 – 93.44) mL/min/1.73m2. APACHE III score was 61 (IQR, 46-78). Among the 2,402 (27.6%) patients known to have AKD on day 14, 1,897 (79%) met MAKE criteria by day 90. However, of the 2,354 (26.8%) patients known to have AKD on day 28, 2,031 (86.3%) met MAKE criteria by day 90. Overall, 182 patients (7.6%) recovered renal function between day 14 and day 28.

Conclusions: Persistent loss of renal function is more accurately assessed at day 28 compared to day 14 as well as risks for dialysis and persistent renal dysfunction in patients with s-AKI. However, day 14 evaluation may allow an early opportunity to focus attention on those patients who have not yet demonstrated evidence of renal function recovery.

Funding: Commercial Support - Atox Bio, Ness Ziona, Israel.
SA-PO155
Fluid Overload Is a Major Predictor for Mortality in Critically Ill Patients with Cirrhosis and AKI
Mohit Gupta,1 Russell E. Rosenblatt,2 Brett E. Fortune,1 Michelle L. Lubetzky,3
1Weill Cornell Medical College, New York, NY; 2Weill Cornell Medicine, New York, NY; 3Division of Nephrology and Hypertension, New York, NY.

Background: Fluid overload is associated with poor outcomes in critically ill patients with acute kidney injury (AKI), but data on whether this applies to patients with cirrhosis are limited. In the setting of portal hypertension, management of AKI can be challenging due to systemic vasodilatation and ineffective renal arterial blood flow. This study aims to determine whether fluid overload had a detrimental effect on critically ill patients with cirrhosis and AKI.

Methods: Clinical and demographic data from 81 hospitalized patients with cirrhosis transferred to the ICU with AKI were collected from a single academic medical center from 2012-2018. Fluid overload was defined as >10% weight gain after the first 3 days in ICU. The primary endpoint was 14-day survival after hospital admission. Kaplan-Meier survival and adjusted Cox hazards analyses were performed.

Results: There were no significant differences between the two groups in terms of age, sex, or etiology of cirrhosis. Non-survivors had a higher MELD-Na when compared to survivors (30 vs 22.5, p<0.001) at the time of transfer to ICU. Fluid overload in the first 3 days of ICU stay, oliguria, and the use of renal replacement therapy (RRT) were highly associated with mortality (p=0.04, 0.0004 and 0.01 respectively). Unadjusted Kaplan-Meier survival analysis demonstrated inferior 14-day survival for patients who developed fluid overload (36% vs 73%) while in ICU (log-rank p=0.006; Figure 1). A multivariable Cox Hazards model, adjusting for age, MELD-Na, and RRT, demonstrated that fluid overload after 3 days following ICU transfer was associated with a 2.45-fold increased risk of mortality (p=0.02).

Conclusions: Our data demonstrate that fluid overload in critically ill patients with cirrhosis and AKI is a major predictor for short-term mortality. Prospective studies that focus on restrictive fluid management are warranted to improve care for this high-risk population.

SA-PO156
Similarity of Outcomes in Hepatorenal Syndrome and Other Forms of AKI in Cirrhosis
Maria Soledad Rivera,1,2 Juan Carlos Q. Velez,1,2,3 Ochsner Clinical School, The University of Queensland, New Orleans, LA; 2Ochsner Clinic Foundation, New Orleans, LA.

Background: Recent data suggests that severe AKI from either hepatorenal syndrome type 1 (HRS-1) or acute tubular injury (ATI) may carry similar mortality, challenging the previous notion of a more ominous prognosis in HRS-1. However, those studies are confounded by uncertainties in adjudication of diagnosis imposed by retrospective designs and by the inherent limitations of the International Club of Ascites (ICA) criteria. Thus, we aimed to examine outcomes of AKI in cirrhosis via a prospective design.

Methods: We established prospective data collection in cirrhotics with AKI stage ≥ 2 (AKIN) over 1.5 years. To reduce uncertainty in diagnosis, we supplemented the standard ICA criteria for HRS-1 with supportive phenotypic criteria: urine Na <20 mEq/L, urine volume <500 ml, mean arterial pressure <80 mmHg, serum Na <135 mEq/L and absence of evidence of ATI by urine sediment microscopy (MicroExU Sed) using the Chawla score (CS). “Definite HRS-1” (Def-HRS) was assigned to those who met all ICA and supportive criteria. “No HRS-1” (No-HRS) was assigned to those with ≥1 unmet ICA criteria or CS for ATI. “Possible HRS-1” (Poss-HRS) was assigned to those who met the ICA criteria but did not meet all supportive criteria, lacked MicroExU Sed or had a CS equivocal for ATI. Outcomes chosen: need for dialysis (RRT), discharge to hospice (Hosp), liver transplant (LT) and death at 1, 3- and 6-months post-AKI.

Results: We included 133 patients (40% women, age 58 (25-87)) in our cohort. MicroExU Sed was done in 88 (66%) patients. We categorized 29 (22%) patients as Def-HRS, 24 (18%) as Poss-HRS and 60 (45%) as No-HRS. Baseline serum creatinine [2.6 (2.4-3.1), 2.4 (2.2-3) and 2.8 (2.3-3.6) mg/dL] and bilirubin [5.6 (2.3-15.6), 5.4 (2.1-14.6) and 5.6 (2.3-14.5) mg/dL] were comparable for the 3 groups. At 30 days, need for RRT was 18%, 21% and 36% for Def-HRS, Poss-HRS and No-HRS, respectively. Mortality rates at 1, 3 and 6 months were: Def-HRS: 21%, 21% and 24%; Poss-HRS: 29%, 33% and 42%; and No-HRS: 35%, 43% and 44%, respectively. After 6 months, LT occurred in 15%, 17%, and 24% for each of the 3 groups, respectively.

Conclusions: Our prospective cohort with stringent adjudication of diagnosis indicates that HRS-1 is not associated with more ominous clinical outcomes compared to other forms of AKI in cirrhosis.

SA-PO157
A Decision Tree to Predict Renal Replacement Therapy Requirement in Rhabdomyolysis-Induced AKI
Ismael A. Gómez Ruiz,1 Ricardo Correa-Rotter,2 Luis E. Morales-Buenrostro,2 Juan M. Mejia-Vileit,2 Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; 1Instituto Nacional de Ciencias Médicas y Nutricion Salvador Zubiran, Mexico City, Mexico, 3Instituto Nacional de la Nutrición, Mexico City, Mexico.

Background: Rhabdomyolysis-Induced Acute Kidney Injury (RI-AKI) develops in 10-40% of patients who present rhabdomyolysis. When damage is severe enough to develop complications such as life-threatening hyperkalemia or anuria, up to 85% of patients will require renal replacement therapy (RRT). The aim of the present study was to study admission variables that predict RRT requirement.

Methods: Retrospective cohort study. All patients hospitalized for RI-AKI between 2007-2017 were included. Patients were divided according to RRT requirement and their admission parameters compared with Mann-Whitney’s U test. Using ROC curves, we determined the best cut-off for lactate dehydrogenase (LDH), creatinine kinase (CK) and the MacMahon score to predict RRT requirement and a decision tree was generated.

Results: We identified 42 RI-AKI hospitalizations. All patients had CK<5000 U/L. The main etiologies were drug-induced (41%) and excessive physical activity (21%). Nine patients (21%) developed stage 1 AKI, 5 (12%) stage 2 AKI and 28 (67%) stage 3 AKI. Twenty-two patients (52%) required RRT. The most frequent indications for RRT initiation were anuria (64%) and hyperkalemia (32%). Intermittent hemodialysis was used in 52% of cases. The median time on RRT was 17.5 days (range 4-59). Five patients (12%) died during hospitalization due to infectious causes. On follow-up, 6 patients (14%) developed CKD. Patients with RRT requirement presented with higher serum phosphorus (6.2mg/dl [5.5-7.6] vs. 3.3mg/dl [3.0-3.9], p<0.001), potassium (5.5mEq/l [4.8-6.3] vs. 4.3mEq/l [3.6-4.8], p<0.001) and LDH (2124 U/l [1067-3193] vs. 553 U/l [322-744], p<0.001). The AUC of LDH, MacMahon score and CK to predict RRT requirement were 0.873, 0.900 and 0.620 respectively. A decision tree was generated and shown in Figure 1.

Conclusions: A simple decision tree based on LDH levels and the MacMahon score at presentation can predict RRT requirement in RI-AKI.

SA-PO158
Dyschloremia and Prognosis in Patients with AKI Requiring Continuous Renal Replacement Therapy
Dong Ho Shin. College of Medicine, Hallym University, Seoul, Republic of Korea.

Background: Dyschloremia is common in critically ill patients. There has been some interest in the low or high serum chloride levels as poor prognostic factor of them. However, little is known about the impact of dyschloremia in patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT).

Methods: A total of 980 patients who received CRRT for AKI between 2009 and 2018 were collected and divided into 3 groups according to the serum chloride levels at the timing of CRRT. Thirty-day all-cause mortality and continued dialysis dependence after hospital discharge was compared among groups.

Results: The hypochloremia group (serum chloride < 98mEq/L, n = 190), normochloremia group (98 ≤ serum chloride ≤ 110 mEq/L, n = 647), and hyperchloremia groups (serum chloride > 110 mEq/L, n = 143) were divided based on the reference values. Serum creatinine (Cr) and blood urea nitrogen (BUN) were significantly higher in hypochloremia and hyperchloremia group. On multivariate logistic regression, dyschloremia group (odd ratio, 1.38; 95% confidence interval, 1.12 - 1.69; p = 0.02) and hyperchloremia group (odd ratio, 1.57; 95% confidence interval, 1.32 - 2.54; p = 0.04) were significantly associated with mortality. In continued dialysis dependence after hospital discharge, similar trends were observed. Moreover, Kaplan-Meier analysis
revealed that mortality was significantly higher in hypochloremia and hyperchloremia groups than normochloremia group.

Conclusions: This study showed that dyschloremia was a predictor for poor prognosis in patients with acute kidney injury requiring CRRT.

SA-PO159

A Non-Steady State Adaptation of the CKD-EPI Equation

Florian Buchkremer, Andreas H. Bock, Stephan Segerer. Kantonsspital Aarau, Aarau, Switzerland.

Background: The CKD-EPI equation is one of the most widely used estimates of kidney function. It is commonly calculated whenever a plasma creatinine (pCr) is measured, although only valid when pCr is stable. Chen proposed a “kinetic GFR” (JASN 24, 877-888 (2013)) for non-steady state conditions. Despite its name it essentially estimates a creatinine clearance (cCr). The goal of our calculations was to develop a true kinetic eGFR estimation and to improve the underlying kinetic clearance formula by explicitly including creatinine generation rate (cgr), the creatinine distribution volume (vD), and accounting for possible changes in distribution volume (vDlt). Methods: The pharmacokinetics of creatinine are comprehensively described by equation A. To solve for cCr requires an iterative process, so a simplified form has been used, which we modified to allow for corrections of vDlt (equation B). In steady state cCr is creatinine excretion rate (which equals cgr) divided by the pCr. To convert our kinetically determined cCr into CKD-EPI based eGFRs, we divided cgr by cCr and calculated a virtual steady state pCr. We then inserted this term into CKD-EPI. Cgr and vD were estimated with published formulas (incorporating age, gender, race, weight and height). We integrated all modifications into four final kinetic CKD-EPI formulations for female and male, as well as black and non-black, respectively.

Results: The comparison of cckr values obtained by equation B and the “gold standard” equation A demonstrated excellent agreement across physiologically plausible ranges of their variables per1, per2, vDlt, vDlt, time interval (t) and cCr. The final kinetic CKD-EPI equations were tested for sensitivity to deviations of cgr and vD from their estimated values. We show that differences within clinically meaningful ranges can have significant effects on the kinetic GFR. Therefore, cgr and vD need to be checked for plausibility and adjusted (e.g. according to muscle mass, volume status) in individual patients.

Conclusions: We have developed a non-steady state adaptation of the CKD-EPI equation.

Funding: Private Foundation Support

SA-PO160

How to Estimate Kidney Function in AKI via the Basic Clearance: Role of the True Average (Creatinine)

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Background: The basic clearance formula UsxVP has a single Plasma creatinine ([Cr]), so it seems to apply only in the steady state. Can UsxVP be used in the non-steady state when there are multiple values of P? We postulate that if all the P’s in a [Cr] trajectory are represented by a “true average” [Cr], then dividing by this one P will recreate the kinetic GFR.

Methods: Working from any differential equation that models creatinine kinetics, we can take the novel step of using the fundamental theorem of calculus at the start. This produces a definite integral that calculates the average (not the simple mean) of a [Cr] vs. time function, our candidate true average [Cr]. It ends up in the denominator after solving for kinetic GFR, fitting the template of UsxVP.

Results: To use the true average [Cr] to compute kinetic GFR, we present two techniques, a graphical one and a numerical one—Newton’s method. Both yielded identical answers for kinetic GFR, verifiable by a gold standard technique. But the true average method arrived at the answer faster than the gold standard and without any false solutions. In analyzing a recent case, the kinetic GFR aided clinical decision-making on a 74-year-old man whose creatinine rose subacutely from 1.10 to 9.57 mg/dL. Intermittent dialysis was done, giving the [Cr] plot a sawtooth pattern (Fig., in purple). Despite an overall decline in [Cr] at first, the kinetic GFR (in blue) showed no improvement in his kidney function, since the “valleys” in between dialyses sank down to the same low level. Later, a renal biopsy (3/26) revealed acute interstitial nephritis, and prednisone was started (3/28). The next kinetic GFR valley (3/29) was slightly higher, hinting at an early renal recovery. The valleys kept increasing (3/31-4/5), telling us that the steroid was working and so dialysis was stopped.

Conclusions: The clearance paradigm applies to the non-steady state as well if the true average [Cr] is the divisor, providing a fundamental strategy to deduce the kinetic GFR from the plasma [Cr] trends occurring in real-life acute kidney injury or renal recovery.

Kidney recovery assessment in patients discharged with AKI requiring hemodialysis to outpatient centers

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Background: As of January 2017, patients with acute kidney injury requiring dialysis (AKI-D) can be discharged to outpatient centers for continued hemodialysis (HD) support. We aimed to examine kidney recovery and time-to-recovery in these patients.

Methods: Single-center, prospective cohort study of 118 adult patients who were admitted to the University of Kentucky Hospital (7/2017-2/2019), suffered from AKI-D and were discharged to non-academic affiliated outpatient HD centers. Kidney recovery was defined as the patient being alive and no longer requiring HD and was assessed at 30-day intervals up to 90 days post discharge.

Results: Of the 118 patients diagnosed with AKI-D during the index hospitalization, 15 patients were declared ESKD prior to discharge. We excluded patients that were prisoners (n=2) or were lost to follow-up (n=19). There were 5 patients that were misclassified as ESKD at their HD center despite being discharged as AKI-D. Among the remaining 77 patients, mean (SD) age was 54.4 (16.0) years; 61% were male and 88.3% white. Overall 29 (37.6%) patients recovered kidney function, about two-thirds of them within the first 30 days of hospital discharge [Figure].

Conclusions: At least 1 out of 3 AKI-D patients discharged to outpatient HD units with continued HD need recovered kidney function within 90 days of hospital discharge. The majority of patients recovered kidney function within 30 days of discharge, illustrating a critical window for surveillance and intervention. Future studies should focus on identifying best practices to promote recovery in this susceptible population.
Methods: Patients with severe AKI treated with CRRT in the first affiliated hospital of Nanjing Medical University from Sep 2016 to Sep 2018 were prospectively enrolled, and divided into death group and survival group according to 28-day survival. Cox regression was used to analyze the association between 28-day survival and tear Tissue Index (TLT), fat Tissue Index (FTI), the ratio of extracellular water(ECW) and body mass cell (BCM) (ECW/BCM), and overhydration (OH), respectively.

Results: A total of 156 patients were included, including 101 males and 55 females. The average age was 62.7±15.4 years, with an average SOFA score of 9.9±3.9. The 28-day mortality rate was 46.2%. The pre-CRT death odds and ECW/BCM values of the 28-day survival group and death group were 3.08 (1.8, 5.5) vs. 4.23 (3.0, 5.7) (P=0.016), 1.00 (0.76, 1.18) vs. 1.07 (0.88, 1.25) (P=0.333), respectively. Pre-CRT high OH values (HR=0.83, 95%CI=0.72-0.95, P=0.008) and high ECW/BCM values (HR=0.79, 95%CI=1.27-2.62, 0.006) were associated with 28-day death, while LTI and FTI values were not correlated with 28-day death. The changes of OH values (HR=0.83, 95%CI=0.72-0.95, P=0.008), ECW/BCM values (HR=0.79, 95%CI=1.27-2.62, P=0.006) and FTI values (HR=1.12, 95%CI=1.40-1.22, P=0.023) between pre-CRT and the 7th day after CRRT initiation were significantly associated with 28-day mortality in patients who survived 7 days after CRRT initiation. After adjusting for age, gender, and SOFA scores, the high OH value before CRRT, the changes of OH values, ECW/BCM values and FTI values between pre-CRT and the 7th day after CRRT initiation, were independently associated with 28-day death.

Conclusions: In biophysical impedance analysis, the OH value and ECW/BCM value before CRRT is associated with 28-day mortality in patients with AKI, while the nutritional indicator LTI is not significantly related. The correction of fluid overload by CRRT within 7 days may reduce the risk of death.

SA-PO163
Preoperative Low Urine Specific Gravity Levels Predict AKI After Cardiac Surgery
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Background: Acute kidney injury (AKI) is a common and serious complication following cardiac surgery. However, strategies that could effectively stratify AKI risk before cardiac surgery are scarce. Recent investigations identified urinary osmolality to be associated with non-glomerular kidney damage in patients who are at higher risk for CKD progression. Patients with underlying kidney damage, although clinically insignificant, may be prone to cardiac surgery associated AKI. Hypothesizing that urine specific gravity (SG) could reflect kidney damage, the clinical implication of preoperative urine specific gravity on AKI occurrence after cardiac surgery was investigated in subjects with normal kidney function.

Methods: A total of 4135 patients who underwent coronary artery bypass or valvular surgery at Yonsei University Health System from were enrolled. Patients whose the eGFR was lower than 60mL/min/1.73m2 were excluded. Fasting urinary specific gravity was measured from the morning first void a day before the surgery. The patients were divided into tertiles based on urine specific gravity. The primary outcome was the incidence of AKI within 48hours of cardiac surgery. AKI was defined according to Acute Kidney Injury Network criteria.

Results: The mean age of the patients was 60 years and 60% were male. Diabetes consisted of 25.6% of the patients and 54.5% were hypertensive. The mean eGFR and urine specific gravity were 69.7±18.6 (mmol/1.73m2) and 1.02, respectively. AKI developed in 1,089 (26.3%) patients. The incidence of AKI was highest in the lower urine SG tertile group (410, 29.0%) and lowest in the highest tertile group (304, 23.5%) (P < 0.001). Multivariable logistic regression analysis revealed that being included in the lowest preoperative urine SG tertile group was significantly related with higher post cardiac surgery AKI incidence (odds ratio (OR), 1.33; CI, 1.4-1.57; P < 0.001). This association was significant even after adjustments were made for confounding factors.

Conclusions: Low urine SG was associated with increased risk of cardiac surgery associated AKI in patient with normal renal function. Evaluating preoperative urine SG may be useful in stratifying post cardiac surgery AKI risk.

SA-PO164
External Validation of an Electronic Health Record (EHR)-Based Machine Learning Risk Score for Hospital-Based AKI
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Background: We seek to externally validate our previously published EHR-based machine learning AKI risk score in data from a new hospital system.

Methods: All hospitalized patients who had sCr measured at Loyola University Medical Center (LUMC) from 2008 to 2016 were eligible. Patients with a first serum creatinine (sCr)>3.0mg/dL, those who had an ICD codes for CKD Stage 4 or higher, or received renal replacement therapy (RRT) within 48 hours(hrs) of admission were excluded. Demographics, vital signs, laboratory results, and nursing scores were utilized in the previously published gradient boosted machine learning algorithm based on data from the University of Chicago (UofC) to predict SCr-based KDIGO AKI. Areas under the curve (AUC) were calculated in the LUMC cohort, and subgroup analyses were conducted across admission sCr, AKI severity, and hospital location.

Results: Among the 194,930 included LUMC patients, 27,374 (14.0%) developed KDIGO AKI with 7,364 (3.8%) developing Stage 2 and 3,393 (1.7%) requiring RRT. These rates were similar to the UofC cohort (14.4% AKI, 3.5% Stage 2). The AUC (95%CI) of the model in the LUMC cohort was 0.80 (0.80-0.80) for predicting Stage 2 AKI within 48 hours compared to 0.86 (0.86-0.86) in the UofC cohort. The AUC was 0.80 (0.80-0.80) for Stage 3 in 48 hrs in the LUMC cohort. AUCs for subgroups (patient location and admitting SCr) at LUMC (24 and 48 hr predictions) can be found in the table.

Conclusions: We report the first externally validated machine learning EHR-based AKI risk algorithm. EHR data can be used to predict impending AKI prior to significant changes in sCr across different patient locations and baseline sCr values. We are using this validated EHM model in real-time in an active clinical trial seeking to improve AKI outcomes.

Funding: NIDDK Support

Validation of EHR Risk Score in Subgroups Based on Patient Location and Admission sCr

<table>
<thead>
<tr>
<th>Location</th>
<th>Stage 2 AKI</th>
<th>Stage 3 AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUMC</td>
<td>0.79 (0.78-0.80)</td>
<td>0.80 (0.79-0.80)</td>
</tr>
<tr>
<td>UofC</td>
<td>0.86 (0.86-0.86)</td>
<td>0.86 (0.86-0.86)</td>
</tr>
</tbody>
</table>

SA-PO165
Identification and Performance Evaluation of AKI Trajectory Subtypes Associated with Mortality and Kidney Recovery in Critically Ill Patients
Javier A. Neyra,1 Taylor D. Smith,1 Victor M. Ortiz-Soriano,3 Xilong Li,3 Donglu Xie,2 Beverley Adams-Huet,1 Orson W. Moe,1 Robert D. Toto,2 Jin Chen,1 University of Kentucky, Lexington, KY; 1University of Kentucky Medical Center, Lexington, KY; 2University of Texas Southwestern Medical Center, Dallas, TX.

Background: Few risk-prediction models focus on outcomes specific to critically ill patients with AKI. We developed and evaluated the performance of a novel machine learning model called Trajectory of Acute Kidney Injury (TAKI) for the prediction of mortality and kidney recovery.

Methods: Independent cohorts from two academic institutions were used: UK (discovery, n=37,095) and UTSW (validation, n=10,590). Exclusion criteria consisted of age ≤18, eGFR <15 or ESKD, kidney transplant, absence of α2 serum creatinine (Scr) measures, absence of Scr-criteria of AKI in the first 7 ICU days or ICU stay <48 h. First, a trajectory based on KDIGO-AKI Scr-severity classification was composed for every patient using repeated Scr measures up to 7 days. Second, for trajectories with different length, population-based dynamic time-warping was developed for alignment. Third, the distance between any two aligned trajectories was computed and then adjusted using AKI severity. Fourth, hierarchical clustering was adopted with a dynamic merging process to determine the final trajectory subtypes, which were used as features for predicting hospital mortality and major adverse kidney events (MAKE) at 90 days following discharge (composite of death, RRT dependency or inability to recover 50% of baseline eGFR).

Results: The incidence of AKI was 33.4% (UK) and 27.0% (UTSW). Hospital mortality rates were 24.4% and 13.7% and MAKE rates 38.3% and 36.2% in UK and UTSW cohorts, respectively. TAKI identified improving, stationary and worsening trajectories with outcomes beyond severity classification. TAKI improved prediction of mortality and MAKE when added to severity classification of AKI or multigorgan failure scores in both cohorts [Table].

Conclusions: TAKI is a feasible method of AKI subtyping that informs risk-stratification of mortality and kidney recovery in critically ill adults with AKI beyond current AKI severity classification. Further validation is needed.

Performance metrics (95%CI) of TAKI for the prediction of mortality and MAKE (UK cohort)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TAKI</th>
<th>EGR</th>
<th>AUC 95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.74 (0.73-0.75)</td>
<td>0.65</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>MAKE</td>
<td>0.87 (0.86-0.88)</td>
<td>0.72</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.001 for performance comparison to corresponding reference; absolute IDI% (9.2-10.9) and continuous NRI (46.5-61.4)
SA-PO166

Recovery Patterns After AKI Differentiate Risk of Long-Term Adverse Kidney Outcomes

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Background: Whether the trajectory of kidney function 72 hours after AKI informs long-term clinical outcomes, including CKD, dialysis and death, is unknown.

Methods: We prospectively enrolled patients who survived 90 days after hospitalization with or without AKI in ASSESS-AKI. Resolving AKI was defined as a decrease in Scr of 0.3 mg/dL or 25% from maximum in the first 72 hours after AKI diagnosis. Non-resolving AKI was defined as all AKI cases not meeting the ‘resolving’ definition. The primary outcome was a composite of major adverse kidney events (MAKE), defined as incident or progressive CKD, incident dialysis or death. Time to event analysis were completed conditioning on: demographics, comorbidities and KDIGO stage of AKI.

Results: We evaluated 772 participants with AKI and 831 participants without AKI over a median of 4.8 years. Among the AKI group, 479 (62%) had a resolving AKI pattern and 294 (38%) had a non-resolving pattern. The unadjusted incidence rate for MAKE was 5.5 events per 100 patient years in participants without AKI, 11.1 events in resolving AKI and 15.4 events in non-resolving AKI (Figure 1). The adjusted hazard ratio (aHR) for MAKE was higher for both resolving (aHR 1.76, 95% CI 1.17 to 2.63; p=0.006) and non-resolving (aHR 2.54; 95% CI, 1.69 to 3.81; p<0.001) AKI compared to participants without AKI. Within the AKI population, non-resolving AKI was associated with a 45% greater risk of MAKE (95% CI, 17% to 78% greater; p=0.001) compared to resolving AKI. The higher risk of MAKE in non-resolving AKI was due to a higher risk of incident and progressive CKD.

Conclusions: The 72-hour time period post AKI diagnosis distinguishes the risk of MAKE. The identification of AKI recovery patterns may improve patient risk stratification, facilitate prognostic enrichment in AKI clinical trials, and recognize patients who may benefit from nephrology consultation.

Funding: NIDDK Support

Figure 1. Kaplan-Meier plot demonstrates the highest risk for major adverse kidney events (MAKE) among participants in the non-resolving AKI recovery group with a step-wise decrease in risk for MAKE in the resolving AKI group and then in participants without AKI. MAKE is defined as the composite of death, dialysis, CKD incidence, or CKD progression during study follow-up.

SA-PO167

Crizotinib-Induced Pseudo-AKI: A Case Report

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Introduction: The appearance of treatment-related Acute Kidney Injury (AKI) or the worsening of a pre-existing Chronic Kidney Disease (CKD) often limit the correct administration of many potentially life prolonging Oncological treatments. Crizotinib is a multi-kinase inhibitor, used to treat ALK-translocated non-small cell lung cancers (NSCLC). Chronic and acute (mainly due to competitive inhibition of creatinine at renal proximal tubule) kidney failure possibility pre-Crizotinib treatment should be considered.

Case Description: A 59 year old male came to oncometabolic evaluation with stage 5 CKD (creatinine 6.1 mg/dl, era 76 mg/dl, no clinical signs of uremia); he had a solitary kidney after a previous right nephrectomy for urothelial carcinoma, and carried a left ureteral stent for concomitant nephrolithiasis. More importantly, he had a metastatic ALK-translocated NSCLC previously treated with Cisplatin-based chemotherapy (CT), which lead to a first episode of AKI and then to CKD, presently treated with Crizotinib 250 mg b.i.d. with optimal disease control. Creatinine levels worsened from 1.6 mg/dl post nephrectomy, to 2.2 post CT, to 4 mg/dl after Crizotinib. The oncological treatment was thus stopped. When referred to us, a kidney sequential scintigraphy with Tc 99mDTPA was performed, which showed a glomerular clearance of 26 ml/min (vs a CKD-EPI of 9.2 ml/min and a Cockcroft Gault of 13.2 ml/min). We thus postulated that CKD worsening could be due to the inhibition of creatinine tubular secretion by Crizotinib. We thus recommended to restart Crizotinib treatment at the reduced dose of 250 mg q.d., suggesting to perform more frequent uroterial stent changes. Two years after restarting Crizotinib, the patient is still on treatment, with stable oncological disease, as well as renal function.

Discussion: Crizotinib may induce inhibition of creatinine tubular secretion together with creatinine increase, thus mimicking AKI on CKD. This case highlights the importance of renal scintigraphy in assessing these patients, as well as the role of Onco-Nephrologist.

SA-PO168

De Novo Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits After Allogeneic Stem Cell Transplant

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Introduction: Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID) is a rare form of monoclonal gammapathy of renal significance (MGRS). Here we describe an unusual presentation of de novo PGNMID occurring in a patient who underwent allogeneic stem cell transplant two years prior to the diagnosis.

Case Description: A 71-year-old male underwent matched related allogeneic stem cell transplant (SCT) for acute myelogenous leukemia (AML). The donor was the patient’s brother. The patient’s relevant medical problems at the time of transplant included enlarged prostate, status post prostatectomy, and previous acute kidney injury events attributed to sepsis and hypotension in the setting of chemotherapy administered for AML. At the time of transplant, serum creatinine was 1.5 mg/dL (GFR 47 ml/min). Urinalysis was voided and devoid of hematuria and proteinuria. Post SCT, he developed graft vs host disease involving the gastrointestinal tract which was treated with steroids. Subsequent restaging bone marrow biopsies showed no residual AML. Two years post SCT, he developed nephritic syndrome associated with a rapid rise in serum creatinine to 4.5 mg/dL (GFR 16 ml/min), and hematuria. Serum testing showed a monoclonal IgG kappa, and kappa free light chain of 4.8 mg/dL (kappa/lambda ratio of 2). Kidney biopsy revealed a diffuse mesangial and endocapillary proliferative glomerulonephritis with immunofluorescence microscopy revealing capillary loop pseudolinventary reactivity for IgG (2+), kappa (2+), and C3 (3+), with no reactivity for lambda. A subsequent bone marrow biopsy was negative for plasma cell neoplasm or lymphoma as was the flow cytometric analysis.

Discussion: To our knowledge, this is the first reported case of PGNMID following allogeneic SCT. Similar to many other reported cases, a plasma cell clone was not identified via histologic examination of the bone marrow. Given the time of PGNMID diagnosis post SCT, transfer of plasma cell disorder from the donor is one consideration to explore by testing the donor for monoclonal dysproteinemia. This case illustrates the importance of considering MGRS in the differential diagnosis of kidney disease and proteinuria in patients with history of stem cell transplant.

SA-PO169

Ibrutinib-Induced Acute Tubular Injury: A Case Series and Review of the Literature

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Introduction: CLL is the most prevalent form of leukemia in adults. Treatment with Bruton tyrosine kinase pathway inhibitor, ibrutinib has revolutionized its treatment. HTN and tumor lysis syndrome (TLS) with ibrutinib are known but acute tubular injury (ATI)
Severe Placental Insufficiency 3 Years After Treatment with Bevacizumab: An Epigenetic Effect

Dominique C. Pauzier, Nephrology, Centre Hospitalier Universitaire, Lille, France.

Introduction: We report on a patient whose second pregnancy was complicated by severe intra uterine growth retardation and early preeclampsia with the HELLP syndrome, thereby requiring a hysterectomy after she had been treated with Bevacizumab for breast cancer.

Case Description: A 26-year-old patient had had an uneventful first pregnancy in 1998. Ten years later, she was diagnosed with grade I intra ductal triple negative breast carcinoma, and treated with partial mastectomy, chemotherapy associated with Bevacizumab and radiation therapy. Three years later, bilateral ovariectomy was about to be performed, when an unexpected pregnancy was found at echography. The patient elected to pursue this pregnancy. Severe intra uterine growth retardation occurred, and cesarean section had to be performed at 29 weeks of amenorrhea, because of preeclampsia with the HELLP syndrome. Four months later, blood pressure and renal function were normal, and there was no proteinuria. No congenital or acquired thrombophilia was found.

Discussion: Our patient had severe placental insufficiency during her second pregnancy, three years after treatment with conventional chemotherapy and Bevacizumab for breast cancer. Conventional chemotherapy, even if used during pregnancy, is not associated with an increased risk of preeclampsia (1). In non-pregnant patients, Bevacizumab may induce a preeclampsia-like syndrome, which disappears when treatment is stopped (2). In our patient, one may speculate that former bevacizumab treatment caused a long-lasting alteration of the balance of angiogenic and antiangiogenic factors, which was later revealed during pregnancy, a distinctly unusual event in that context. Antiangiogenic drugs can alter the transcription profile of acetylation genes in retinal cells (3). This very unusual observation supports the hypothesis that Bevacizumab may have long-lasting endothelial effects in an epigenetic fashion (4). (1) Massey Shu-Chen et al. Obstet Gynecol 2012; 286: 89-92 (2) Cross SN et al. Rev Obst Gynecol 2012; 5: 2-8 (3) Hamid MA et al. Ophthalmic Surg Lasers Imaging Retina 2018; 49 : S29-33

SA-PO171
Monoclonal Immunoglobulin Tubulointerstitial Deposits in Kidney in Sjogren Syndrome with MALT Lymphoma: Occam’s Razor or Hickam’s Knife

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Introduction: Monoclonal gammopathy is a common phenomenon in patients with MALT (Mucosa Associated Lymphoid Tissue) lymphoma likely due to clonal production of paraproteins by lymphoplasmacytic cells, which responds to B cell directed therapy. We report a case of Sjogren’s disease and MALT lymphoma with rearranged kappa light chain, serum monoclonal gammopathy, and monoclonal IgM-kappa tubulointerstitial deposits in the kidney, that presented with a challenging therapeutic dilemma.

Case Description: 60 yo woman with Sjogren’s disease presented with a subacute rise in creatinine from 1.4 to 1.8 mg/dl and 1 gm proteinuria. Work up was positive for low C3, undetectable C4, positive RF. SIFE showed weak IgM-kappa band, urine immunofixation showed kappa positive urine. Kappa Lambda free light chain ratio was 23. She had a h/o parotid mass 2 years ago, diagnosed on excisional biopsy to be extra-nodal marginal zone lymphoma with IHC positive for CD20 and PC-10 and negative for lambda light chain. Repeat CT showed persistent low level FDG activity in left eye and parotids that was decided to be monitored. A kidney biopsy was obtained that showed IgM kappa lambda tubulointerstitial deposition disease with polytypic chronic active interstitial nephritis. Immunohistochemistry analysis revealed polytypic T cell predominant immunophenotype with no evidence of lymphoma. A subsequent work up included a bone marrow biopsy that showed a polytypic cell population (10.6% of the cells) with a K/L ratio of 3:1. Immunohistochemistry showed polymorphic plasma cells. There was no evidence of myeloma or lymphoma. Considering the above, it was concluded that the low level gammopathy was likely the source of monoclonal protein and a decision was made to treat with B cell directed therapy only.

Discussion: Monoclonal gammopathy has been reported with MALT lymphomas but this is the first case in literature with associated monoclonal IgM-kappa light chain tubulointerstitial deposition disease in the kidney. It is important to work up these patients for another clone producing site since it impacts decision making about immunosuppression. Close follow up is needed for monitoring renal and hematologic recovery.

SA-PO172
Rituximab Administration Unveils Monoclonal Gammopathy of Renal Significance (MGRS)

Itamar Sagiy, Karen Meir, Dvor Rubinger, Moshe E. Gatt, Hadassah Hebrew University Medical Center, Jerusalem, Israel.

Introduction: Cryoglobulinemic renal disease occurs in the presence or the absence of serological markers. In this case type I cryoglobulinemia-associated MGRS was diagnosed after rituximab (Rx) administration.

Case Description: A 52 yr old man was evaluated for moderate proteinuria with no extrarenal manifestations. Laboratory evaluation disclosed low C3 and increased antistreptolysin titer. Ranpirplin treatment did not affect urinary protein excretion. On kidney biopsy, there were PAS positive proteinaceous thrombi obliterating capillary lumens in a focal segmental pattern. These findings were suggestive of cryoglobulinemia. Immunofluorescence revealed intramembranous deposits positive for C3 and IgM κ chains (Figure1). Cryocrit increased from traces to 2% (Table 1). Anti HCV antibodies, rheumatoid factor, ANA, ANCA were negative. No paraprotein was detected. Treatment with Prednisone and subsequently with Rx had no effect. After 6 months the patient developed severe nephrotic syndrome and renal dysfunction. Cryocrit rose to 3% and IgM κ paraprotein appeared for the first time on immunofixation. A bone marrow biopsy showed 4.8% monoclonal plasma cells positive for IgM κ. Treatment with Bortezomib, Cyclophosphamide and Dexamethasone resulted in resolution of nephrotic syndrome and normalization of renal function.

Discussion: B cell suppression after Rx exposed the serum IgMκ originating from a small clone of plasma cell and responsible for MGRS. A Bortezomib based protocol induced complete clinical and serological remission.

Table 1. Clinical course and response to treatment.

<table>
<thead>
<tr>
<th>Year</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine proteinuria</td>
<td>mg/dL</td>
<td>mg/dL</td>
<td>mg/dL</td>
<td>mg/dL</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Serum proteinuria (mg/dL)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dL</td>
<td>mg/dL</td>
<td>mg/dL</td>
<td>mg/dL</td>
<td>mg/dL</td>
</tr>
<tr>
<td>Treatment</td>
<td>Prednisone</td>
<td>Rituximab</td>
<td>Prednisone</td>
<td>Rituximab</td>
<td>Prednisone</td>
</tr>
<tr>
<td>IgM**</td>
<td>SA</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Cyclophosphamide</td>
<td>Dexamethasone</td>
<td>Bortezomib</td>
<td>Cyclophosphamide</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NA:not available; ACE: angiotensin converting enzyme.

*Normal range: 0.26-1.65; ** Immunofixation.

Figure 1.

SA-PO173
Amyloidosis Returns

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Introduction: AL Amyloidosis is the most common type of systemic amyloidosis and frequently involves the kidney. Renal outcomes in renal AL Amyloidosis depend on hematologic remission, initial organ injury and depth of organ response. We describe a case of renal AL amyloidosis who developed worsening kidney function and nephrotic range proteinuria 3 years post ASCT and presented a challenging diagnostic and therapeutic dilemma.

Case Description: A 71 yo male presented with nephrotic syndrome with 5 gms proteinuria and had a renal biopsy revealing renal amyloidosis with lambda restriction. There was 50% interstitial fibrosis and tubular atrophy. Workup showed Igk Lambda monoclonal protein in serum and urine, normal troponin and mildly elevated NT-pro-BNP.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Skeletal survey was negative. ECHO showed EF of >70% with normal wall thickness. Bone marrow (BM) showed 70% cellularity with 15-25% plasma cells cytoplasmic lambda, and CD 38 and 138 were positive. Patient received cyclophosphamide, bortezomib and dexamethasone followed by ASCT. Following transplant, he developed acute kidney injury requiring short term dialysis with creatinine stabilizing at 1.6-1.8 g/dl and a proteinuria of 1.2 g/l. BM biopsy post ASCT was negative. Serum immunofixation (SIFE) was negative. 3 years later, he presented with subacute rise in proteinuria to 8 gms and a serum creatinine of 2.5-3.3 g/dl. He had a second kidney biopsy that showed lambda light chain restricted AL amyloidosis, with global sclerosis or obliteration by amyloid in 42% of glomeruli, tubular atrophy (70% of cortex), diffuse interstitial fibrosis and amyloid deposition. SIFE remained negative and Kappa/Lambda ratio was 1.3. A repeat BM biopsy was negative. Minimal residual disease testing on BM was also negative. There was no evidence of cardiac or hepatic amyloid. Considering the above, this was ascertained to be progression of the original amyloid disease and no further treatment was considered.

Discussion: We present a case of AL amyloidosis treated with chemotherapy and ASCT and remained in complete hematologic remission, but three years later presented with worsening renal failure and proteinuria with repeat kidney biopsy showing extensive amyloid deposits. This case highlights the importance of distinguishing between recurrence and progression of renal amyloidosis post ASCT by detailed hematologic workup and ruling out extra-renal disease.

**SA-PO174**

**Autologous Stem Cell Transplant for the Treatment of Masked Crystal-line Light Chain Tubulopathy and Podocytopathy Causing FSGS in the Context of Monoclonal Gammopathy of Renal Significance**

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**Introduction:** MGRS encompasses a wide spectrum of renal histopathology. Light chain (LC) crystalline podocytopathy causing secondary FSGS has rarely been described. We present a case with masked crystalline tubulopathy and podocytopathy associated with MGRS which was treated with melphalan induction therapy followed by autologous stem cell transplantation (ASCT).

**Case Description:** A 47 year old male presented with nephrotic proteinuria (uPCR 760 mg/mmol), microscopic haematuria and renal impairment (Creatinine 14460μmol/L, eGFR 40 ml/min). Autoimmune, virology screen, Complement were normal. Serum electrophoresis (SPEP) showed IgG kappa paraprotein 11g/L. Serum free light chain (SFLC) ratio was 9.5 (kappa level 91.3mg/l, lambda 9.6mg/l). No cryoglobulin was detected. Renal biopsy showed features of secondary FSGS. Immunofluorescence (IF) was negative for IgG, IgM, IgA, C3, C1q and equal kappa/lambda staining. We performed IF immunofluorescence unmasking crystalline inclusions in podocytes and tubules showing kappa LC restriction. Bone marrow biopsy (BMAT) showed 10-12% plasma cells. Normal skeletal survey. In conjunction, BMAT and renal biopsy results were confirmed with renal biopsy. BMAT showed 10-12% lambda, and CD 38 and 138 were positive. Patient received cyclophosphamide, bortezomib and dexamethasone whereas control arm utilized sunitinib.

**Results:** The randomization ratio was 1:1 in all studies. The 12 statistic for heterogeneity was 0%, suggesting homogeneity across RCTs. The PFS benefit was observed in all IMDC risk groups, including favorable group (HR, 0.70; 95% CI: 0.52-0.90; P = 0.02), intermediate risk group (HR, 0.71; 95% CI: 0.60-0.84; P < 0.0001) and poor group (HR, 0.58; 95% CI: 0.42-0.80; P = 0.0009). The PFS benefit was only noted in PD-L1 positive (≥1%) cohort with HR of 0.66 (95% CI: 0.57-0.77; P < 0.0001).

**Conclusions:** Our study showed that combination of immune checkpoint inhibitor and antiangiogenic therapy significantly improved PFS compared to standard sunitinib in patients with advanced RCC, regardless of IMDC risk categories. However, PFS benefit was only noted in PD-L1 positive cohort and further strategies are warranted in PD-L1 negative subset.

**SA-PO177**

**Incidence of AKI in Melanoma Patients Treated with Immune Checkpoint Inhibitors**

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**Background:** Immune checkpoint inhibition (ICI) has a major clinical success in clinical oncology. Immune-related adverse events (irAEs) are well described toxicities. Unlike other common irAEs, the incidence of renal toxicity is reported 3.8% with varied definitions of AKI. In this study we sought to retrospectively review a single center 10 year experience of patients diagnosed with Melanoma and treated with CPI and evaluate the incidence of AKI and overall survival.

**Methods:** We performed a retrospective chart review from 2008-2018 and extracted all patients treated with CPI. We identified 1691 unique melanoma patients and extracted such cases for this analysis.
all available creatinine. We have defined AKI based on KDIGO guidelines. 1st definition: as >0.5 mg/dl increase in serum creatinine of 0.3 mg/dl within 48 hours and 2nd as 50% relative increase in serum creatinine within 7 days. Time to first AKI was defined as time from treatment initiation to time of AKI. Cumulative incidence rate of AKI after initiation of ICIs were calculated in the presence of death as a competing risk. The effects of covariates on the cumulative incidence function of AKI were evaluated in the univariate setting using Gray’s test. Validity of the proportional cause-specific hazards and sub-distribution hazards assumptions were assessed using the proportionality test on time-varying covariates.

Conclusions: With such a large population of melanoma patients treated with ICI we have not yet accounted for the inclusion of AKI in setting of ICi use and confirmation of incidence that has been inducted. In addition, it’s an expansive look at predictors of AKI and the use of ipilimumab and combinations of ICi more associated with AKI. Impact of AKI on survival is underway.

Funding: Other NIH Support - The University of Texas MD Anderson Cancer Center is supported in part by the National Institutes of Health through Cancer Center Support Grant P30CA16672

SA-PO178
Incidence of Nephrotoxicity Secondary to PD-1/PD-L1 Inhibition: A Single Health Center Experience
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Background: Immuno-check point inhibitors (CPI) such as PD-1/PD-L1 inhibitors alone or in combination with other chemotherapy medications have been used to treat variety of metastatic neoplasms with amazing effects in recent years. However, cases of the nephrotoxicity caused by them not being often. Here we present a single health center experience of identifying CPI associated nephrotoxicities in renal biopsies and their follow-up data.

Methods: Over past 17 months (till April 2019), we have had approximately 620 cases of renal biopsies from our eight-hospital system (4000 beds in total) in Southeast Michigan. Seven indicated native renal biopsies were performed to evaluate renal pathology in patients who were treated with CPI for various metastatic neoplasms, but developed acute kidney injury. Conventional light microscopy, immunofluorescent stains and electronmicroscopy were used to assess renal pathology and clinical correlations were conducted. Results: The cases are summarized in Table below. The identified cases represent 1.1 % of our renal biopsies. Typical acute interstitial nephritis (AIN) (composed of dominant CD3 positive T lymphocytes) was seen in five of seven patients (Table below) but remaining two patients’ biopsies without AIN had either chronic thrombotic microangiopathy (TMA) or acute tubular injury (ATI). Three out the five patients with CPI induced AIN had significant recovery of renal function after steroid treatment, while other two AIN cases had limited renal functional recovery.

Conclusions: Since our first cases seen at the end of 2017, there have been increased incidence of nephrotoxicity cases due to CPI treatment, most characterized by T lymphocytes mediated AIN. Some patients had a good renal function recovery in response to steroid treatment.

Clinical and Pathologic Indices, and Follow-up Renal Function

<table>
<thead>
<tr>
<th>Age/Gender/Treatment</th>
<th>CPI</th>
<th>Polo-G</th>
<th>Rituximab</th>
<th>Follow-up PK/RI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60, renal cell cancers</td>
<td>Optimal</td>
<td>5.5</td>
<td>AIN, moderate</td>
<td>2.47</td>
</tr>
<tr>
<td>62m, lung cancer</td>
<td>Keytruda</td>
<td>2.0</td>
<td>AIN, moderate</td>
<td>1.95</td>
</tr>
<tr>
<td>66m, lung cancer</td>
<td>Keytruda</td>
<td>4.0</td>
<td>AIN, moderate</td>
<td>1.01</td>
</tr>
<tr>
<td>49f, lung adenocarcinoma</td>
<td>Optimal</td>
<td>2.7</td>
<td>AIN, mild</td>
<td>0.90</td>
</tr>
<tr>
<td>87m, melanoma</td>
<td>Optimal</td>
<td>2.0</td>
<td>TMA</td>
<td>1.77</td>
</tr>
<tr>
<td>18m, bladder cancer</td>
<td>Keytruda</td>
<td>2.0</td>
<td>AIN, mild</td>
<td>1.89</td>
</tr>
<tr>
<td>71m, lung cancer</td>
<td>Keytruda</td>
<td>1.9</td>
<td>AIN, mild</td>
<td>1.15</td>
</tr>
</tbody>
</table>

M - male; F - female

SA-PO179
A Single-Institution Study of Renal Outcomes in Patients Receiving Checkpoint Inhibitors

Background: Checkpoint inhibitors (CPI) are becoming more widely used for various malignancies. The reported incidence of renal toxicities has varied, with a lower incidence reported in clinical trials but significantly higher in follow up retrospective cohorts. Here, we present a single-institution retrospective study monitoring renal function in patients receiving CPI treatment.

Methods: An IRB-approved retrospective analysis was performed using patients seen at Moffitt Cancer Center between 1/1/2015 and 1/1/2016 who were receiving CPI therapy (ipilimumab, nivolumab, pembrolizumab or any combination). Selected patients had up to 12 months follow up including laboratory analysis of renal function. If available, serum electrolytes and urine studies were also collected. Primary endpoint was acute kidney injury (AKI), defined as increase in serum creatinine by > 0.3 mg/dl or ≥ 50% from baseline.

Results: 206 patients were selected with most common diagnoses of melanoma (81%) or NSCLC (12%). Most patients (79%) also had stage 4 disease. There were 19 patients who had AKI, with a median age of 73 vs 68 in the non-AKI group (p = 0.057). There was no difference in HTN, DM, CKD stage, baseline creatinine, or baseline blood pressure between groups. There was no correlation between AKI and specific CPI therapy or combined CPI therapy. In the AKI group, there was a higher incidence of concomitant antihistamines (42% vs 15%, p = 0.003) and diuretics (37% vs 17%, p = 0.03). In the AKI group, 10 discontinued all CPI therapy due to disease status (progression or surveillance).

Conclusions: CPI had AKI associated with autoimmune toxicity (2 colitis, 1 pancreatitis, 1 autoimmune nephritis) that resolved with steroids and stopping/changing CPI. 6 patients continued therapy without interruption, 4 had resolution of AKI. 5 patients had increasing SBP (>20 mmHg) at the time of AKI.

SA-PO180
Incidence of Rash and Palmar-Plantar Erythrodysesthesia in Patients with Advanced Renal Cell Carcinoma Treated with First-Line Combination Therapy with Checkpoint Inhibitors
Yvette Canzian1, Dia R. Aftieh2,3,4,5,6,7,8, R. Anna Sultan,2 Vaqar Ahmed,1 Maung Htain K. Lin,7,8 Thura W. Hutm,9 Kim Phung L. Nguyen,3,4,5,6,7,8,9 Sriram Swarup,1 Kyaw Z. Thein,10,11 UTHealth, Houston, TX;5 Texas Tech University Health Sciences Center, Lubbock, TX;4 Dallas Nephrology Associates, Lubbock, TX;4 Charles Wilson VA outpatient clinic, Houston, TX;11 Aberdeen Royal Infirmary, Colchester, Essex, United Kingdom;12 McGovern Medical School - UTHealth - Houston, Houston, TX;5 University of Texas Health Science Center at Houston, McGovern Medical School, Houston, TX;3 The University of Texas MD Anderson Cancer Center, Lubbock, TX;5 Texas Tech University Health Sciences Center, Lubbock, TX.

Background: Renal cell carcinoma (RCC) is the most common form of kidney cancer and clear cell RCC, the most common histology, harbors genetic abnormalities involved in angiogenesis via production of vascular endothelial growth factor (VEGF). Sunitinib has been the standard first-line treatment of advanced RCC for the past decade with notable dermatologic toxicities. We present a single institution retrospective study of randomized controlled trials (RCT) to determine the risk of rash and palmar-plantar erythrodysesthesia (PPE) with newer first-line combination therapies with checkpoint inhibitors.

Methods: PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through May 2019 were queried. RCTs utilizing upfront checkpoint inhibitors combination therapy in patients with advanced RCC were incorporated. The primary meta- analytic approach was a random effects model using the Mantel-Haenszel (MH) method. It was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI).

Results: Four phase III RCTs including 3758 patients with advanced RCC were eligible. The study arm used nivolumab+ ipilimumab, pembrolizumab+ axitinib, avelumab+ axitinib or atezolizumab+ bevacizumab while control arm utilized sunitinib. The randomization ratio was 1:1 in all studies. The I2 statistic for heterogeneity was 98%, suggesting some heterogeneity among RCTs. Any-grade PPE was reported in 295 (15.8%) vs 205 (11.0%) in control group with RR of 1.43 (95% CI: 1.21 –1.69, P < 0.001). High-grade PPE was noted in 47 (2.5%) vs 124 (6.6%) in control group with RR of 2.58 (95% CI: 1.87 –3.53, P < 0.001). Any-grade PPE was 289 (15.5%) in study arm vs 741 (39.8%) in control arm. The pooled RR was statistically significant at 0.21 (95% CI: 0.06 –0.71, P = 0.01). High-grade PPE was noted in 47 (2.5%) vs 124 (6.6%) in control group with RR of 0.20 (95% CI: 0.03 –1.59, P = 0.13).

Conclusions: Upfront checkpoint inhibitors combination therapy notably decreased the risk of any-grade PPE, a major cause of morbidity and one of the feared dermatological toxicities, with a RR of 0.21, despite increasing the risk of any-grade rash.

SA-PO181
Monoclonal Immunoglobulin Deposition Disease: Experience in a Single Institution
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Background: Recently described proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGNMID) has become of interest as it typically has clinically significant glomerulonephritis, with a membranoproliferative (MPGN) pattern on light microscope, and selective glomerular deposition of an entire monoclonal immunoglobulin by IF. There is often no hematologic malignancy to explain the findings, leading to therapeutic difficulties.

Methods: We reviewed our MN cases (7/1/2017-5/1/2019).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: The prevalence of MIDD is 3% (28/860), including entire monoclonal immunoglobulin light and heavy chain deposition disease (L&HCDD, n=12), renal light chain (AL) amyloidosis (n=13), κ light chain deposition disease (KCDD, n=1), and γ heavy chain deposition disease (HCDD, n=2). The L&HCDD group had 9 cases of monoclonal IgG deposition disease (PGNMID), with a predominant MPGN pattern, and 3 cases of monoclonal IgA DD, with a predominant mesangial glomerular involvement. Bone marrow (BM) was biopsyed in 6/12 of the L&HCDD cases; 3 showed abnormalities. Serologically, 6/12 had no M-spike; 1 case with M-spike had negative BM workup; 1 case had an M-spike without BM biopsy; and 1 case had no serological workup. 7/9 PGNMID cases received bortezomib based treatment. Pre- and post-treatment proteinuria was 8.76±9.95 and 1.75±2.06; creatinine was 1.97±0.64 and 1.94±0.61mg/dL. Other MIDD cases had a clear connection with BM malignancy: multiple myeloma in 9/13 amyloid cases and all HCDD and KCDD cases; 1 case had a negative BM evaluation but had a lgG-A circulating paraprotein.

Conclusions: L&HCDD is almost as common as AL amyloidosis, and much more common than LCDD or HCDD. Despite not identifying a monoclonal disease in many of our PGNMID cases, bortezomib based treatment resulted in good renal outcomes.

SA-PO183
Impact of Autologous Stem Cell Transplantation on Renal Response in Multiple Myeloma Patients with Advanced Renal Failure
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Background: This study aimed to evaluate the impact of autologous stem cell transplantation (ASCT) on renal outcomes of multiple myeloma (MM) patients who had advanced renal failure with estimated glomerular filtration rates (eGFR) ≤60 ml/min/1.73m² at the time of transplantation.

Methods: In our ASCT database from July 2009 to September 2018, 76 MM patients with median eGFR of 36.0 (range, 5.4-59.8) ml/min/1.73m² at ASCT were included: 47 (61.8%) with eGFR ≤30 and <60ml/min/1.73m²; 16 (21.1%) with eGFR 30≤ and <60ml/min/1.73m²; and 13 (16.9%) with eGFR <15ml/min/1.73m² and/or hemodialysis-dependent. Myeloma and renal response after ASCT were evaluated using the international myeloma working group response criteria.

Results: During median follow-up of 37.3 (range 0.9-108.3) months, transplant-related mortality occurred in seven patients (9.1%). Overall myeloma response was achieved in 70 patients (92.1%): 6 (7.9%) of partial response (PR), 12 (15.8%) of very good partial response (VGPR), and 52 (65.8%) of complete response (CR). Median year-probability of myeloma progression-free survival (PFS) and overall survival were 23.2 (95% CI, 16.9-32.1) and 61.5 (95% CI, 43.6-69.8) months, respectively. Among 20 patients (26.3%) who achieved renal response, including 19 (25.0%) of renal CR and 1 (1.3%) of renal PR, median time to achieve partial response was 267 days (range, 3-2022). In subgroup (n=29) with baseline eGFR <30 ml/min/1.73m², 21 patients (53.8%) achieved renal response after median 53 (3-1756) days post ASCT. In multivariate analysis, IgA type, advanced eGFR (≤30 ml/min/1.73m²), and shorter duration from diagnosis to ASCT (<6 months) were associated with higher cumulative rate for achieving renal response.

Conclusions: Clinical outcome of myeloma patients after ASCT was favorable. Patients with advanced renal failure may benefit from early ASCT.

SA-PO184
Monoclonal Gammopathy-Associated Thrombotic Microangiopathy
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Background: Thrombotic microangiopathy (TMA) is characterized by end-organ damage and classic histopathologic findings secondary to endothelial injury. Microangiopathic hemolytic anemia (MAHA) often accompanies TMA. TMA in the setting of monoclonal gammopathy has been reported after hematopoietic stem cell transplant or with proteasome inhibitors in multiple myeloma (MM) but it is less clear if the monoclonal gammopathy itself may be involved in pathogenesis.

Methods: Cases were obtained from 6 institutions in the United States and Canada. TMA was confirmed histologically (kidney biopsy) or evidence of MAHA with thrombocytopenia (platelet count less than 150 x 10^9/L) and schistocytes, elevated lactate dehydrogenase (LDH), decreased haptoglobin, and indirect hyperbilirubinemia.

Results: Of the 9 patients, (33.3%) were female. The median age was 66 years. Five patients had MM (4 were treatment naive, 1 previously received melphalan and prednisone), one had Waldenstrom macroglobulinemia (WM), and 3 had monoclonal gammopathy of undetermined significance. The patient with WM had previously been treated with cyclophosphamide, rituximab and dexamethasone. No patient had otherwise received any medication associated with drug-induced TMA. All patients had renal involvement and a median creatinine of 3.3 mg/dL. Seven patients had a kidney biopsy and all demonstrated TMA. Median hemoglobin and platelet count were 108 g/L and 147 x 10^9/L, respectively. Six patients had thrombocytopenia but only 4 had evidence of MAHA. No patient had GI symptoms. ADAMTS13 level was only obtained in 1 patient and was non-deficient at 27%. Complement levels (C3, C4, total complement) were normal in 5 patients, and 1 patient had a low C4. Genetic testing for mutations in the alternative complement pathway were performed in 2 patients and were normal. Three patients were treated with plasma exchange, 1 patient initially improved but died of multiorgan failure 6 days after presentation. One patient is awaiting treatment plan from hematology. The others have had resolution of TMA without recurrence after treatment of their disease. Most of the patients received eculizumab.

Conclusions: This study suggests that monoclonal gammopathies are associated with TMA. Disease-directed therapy should be considered first-line treatment of TMA, in addition to PLEX if there is ADAMTS13 deficiency.

Funding: Commercial Support - Tokuda, Pfizer, Prothena, Celgene, Janssen, and Alnylam, Government Support - Non-U.S.
SA-PO185
Tubulointerstitial Lesions Associated with Monoclonal Gammapathies of Renal Significance
Afonso Santos,1 Ana Gaspar,2 Anna Lima,1 Rita Theias Manso,1 Karina Soto,1,2 Pathology, Hospital Fernando Fonseca, Lisbon, Portugal; 3NOVA Medical School of Lisbon, CEDOC, Lisbon, Portugal; 4Nephrology, Hospital Fernando Fonseca, Lisbon, Portugal.

Background: Monoclonal gamopathy of renal Significance (MGRS) is not a renal disease, however, some patients presented with symptoms and signs related to renal involvement. Aims: To assess the incidence and histopathological features of monoclonal gammapathies in patients with MGRS.

Methods: A retrospective analysis was performed. Patients with renal symptoms (hematuria, proteinuria, nephrotic syndrome) and/or laboratory evidence of renal tubulopathy were included. Renal biopsies were performed using standard techniques. The histopathological features of monoclonal gammapathies are broad, and they are usually associated with interstitial inflammatory reactions.

Results: A total of 129 patients who performed kidney biopsy, 21 patients were initially excluded. The histopathological features of monoclonal gammapathies are broad, and they are usually associated with interstitial inflammatory reactions.

Conclusions: Monoclonal gammapathies of renal significance are often associated with interstitial inflammatory reactions; a subset of such patients may be diagnosed by the International Kidney and Monoclonal Gammapathy Research Group.

SA-PO186
Effect of Bortezomib and Male Sex on the Risk for Developing Tumor Lysis Syndrome in Patients with Multiple Myeloma: A Retrospective Study
Masahiro Kondo,1 Yuji Hotta,2 Karen Yamauchi,1 Hirokazu Komatsu,3 Shin-suke Iida,1 Kazunori Kimura.1,2 Department of Pharmacy, Nagoya City University Hospital, Nagoya, Japan; 3Department of Hospital Pharmacy, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan; 4Department of Hematology and Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

Background: Tumor lysis syndrome (TLS) causes acute kidney injury and is a complication of cancer chemotherapy. TLS risk is classified by malignant disease type. Although multiple myeloma (MM) is a low-risk disease, treatment by novel therapies, including bortezomib, may increase TLS risk. This risk was investigated for patients with MM.

Methods: Retrospectively investigated the incidence of laboratory TLS in patients who received primary therapy for untreated symptomatic MM between May 2007 and December 2017. As sensitivity analyses, landmark analyses were conducted with day 0, 100, 180, and 365 days post-transplant as landmark time points. As sensitivity analyses, landmark analyses were conducted with day 0, 100, 180, and 365 days post-transplant as landmark time points.

Conclusions: Bortezomib may increase TLS risk, particularly among male patients with MM. Thus, TLS risk should be evaluated based on multifactorial.

SA-PO187
Assessment of Renal Impairment on the Prognosis of Newly Diagnosed Multiple Myeloma
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Background: The renal impairment (RI) at multiple myeloma (MM) ranged from 20 to 90% and RI is associated with reduced survival. The new criteria from the International Myeloma Working Group (IMWG) defined RI as serum creatinine (SCr) > 2.0 mg/dL or eGFR < 40 ml/min/1.73 m². If these definitions are associated to overall survival (OS) is still debatable.

Methods: All patients with newly diagnosed MM (up to three months) admitted for treatment at the Sao Paulo State Cancer Institute, between February 2012 and May 2016, were followed for a minimum of three years. Exclusion criteria were: age < 18 years; pts on dialysis; initiation of MM treatment before recruitment or exams; pts with follow up and overall survival after ASCT.

Conclusions: KDIGO CKD definition seems to be superior to the IMWG criteria to assess the impact of RI on the prognosis of newly diagnosed MM pts. Markers of higher burden of disease are strongly related to reduced survival.

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SA-PO188
Impact of Autologous Stem Cell Transplant in Myeloma Patients on Renal Function, Progression-Free Survival, and Overall Survival: A Longitudinal Analysis
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Background: Renal impairment has been negatively associated with progression free survival (PFS) and overall survival in patients diagnosed with multiple myeloma (MM). Autologous stem cell transplantation (ASCT) has been shown to reduce serum creatinine (SCr) < 2.0 mg/dL (P=0.703), eGFR < 40 ml/min/1.73 m² (P=0.414). Variables related to low OS were CKD 3 (P=0.011), ISS-III (P=0.011) and B2M > 3.5 mg/L (P=0.0001). Elevated LDH value was marginally related to reduced OS (P=0.090). On Cox regression model, B2M = 3.5 mg/L (HR: 1.68; 95% CI: 1.12 – 2.63) and abnormal LDH (HR: 1.61 [1.01 – 2.56]) were associated with lower OS.

Conclusions: KDIGO CKD definition seems to be superior to the IMWG criteria to assess the impact of RI on the prognosis of newly diagnosed MM pts. Markers of higher burden of disease are strongly related to reduced survival.

Funding: Private Foundation Support
SA-PO189

Rate and Predictors of Developing Monocalon Gammapathy of Renal Significance (MGRS) Lesion on Renal Biopsy in Patients with Positive Monoclonal Studies

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Background: Monoclonal gammopathy (MG) can cause renal damage in a subset of patients known as MGRS. However, the rate of finding an MGRS lesion on a biopsy in a patient with MG and the clinical factors that would predict the likelihood of finding such lesions remains unknown.

Methods: We identified all patients that had a positive serum MG based on a positive serum electrophoresis or immunofixation between 2013 through 2018 at the Mayo Clinic Rochester. We then excluded those patients who had a diagnosis of multiple myeloma, amyloidosis, or those with a renal transplant.

Results: We identified 4257 patients who met the inclusion criteria, of which 105 had a renal biopsy (2.47%). Of the 105 patients, 25 (23.8%) had an MGRS lesions. The most common MGRS lesions included proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGNMID) (n=10, 40%) followed by cryoglobulinemic vasculitis (n=5, 20%). In the remaining 80 patients, the most common lesions included arteriosclerosis (n=19, 23.75%), diabetic nephropathy (n=14, 17.5%), ANCA associated vasculitis (n=8, 8.8%) and IgAN (n=8, 8.8%). At the time of renal biopsy, there were no differences in age, sex, serum creatinine, hemoglobin and type of light chain between 2 groups. Compared to non-MGRS patients, MGRS patients had a significantly higher systolic blood pressure (p = 0.03) and more likely to have IgG heavy chain (p =0.03). Hematuria at time of the renal biopsy was the most significant predictor of finding an MGRS lesion with an OR of 6.21 (2.1-18.3, P=0.0003), followed by proteinuria >3 g/d with OR of 2.61 (1.01-6.7, p=0.04), and an elevated ratio of affected/unaffected light chain (OR= 1.0, 1.01-1.16, p=0.0001). Having a combination of hematuria and proteinuria 2 g/day was also highly predictive with an OR of 5.67 (2.0-16.1, P=0.001).

Conclusions: Among patient with a positive MG who had a renal biopsy in the absence of amyloidosis, 75% had a lesion unrelated to the MG with arteriosclerosis and DN being the most common findings. Hematuria, nephrotic range proteinuria or high risk features (hematuria=proteinuria2 g) were the strongest predictors of finding an MGRS lesion.

SA-PO190

Twenty-Eight Treatments of Acute Renal Failure Secondary to Multiple Myeloma (MM) with High Cutoff (HCO) Filters

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Background: Our hospital is a reference in Spain for the treatment of acute renal failure secondary to multiple myeloma with HCO filters. We present our experience with 28 treatments.

Methods: Treatment indication required the diagnosis of MM, the presence of AKI requiring dialysis, a free light chains (FLC) level greater than 500 mg/L. The patients were analytically monitored by blood sampling at the start and the end of the hemodialysis session. The dialysis protocol used was the following: daily dialysis for 6 sessions, ultrapure water, HCO filter of 2.1 meters. To pass then to dialyze every other day until reaching sFLC levels below 500 mg/L, or until the recovery of a renal function. The duration of the sessions was 6 hours. 2 vials of 20% human albumin, 50 mL, were infused in aprotocled manner during the last half hour of dialysis.

Results: 28 treatments were performed on 25 patients. The average age of the patients was 60.2 years; 17 men and 8 women. The chemotherapy regimen was based on Bortezomib and Dexamethasone as first line. 24 of the 28 cases (85.7%) had a renal recovery to allow independent dialysis. At 3 months, the number of patients who remained independent of dialysis was 21 of the 28 cases treated (75%), 13 patients presented MM with Lambda chains and 12 were kappa. The average reduction of FLC by dialysis session was 63%. The reduction in sFLC beginning and the end of the treatment reached an average of 91%. Reviewing our data in May 2019, after 8 years of treatment, we have found that 52% of patients live independently of dialysis, we have also compared our results with the studies that more patients have treated and we have proven that our results are better.

Conclusions: Given our experience, we believe that prolonged hemodialysis with HCO filters is effective, safe and with a high rate of renal recovery. Therefore it should be the treatment option chosen, together with chemotherapy, in all patients with multiple myeloma, cylinder nephropathy and acute renal failure requiring dialysis.

SA-PO191

Incidence of Hypertension and Hypothyroidism in Patients with Advanced Renal Cell Carcinoma Treated with First-Line Combination Therapy with Checkpoint Inhibitors

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Background: Utilizing immunotherapies and antiangiogenic agents has become a fundamental paradigm shift in the treatment of advanced renal cell carcinoma (RCC). Inhibition of vascular endothelial growth factor (VEGF) has antiangiogenic and immunomodulatory effects. Combination of these therapies has also shown to have synergistic antitumor activities and survival benefits. Yet, there are considerable safety concerns. We conducted a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of hypertension and hypothyroidism.

Methods: PUBMED, MEDLINE, EMBASE databases and meeting abstracts from inception through May 2019 were queried. RCTs utilizing upfront checkpoint inhibitors combination therapy in patients with advanced RCC were incorporated. The primary meta-analytic approach was a random effects model using the Mantel-Haenszel (MH) method. It was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI).

Results: Four phase III RCTs including 3758 patients with advanced RCC were eligible. The study arm n/volumub+ ipilimumab, pembrolizumab+ axitinib, avelumab+ axitinib or atezolizumab+ bevacizumab while control arm utilized sunitinib. The randomization ratio was 1:1 in all studies. The I2 statistic for heterogeneity was 98%, suggesting some heterogeneity among RCTs. Any-grade hypertension was reported in 567 (30.4%) vs 746 (40.1%) in control group with RR of 0.54 (95% CI: 0.27 –1.07, P = 0.008). High-grade hypertension was reported in 273 (14.6%) in study arm vs 317 (17.0%) in control arm (RR, 0.63; 95% CI: 0.30 –1.30, P = 0.21). Any-grade hypothyroidism was 450 (24.1%) in study arm vs 388 (20.8%) in control arm. The pooled RR was not statistically significant at 1.22 (95% CI: 0.76 –1.95, P = 0.41). High-grade hypothyroidism was noted in 5 (0.27%) vs 4 (0.22%) in control group with RR of 1.23 (95% CI: 0.33 –4.67, P = 0.76).

Conclusions: Our meta-analysis demonstrated that there was no significant increase in the risk of hypertension and hypothyroidism in upfront combination therapy group compared to standard sunitinib arm, despite achieving higher survival benefits.

SA-PO192

Graft vs. Kidney Disease in Recipients of Hematopoietic Stem Cell Transplantation: A Need for More Kidney Biopsies

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Background: Kidney biopsies are seldom done in patients with AKI after Hematopoietic Stem Cell transplant (HSCT). Graft versus kidney disease (GVKD) has not been well described. We aimed to assess the clinical and pathologic findings of patients with AKI after HSCT who received a kidney biopsy.

Methods: We conducted a chart review of 15 HSCT patients who underwent 17 kidney biopsies for AKI.
Results: Clinical characteristics and pathology results are listed in Table 1. Most patients who underwent kidney biopsy had both AKI and proteinuria. The most common biopsy finding was a mix of interstitial inflammatory cell infiltrate (GvKD) combined with acute or chronic endothelial injury, TMA (n=7, 41%). Other biopsy diagnoses included acute and chronic TMA, GvKD, acute tubular injury, and polyomavirus BK nephropathy. Immunohistochemical staining for C5b-9 was done on 7 biopsies with acute or chronic TMA and was positive in all 7. In 3 patients with GvKD and interstitial cell infiltrate, staining for granzyme B and CD3 was positive. Figure 1 demonstrates the pathology findings of a patient with AKI and biopsy diagnosis of GvKD with inflammatory cell infiltrate and chronic tubular injury. IHC was positive for both granzyme B in the interstitium and C5b-9 in the glomeruli and arterioles (Figure 1).

Conclusions: There is a range of pathologic findings in patients with AKI after HSCT. To understand the pathogenesis and explore therapies for AKI in HSCT we recommend a lower threshold for kidney biopsy in these patients.

Methods:

High Dose Methotrexate (HD MTX) defined as ≥ 1000 mg/m² is used to treat several tumors including lymphomas, leukemias and osteosarcoma. In a multicenter study in patients with osteosarcoma treated with HD MTX, Widemann et al reported a rate of AKI (defined as elevation in Cr ≥ 1.5 fold increase in baseline serum creatinine within 4 days after HD MTX) of 1.8%. We aimed to look at the rate of AKI in patients receiving HD MTX across the range of primary tumors for which the drug has an indication.

Methods: Data was collected on all adult patients (>18 years) who received HD MTX for all diagnoses from 01/01/2003 – 12/31/2013 at a single academic medical center. We excluded patients who had received prior or concurrent cisplatin®/ifosfamide. AKI with HD MTX was defined as 1.5 fold increase in baseline serum creatinine within 4 days after HD MTX. Clinical and demographic data were collected. Data on cumulative dose (CD) of HD MTX and number of cycles was obtained in both groups.

Results: The observed rate of AKI was 32.1% (282/880). The most common malignancies treated with HD MTX were lymphoma (75.0%) and leukemia (13.6%). Table 1 shows that advanced age (64 vs 57, p<0.0001) was associated with a higher rate of AKI. CKD III was associated with a lower rate of AKI (19.5 vs 80.5, p=0.01). The (CD) of HD MTX in patients who developed AKI was lower in comparison to those without AKI (1388 ± 1035 mg vs 22820 ± 16538 mg, p<0.0001). The number of cycles for HD-MTX was lower in patients who developed AKI (2.5 vs 4.4, p=0.001).

Conclusions: This study is the largest single center report on the rate of AKI following HD MTX treatment across all tumor types for which the drug has an indication. Lower cD is corresponding to CKD III and shorter duration of treatment with HD MTX were associated with a lower rate of AKI. A lower (CD) of HD MTX was associated with a higher risk of AKI. These findings suggest that clinicians are reducing the dose of HD MTX in patients with CKD or following an episode of AKI. Future studies on the impact of AKI on long-term renal function in patients receiving HD MTX would assess whether such dose modification is necessary and what the effect is on long-term survivorship.

Methotrexate-Induced AKI: A Retrospective Study

Rohit Gupta,1 Shenon Latcha,2 Elyn Riedel,2 (New York Presbyterian - Weill Cornell, New York, NY, 1Memorial Sloan Kettering Cancer Center, New York, NY.

Background: High Dose Methotrexate (HD MTX) defined as a 1000 mg/m² is used to treat several tumors including lymphomas, leukemias and osteosarcoma. In a multicenter study in patients with osteosarcoma treated with HD MTX, Widemann et al reported a rate of AKI (defined as elevation in Cr ≥ 1.5 fold increase in baseline serum creatinine within 4 days after HD MTX) of 1.8%. We aimed to look at the rate of AKI in patients receiving HD MTX across the range of primary tumors for which it is indicated.

Methods: Data was collected on all adult patients (>18 years) who received HD MTX for all diagnoses from 01/01/2003 – 12/31/2013 at a single academic medical center. We excluded patients who had received prior or concurrent cisplatin®/ifosfamide. AKI with HD MTX was defined as 1.5 fold increase in baseline serum creatinine within 4 days after HD MTX. Clinical and demographic data were collected. Data on cumulative dose (CD) of HD MTX and number of cycles was obtained in both groups.

Results: The observed rate of AKI was 32.1% (282/880). The most common malignancies treated with HD MTX were lymphoma (75.0%) and leukemia (13.6%). Table 1 shows that advanced age (64 vs 57, p<0.0001) was associated with a higher rate of AKI. CKD III was associated with a lower rate of AKI (19.5 vs 80.5, p=0.01). The (CD) of HD MTX in patients who developed AKI was lower in comparison to those without AKI (1388 ± 1035 mg vs 22820 ± 16538 mg, p<0.0001). The number of cycles for HD-MTX was lower in patients who developed AKI (2.5 vs 4.4, p=0.001).

Conclusions: This study is the largest single center report on the rate of AKI following HD MTX treatment across all tumor types for which the drug has an indication. Lower cD is corresponding to CKD III and shorter duration of treatment with HD MTX were associated with a lower rate of AKI. A lower (CD) of HD MTX was associated with a higher risk of AKI. These findings suggest that clinicians are reducing the dose of HD MTX in patients with CKD or following an episode of AKI. Future studies on the impact of AKI on long-term renal function in patients receiving HD MTX would assess whether such dose modification is necessary and what the effect is on long-term survivorship.
SA-PO195

AKI in Critically Ill Patients After Oncological Surgery: Risk Factors and Mortality

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Background: Acute kidney injury (AKI) is a frequent complication in critically ill patients, major surgery is the second most important cause of AKI. In cancer patients AKI is associated with increased mortality, therefore it is necessary to identify modifiable risk factors for its prevention. Previous scores aimed to predict AKI in general surgery have shown poor predictive value in patients undergoing oncological surgery, possibly because these scores do not consider previously administered radiotherapy or chemotherapy. The aim of the present study was to validate the incidence, mortality and risk factors for AKI development, defined by KDIGO criteria in patients admitted to the intensive care unit (ICU) in the first 24 hours after major oncological surgery.

Methods: We conducted a retrospective analysis using a logistic regression model to evaluate the association between preoperative and intraoperative variables and AKI, and a Cox regression model to evaluate factors associated with 12-month mortality.

Results: We included 434 patients, with a median follow-up of 432 days. We included 171 men (39%), with a median age of 53 years (IQR 41-63). All patients had solid tumors, most from gastrointestinal origin (124 patients, 29%) and female reproductive system (98 patients, 23%), and 294 (68%) underwent abdominal surgery. We diagnosed AKI in 264 (60.8%) patients: 135 (31.1%) stage-1, 66 (15.2%) stage-2 and 63 (14.5%) stage-3 AKI. In multivariate analysis, abdominal radiography (OR 2.57, 95% CI 1.25-5.29, p=0.010), abdominal surgery (OR 2.46, 95% CI 1.31-4.62, p=0.005), surgical packing (OR 4.12, 95% CI 1.97-8.61, p=0.000) and sepsis (OR 2.39, 95% CI 1.31-4.37, p=0.005) were independent risk factors for AKI development, while pre-surgical albumin (OR 0.45 95% CI 0.32-0.63, p=0.000) and intraoperative urine output (OR 0.81, 95% CI 0.70-0.94, p=0.009) were protective factors. During the 12-month follow-up 108 patients died (25.3%), 75 (17.2%) died of AKI. Male gender, age, diabetes, hypertension were associated with higher risk of developing AKI. Contrast renal injury, followed by hypovolemia. There were 13 patients where the acute kidney injury was attributed to drugs. The drugs were NSAIDS, Lenalidomide, Methotrexate, Ibrutinib, Pamidronate, Gemicitabine, Venurlafnil and Crizotinib. Patients with acute kidney injury demanded to above drugs had either a dose reduction or change in chemotherapy regimen. None of the patients had a renal biopsy to confirm drug-induced pathology. However all of the patients had resolution of AKI after stopping the drug or changing the regimen. Also of note, only one patient with Pamidronate induced acute kidney injury was referred to nephrology service. Looking at individual cancer types, 5 out of 10 patients (50%) with RCC developed acute kidney injury followed by lymphoma, prostate and myeloma. Factors associated with acute kidney injury, higher ECOG score, diabetes and hypertension were associated with higher risk of developing acute kidney injury. Contrast to other published papers, having metastatic disease and ACE inhibitors was not associated with higher risk of acute kidney injury. Acute kidney injury is associated with increased mortality. We observed the same trend in our study. Without adjusting for confounding factors, mortality in the acute kidney group at 6, 12 and 18 months was 15%, 31% and 46% compared to Non AKI group, which was 5%, 26% and 43%.

Conclusions: AKI is common in patients with malignancies and its associated with high mortality.

SA-PO196

AKI After Radical Nephrectomy as Risk Factor for CKD: Retrospective Analysis from an Italian Cancer Center

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Background: Radical nephrectomy is a significant risk factor for chronic kidney disease (CKD), and there are few reports on the renal outcome after radical nephrectomy for cancer. The aim of this study was to determine the incidence of AKI and whether postoperative AKI is associated with new-onset CKD after radical nephrectomy for renal cell cancer (RCC).

Methods: We conducted a retrospective study of 837 adult patients (~40 years old), from two major Cancer Centers with normal renal function who underwent unilateral radical nephrectomy for a solitary renal cortical tumor and were pathologically diagnosed with RCC between January 2010 and February 2019. Post-operative AKI was classed using risk, injury, failure, loss and end-stage kidney disease (RIFLE) criteria. CKD was defined as a decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m2.

Results: According to the RIFLE criteria, 258 of 278 patients fell into the AKI risk category 1, 21 patients fell into the AKI injury category and 6 patients fell into the AKI failure category. Multivariate analysis revealed as major result that higher preoperative GFR was an independent risk factor for postoperative AKI, although older age, male gender higher body mass index, smaller RCC size were independent risk factors too. New-onset CKD was more prevalent in the AKI risk group than in patients without AKI 1 year after surgery (56.1% versus 43.9%, respectively) and 3 years after surgery (52% versus 31%). Patients who experienced post-operative AKI had a 5.1-fold higher risk of new-onset CKD after multiple adjustments, that confirms our recent study.

Conclusions: AKI after radical nephrectomy in patients is a potent risk factor for new-onset CKD. Prevention of post-operative AKI, but also the assessment of kidney function pre-nephrectomy, is essential for reducing the incidence of CKD after nephrectomy.

SA-PO197

AKI in Patients with Haematological and Solid Organ Malignancy Receiving Chemotherapy

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Background: The aim of this study was to look at the incidence of acute kidney injury and its clinical correlates in patients with haematological and solid organ malignancies receiving chemotherapy.

Methods: All patients, more than 18 years of age receiving outpatient chemotherapy, for solid organ and haematological malignancies at our hospital from Jan 2016 to Dec 2016. Incidence of acute kidney injury was computed and its causes and clinical correlates were analyzed using univariate analysis and multivariate logistic regression.

Results: 592 patients were included in the study. Acute kidney injury during the one-year course of chemotherapy was seen in 158 patients (27.24%). Pre-renal acute kidney injury was seen in 82 patients (51.8%) and intrinsic renal in 20 patients (12.65%) and post renal cause in 35 patients (22.15%). Sepsis was the most common cause of acute kidney injury, followed by hypovolemia. There were 13 patients where the acute kidney injury was attributed to drugs. The drugs were NSAIDS, Lenalidomide, Methotrexate, Ibrutinib, Pamidronate, Gemicitabine, Venurlafnil and Crizotinib. Patients with acute kidney injury demanded for above drugs had either a dose reduction or change in chemotherapy regimen. None of the patients had a renal biopsy to confirm drug-induced pathology. However all of the patients had resolution of AKI after stopping the drug or changing the regimen. Also of note, only one patient with Pamidronate induced acute kidney injury was referred to nephrology service. Looking at individual cancer types, 5 out of 10 patients (50%) with RCC developed acute kidney injury followed by lymphoma, prostate and myeloma. Factors associated with acute kidney injury, higher ECOG score, diabetes and hypertension were associated with higher risk of developing acute kidney injury. Contrast to other published papers, having metastatic disease and ACE inhibitors was not associated with higher risk of acute kidney injury. Acute kidney injury is associated with increased mortality. We observed the same trend in our study. Without adjusting for confounding factors, mortality in the acute kidney group at 6, 12 and 18 months was 15%, 31% and 46% compared to Non AKI group, which was 5%, 26% and 43%.

Conclusions: AKI is common in patients with malignancies and its associated with high mortality.
Methods: We conducted a retrospective cohort study of patients receiving ICI at our center from 2010 to 2017 via electronic health record. The primary outcome was AKI [an increase of at least 50% from baseline serum creatinine (SCr)]. Risk factors for AKI were assessed using logistic regression. Survival among those with and without AKI was compared using time-to-event analysis.

Results: Among 309 patients on ICI, 52 (17%) developed AKI (KDIGO Stages 1: 9%, 2-4%, 3-4%). AKI was associated with other immune-related adverse events (IRAEs) [odds ratio (OR) 3.2 (95% CI: 1.6-6.1), p < 0.001], hypertension [4.3 (1.8-6.1), p = 0.001] and cerebrovascular disease [9.2 (2.1-40.0), p = 0.001]. Baseline SCr, cancer and ICI type were associated with AKI. Use of ACEi/ARB [OR 0.7 (0.4-1.5), p = 0.001] and corticosteroid treatment [OR 1.9 (1.3-3.6), p = 0.03] were associated with AKI. In the multivariable analysis, AKI was associated only with other IRAE [2.82 (1.45-5.48), p = 0.002] and hypertension [2.96 (1.33-6.59), p = 0.008]. AKI was associated with increased risk of mortality [hazard ratio 1.1 (0.8-1.5), p = 0.56].

ICl nephrotoxicity was attributed via biopsy or nephrologist assessment in 12 patients (6 intestinal nephritis, 2 membranous nephropathy, 2 minimal change disease, 2 thrombotic microangiopathy). Re-challenge with ICI occurred in 12 patients with AKI, 1 (8.3%) had recurrent AKI.

Conclusions: AKI incidence during ICI therapy may be greater than previously reported and several etiologies must be considered. A minority of patients undergoing kidney biopsy. The development of other IRAE is associated with AKI risk. AKI was not associated with worse cancer survival.

**SA-PO200**

Kidney Dysfunction in Head and Neck Squamous Cell Carcinoma Patients After Cisplatin-Based Concurrent Chemoradiation in a Long-Term (LT) Follow-Up: A Cross-Sectional Study

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**Background:** Cisplatin-based concurrent chemoradiation (CRT) offers to head and neck squamous cell carcinoma (HNSCC) patients (pts) better overall survival, but is associated with acute and late toxicity. Here we aimed to study the frequency of kidney dysfunction in HNSCC pts treated with CRT with curative intent in a LT follow-up.

**Methods:** Cross-sectional study of pts treated at São Paulo State Cancer Institute under regular follow-up. Eligible pts had to be diagnosed with HNSCC and treated with CRT (adjuvant or definitive), with no evidence of disease (NED) for at least 2 years after CRT. Chronic kidney disease (CKD) was defined as glomerular filtration rate (eGFR) < 60 mL/min/1.73m2. eGFR was estimated by the CKD-EPI equation.

**Results:** 120 pts were studied, median age 59 y.o. (21-78), being 88% (73%) male. The most common primary site was oropharynx (50 pts, 42%), followed by larynx (29 pts, 23%), oral cavity (23 pts, 19%), hypopharynx (9 pts, 8%) and nasopharynx (9 pts, 8%). Pts were staged as T3-T4 (87 pts, 75%) or N+ (86 pts, 72%). Comorbidities, such as hypertension or diabetes, were reported by 38 pts (32%). Most of the patients (107 pts, 97%) were ECOG-PS 0 or 1. CRT was administered either as adjuvant (59 pts) or definitive (61 pts) therapy, with a median RT dose of 70 Gy concurrently delivered with cisplatin (total median dose 300mg/m2, ranging from 100-300). Cisplatin-based induction chemotherapy was administered before CRT in 32 pts (total median cisplatin dose 225mg/m2, range 75-350). On follow-up of 42 months (24-125) after CRT, we detected a significant increase of serum creatinine (1.01±0.35 mg/dl) in comparison with baseline values (0.84±0.18 mg/dl) (p < 0.001), and a decrease of eGFR (78.2±20 ml/min) versus baseline (93.1±19 ml/min) (p < 0.001). Baseline (pre-treatment) eGFR was in range of 60 mL/min in only 4 pts (14%). In this analysis, eGFR was below 60 mL/min in 16 pts (14%) (p = 0.004). 44 pts (40%) had a decrease in eGFR above 5 ml/min/1.73m2/year. No clinically significant electrolyte abnormalities were detected and no pts were on dialysis at the end of follow up.

**Conclusions:** Chronic kidney disease features were frequently diagnosed in HNSCC pts with NED in a LT follow-up after CRT and may contribute to overall morbidity in these pts.

**SA-PO202**

Mortality Rates and Geographic Distribution of Kidney Cancer in Peru

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**Background:** Recent data showed decreasing prevalence rates of kidney cancer in the world. However, the epidemiology of kidney cancer in South America remains poorly explored. This study aims to illustrate the case of Peru.

**Methods:** Secondary data analysis from the Deceased Registry of the Peruvian Ministry of Health (PMH) database (2010 – 2015), which included reports from health care facilities located in 24 provinces, grouped into 3 regions: coast, highlands, and rainforest. Code 189 was used to identify deaths from kidney cancer based on ICD 9th Revision. Deaths were classified according to the birthplace. Calculations were made assuming an underreporting rate of 40%, as estimated by the PMH. We computed age-standardized mortality rates (ASMR, world population) per 100,000 person-year. Cluster map was developed to visualize data across regions.

**Results:** A total of 2074 kidney cancer deaths in Peru were identified. ASMR (per 100,000 individuals) due to kidney cancer increased in men by 15.3%: from 1.30 (2010-2012) to 1.50 (2013-2015). Similarly, ASMR (per 100,000 individuals) increased among women by 22.6%: from 0.70 (2010-2012) to 0.86 (2013-2015). When stratified by regions, people in the coast had the highest ASMR, in both men (1.83 - 1.99 per 100,000 individuals) and women (0.94 - 1.14 per 100,000 individuals); mainly in the provinces of Lima and Tacna. The lack of healthcare access for early detection and limited coverage for treatment may play a role in the observed kidney cancer-related mortality rates in Peru. Further studies are warranted to identify modifiable epidemiological risk factors associated with kidney cancer in this country and region.

**Provincial, regional and national age-standardized kidney cancer mortality rates per 100,000 in men and women in 2010-2012 and 2012-2015, and rate percentage change**

<table>
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<tr>
<th>Region</th>
<th>2010-2012</th>
<th>2011-2013</th>
<th>% change</th>
<th>2009-2012</th>
<th>2012-2015</th>
<th>% change</th>
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<tr>
<td>Peru</td>
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<td>1.50</td>
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<td>Coast</td>
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<td>0.94</td>
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<tr>
<td>Highlands</td>
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<td>Amazon</td>
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<td>52.3</td>
<td>0.07</td>
<td>0.18</td>
<td>61.5</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

815
SA-PO203

AKI and CKD Prevalence in Pediatric Neuro-Oncology Survivors
Elizabeth J. Romps, Kelli A. Krallman, Ralph Salloum, Stuart Goldstein. Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: In facing an oncologic diagnosis, the pediatric patient may face a host of comorbid diagnoses resulting of required treatments. These diagnoses will often influence life-long follow-up. The nephrologic impact of multimodal treatment regimens for childhood central nervous system (CNS) tumors is a topic of particular interest.

Methods: A pediatric CNS tumor survivor clinic follows patients who have been in remission for a minimum of 5 years. Medical records of 211 patients were examined for renal sequelae of CNS tumor treatment. Patients were classified as having Acute Kidney Injury (AKI), using KDIGO definitions, if more than 2 serum creatinine (Scr) results were available over a 48hr period for trending. Patients were assessed for Chronic Kidney Disease (CKD) using nuclear or estimated GFR, positive proteinuria (PU) and/ or microalbuminuria (MAU), and renal ultrasound. Stage I is defined as GFR >120, on 2+ measurements, with PU/MAU. Stage II is defined as GFR 90-120, and Stage III is defined as GFR 60-89. Patients with an abnormal renal ultrasound, or with PU/MAU but a normal or above normal GFR, were classified as having a marker of CKD.

Results: Survivors range in age from 7 to 53 years old, with the median age of 21. Eleven of the 211 patients could not be assessed for AKI due to inadequate Scr results. Of the remaining 200 patients, 11 (5.5%) experienced AKI. Evidence of CKD was observed in 62/211 patients (29.4%), six of whom previously had AKI. Of those with CKD, 15 (24.2%) had stage I, 27 (43.5%) had stage II, and 2 (3.2%) had stage III. The other 18 (90.9%) had either persistent PU/MAU with normal or above normal GFR and/ or abnormal renal ultrasound.

Conclusions: Surveillance post AKI and mitigation of CKD after cancer remission helps to reduce additional burden from pediatric cancer survivors. The high prevalence of CKD markers demonstrates that CNS tumor treatment may cause significant subclinical renal damage during the acute treatment phase. Additional work should be done to assess the incidence of kidney disease in this population, and structure ideal follow-up.

SA-PO205

Predictors of Mortality in Patients with CKD and Cancer
Antonio Abel Portela Neto,1,2 Marcella M. Frediani,1 Renato A. Caires,1 Fernanda O. Coelho,1 Francisco Z. Mattioli,1 Veronica Torres,1 Elerson Costalonga,1 1Sao Paulo State Cancer Institute - USP, Sao Paulo, Brazil; 2University State of Sao Paulo, Sao Paulo, Brazil.

Background: Cancer patients have a high prevalence of chronic kidney disease (CKD). The aim of this study was to assess prognostic factors for death in cancer patients with CKD.

Methods: Among 516 outpatients with cancer referred to nephrology evaluation (2009-13), 251 had CKD according KDIGO definitions and at least 3 months of follow up. Clinical and biochemical data were retrieved from patient medical records. The Cox regression was used to examine the predictors of mortality.

Results: After a mean follow-up of 4.2±2 years, the mortality rate observed was 57%. The patients features are shown in Table 1. In the Cox regression analyses, ongoing chemotherapy [aHR=2.4; CI 1.3-4.5, p=0.004], Karnofsky index < 80 [aHR=2.1; CI 1.3-3.9, p=0.025], and eGFR < 30 ml/min/1.73m2 [aHR= 1.9; CI 1.0-3.6, p=0.03] were the independent predictors of mortality in our population. Of note, kidney dysfunction remained an independent risk factor for mortality even after adjustments for age and the presence of metastasis.

Conclusions: Patients with cancer and CKD have a poor prognosis. Ongoing chemotherapy, Karnofsky index, and an eGFR lower than 30 ml/min/1.73m2 were independent factors associated to mortality.

Table 1. Baseline Features

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>65-182</th>
<th>&lt;65</th>
<th>(p)</th>
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<tbody>
<tr>
<td>Female (%)</td>
<td>25</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>66</td>
<td>62</td>
<td>0.005</td>
</tr>
<tr>
<td>Ongoing Chemotherapy (%)</td>
<td>90</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Karnofsky status &gt; 80 (%)</td>
<td>35</td>
<td>20*</td>
<td></td>
</tr>
<tr>
<td>eGFR  &gt; 30 (%)</td>
<td>36</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Serum albumin &gt; 4 g/dL (%)</td>
<td>64</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (%)</td>
<td>86</td>
<td>82</td>
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</tbody>
</table>

Results are expressed as mean±SD and percentage. * < 0.05 vs Death group.

SA-PO204

Cancer Risk and Mortality in Patients with CKD: A Population-Based Cohort Study
Abhijit Kitchlu,1 Jennifer Reid,1 Nivethika Jeyakumar,2 Alejandro Y. Meraz-Munoz,3 Christopher T. Chan,1 Amit X. Garg,1 Joseph Kim,1 Eitan Amir,1 Ron Wahl,2 1University of Toronto, Toronto, ON, Canada; 2St. Michael’s Hospital, Toronto, ON, Canada; 3London Health Sciences Centre, London, ON, Canada; 4Toronto General Hospital, Toronto, ON, Canada; 5Princess Margaret Cancer Centre, Toronto, ON, Canada; 6ICES, London, ON, Canada; 7Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico; 8Toronto General Hospital, University Health Network, Toronto, ON, Canada.

Background: Patients with chronic kidney disease (CKD) may be at increased risk for cancer. CKD may also confer worse cancer outcomes. Existing data is limited and conflicting regarding the associations between kidney function and outcomes in specific malignancies.

Methods: We conducted a population-based cohort study of all Ontario residents 18 years or older with available serum creatinine data in the Ontario Laboratory Information System or inclusion in the Canadian Organ Replacement Register as chronic dialysis or kidney transplant patients between April 1, 2007 and October 31, 2016. We categorized patients according to CKD status [estimated glomerular filtration rate (eGFR) <60, 45-59, 30-44, 15-29, <15 ml/min/1.73m2, dialysis and transplant recipients] and assessed overall and site-specific cancer incidence and mortality using multivariable Cox models, accounting for competing risks.

Results: Among 5,871,837 individuals with eGFR data, 29,809 on dialysis and 4,951 kidney transplant recipients there were 325,895 cancer diagnoses over 29,993,847 person-years of follow-up. Relative to patients with eGFR >60 ml/min/1.73m2, total cancer incidence was increased in patients with CKD (stages 3a to 5), adjusted hazard ratios (aHR) 1.07, 95%CI: (1.05, 1.09), 1.04 (1.02, 1.07), 1.01 (0.98, 1.05), 1.13 (1.02, 1.25) on dialysis: 1.31 (1.25, 1.38), and transplant recipients: 1.22 (1.09, 1.36). The risks of bladder, kidney cancer and myeloma were particularly high in patients with CKD. Cancer-specific mortality was increased in CKD stages 3a to 5, aHR: 1.21 (1.17, 1.25), 1.30 (1.25, 1.35), 1.45 (1.37, 1.54), 1.41 (1.20, 1.67), dialysis: 1.36 (1.24, 1.49) and transplant: 1.46 (1.16, 1.84). Kidney cancer and myeloma mortality was observed to progressively increase with worsening baseline kidney function. Patients on dialysis had increased risk of mortality related to bladder, kidney cancer and myeloma.

Conclusions: Overall cancer incidence was increased in patients with CKD (stages 3a to 5) and end-stage kidney disease. CKD is associated with increased risks of bladder, kidney cancer and myeloma. Cancer-related mortality in patients in CKD is also increased in patients with CKD, on dialysis and post-kidney transplant. Strategies to address the increased burden of cancer in the CKD population are needed.

Funding: Government Support - Non-U.S.

SA-PO206

Study of Relationship Between Etiology of ESRD and Cancer Incidence in Chronic Hemodialysis Patients
Leonid Feldman,1,2 Anna Katkov,1,2 Lusia Merkin,2,3 Marieta Haimov,1 Zvi Barnea,1,2 Rehav Cernes,1,2 Ronen Brenner.1,2 1Nephrology and Hypertension Department, Wolfson Medical Center, Holon, Israel; 2Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; 3Oncology Department, Wolfson Medical Center, Holon, Israel.

Background: Previous research has shown that patients with end-stage renal disease (ESRD) treated with dialysis are at increased risk of cancer development. The aim of the present study was to examine a relationship between etiology of ESRD and cancer incidence in patients treated with chronic hemodialysis (HD).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
**SA-PO207**

**Dialysis Does Not Affect Outcomes in Stage IV Cancer Patients Admitted to the Intensive Care Unit with AKI at a Comprehensive Cancer Center**

*Ali Abubakr 1, Maen Abdellah 1, Juhee Song 2, Sreedhar A. Mandayam 1, Joseph L. Nates 1, Alvin H. Moss 3, Paul M. eBay 1, Virginia University, Morgantown, WV; 4University of Texas MD Anderson Cancer Center, Houston, TX; 5Houston Methodist Cancer Center, Houston, TX.*

**Background:** In advanced cancer patients, prolongation of life with treatment may incur substantial emotional and financial expense. Since acute kidney injury (AKI) in hospitalized cancer patients is known to be associated with poor survival, we investigated whether dialysis use in the intensive care unit (ICU) was a significant independent predictor of worse outcomes.

**Methods:** We retrospectively reviewed patients admitted in 2005-2014 who were diagnosed with stage IV solid tumors, had acute kidney injury and a nephrology consult. The main outcomes were survival from ICU admission, inpatient mortality and long-term survival after hospital discharge. Log-rank tests and Cox proportional regression were used to compare survival between dialysis and non-dialysis groups. Propensity score matched landmark survival analyses was performed with two landmark time-points chosen at day 2 and at day 7 from ICU admission.

**Results:** Of 465 patients, 176 needed renal replacement therapy. Landmark analyses at day 2 and day 7 from ICU admission showed no difference in dialysis was not associated with worse mortality during ICU admission (HR, 0.926, p=0.6657); adjusting for age, baseline serum albumin, baseline creatinine, baseline, and baseline max SOFA. In the multivariable logistic regression model after adjusting for baseline serum albumin and baseline maximum SOFA, the patients who received dialysis was not less likely to be discharged alive than non-dialysis patients (p=0.9892). To evaluate the impact of dialysis on long-term survival we evaluated 189 patients who were discharged alive. There was not a longer-term survival benefit after discharge for patients who received dialysis.

**Conclusions:** Our data found that receiving dialysis in the ICU did not adversely affect survival to discharge and long-term survival after discharge for patients with stage IV cancer with AKI. Dialysis itself contributed little harm or benefit to survival after discharge of the patient. Prolongation of suffering with no meaningful longer-term survival benefit should be avoided, and a shared decision-making discussion prior to hospital admission should be encouraged for the initiation of dialysis in stage IV cancer patients with acute kidney injury.

**Funding:** Other NIH Support - NCI

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**SA-PO208**

**Calendar Trends in Cancer Incidence Among US Kidney Transplant Recipients**

*Christopher D. Blosser,1,2 Gregory Haber,1 Eric A. Engels,3 University of Washington, Seattle, WA; 2Seattle Children’s Hospital, Seattle, WA; 3National Cancer Institute, Bethesda, MD.*

**Background:** Kidney transplant recipients (KTRs) are at 2-4 times greater risk of cancer compared with the general population, and older recipients are at highest risk. Kidney allograft survival is improving with newer immunosuppression and allocation policies. We assessed the changes in incidence of cancers after kidney transplantation over time.

**Methods:** We compared the incidence of cancer in first time kidney-only transplant recipients within three ten-year calendar intervals (1987-1996, 1997-2006, 2007-2016) characterized through linkage of SRTR and cancer registry databases from 17 U.S. states and data from the Transplant Cancer Match Study. KTRs were excluded for a cancer diagnosis before or within 90 days post-transplant, if transplanted before cancer registry coverage, or HIV infection. First cancers were identified from cancer registries if <5 years of transplant. We analyzed overall cancer and post-transplant cancers: colorectal, lung, melanoma, prostate, kidney and non-Hodgkin lymphoma (NHL). Non-melanoma skin cancer is not reported to cancer registries. Poisson regression was used to compare incidence rate ratios (IRR) across time intervals among KTRs with the earliest era as the reference, and adjusted for risk factors including age at transplant, gender, primary cause of ESRD, time on transplant waiting list, BMI, type of kidney donor, and maintenance immunosuppression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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**SA-PO209**

**Risk Factors for Advanced Colorectal Neoplasia in CKD**

*Eric H. Yu,1,2 DETECT Study Investigators,1 School of Public Health, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia; 3Centre for Kidney Research, Children’s Hospital at Westmead, Sydney, NSW, Australia.*

**Background:** Colorectal cancer is common in people with chronic kidney disease (CKD), but the risk factors are poorly understood. The aim of this study is to identify risk factors for advanced colorectal neoplasia in people with CKD (as a sub-study of DETECT). **Methods:** People with CKD (stages III-V, dialysis and transplant) across eleven sites in Australia, New Zealand, Canada and Spain were screened for colorectal neoplasm using fecal immunochemical test (FIT). Advanced colorectal neoplasia was identified through a 2-step verification process with colonoscopy following a positive FIT and 2-year clinical follow-up for all patients. Potential risk factors for advanced colorectal neoplasm at different CKD stages were assessed using multivariable logistic regression.

**Results:** A total of 1706 patients received FIT screening (791 CKD III-V, 418 dialysis, 497 transplant). 323 (18.9%) had colorectal positive FIT and 103 advanced colorectal neoplasia (44 CKD III-V, 31 dialysis, 28 transplant) were identified (overall detection rate 6%). At follow-up, 14 additional advanced neoplasia (10 CKD III-V, 3 dialysis, 1 transplant) were identified. Across CKD stages, older age and male sex were risk factors for advanced colorectal neoplasia (figure). Current smoking use was associated with advanced colorectal neoplasia among those with CKD III-V (odds ratio 2.3, 95% CI 1.1-4.9). For those on dialysis, patients with diabetes experienced 2.1 times greater odds of advanced colorectal neoplasia (95% CI 1.0-4.4). For kidney transplant recipients, daily anticoagulant use was associated with increased odds of advanced colorectal neoplasia [OR 4.5 (95% CI 1.5-13.4)].

**Conclusions:** Increasing age, smoking, male sex and having diabetes are associated with advanced colorectal neoplasia in patients with CKD. The observed increased risk associated with anticoagulation use in transplant recipients may be due to increased detection by FIT.

**Funding:** Government Support - Non-U.S.

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**SA-PO210**

**Increased Risk of Cutaneous Squamous Cell Carcinoma in Organ Transplant Recipients and Patients on Chronic Dialysis: A Cancer Registry-Based Study in Taiwan**

*Yuh-Mou Suen,1,2 Department of Internal Medicine, Taipei Medical University-Wan Fang Hospital, Taipei, Taiwan; 3Department of Internal Medicine, Taipei Medical University, Taipei, Taiwan.*

**Background:** Organ transplant recipients (OTRs), patients on chronic dialysis, and those with chronic kidney disease (CKD) have immune dysregulation and are at higher risk of skin cancers. However, the predominant histological skin cancer subtype in these populations has not been well-investigated among Asians. This study aimed to investigate the predominant histological skin cancer subtype among OTRs, patients on chronic dialysis, and those with CKD in Taiwan.

**Methods:** We obtained data between 2007 and 2014 from the Taiwan Cancer Registry Database and the National Health Insurance Research Database. The proportions of certain histological skin cancer subtypes in OTRs, patients on chronic dialysis, and those with
CKD were compared against those in the control group using a generalized estimating equation (GEE) regression model.

Results: Among 23,644 patients with skin cancer, 53 were OTRs, 225 had chronic dialysis, 1,792 had CKD, and 21,544 were placed in the control group. The proportions of squamous cell carcinoma (SCC) were 52.8%, 47.8%, 40.1%, and 33.5%, respectively. Compared to the control group, OTRs (1.99-fold) and chronic dialysis patients (1.25-fold) were found to have higher risk of developing SCC than other skin cancers after adjustment for potential confounding factors. Other subgroups or covariates associated with increased SCC risk included CKD patients aged <70 years (vs. control group; 1.3-fold), female sex (vs. younger age; 2.86-fold), male sex (vs. female sex; 1.1-fold), and Saudi Arabia (vs. north-Saudi Arabia; 1.1-fold).

Conclusions: OTRs and patients on chronic dialysis had a greater risk of developing SCCs than other skin cancer subtypes.

SA-PO211
Diversity of Nutritional Status in Patients with Cancer and CKD
Micheline T. Souza,1 Luiz A. Gil,2 Renato A. Aires,3 George B. Coura-Filho,1 Elerson Costalonga,1 Marcelo T. Sapienza,1 Andrew S. Levy,2 Lesley Inker,3 Emmanuel A. Burdman,4 Veronica Torres,1,2 ICESP, Sao Paulo, Brazil; 3Sao Paulo State Cancer Institute - USP, Sao Paulo, Brazil; 4School of Medicine, University of Sao Paulo, Sao Paulo, Brazil; 5University of Sao Paulo School of Medicine, Sao Paulo, Brazil; 6University of Sao Paulo, Sao Paulo, Brazil; 7HCFMUSP, Sao Paulo State Cancer Institute - USP, Sao Paulo, Brazil; 8Tufts Medical Center, Boston, MA.

Background: Cancer patients (pts) constitute a population with heterogeneous range of nutritional status. There is scanty prospective data on nutritional aspects of cancer pts with chronic kidney disease (CKD).

Methods: A group of solid cancer pts with CKD (not in dialysis) admitted for treatment (AT) or already in follow-up (FU) at a cancer hospital in Brazil (São Paulo State Cancer Institute) was prospectively evaluated between April 2015 and October 2017. Patients underwent an evaluation including bioimpedance exam, weight, height and subjective nutritional assessment questionnaire (PG-SGA), assessment of the glomerular filtration rate through 51 Cr-EDTA (GFR), serum creatinine (SCr) and albumin (Alb). Chronic Kidney Disease (CKD) was defined as rGFR <60 ml/min/1.73 m2. Sarcopenia was defined when BMI was equal to or lower than 22 kg/m2 and the arm muscle area index was lower than 7.15 cm2/m2.

Results: One hundred sixty-six one pts were enrolled. Pts characteristics were age 69.92 ± 10.46 years, 61.5% male, 72% AT. Most common tumor origins were: genitourinary tract 41%; gastrointestinal tract 12.4%, breast cancer 13.7%. ECOG was 0-1 in 89.5%, >2 in 5.2% of pts. Sarcopenia was observed in 28.6% of pcts and 81.4% of pcts were considered well nourished by PG-SGA. AT and FU pcts presented no difference in either albumin and SCr and BMI. AT pcts presented higher BMI (27.1 [24.2 – 30.2] vs 25.10 [22.2 – 28.7], P=0.330 and higher subjective nutritional assessment questionnaire (PG-SGA), assessment of the glomerular filtration rate through 51 Cr-EDTA (GFR), serum creatinine (SCr), standardized to the isotope-dilution mass spectrometry reference method. rGFR and GFR were expressed as ml/min/1.73 m2. Results: Patients were 59.4 ± 10.6 y, 50.2% male, 97.9% white. Renal tumor had 3.50 (2.70 – 4.72) cm at largest diameter and was malignant (histology confirmed post surgery) in 85% of cases. Comparing renal function before surgery, SCr was 0.86 (0.74 – 1.10) mg/dL, rGFR was 81.1 ± 22.5 and GFR < 60 was observed in 18% of pts. eGFRs using the CKD-EPI, mGFR and CG equations were 80.6 ± 20, 77.3 ± 28.0, and 89.2 ± 30.6, respectively. CG and mGFR showed significant differences in the means from the paired t-test when compared to mgFR (P<0.05) (Figure 1 - Table 1). CKD-EPI equation demonstrated satisfactory precision and higher accuracy (Figure 1 - Table 2).

Conclusions: CG and mGFR equations performed poorly compared with mgFR in this group of patients with renal tumors. CKD-EPI equation demonstrated adequate performance and should be considered when deciding upon surgical strategies in the setting of renal tumors.

SA-PO212
Obesity and Renal Outcome in Patients with Renal Cell Carcinoma
Sewon Oh,1 Kyungmi A. Lim,1 Jihyun Yang,2 Myung-Gyu Kim,3 Sang-Kyung Jo,4 Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea; 5Korea university medical college, Seoul, South Africa; 6Korea University Hospital Seoul, Seoul, Republic of Korea.

Background: Epidemiologic studies has shown obesity is associated with renal cell carcinoma (RCC). Obesity causes dysregulation of adipokines, activation of inflammatory cytokines, angiogenesis, and may lead to development of RCC and renal injury. We evaluate the relationship of obesity with the risk of RCC and renal outcomes in urologic cancers. In addition, we evaluate the effect of inflammation on the risk of RCC.

Methods: A total of 6,218 patients were enrolled in patients diagnosed with urological cancer at two University Hospital from 2001 to 2019. Obesity was defined as body mass index (BMI) ≥ 30 kg/m2. Results: The mean age of the patients was 65.5 ± 10.6 years and 87.3% was male. Of 6,218 patients, 1011 were diagnosed with RCC, 2002 with urothelial cancer, 136 with genital cancers and 2979 with prostate cancers. RCC was significantly related to younger age, diabetes, higher BMI, CRP and monocyte count. RCC showed 1.584-fold increased risk of obesity than prostate cancer (95% CI, 1.097-2.288). Compared to non-obese patients, obesity was associated with risk of RCC in urologic cancers (RR, 1.901, 95% CI, 1.631-2.247). Serum monocyte count is a stronger risk factor for the risk of RCC (RR, 3.461; 95% CI, 1.079-11.095) in obese patients than non-obese patients (2.714, 95% CI, 1.648-2.867). Obese patients showed higher incidence of 30% and 40% eGFR decline in urologic cancers during 7.7±1.2 years of mean follow up (P=0.05). Obesity was related to increased risk of 40% eGFR decline in urologic cancers by multivariate analysis (1.596, 95% CI, 1.074-2.371).

Conclusions: Obesity was significantly associated with the prevalence of RCC than other urologic cancers. Serum monocyte count is a stronger risk factor for the RCC in obese patients. Obese patients had significant worse renal outcomes in urologic cancers.

SA-PO213
Comparing Gomerular Filtration Rate Equations with 51 Cr-EDTA in Patients with Renal Tumors
Gilberto J. Rodrigues,1 Giuliano B. Guglielmetti,3 Veronica Torres,2 Elerson Costalonga,2 Maurício Cordeiro,2 Renato A. Aires,3 William C. Nahas,7 ICESP - USP (Sao Paulo State Cancer Institute, University of Sao Paulo), Sao Paulo, Brazil; 2Sao Paulo State Cancer Institute - USP, Sao Paulo, Brazil; 3University of Sao Paulo, Sao Paulo, Brazil; 4University of Sao Paulo School of Medicine, Sao Paulo, Brazil; 5University of Sao Paulo, Sao Paulo, Brazil; 6University of Sao Paulo School of Medicine, Sao Paulo, Brazil; 7Korea University Guro Hospital, Seoul, Republic of Korea.

Background: Assessment of glomerular filtration rate (GFR) is a crucial element to plan surgical strategies in patients with renal tumors. However, the estimate GFR (eGFR) trough equations was not validated in these patients. The aim of this study is to compare the performance of Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI), abbreviated Modification of Diet in Renal Disease (aMDRD) and Cockcroft-Gault (CG) equations with 51Cr-EDTA in patients with renal tumors eligible to surgical treatment.

Methods: Prospective evaluation of 142 outpatients with renal tumors and submitted to partial nephrectomy at Sao Paulo State Cancer Institute between April 2013 and November 2018. All patients were evaluated before surgery with 51 Cr-EDTA (GFR) and serum creatinine (SCr), standardized to the isotope-dilution mass spectrometry reference method. eGFR and GFR were expressed as ml/min/1.73 m2.

Results: Patients were 59.4 ± 10.6 y. 50.2% male, 97.9% white. Renal tumor had 3.50 (2.70 – 4.72) cm at largest diameter and was malignant (histology confirmed post surgery) in 85% of cases. Comparing renal function before surgery, SCr was 0.86 (0.74 – 1.10) mg/dL, rGFR was 81.1 ± 22.5 and GFR < 60 was observed in 18% of pts. eGFRs using the CKD-EPI, aMDRD and CG equations were 80.6 ± 20, 77.3 ± 28.0, and 89.2 ± 30.6, respectively. CG and aMDRD showed significant differences in the means from the paired t-test when compared to mgFR (P<0.05) (Figure 1 - Table 1). CKD-EPI equation demonstrated satisfactory precision and higher accuracy (Figure 1 - Table 2).

Conclusions: CG and aMDRD equations performed poorly compared with mgFR in this group of patients with renal tumors. CKD-EPI equation demonstrated adequate performance and should be considered when deciding upon surgical strategies in the setting of renal tumors.

SA-PO214
Dipstick Proteinuria and Cancer Incidence: A Nationwide Popula- tion-Based Study
Shin-Young Ahn,1,2 Gang Jeo Ko,1,2 Young-Joo Kwon,1,2 Korea University Medical Center, Korea University Guro Hospital, Seoul, Republic of Korea; Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea.

Background: Proteinuria is a representative indicator of chronic kidney disease (CKD) and an independent risk factor for both cardiovascular and non-cardiovascular mortality. Given that a major cause of non-cardiovascular mortality is malignancy, the association between proteinuria and malignancy has been discussed for several decades. We evaluated the clinical implication of dipstick proteinuria as a predictor for malignancy using nationwide population-based data.

Methods: We included subjects who had undergone a medical examination in 2009 (index year) among 10,505,818 participants. We excluded subjects who did not satisfy the inclusion criteria. Finally, 9,714,387 subjects were included in this study and were followed from the index year to December 31, 2017. We categorized the results of dipstick proteinuria into three groups; negative (-), trace (+), overt proteinuria (more than 1+).
Results: The participants with overt proteinuria were more likely to be older, have hypertension, diabetes, and dyslipidemia. During the follow-up period, we observed that overt proteinuria at baseline correlated with the risk of overall cancer incidence, even after it was adjusted by age, gender, smoking history, degree of exercise and diabetes (HR 1.151, 95% CI, 1.133 – 1.169, referenced to no proteinuria). In terms of site-specific cancer incidence, no significant risk of colorectal, liver, lung, cervical, esophagus, kidney, bladder, and prostate cancer incidence gradually increased in proportion to the degree of proteinuria. In order to observe the risk of cancer incidence according to the change in proteinuria, we used the same participant’s records from the 2005 NHHD (National Health Insurance Database). We demonstrated that the risk of cancer incidence increased proportionally according to the changes in dipstick proteinuria over four years.

Conclusions: We elucidated the dose-response relationship between the degrees of dipstick proteinuria and the graded risk of overall and site-specific cancer development. We also observed that the long-term risk of cancer incidence increased proportionally according to the changes in dipstick proteinuria over four years.

SA-PO215
Combining a Digital Platform and Point-of-Care (POC) Testing to Extend Kidney Patient Participation in Cancer Trials: Technical Feasibility and Patient Acceptability Study (IDecide Program)
Leanne A. Oden,1 Sandip Mitra.2 Digital Experimental Cancer Research Team 1Manchester Royal Infirmary, Manchester, United Kingdom; 2Manchester University Hospitals, UK, Sale, United Kingdom.

Background: Recruitment to cancer clinical trials is an ongoing challenge and usually limited to patients with preserved kidney function. Eligibility often restricts recruitment to those with an eGFR of >50ml/min, this is arbitrary and not a risk-based approach driven by current clinical science. Due to the increased survival rates for both conditions, there is a significant population with both cancer and reduced kidney function. The aim of this body of research is to assess whether new technological advances in POC creatinine meters and digital science can be used to modernise eligibility criteria in oncology clinical trials.

Methods: Three POC devices were evaluated for usability, size and complexity. A smart phone app was developed, which captures device data and sends securely to a Cloud environment. Creatinine testing, calibration and patient acceptability in the hospital was conducted over a 2 week period with 17 interactions (patient/carer/nurse), including 2 patient focus group with 8 participants from oncology and nephrology backgrounds.

Results: The Nova Biomedical Creatinine StatSensor® was the device chosen to enable home creatinine readings with good user feedback and stable performance characteristics. The app user interface design was acceptable with patients based on patient acceptability testing.

Conclusions: This initial proof of concept successfully demonstrated that creatinine can be measured by a POC device, the data captured by an app and reported in near-real time. We have now developed a clinical rules engine based on the NHS/NICE published algorithm for AKI; and will be applying this to a clinical trial to detect AKI in patients receiving chemotherapy to quantify the potential clinical benefits. We aim that this will be the first step in a body of work to challenge traditional eligibility criteria for clinical trials and improve outcomes for this population of patients, through first improving their recruitment to cancer clinical trials.

SA-PO216
Effect on Renal Function of Repeated Administerations of Contrast Media in Cancer Patients Nephrectomized for a Metastatic Renal Cell Carcinoma: A Retrospective Italian Study
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Background: Patients with renal carcinoma (RCC) presents with concomitant chronic kidney disease (CKD) with a frequency of about twice that of the general population; moreover, being often nephrectomized and therefore with a reduced renal functional reserve (RFR), they also present a higher incidence of acute kidney failure (AKI). Thus, we decided to evaluate the progression of renal impairment in metastatic RCC through personalized risk-based monitoring. We created an approach that explored the potential and acceptability of using a POC device, data capture via a smartphone, and risk-categorisation through an Acute Kidney Injury (AKI) algorithm, to enable decision-making and the first step in addressing this unmet clinical need.

Methods: We recruited 76 cancer patients with overt proteinuria (≥250 mg of dipstick protein per 24 hours) in our Kidney Function Monitoring Program (KFMP), according to the changes in dipstick proteinuria over four years. We created a cohort of patients that is not observed in the other populations of patients considered, and that it could have been caused by the additional effect of the antiangiogenic drugs used. No correlations were found between renal function and the time elapsed between nephrectomy and the first CT scan.

Conclusions: In our nephrectomized patients, CT contrast medium appears to play a secondary role on the incidence of AKI, or on worsening of CKD. We should therefore be more liberal in the use of contrast medium, even in nephrectomized cancer patients.

SA-PO217
Persistence of CKD and Hypertension at 12 Months After Cisplatin Therapy in Children
Asaf Lebel,1 Kelly McMahon,1 Vedran Covcokovic,2 Jasmine Lee,2 Mariya Yordanova,1 Louis Huynh,3 Frédéric Crépieu-Hubert,4 Tom D. Blydt-Hansen,5 Cherry Mammens,6 Maury N. Pinsk,7 Shahrad R. Rasskehr,8 Kirk R. Schultz,9 Ross T. Tsuyuki,10 Michael Zappitelli.2,4 Research Institute, McGill University Health Centre, Montreal, QC, Canada; 2The Hospital for Sick Children, Toronto, ON, Canada; 3Montreal Children’s Hospital, Montreal, QC, Canada; 4School of Medicine, Queen’s University, Kingston, ON, Canada; 5University of British Columbia, Vancouver, BC, Canada; 6British Columbia Children’s Hospital, Vancouver, BC, Canada; 7University of Manitoba, Winnipeg, MB, Canada; 8University of Alberta, Edmonton, AB, Canada; 9University of Toronto, Toronto, ON, Canada; 10McGill University, Montreal, QC, Canada.

Background: Cisplatin (CisP) commonly causes acute kidney injury (AKI). Late CisP-nephrotoxicity (chronic kidney disease (CKD); hypertension (HTN)) is poorly characterized in children. We determined prevalence and progression of CKD and HTN 3 and 12 months (m) post-CisP therapy, and if CisP-AKI is associated with these outcomes.

Methods: 12 Canadian-site prospective cohort study. Protocol: Children treated with CisP were followed during cancer therapy (labs, clinical data) and at 3 and 12m post-CisP therapy completion (blood pressure [BP], blood and urine collection). AKI during cancer therapy: defined per KDIGO serum creatinine criteria. Outcomes: a) CKD: eGFR <90ml/m²; b) elevated BP and HTN, per 2017 child HTN guidelines. Paired t-tests and McNemar’s test used to determine if outcome prevalence differed from 3 to 12 m. Logistic regression (odds ratio [OR], 95% CI) used to determine relation of AKI with 3 and 12m CKD and HTN.

Results: Of 159 patients (50.3% male; median age 5.5 [IQR 2.4–11.9] yrs), 37% developed AKI. Figure (1): There was no significant change in 3 vs 12m prevalence (McNemar p-values all >0.05) of any outcomes (CKD: 44% and 39%, respectively; HTN: both 17%). eGFR was significantly lower at 12 vs. 3m (Figure 2, median [IQR] 133.8 [52.1] vs. 120.6 [37.4], respectively, p-value <0.001). AKI during CisP therapy was associated with 3 and 12m CKD (OR 2.2 [95% CI 1.2-4.4] and 2.8 [95% CI 1.4-5.6], respectively) but not HTN (OR 1.6 [95% CI 0.7-3.9] and 2.1 [95% CI 0.9-5.1], respectively).

Conclusions: CKD and HTN were common and persisted from 3m to 12m after cancer therapy completion. AKI was associated with later CKD but not HTN. Research on interventions to prevent AKI and reduce post-CisP CKD and HTN is needed.

Funding: Government Support - Non-U.S.
SA-PO218
Anemia Management in Hemodialysis Patients: How Much Better Can We Do?
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Germany.

Background: The goal of anemia management with erythropoiesis-stimulating
agents (ESA) is to achieve target hemoglobin (Hgb) levels while keeping drug doses
low. Built on a physiology-based mathematical model of erythropoiesis (Fuertinger et al.,
PLoS ONE 2018), we developed an optimal control algorithm for individualized methoxy
polyethylene glycol-epoetin beta (Mircera®) dose optimization.

Methods: The designed algorithm is a model predictive controller (MPC) that aims
to stabilize Hgb levels at 10.5 g/dl. We compared the MPC administration regimens to a
standard treatment protocol (STP) in an in-silico study for 6,659 chronic hemodialysis (HD)
patients over a period of one year. Based on the Hgb levels obtained by the protocol,
the in-silico population was divided into Hgb cyclers (cycles with amplitude >1.5 g/dl and
duration >8 weeks, at least two cycles per year) and non-cyclers as defined by Fishbane &
Berns (Kidney Int., 2015) yielding 1,987 cyclers.

Results: For non-cyclers, the MPC and STP regimens produced similar outcomes with
respect to achieving Hgb targets and ESA usage. However, for cyclers, the MPC
outperformed the STP. Cyclers’ percentage of Hgb values within the target range of 10-
11.5 g/dl for both treatment approaches are shown in Figure 1. The MPC lead to 91% of
cyclers with at least 80% of Hgb values within the range and lowered the monthly
Mircera® dose on average by 30%.

Conclusions: Our analysis shows a clear potential for better anemia management in
Hgb cyclers as a subpopulation of HD patients: The MPC stabilized Hgb levels with a
significantly reduced amount of Mircera® in this in-silico study. For non-cyclers, the
STP could not be outperformed. Clinical studies are warranted to validate these
findings.

SA-PO219
Anemia Disrupts Renal Compensatory Responses After Uninephrectomy in Mice
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Background: Kidneys with functional nephrons are essential for our life, but the
numerous factors could reduce the numbers of nephron day by day. Kidney has ability
to adapt its size and function against the nephron loss to maintain total renal function,
for example, in both donor and recipient in renal transplantation. However, the factors that
regulate this compensation have not been fully clarified yet. Hereby we examined the
effects of erythropoietin (EPO)/anemia on the compensatory renal hypertrophy in mouse
model of renal anemia.

Methods: The mice lacking renal EPO production were used.

Results: The anemic mice showed renal compensatory responses, such as GFR more
than half and cell hypertrophy, similar to normoxemic mice at week 1 after unilaterial
nephrectomy (UNX). However, the compensation was disrupted only in anemic mice at
week 4 after UNX; the mice lacking EPO receptor in the kidney showed successful
compensation. The disruption was accompanied by the increased oxidized glutathione
and decreased reversible phosphorylation of ribosomal protein S6, a marker of mTOR activation,
which was decreased after successful compensation in the normal mice. In the renal
interstitium of anemic mice at week 4 of UNX, the number of cells promoting eop gene
transcription (but disable to produce EPO protein in the mice) was reduced even under
the anemia, and the number of α-smooth muscle actin-positive cells was increased,
suggesting the transdifferentiation of EPO-producing cells. These changes were restored by
the supplementation of EPO.

Conclusions: Anemia does not affect the onset of compensatory renal hypertrophy
after UNX, but disrupts the persistent compensation process.

Funding: Government Support - Non-U.S.

SA-PO220
Patient-Specific Characteristics of Erythropoiesis and Their Influence on
Hemoglobin Stability
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Germany.

Background: In hemodialysis (HD) patients treated with erythropoiesis-stimulating
agents (ESA) maintaining hemoglobin (Hgb) levels within recommended ranges is
difficult. Many patients express Hgb excursions above and below the target range over
the course of a year. This Hgb variability is associated with clinical events and ESA
dose changes. This study investigates differences in biological key characteristics of
erythropoiesis in HD patients and its influence on Hgb stability.

Methods: We adapted a comprehensive mathematical model of erythropoiesis to
individual HD patients treated with methoxy polyethylene glycol-epoetin beta to estimate
key characteristics of their red blood cell (RBC) reproduction cycles (Fuertinger, Plos One
2018), including RBC lifespan, endogenous EPO levels, ESA half-life and ESA influence
on apoptosis and maturation velocity of RBC progenitors. In-silico tests were performed to
distinguish Hgb “cyclers” from “non-cyclers” (criteria per Fishbane & Berns, Kidney
Int. 2005). Estimated physiological parameters are depicted as violin plots, groups are
compared by t-test.

Results: We estimated patient-specific characteristics of erythropoiesis in 6659 HD
patients (∼46 %, Black: 43.4 %, mean ± SD: age 64 ± 14 years, BMI: 29.4 ± 7.6 kg/m²).
28.9 % were categorized as Hgb cyclers. Figure 1 compares erythropoiesis characteristics
between cyclers and non-cyclers. We observed a statistically significant difference
between Hgb cyclers and non-cyclers in RBC lifespan (meansSD: 72±18 vs 78±21 days),
endogenous EPO levels (13±8 vs 18±8 U/I), ESA half-life (159±46 vs 115±57 hours) and
anti-apoptotic effects.

Conclusions: Patient-specific parameter estimates suggest that certain underlying
biological characteristics may predispose patients to Hgb cycling. A better understanding
of these effects could permit tailoring anemia algorithms to this subgroup to improve their
Hgb variability and eventually clinical outcomes.
Methods: The effects of uremic toxin on red blood cell development was evaluated using hematopoietic stem cell (HSC) cultures. HSCs were isolated from umbilical cord blood using magnetic cell sorting to indicate CD34 positive cells. HSCs were then grown in differentiation medium combination with various concentrations of indoxyl sulfate (IS). Cell proliferation, viability, cell morphology, and erythroid specific markers were identified.

Results: The lower cell number in HSCs treated with IS was investigated in a dose-dependent manner. Proliferation and the percent viability of CD34 positive cells cultures were observed with culture medium containing 0 (control), 25, 50, 100, and 200 µg/mL IS showing a dose-dependent trend to decline as demonstrated by lower numbers of CD235 and CD71 positive cells. Mature cells were counted using morphology assessments.

Conclusions: These findings indicate that uremic toxin IS appears to be a factor governing the functional roles of HSCs. However, pathogenesis of anemia involves multi-step processes that might be affected by the other types of uremic toxins and factors.

Funding: Government Support - Non-U.S.

SA-PO223
LDL Lipidome and Erythropoiesis Stimulating Agent Response in Hemodialysis Patients
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Background: Anemia management in end-stage renal disease (ESRD) is difficult due to variable erythropoiesis stimulating agent (ESA) response. Hemodialysis alters lipoprotein composition. Additionally in vitro erythropoietin burst assays respond to changes in lipoprotein supplementation; suggesting a role in RBC formation. We have previously shown HDL, proteome differs with ESA response in maintenance hemodialysis (HD) patients. We hypothesized HD patients ESA response was associated with HDL/LDL composition.

Methods: HDL & LDL were isolated by dextran sulfate precipitation (n=105 patient samples). Purity was assessed by immuno blot and proteinomics. Total cholesterol (Cho), phospholipid (PL) and triacylglycerol (TAG) were quantified by enzyme assay. Avant SPLASH™ LipidMix® standards were added before Bligh-Dyer LDL lipid extraction. LC/MS-derived informatics used Waters UPLC-Syapt G2-Si Q-Tof MSE (+/- ion modes) with Progenesis Q I + LipidMAPS database. Data were normalized to internal ion-scan and total-in and close-up; Cho results filtered based on mass accuracy (<1 ppm), fragmentation score, and isotopic matching. Categorical differences (ESA naïve (38), ESA hyper (23)), ESA normal (22), and ESA hypo (22) responders) were analyzed by ANOVA, and continuous differences with Spearman correlation.

Results: LDL Cho but not HDL Cho was negatively correlated (p<0.05) with ESA utilization. Lipidomics identified 222 LDL-associated lipids including 36 different by ANOVA (p<0.05): 22 increased and 3 decreased with ESA dose response. 11 lipids changed with EPO use relative to EPO naïve patients. Post-hoc test showed significant increase of four lipids (hyper-to-hypo-EPO response) including a cholesterol ester, a ceramide, and a vitamin D3 analogue. Spearman analysis revealed LDL lipid correlation to EPO dose (10), ESA response index (7), to d12 (12), hepcidin (3), and CRP (2); including polyunsaturated (PU)-ceramides, lysophosphatidylcholine, oxidized phosphophyleolipid, Cho-esters and a statin.

Conclusions: In this study poor HD patient-ESA dose was associated with low LDL Cho levels suggesting ESA hypo-response is associated with LDL lipoprotein composition including lipids associated cytokotaxicity, proatherogenic pathways and a statin. Future/ongoing work addresses anti-atherogenic markers and ESA response.

Funding: NIDDK Support, Clinical Revenue Support

SA-PO224
Hemodialysis Augments Red Blood Cell Death and Intracellular Hypoxia
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Background: Previous studies have shown that uremia increases red blood cell (RBC) death (eryptosis) in hemodialysis patients, possibly aggravating their anemia. The present study tests the hypothesis that hemodialysis (HD) triggers eryptosis, as indicated by phosphatidylserine (PS) exposure, and calcium influx into RBC. In addition, we explored levels of RBC intracellular hypoxia.

Methods: RBC were obtained from healthy subjects (CON-RBC; n=8) and ESRD patients (HD-RBC; n=10) pre- and post-HD. Using flow cytometry, PS exposure (fluorescein-labeled annexin V), calcium influx (fluorescein-labeled calcium indicator Fura-2AM), and intracellular level of hypoxia (Hypoxia Green probe) were determined. Results are expressed in mean fluorescence units (MFU). We compared these parameters between healthy controls and pre- and post-HD, respectively.

Results: The age of the healthy subjects was 34.8±17.3 years, 20% were male. The patients were 73% males, the age was 58.1±18.1 years. Compared to CON-RBC, PS exposure, calcium influx, and levels of intracellular hypoxia were increased in HD-RBC pre- and post-HD, respectively. In addition, HD treatment was associated with significantly increased PS exposure and intracellular hypoxia (Table 1).

Conclusions: Taken together, our results suggest that HD increases RBC hypoxia, eryptosis, and RBC calcium influx. Lower oxygen levels in HD-RBC could be due to either an impaired uptake or enhanced release of oxygen. Oxygen-sensitive intracellular responses may regulate RBC lifespan.

Funding: NIDDK Support, Other NIH Support - NHLBI U01 HL117684 to DMP, Private Foundation Support
Two Phase 3, Multicenter, Randomized Studies of Intermittent Oral Roxadustat in Anemic CKD Patients on (PYRENEES) and Not on (ALPS) Dialysis

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Background: Roxadustat is an oral HIF-PHI in late-stage development for treatment of CKD anemia.

Methods: Two phase 3 European studies enrolled non-dialysis-dependent (NDD; ALPS) and dialysis-dependent (DD; PYRENEES) patients with CKD anemia. In the double-blind NDD study, patients with hemoglobin (Hb) ≥10 g/dL not treated with erythropoietin-stimulating agents (ESAs) were randomized (2:1) to oral roxadustat or placebo for 52-104 weeks. In the open-label DD study, stable hemodialysis or peritoneal dialysis patients with Hb 9.5-12 g/dL treated with ESAs were randomized (1:1) to oral roxadustat or ESAs for 52-104 weeks. Primary endpoints were change of average Hb levels at Weeks 28-52 from baseline. Secondary endpoints included change of average low-density lipoprotein cholesterol (LDL) at Weeks 12-28 from baseline, time to use of rescue therapy (ie, transfusion, ESA, IV iron, NDD study), and mean monthly IV iron use through Week 36 (DD study). Occurrence of adverse events (AEs) was also assessed.

Results: The NDD study randomized 594 patients to roxadustat (n=391) or placebo (n=203); the DD study randomized 836 patients to roxadustat (n=415) or ESA (n=421). Mean (SD) change of average Hb levels at Weeks 28-52 from baseline was 1.988 (0.953) for roxadustat and 0.406 (0.979) for placebo (P<0.001) in NDD patients and 0.396 (0.773) for roxadustat and 0.183 (0.860) for ESA in DD patients (P<0.001). The LS mean difference (95% CI) in LDL at Weeks 12-28 was -0.701 (-0.83, -0.57; P<0.001) mmol/L vs placebo in NDD patients and -0.377 (-0.451,-0.304; P<0.001) mmol/L vs ESA in DD patients. In NDD patients, roxadustat was superior to placebo in use of rescue therapy (hazard rate [95% CI], 0.238 [0.17, 0.33; P<0.001]). In DD patients, roxadustat was superior to ESA in mean monthly IV iron use (LS mean difference [95% CI], -31.9 [-41.4, -22.4]; P<0.001). Common AEs in both treatment groups were ESRD, hypertension, peripheral edema, and decreased GFR in NDD patients, anemia, arteriovenous fistula thrombosis, headache, and diarrhea in DD patients. Roxadustat safety data will be integrated across all trials.

Conclusions: Roxadustat was effective in achieving and maintaining Hb levels compared with placebo and ESA in NDD- and DD-CKD patients.

Funding: Commercial Support - Astellas Pharma Inc.

Phase 3, Multicenter, Randomized, Open-Label, Non-Comparative Study of Intermittent Oral Roxadustat in ESA-Naive CKD Patients Not on Dialysis in Japan

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Background: Roxadustat, an oral HIF-PHI, is in late-stage development for treatment of chronic kidney disease (CKD) anemia. This phase 3 study evaluated efficacy and safety of oral roxadustat in erythropoiesis stimulating agent (ESA)-naive non-dialysis-dependent (NDD)-CKD patients not on dialysis. A total of 99 patients were treated with roxadustat or placebo.

Methods: Multicenter, 24-week, Japanese study of NDD-CKD ESA-naive anemic (hemoglobin[Hb]<10.5 g/dL) patients. Patients were randomized to roxadustat (initial dose of 50 mg or 70 mg) three times weekly; dose was adjusted to maintain Hb at 10-12 g/dL. Efficacy endpoints were response rate (Hb ≥10.0 g/dL and an increase ≥1.0 g/dL from baseline) at end of treatment; average Hb levels at Weeks 18-24; change of average Hb levels at Weeks 18-24 from baseline; maintenance rate of target Hb level (proportion of patients achieving average Hb level of 10-12 g/dL at Weeks 18-24); rate of rise in Hb (g/dL/week) from Week 0 to Week 4, time of discontinuation before Week 4.

Results: Of 100 randomized patients, 99 started on 50 mg (n=49) or 70 mg (n=50) roxadustat. Response rate (95% CI) from baseline to end of treatment was 95.9 (83.1, 97.8)% and 100.0 (92.9, 100.0)% in the 50-mg and 70-mg groups, respectively. Mean (SD) of average Hb levels at Weeks 18-24 was 11.2 (0.57) g/dL and 11.23 (0.67) g/dL in the 50-mg and 70-mg groups, respectively. Mean (SD) change of average Hb levels at Weeks 18-24 from baseline was 1.39 (0.93) and 1.30 (0.80) g/dL in the 50-mg and 70-mg groups, respectively. Maintenance rate (95% CI) of target Hb level during Weeks 18-24 among patients with ≥1 Hb value at Weeks 18-24 was 88.4 (75.4, 92.6)% and 88.9 (75.9, 93.5)% in the 50-mg and 70-mg groups, respectively. Mean (SD) rate of rise in Hb from Week 0-4 was 0.291 (0.197) g/dL/week and 0.373 (0.235) g/dL/week in the 50-mg and 70-mg groups, respectively. The most common AEs were nasopharyngitis (20.2%), hypertension (6.1%), diarrhea (5.1%), and hyperkalemia (5.1%).

Conclusions: Roxadustat was effective in achieving and maintaining Hb levels with the target range at both starting doses and in Japanese ESA-naive NDD-CKD patients with a favorable safety profile. The rate of rise of Hb was dose-dependent.

Funding: Commercial Support - Astellas Pharma Inc.
Anemia and Iron Metabolism: Clinical

Anemia and Iron Metabolism: Clinical

Ponce, PR; 3Nephrology Associates Medical Group, INC, Riverside, CA

Cameron Chao

Dialysis and Non-Dialysis Patients with CKD

Roxadustat for the Long-Term Maintenance Treatment of Anemia in

SA-PO231

SA-PO232

Friday, Saturday

Funding: Commercial Support - Fibrogen Inc.

Funding: Commercial Support - AstraZeneca

SA-PO229

Randomized, Open-Label, Active-Controlled (Darbepoetin Alfa), Phase 3 Study of Vadadustat for Treating Anemia in Non-Dialysis-Dependent

CKD Patients in Japan

Miyamoto,1 Takashi Nagaoka,1 Yoshikazu Kondo,2 Yoshimasa Kokado,3 Kiichiro Ueta,2 Genki Kaneko,2 Masashi Shiosaka,2 Yutaka Kagawuchi,2 Yasuhiro Komatsu,3 the University of Tokyo School of Medicine, Tokyo, Japan; 4Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan; 5Gunma University, Graduate School of Medicine, Maebashi, Gunma, Japan.

Background: This open-label, active-controlled Phase 3 study (NCT03329196) evaluates the efficacy and safety of vadadustat (VDT), an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, in 304 nondialysis dependent (NDD) chronic kidney disease (CKD) subjects with anemia in Japan for 52 weeks. Prespecified primary analysis results at 24 weeks are presented here.

Methods: NDD-CKD subjects with anemia receiving (conversion) or not receiving erythropoiesis stimulating agents (correction) were randomized to VDT (n=151) or darbepoetin alfa (DA) group (n=153). After initial VDT dose of 300 mg daily, doses were adjusted within 150–600 mg to achieve and maintain target hemoglobin (Hb) of 11–13 g/dL. Primary endpoint was average Hb at weeks 20 and 24. Noninferiority of VDT to DA was tested using mixed model for repeated measures. Iron parameters were measured.

Results: Safety was assessed up to 24 weeks.

Results: LS Mean of the average Hb at weeks 20 and 24 was 11.66 (VDT: 95% CI: 11.49 to 11.84) and 11.93 (DA: 11.76 to 12.10) g/dL; 95% CI of both groups were within the target Hb of 11–13 g/dL. Difference in LS Mean between the groups was −0.26 g/dL (−0.50 to −0.02); the 95% CI lower limit was above the predefined noninferiority margin of −0.75 g/dL, demonstrating the noninferiority of VDT to DA. VDT improved mean Hb from baseline of 10.68 to 11.27 g/dL at week 24 (conversion, n = 80) and 10.17 to 11.85 g/dL (correction, n = 71). VDT regimen was associated with significant increases in total iron-binding capacity and decreases in hepcidin from baseline to week 24, not found in the DA group. At least one adverse event (AE) was seen in 72.2% (VDT) and 73.2% (DA) subjects. The most common AEs in the VDT group were nasopharyngitis (VDT: 14.6%, DA: 12.4%), diarrhea (VDT: 10.6%, DA: 3.3%), and constipation (VDT: 5.3%, DA: 3.3%). The serious AEs were 13.9% (VDT) and 14.4% (DA). No serious AE was considered related to the study drug.

Conclusions: VDT was effective as DA in controlling Hb within the target range in both conversion and correction without new safety concerns, indicating the usefulness of VDT for treating anemia in Japanese NDD-CKD patients.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation

SA-PO230

An Open-Label Extension Study to Evaluate the Efficacy and Safety of Roxadustat for the Long-Term Maintenance Treatment of Anemia in

Dialysis and Non-Dialysis Patients with CKD

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Background: Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that stimulates erythropoiesis via increasing endogenous erythropoietin, and regulates iron metabolism.

Methods: In this open-label, extension study, subjects with dialysis-dependent (DD-CKD) and non-dialysis-dependent chronic kidney disease (NDD-CKD) who have completed the treatment period of a phase 2 roxadustat anemia study in the U.S. were enrolled and treated with roxadustat. Subjects continued to receive roxadustat at the same dose for up to 30 months. Adjustment was required, followed by dose titration to Hb levels. Mean Hb values, total weekly roxadustat doses and dose frequencies over time were evaluated. Safety and tolerability were assessed by adverse events, vital signs, electrocardiogram findings, and clinical laboratory values.

Results: Fifteen subjects with NDD-CKD (n=14) and DD-CKD (n=1) were enrolled and treated. One subject with DD-CKD who withdrew consent two weeks after enrollment and one other subject with DD-CKD were excluded from the analyses. Among the 13 NDD-CKD patients, mean age was 65.7 years; range, 38 - 78 years; 61.5% (8/13) were women; 23.1% (3/13) were white. Baseline Hb levels averaged 10.2 g/dL [range, 8.7 - 11.2 g/dL] and eGFR averaged 26.1 mL/min; [range, 7.3 - 48.2 mL/min]. At the time of enrollment, 7.7% (1/13) of subjects were on TIW dosing regimen, 69.2% (9/13) on BIW, 15.4% (2/13) on QW, and 7.7% (1/13) were on QOW dosing regimen. The total mean weekly dose of roxadustat was 241.2 mg; [range, 73.7 - 517.9 mg]. The safety and tolerability profiles observed were as expected for this patient population.

Conclusions: In this cohort of patients with NDD-CKD, long-term use of roxadustat for the treatment of anemia resulted in an Hb response in 77% of all patients with a safety profile consistent with the population of patients under study.

Funding: Commercial Support - Fibrogen Inc.
SA-PO233
Understanding Patient Perspectives of the Impact and Treatment of CKD Anemia: A Patient Survey in China
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Background: Anemia is a common complication of CKD that may reduce patients’ quality of life (QoL) and/or require treatment. The objective of this study was to assess the QoL, burden, knowledge, and management of CKD anemia in a sample of Chinese pts.

Methods: In August–September 2018, a quantitative, online survey was administered to 500 Chinese pt volunteers aged ≥18 years with self-reported CKD with or without anemia; pts with cancer were excluded. Pts were recruited via online communities, pt associations, online support groups, and direct pt referrals. This 27-question survey explored pt knowledge of anemia, its management, impact on QoL, information sources for the condition, and effects on the healthcare practitioner–pt relationship. Data collected from the survey were aggregated and anonymized to protect pt confidentiality.

Results: Overall, data were evaluable for 456 pts, 44% female, mean age 41.0 years, and 23% reported receiving a CKD diagnosis stages 3–5, the remaining 77% had CKD stage 1 or 2, and did not know the stage. Of the entire cohort, 32% of pts reported being told they had anemia, 73% did not know their hemoglobin (Hb) level or had not had a blood test in the previous year. Of pts told they had anemia (n=148), most reported feeling ill (86%), lack of energy (75%), nausea (72%), pain (69%), and sadness and/or depression (61%). For these pts, a negative impact of CKD anemia on QoL was perceived: 66% reported less energy, 54% reported more sadness/depression, 50% felt they were more ill, 37% worried more that their condition was worsening, and 29% reported less ability to work. Awareness of the link between CKD and anemia was common (87%), and 71% thought that their anemia was well or very well managed: 64% reported taking iron supplements; 69% had received dietary advice; 26% were given erythropoiesis-stimulating agents; and 31% had received blood transfusions.

Conclusions: Chinese pts perceived that CKD anemia had a negative impact on their QoL. Although pt knowledge of anemia was varied, perceptions of its management were geared to positive. There are opportunities for improving pt education on the association between CKD and anemia, improving Hb testing and monitoring, and increasing use of treatments to avoid blood transfusions.

Funding: Commercial Support - AstraZeneca

SA-PO234
Role of Nephrology Pharmacists in the Management of Anemia in Outpatient Dialysis Units: A Canadian Model
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Background: Hemodialysis patients frequently suffer from anemia. Proper utilization of therapies such as iron and erythropoiesis-stimulating agents (ESAs) are crucial to attain established hemoglobin targets. The purpose of this study was to evaluate the clinical and financial impact of nephrology trained pharmacists on anemia management in these patients.

Methods: A retrospective study of patients who received hemodialysis between Jan 2010 and Dec 2011 in the outpatient hemodialysis units. In Dec 2010, pharmacists were tasked to manage anemia under medical directive. Primary endpoints were compared across years (2010 vs. 2011) using a mixed-effects model strategy. An unstructured random effects correlation matrix was utilized to capture patient-level variation in 2010 and 2011 separately.

Results: Of 202 patients, 163 contributed in both years, 57% were males, age 65.18±16.3 years. Hemoglobin levels were 10.95±0.95 and 10.83±0.94 mg/dL in 2010 vs. 2011, respectively (p=0.158), while the transfusion rate was 1.3% and 1.8%, respectively, p=0.196. Ferritin levels 273.5±215 and 317.1±123, p=0.0019, iron saturation 0.30±0.11 and 0.39±0.05, p=0.838, and Iron dose 215.4±100.2 mg and 317.1±123.7 mg, respectively, p=0.996. Finally, the average weekly ESA use in 2010 was 123.7 mg, respectively, p=0.05, while the transfusion rate was 1.3% and 1.8%, respectively, p=0.838, and Iron dose 215.4±100.2 mg and 317.1±123.7 mg, respectively, p=0.996. The average ESA use in 2010 vs. 2011, p=0.158, while the transfusion rate was 1.3% and 1.8%, respectively, p=0.838, and Iron dose 215.4±100.2 mg and 317.1±123.7 mg, respectively, p=0.996. Finally, the average weekly ESA use in 2010 was 123.7 mg, respectively, p=0.05, while the transfusion rate was 1.3% and 1.8%, respectively, p=0.838, and Iron dose 215.4±100.2 mg and 317.1±123.7 mg, respectively, p=0.996. Finally, the average weekly ESA use in 2010 was higher and trending up over time.

Conclusions: Similar models are applied throughout our dialysis service. We tracked laboratory values and medications. We performed root cause analysis (RCA) routinely to analyze and resolve challenges to achieve goals. Patients in ferritin target (200-800) improved (55% vs 69% p<0.005) without affecting iron saturation. Weekly Aranesp dose was reduced with the ANM model from 45mcg to 39mcg and monthly Mircera dose from 151mcg to 127mcg. Simple cost-effectiveness analysis (saving in ESA consumption-nurse salary) showed estimated annual cost saving of 70000 dollars. Our RCA showed that the main cause of failure was compliance with visits and ESA shots. Based on our RCA we built a unique anemia management algorithm for PD (Figure 1).

Funding: Commercial Support - AstraZeneca

SA-PO235
Anemia Nurse Manager in Peritoneal Dialysis: A Retrospective Study from Qatar

Background: Anemia management is challenging in peritoneal dialysis (PD) patients (home-based with dependence on patients’ compliance). We implemented a special nursing anemia nurse manager (ANM) model with nephrologist’s supervision in PD to achieve better hemoglobin (Hg) targets. We performed a retrospective study to evaluate outcomes and cost effectiveness of the new model.

Methods: Our PD ANM is a PD nurse who was trained for 4 months (8/2017) by a nephrologist. The program expanded gradually to include all PD patients by 1/2018. Our PDANM role includes lab review, medications adjustments, patients’ education and act as a focal point for anemia. We reviewed patients record for 1 year (1/2018-12/2018). We tracked laboratory values and medications. We performed root cause analysis (RCA) routinely to analyze and resolve challenges to achieve goals.

Results: PD census mean was 180 patients during study period (1/2018-12/2018). ANM model achieved a significant improvement in PD patients with Hg in target range (10-12g/dL) (54% in 1/2018 vs 75% in 12/2018 p=0.0004). Number of patients with extreme Hg (<9 g/dl or >13 g/dl) improved from 18% to 12% in the same period (p=0.03). Patients in ferritin target (200-800) improved (55% vs 69% p=0.005) without affecting iron saturation. Weekly Aranesp dose was reduced with the ANM model from 45mcg to 39mcg and monthly Mircera dose from 151mcg to 127mcg. Simple cost effectiveness analysis (saving in ESA consumption-nurse salary) showed estimated annual cost saving of 70000 dollars. Our RCA showed that the main cause of failure was compliance with visits and ESA shots. Based on our RCA we built a unique anemia management algorithm for PD (Figure 1).

Conclusions: Anemia management in PD was successfully shifted to our new ANM model. We were successful to achieve and maintain patients within anemia targets. The model was cost effective. We collaborated with a hematologist to address challenges. Similar models are applied throughout our dialysis service.
SA-PO236
Association Between Serum Total Bilirubin Levels and Mortality in Dialysis Patients
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Background: Serum bilirubin may have a potent antioxidant effect and may be associated with protection from cardiovascular disease (CVD) in non-dialysis patients. It is unknown if serum bilirubin levels (sTB) can predict subsequent mortality risk following dialysis initiation in patients at high risk of developing CVD.

Methods: We identified 3,769 patients who transitioned to maintenance dialysis in a large US dialysis organization (2007–2011) and had available sTB data at baseline. Patients with abnormally high (>1.3 mg/dL) and low (<0.1 mg/dL) sTB or liver disease were excluded from the cohort. We divided patients into 12 groups based on their sTB levels (0.1–<0.3 [ref.], 0.3–<0.4, 0.4–<0.5, 0.5–<0.6, 0.6–<0.7, 0.7–<1.3 mg/dL) and age (<65 years, ≥65 years).

Results: Both factors and strata of increasing age were modestly associated with CKD progression at 5 y; p < 0.05). Both factors and strata of increasing age were modestly associated with CKD progression at 5 y; p < 0.05).

Conclusions: In contrast to conventional standards, higher sTB levels within normal ranges are associated with higher mortality in incident dialysis patients. Aging and uremia under dialysis might attenuate an antioxidant effect of bilirubin. Whether bilirubin can be used as an independent risk factor for mortality in dialysis patients warrants additional studies.

Funding: NIDDK Support

SA-PO237
CKD Anemia Epidemiology and Associated Outcomes in Non-Dialysis-Dependent Patients
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Background: Anemia is a well-known CKD complication associated with increased risk of red cell transfusions (RBCs), low quality of life, and adverse outcomes such as cardiovascular events and mortality. Current treatments including erythropoietin-stimulating agent (ESA) have not been shown to improve clinical outcomes in non-dialysis dependent (NDD) CKD patients. The aim of this study was to generate real-world evidence regarding the epidemiology and selected clinical outcomes of anemia and in NDD patients.

Methods: Data for this retrospective, observational study was extracted from Henry Ford Health System databases. Adults with NDD CKD (estimated GFR <60 ml/min/1.73m2) according to Asia-Pacific classification. Central obesity was defined as waist circumference according to Asian-Pacific threshold (male ≥90cm, female ≥80cm). Hemoglobin levels were measured yearly during a mean follow-up period of 37.5±22.1 months. Anemia was defined as hemoglobin <13.0 g/dL in men and 12.0 g/dL in women. Iron deficiency was defined as serum ferritin <100 ng/mL or transferrin saturation <20%.

Results: The prevalence of underweight, normal weight, overweight, and obese was 2.4%, 29.4%, 26.5%, and 41.7%, respectively. Overall, 44.0% of patients were anemic and 55.0% of patients had iron deficiency. Obese patients had the highest hemoglobin concentration compared with other BMI groups (P < 0.001) and erythropoietin stimulating agent (P < 0.015) were significantly decreased in high BMI categories. BMI was positively associated with hemoglobin in multivariable linear regression analysis with adjustment (b = 0.16; 95% confidence interval [CI], 0.22–0.61; P < 0.001). Central obesity was also positively associated with hemoglobin (P < 0.001).

Among 1,165 patients without anemia at baseline, 414 (35.5%) patients developed anemia during a follow-up period. In multivariable Cox regression analysis after adjustment, obese patients had a significantly higher risk of anemia development than those in the normal weight patients (HR, 0.76; 95% CI, 0.58–0.99; P = 0.046).

Conclusions: Obese patients had the highest hemoglobin concentration and had a significantly lower risk of anemia development than those in the normal weight patients.

SA-PO238
Anemia, Iron Status, and Anemia Development in Relation to Body Mass Index in Nondialysis CKD Patients: The Results from the KNOW-CKD Study
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Background: Anemia and iron deficiency are frequent findings in obese subjects. However, there were inconsistent results in adult studies. We aimed to investigate anemia, iron status, and anemia development in relation to body mass index (BMI) in chronic kidney disease patients.

Methods: This prospective study included 2,214 patients from the KNOW-CKD study (Korean Cohort Study for Outcome in Patients With Chronic Kidney Disease), after excluding 24 patients without data on BMI. Participants were classified by BMI categories as underweight (<18.5 kg/m2), normal weight (18.5 to <23 kg/m2), overweight (23 to <25 kg/m2), and obese (≥25 kg/m2) according to Asia-Pacific classification. Central obesity was defined as a waist circumference according to Asian-Pacific threshold (male ≥90cm, female ≥80cm).

Results: Out of 933,463 CKD patients included, 21.6% were anemic. Among patients with anemia, iron deficiency (IDA) was associated with adverse outcomes (hospitalization, dialysis and mortality) in those with CKD.

Methods: Non-dialysis patients followed in the Veterans Administration with hemoglobin level measured within 90 days of the date of the second eGFR < 60 ml/min/1.73m2 were included. Logistic regression, multivariable Cox proportional hazard regression, and poisson regression models adjusted for demographics and comorbidities were used to assess following outcomes: a) prevalence and correlates of absolute (TSAT < 20%, ferritin <100ng/ml), functional IDA (TSAT < 20%, ferritin 100-800 ng/ml) and b) association of absolute and functional IDA, those with Ferritin >800 ng/ml with mortality, dialysis and cardiovascular hospitalization.

Results: Out of 933,463 CKD patients included, 21.6% were anemic. Among patients with anemia with TSAT/Ferritin data, 50% did not have iron deficiency, 30% had absolute IDA, and 19% had functional IDA. Median follow-up was 3.9 years for mortality and 3.6 years for dialysis. Absolute IDA was not associated with an increased risk of mortality and dialysis but had higher risk of 1-year (RR 1.18, 95% CI: 1.11–1.26) and 2-year cardiovascular hospitalization (RR 1.10, 95% CI: 1.04–1.16) [FIGURE]. CKD patients with functional IDA had a higher risk of mortality along with a higher risk of 1-year and 2-year cardiovascular hospitalization. Ferritin > 800 mg/ml (treated as a separate category) was only associated with an increased risk of mortality.

Conclusions: In a large population of CKD patients with anemia, functional IDA was associated with a higher risk of mortality and cardiovascular hospitalization while absolute IDA was associated with a higher risk of hospitalization.

Funding: Commercial Support - AstraZeneca
SA-PO240
Prevalence and Risk Factors of CKD Anemia in the United States
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Background: The most recent estimate to date of the prevalence of anemia in patients with chronic kidney disease (CKD) in the US is supported by data from US National Health and Nutrition Examination Survey (NHANES) in 2007-2010. We analyzed the NHANES database from 1999 to 2016 to update the prevalence of anemia among the US adult population with CKD and investigate risk factors.

Methods: CKD stage was assessed using the estimated glomerular filtration rate (eGFR) derived from serum creatinine using CKD-EPI equation. Anemia was defined as hemoglobin ≤13 g/dl in men and ≤12 g/dl in women, and severe anemia as hemoglobin (Hb) <10 g/dl (per KDQI guidelines). Pregnant women were excluded. NHANES participants who had received dialysis treatment in the 12 months before the survey were considered as presenting CKD stage 5 but were excluded for estimation of prevalence of anemia. Associations between anemia and CKD stage, age, sex, race/ethnicity, smoking status, diabetes, hypertension, and body mass index were investigated. A logistic regression multivariate model was fit using a stepwise downward approach.

Results: Median age (yrs) of all the NHANES participants with CKD was 73.4 (interquartile range: 60.7, 81.0); 59.8% (95% CI: 57.7, 61.1) were female; 9.8% (95% CI: 8.4, 11.1) were African-American; and 25.1% (95% CI: 23.3, 26.8) reported diabetes mellitus. Prevalence estimates of anemia and severe anemia in 2015-2016 were 23.5% (95% CI: 19.4, 27.7) and 1.2% (95% CI: 0.4, 2.0), respectively. Association between CKD stage and anemia severity are shown in the Table.

Conclusions: Only a small fraction of CKD patients with anemia present with Hb <10 g/dl, and are eligible for treatment. The risk of anemia and severe anemia is markedly increased in patients with lower eGFR.

Funding: Commercial Support - AstraZeneca

SA-PO241
A Faster Decline of Residual Kidney Function and Erythropoiesis-Stimulating Agent (ESA) Hyporesponsiveness in Incident Hemodialysis Patients
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Background: In dialysis patients, resistance to ESA is associated with worse outcomes such as higher death risk. Prior studies have demonstrated that a slower loss of residual kidney function (RKF) is associated with better outcomes. However, little is known about the relationship between RKF decline and resistance to ESA.

Methods: The odds of ESA hyporesponsiveness with RKF decline in the first year were examined across four strata of annual changes in residual renal urea clearance ([KRU], ~3.0 to ~1.5, ~1.5 to ~0.5, ~0.5 to 0, ~0 mL/min/1.73m2) and urinary volume (~<600, ~600 to ~<100, ~100 to 0, ~0 mL/day). Logistic regression models adjusted for demographic, clinical characteristics and laboratory variables were used in 5,239 incident HD patients from 1/1/2007-3/31/2010.

Results: The median (interquartile range) baseline values of the annual changes in KRU and urinary volume were ~1.2 (~2.8, 0.1) mL/min/1.73m2 and ~250 (~600, 100) mL/day, respectively. A faster RKF decline in the first year of HD initiation was associated with higher odds of ESA hyporesponsiveness (Figure). These associations remained robust across adjustment for laboratory variables and consistent in subgroup analyses across strata of baseline RKF, age, sex, race, diabetes, congestive heart failure, hemoglobin, and serum albumin. Similar results were found using urinary volume as another index of RKF (Figure).

Conclusions: A faster RKF decline during the first year of dialysis was associated with hyporesponsiveness to ESA among incident HD patients. Future studies are necessary to explain the underlying mechanisms of this association.

Funding: NIDDK Support

SA-PO242
Prevalence of CKD Anemia in Non-Dialysis-Dependent Patients Using Linked US Claims and Electronic Health Record Data
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Background: Novel strategies for the management of anemia, a complication of chronic kidney disease (CKD), are in development. Insights into CKD-related anemia burden, associated outcomes, and resource utilization are needed from representative non-dialysis dependent CKD populations receiving high-quality clinical care. The primary study objective was to describe baseline patient characteristics, comorbidities, and anemia prevalence in non-dialysis-dependent (NDD) CKD patients in US real-world practice.

Methods: This retrospective observational study evaluated the integrated Limited Claims and Electronic Health Record Data (IBIM Health, Armonk, NY). The study cohort included patients aged ≥18 years with ≥2 eGFR measures ≤60 mL/min/1.73 m2 at least 90 days apart. Anemia was defined as the first observed hemoglobin (Hb) <10 g/dl. The baseline period was defined as the date of the second confirmatory eGFR ≤60 months. Baseline anemia prevalence, demographics, comorbidities, laboratory measurements, and selected medications were extracted and analyzed for the period from January 1, 2012 and September 30, 2017. Descriptive data were summarized, and no inferential statistics were performed.

Results: The study cohort (N = 33,088) was 57% female and mean (±SD) age was 70 (±13) years. The proportion of patients across CKD stages at baseline was: 3a (56%), 3b (23%), 4 (8%), and 5 (15%). Baseline comorbidities included type 2 diabetes mellitus (31%), cardiovascular disease (49%), heart failure (23%), and hyperlipidemia (62%). Median baseline (interquartile range) Hb was 12.4 (11, 13.6) g/dl, creatinine 1.3 (1.1, 1.7) mg/dl, ferritin 116 (53, 244) ng/ml, and total iron binding capacity 303 (254, 349). Baseline anemia prevalence was 30% (N = 9909/33,088). Erythropoiesis-stimulating agents (ESAs) were prescribed in 0.6% of all patients at baseline, and usage increased by worsening Hb strata (0.1% in Hb >12, 1.0% in Hb 10-11.9, 2.3% in Hb 9-8.9, and 2.6% in Hb <8 g/dl).

Conclusions: Anemia is a frequently observed complication of CKD in NDD patients and co-exists with other comorbidities. Baseline utilization of ESAs was very rare, and should increase when associated with decreasing Hb in a large US cohort of NDD patients with anemia.

Funding: Commercial Support - AstraZeneca

SA-PO243
A Rapid Decline of Residual Kidney Function and Anemia in Hemodialysis Patients
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Background: Patients on dialysis commonly develop anemia due to the kidney’s critical role in red blood cell production. Slower residual kidney function (RKF) decline on dialysis is associated with better outcomes. We hypothesized that a faster decline in RKF may be associated with a higher odds of developing anemia in the incident hemodialysis (HD) patients.

Methods: The associations of decline in RKF with anemia were examined retrospectively across four strata of annual change in RKF (residual renal urea clearance [KRU], ~<3.0, ~3.0 to ~<1.5, ~1.5 to <0, ~0 mL/min/1.73m2) and urinary volume (~<600, ~600 to ~<100, ~100 to 0, ~0 mL/day). Logistic regression models adjusted for clinical characteristics and laboratory variables in 5,403 incident HD patients of a large US dialysis organization between January 1, 2007 and December 31, 2011.

Results: A total of 5,291 (98%) patients used erythropoiesis-stimulating agents (ESAs) during the first year of HD initiation. The median baseline values of the annual change in KRU and urinary volume were ~1.2 (interquartile range [IQR]: ~2.8 to 0.1) mL/min/1.73m2 and ~250 (~600, 100) mL/day, respectively. Multivariate logistic regression models revealed that the fastest RKF decline in the first year of HD was associated with higher odds of anemia (Figure). These associations remained robust against adjustment for
SA-PO244

Iron Deficiency Anemia in Clinical Practice: Can Virtual Patient Simulation Improve Management?

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Background: We sought to determine if an online, virtual patient simulation (VPS)-based continuing medical education (CME) intervention could improve performance of nephrologists and primary care physicians (PCPs) in diagnosing and managing iron deficiency anemia (IDA).

Methods: The intervention comprised two case pages where learners ordered lab tests, made diagnoses, and prescribed treatments similar to practice. Tailored clinical guidance (CG), based on current evidence and expert recommendation, was provided following each decision, followed by the opportunity for the learner to modify to their decisions. Decisions were collected post-CG and compared with each user’s baseline (pre-CG) decisions using a 2-tailed paired t-test to determine P values. The activity launched March 1, 2019; data were collected for initial abstract submission through May 22, 2019.

Results: To date, 11 nephrologists and 47 PCPs have participated (larger sample size expected by ASN conference). Case 1: IDA diagnosis: 22% absolute improvement among nephrologists (22% pre-CG vs 44% post-CG; P=.18), 5% improvement among PCPs (53% pre-CG vs 58% post-CG, P=.16). Diagnosis of chronic kidney disease stage 5: 33% absolute improvement among nephrologists (6% pre-CG vs 33% post-CG; P<.001), 34% improvement among PCPs (16% pre-CG vs 50% post-CG; P<.001). Dialysis referral: 22% absolute improvement among nephrologists (22% pre-CG vs 44% post-CG; P=.18), 21% improvement among PCPs (21% pre-CG vs 42% post-CG; P=.05). Initiate oral iron replacement: 22% absolute improvement among nephrologists (22% pre-CG vs 44% post-CG; P=.18), 32% improvement among PCPs (39% pre-CG vs 71% post-CG; P<.001). Case 2: IDA diagnosis: 27% absolute improvement among nephrologists (27% pre-CG vs 54% post-CG; P=.08), 21% improvement among PCPs (30% pre-CG vs 52% post-CG, P<.001). Diagnosis of chronic kidney disease stage 4: 36% absolute improvement among nephrologists (27% pre-CG vs 63% post-CG; P<.001), 32% improvement among PCPs (17% pre-CG vs 49% post-CG; P<.001). Initiate oral iron replacement: 36% absolute improvement among nephrologists (56% pre-CG vs 82% post-CG; P<.001), 21% improvement among PCPs (9% pre-CG vs 57% post-CG; P<.001).

Conclusions: VPS that immerses and engages specialists in an authentic and practical learning experience can improve evidence-based clinical decisions related to diagnosis and management of IDA.

SA-PO245

Ferric Citrate Hydrate on Anemia Management in Hyperphosphatemia Hemodialysis Patients with or without Diabetes: ASTRIO Study

Supplementary Analysis

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Background: It is reported that patients with diabetes in hemodialysis (HD) tend to be treated with higher ESA dose. The relationship is bi-directional, iron affects glucose metabolism and glucose metabolism affects iron metabolism pathway. In ASTRIO Study, Ferric Citrate Hydrate (FC) reduced dose of ESA. The effect of FC on anemia management in hemodialysis diabetes patients has not been extensively evaluated.

Methods: ASTRIO was a prospective, randomized, multicenter, 24-week study. 93 hyperphosphatemia HD patients who had been taking non-iron based phosphate binders (PBs) were randomized to FC group (n=48) or Control group (n=45). In Control, patients maintained treatment with their existing PBs. Serum P and Hb were controlled within 3.5 to 6.0 mg/dL and 10.0 to 12.0 g/dL, respectively. Oral iron was prohibited in Control group. Intravenous iron was permitted if iron replacement therapy was required, at the physician’s discretion. The primary endpoint was change in ESA dose from baseline to the end of treatment (EOT); we evaluated a stratified analysis for diabetes patients whose main underlying disease is diabetic nephropathy.

Results: Serum P and Hb were maintained in both groups. Regardless of whether patients have diabetes or not, ESA doses decreased in FC group.

Conclusions: The effect of FC on anemia management in hyperphosphatemia HD was comparable between diabetic and non-diabetic patients.
and cancer (cancer-related mortality and tumor progression and recurrence) related AEs, and opportunistic infections by ophthalmologists during treatment.

Results: AEs in each AESI category were pooled from 549 patients (n=319; daprodustat, n=230; ESA) and 487 patients (n=313, n=174) in ND and HD patients, respectively. Median exposure (days, daprodustat vs. ESA) in ND and HD patients was 172.5 vs. 169.1, respectively. In ND patients, the incidence (daprodustat vs. ESA) of ocular, cardiovascular, and cancer related AEs were 3% vs. 3%, 3% vs. 6% and 1% vs. 1%, respectively. In HD patients, these were respectively 2% vs. 2%, 7% vs. 7% and 1% vs. 1%. The incidence of ophthalmological findings were 11% vs. 10% in ND patients and 8% vs. 6% in HD patients. There was no meaningful difference in the frequencies of the predefined AESIs or ophthalmological findings between the treatment groups in ND and HD patients.

Conclusions: Daprodustat showed no new safety concerns in these predefined AESIs in these clinical studies, but further investigation will be needed.

Funding: Commercial Support - GlaxoSmithKline

SA-PO248

Comparison Between a Novel Lactate Immunoassay and LC-MS/MS for Hepcidin-25 Measurement

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Background: Hepcidin-25 is an iron regulatory factor in the in vivo evaluation of iron dynamics and plays an important role in determining the development and severity of anemia in patients with chronic kidney disease. Although the golden standard of measurement of hepcidin-25 is the LC-MS/MS method, results cannot be obtained immediately at the clinical site. However, the latest immunoassay (LIA) can be performed using general clinical laboratory equipment, and the results obtained quickly. Our aim was to measure hepcidin-25 by LIA and LC-MS/MS and compare the two methods.

Methods: Hepcidin-25 was measured by LIA and LC-MS/MS in 134 hemodialysis patients. We used a hepcidin-25 specific reagent (FUJIFILM Wako Pure Chemical Corporation) and the ICA-BM6050 automatic analyzer for LIA and the 4000 QTRAP LC-MS/MS system for LC-MS/MS. The results obtained by the two methods were compared by standard major axis regression.

Results: The standard major axis regression equation between the two methods was \( y = 0.995x + 0.5 \) (\( r = 0.998, p < 0.001 \)). The correlation between the two methods was very strong and the measured values were almost identical.

Conclusions: The performance of LIA was equivalent to that of LC-MS/MS for hepcidin-25 measurement. LIA can be performed using general clinical examination apparatus and has a higher processing speed than LC-MS/MS. Therefore, measurement of hepcidin-25 by LIA may potentially be useful for routine laboratory testing.

SA-PO249

Hemoglobin Cycling Induced by Delayed Patient-Therapy Feedback During ESA Treatment

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Background: Chronic kidney disease (CKD) commonly entails anemia, leading to poor patient outcomes. During treatment of anemia with erythropoiesis-stimulating agents (ESAs), patients frequently experience hemoglobin (Hgb) “cycling” periods during which the patient’s Hgb levels periodically over- and undershoot a defined target range of 10–11.5 g/dL. Using a computational model of anemia treatment (“Virtual Anemia Trial”; Fuertinger et al., CPT Syst. Pharmacol. 7(4) 219, 2018), we aimed to detect treatment-related causes of this behavior.

Methods: We carried out Virtual Anemia Trials with 6659 virtual patients (“avatars”) under 4 different anemia treatment protocols (a-d) for one simulated year of treatment. Avatars differed in endogenous EPO levels, total blood volume, and ESA half-life. Treatment protocols differed in ESA-dosing charts (steps between doses and administration frequency) and the criteria that determine ESA dose recommendations based on the patient’s Hgb history (i.e., critical Hgb levels and/or rates of change).

Results: The 4 treatment protocols yielded different distributions of Hgb amplitudes (difference between maximum and minimum Hgb in the second half of the simulated patient year), with a mean s.d. given by (a) 1.7 ± 1.5 g/dL, (b) 1.7 ± 1.4 g/dL, (c) 1.6 ± 1.3 g/dL, and (d) 1.1 ± 1.0 g/dL, respectively (see Figure). Except for (a) vs. (b), differences between the corresponding distributions were statistically significant when pairwise compared (Pearson chi-squared test; \( p < 0.05 \)).

Conclusions: Our results suggest that certain treatment protocols can augment Hgb cycling instead of preventing it. Analysis of the differences between probed treatment protocols reveals two treatment-related causes for Hgb cycling: (i) too late ESA dose changes in response to falling/rising Hgb levels and (ii) too extreme dosing decisions (e.g., complete ESA hold for a too long time) that prevent Hgb levels from remaining within target after transiently reaching it. Based on these insights, existing treatment protocols may be modified to reduce patients’ Hgb cycling.

Funding: Commercial Support - Fresenius Medical Care Germany

SA-PO250

The Alteration of Non-Transferrin-Bound Iron (NTBI) and Malondialdehyde (MDA-LDL) in Hemodialysis (HD) Patients

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Background: OIA is not considered to increase NTBI because of slow iron adsorption rate. Aim of this study is to assess the alteration of NTBI and an oxidative stress marker, MDA-LDL after single dose ESA.

Methods: 25 HD patients without any iron load within 4 weeks, whose Hb<12g/ dl, ferritin<100ng/ml and CRP<1.0mg/dl and 13 healthy volunteers received oral ferrous sulfate 105mg. 21 HD patients without OIA were as HD control. We evaluated the following markers before and at 1, 2, 3, 4 and 48 hours (hrs) after OIA: MDA-LDL, NTBI, hepcidin-25(HPC), serum iron(Fe), TSAT, ferritin, selenium(Se) and standard hematological parameters. Vitamin C(VC) were measured before and at 4 and 48hrs. MDA-LDL was measured by ELISA. NTBI was measured by recently described reliable method(Clin Chim Acta347:129-135, 2014).

Results: Fe, TSAT and NTBI increased after OIA and reached the peak at 4hrs, ferritin also increased at 48hrs in both HD patients and healthy control. In HD control without OIA, they did not change. NTBI and HPC basal levels were higher in healthy control than in HD patients. MDA-LDL before OIA was not different between the two groups. MDA-LDL increased from 1 to 4hrs during HD and returned to the basal level at 48 hrs irrespective of OIA, however, in healthy control, no significant alteration was observed. In HD patients, Se level before OIA was a negative predictor for Log(MDA-LDL) before OIA by stepwise analysis(\( p=0.459, p=0.021, R^2=0.21 \)). In healthy control, NTBI before OIA was a predictor for Log(MDA-LDL) before OIA(\( p=0.768, p=0.002, R^2=0.589 \)). Percentage of hypo-hemoglobinised (HypoHe) in HD patients (\( p=0.443, p=0.027, R^2=0.196 \)) and HPC in healthy control (\( p=0.637, p=0.019, R^2=0.406 \)) before OIA were negative predictors for the maximum level of NTBI after OIA, respectively. Antioxidants, Se and VC basal levels were lower in HD patients. Se level did not change during HD. VC level decreased after HD and recovered at 48 hrs.

Conclusions: NTBI significantly increased after OIA. However, MDA-LDL significantly increased during HD session irrespective of OIA, whereas it did not change in healthy control after OIA. Although OIA increased NTBI, it had little influence on the MDA-LDL level. This may result of the exquisite balance of the oxidative stress and the antioxidant activity.

SA-PO251

Impact of a Novel Dose Calculation Method for Erythropoiesis Stimulating Agents on Renal Anemia Therapy in Hemodialysis Patients

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Background: Patients with end-stage renal disease requiring dialysis therapy have poor prognosis compared with normal population. Renal anemia is a common comorbidity and is a major cause of morbidity and mortality among hemodialysis patients. For treatment of renal anemia, empiric erythropoiesis stimulating agents (ESA) dosing method is generally used in hemodialysis patients and standardized method are shown by Fishbane et al. in 2005. However, hemoglobin (Hb) levels are not always within target range for favorable prognosis according to anemia guidelines. We developed a new method for ESA dose determination that uses individual increase value and individual decrease value calculated from Hb variability. Individual increase value and individual decrease value mean real response of Hb increase under maximum ESA dose and natural HB decrease without ESA per week, respectively. There has never been a reliable and valid method to calculate individual increase and decrease values before the new method. The aim of this study was to estimate effectiveness of the new method for ESA dosing.

Methods: This was a 6-month randomized, controlled, parallel-group study in hemodialysis patients with renal anemia treatment. Patients were assigned to two groups receiving epoetin beta (EPO) dosing by new method and standardized method. The target range of Hb was set at 10.0 to 11.0 g/dL. EPO doses for two weeks were determined at every two-week Hb measurement. Iron was administered when ferritin was below 100 ng/ml or transferrin saturation below 20%.

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Anemia and Iron Metabolism: Clinical
Poster/Saturday

Results: One-hundred and two patients were enrolled (61 men, 41 women; mean age 68.9 ± 12.5 years). There was no difference in baseline characteristics between the two groups. At end of study, mean Hb levels were not different between the new method group and standardized method group (10.5 ± 0.7 g/dL vs. 10.5 ± 0.7 g/dL, P = 0.936). The ratio of patients with Hb levels within target range were significantly different between the new and standardized method groups (75% vs. 50%, P = 0.021 by chi-square tests). Required EPO dose were not different between the new and standardized method groups (2578.1 ± 1851.2 IU/w vs 3046.9 ± 2627.3 IU/w, P = 0.359). There were no adverse events related to the new method.

Conclusions: The new method for EPO dosing is superior to existing standardized EPO dosing method.

SA-PO252

Modulation of Circulating Endothelial Progenitor Cells by Erythropoiesis-Stimulating Agent in Patients with Hemodialysis
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Background: Recent studies have suggested that erythropoiesis stimulating agent (ESA) may accelerate not only anigenesis, but also vasculogenesis, beyond erythropoiesis.

Methods: We conducted a 12-week prospective study in 42 dialysis patients; 11 patients were treated with recombinant human erythropoietin (rhEPO) (EPO group, 5487.5 ± 735.1 IU/week), 11 patients with darbepoetin (DA) (DA group, 41.6 ± 4.7 µg/week), 10 patients with epoetin β pegol (CERA group, 49.5 ± 16.5 µg/week) and 10 patients with no ESAs (no-ESA group). Vascular mediators comprising EPCs, vascular endothelial growth factor, matrix metalloproteinase-2 (MMP-2), and high-sensitivity C-reactive protein were measured at 0 and 12 weeks. EPCs were measured by flow cytometry as CD34+CD133+ cells.

Results: In the EPO and CERA group, EPC count increased significantly from 0 to 12 weeks in a dose-dependent manner (EPO, r = 0.77, p = 0.01, CERA, r = 0.72, p = 0.01). In the DA group, the EPC number did not change at 12 weeks. Furthermore, serum levels of the above biomarkers except EPC were not affected by ESA in all groups.

Conclusions: We speculate that the pleiotropic effects of each ESA types beyond their hematopoietic effects may differ in ESKD patients.

Funding: Clinical Revenue Support

SA-PO253

Model Predictive Control (MPC) for Iron Dosing for the Management of Anemia
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Background: Recent studies have shown that ESA management can be improved using computer based tools to determine the dose of an erythropoietic stimulating agent (ESA). We tested the hypothesis that similar improvements can be achieved for iron dosing.

Methods: A ferrokinetic model was developed based on published data from iron studies. The model predicts monthly change in Tsat and Ferritin in response to a dose adjustment of iron sucrose. Using this model, a dose adjustment algorithm was designed using principles of Model Predictive Control. The dosing objective was to drive Tsat to a physician-specified target value of 35 without exceeding an upper Ferritin threshold, also based on the current monthly lab draw and patient’s own historical data. These predictions were then provided to anemia managers along with interpretive guidance from the development team.

Results: Incorporation of this form of decision support into the anemia management protocols significantly increased the number of Hgb readings below 10 g/dL decrease from 23.7% pre-intervention to 19.5% post intervention (p=0.044). There was an increase from 10.8 g/dL to 11.2 g/dL in the average patient mean Hgb (p=0.09) and a 77.3% decrease in the average patient Hgb variance (p=0.01). Overall, there was a 32.7% decrease in the average per treatment ESA dose (p=0.01).

Conclusions: Incorporating decision support from a predictive algorithm into an existing anemia management protocol resulted in a decrease in overall ESA use while decreasing patient Hgb variability. Small study population was a limitation to this study.

SA-PO254

Using a Predictive Algorithm to Provide Decision Support in Anemia Management
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Background: Anemia in hemodialysis is very common with most receiving erythropoietin stimulating agent (ESA) therapy. Most ESA dosing protocols are based on manufacturer recommendations and clinical experience. They are standardized across entire dialysis populations and do not account for individual response. To improve anemia management, we developed a predictive algorithm to forecast 1, 2 and 3 month hemoglobin (Hgb) values as a way of providing decision support for monthly ESA dose adjustments.

Objectives: To determine if the addition of future Hgb predictions to the information currently provided to anemia managers will result in a reduction in Hgb variability, an increase in the number of Hgb observations within the target range, and a decrease in the average per treatment ESA use.

Methods: We developed a predictive algorithm utilizing historic electronic medical record (EMR) data collected during the 2009-2017 time period. The data set included dialysis sessions, ESA administered, intravenous iron, Hgb, ferritin, and transferrin saturation (Tsat %). Following algorithm development, we conducted a 10 month (July 2018 to April 2019) QI project with approximately 20 patients in an academic dialysis center. Each month, future hemoglobin predictions were provided for 1, 2, and 3 months ahead. The current monthly lab draw and patient’s own historical data. These predictions were then provided to anemia managers along with interpretive guidance from the development team.

Results: Incorporation of this form of decision support into the anemia management protocols significantly increased the number of Hgb readings below 10 g/dL decrease from 23.7% pre-intervention to 19.5% post intervention (p=0.044). There was an increase from 10.8 g/dL to 11.2 g/dL in the average patient mean Hgb (p=0.09) and a 77.3% decrease in the average patient Hgb variance (p=0.01). Overall, there was a 32.7% decrease in the average per treatment ESA dose (p=0.01).

Conclusions: Incorporating decision support from a predictive algorithm into an existing anemia management process resulted in a decrease in overall ESA use while decreasing patient Hgb variability. Small study population was a limitation to this study.

SA-PO255

Contemporary Management of Anemia and Associated Risk Across the Spectrum of CKD: A Nationwide Analysis from the Swedish Renal Registry
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Background: The last decade has seen noteworthy changes in renal anemia guidelines. Here we explore the current management of renal anemia and associated cardiovascular (CV) risk in a contemporary nationwide cohort of chronic kidney disease (CKD) patients in Sweden.

Methods: Observational analysis from the Swedish Renal Registry, including nephrologist-referred adult CKD patients during 2015. The epidemiology and treatment of anemia across the spectrum of stage 3b-5 non-dialysis-dependent (NDD) and dialysis-dependent (DD) CKD were assessed. Logistic regression and Cox proportional hazard models were employed to explore the associations between anemia management, Creatinine protein (CRP), erythropoietin resistance index (ERI [erythropoiesis-stimulating agent (ESA) dose/weight]/hemoglobin [Hb]), and subsequent risk of major adverse CV events.

Results: Data from 14,415 (NDD, 11,370; DD, 3,045) patients were included. Approximately 60% of NDD CKD patients had anemia (World Health Organization definition: Hb <12 g/dL for females; Hb <13 g/dL for males) compared with 93% of DD patients. The proportions of NDD patients who received iron (oral or intravenous) and/or ESA therapy were 21% and 24%, respectively; the proportions of DD patients were 62% and 82%, respectively. In both NDD and DD populations, about half of the patients receiving ESA had Hb levels between 10-12 g/dL; 27% had Hb >12 g/dL and 14% had

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HB <10 g/dL. Use of high-dose ESA (>6000 IU/week) was relatively common even among patients at earlier stages of CKD (~25%). The use of high versus low (<3000 IU/week) median (3000-6000 IU/week) dose ESA was associated with increased systemic inflammation in cross-section (CRP >5 mg/L; odds ratio, 1.68 [95% CI: 1.45-1.94]), with a 40% higher risk of CV events (adjusted hazard ratio [HR], 1.40 [95% CI: 1.16-1.69]). Patients with high (0.81-12.0) versus low (0.0-4) ERI had a 2-fold higher risk of CV events (adjusted HR, 1.98 [95% CI: 1.61-2.43]). Treatment with iron was not associated with CRP levels or CV risk.

Conclusions: Anemia continues to be a highly prevalent complication among community-dwelling adults with CKD. Given the guideline recommendations, the use of iron was unexpectedly low. High doses of ESA and high ERI predicted increased CRP levels and subsequent CV risk.

Funding: Commercial Support - Astellas Pharma Inc

SA-PO256

Evaluating Anemia in Acutely Ill Patients
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Background: Anemia of chronic kidney disease (CKD) is one of the most common long-term complications as kidney failure progresses. The pathogenesis is multifactorial, but decreased erythropoietin production has a main role in later stages of CKD. The prevalence is approximately 33-67%. Treatment options include erythropoietin stimulant agents (ESA) once iron deficiency has been treated and contraindications have been evaluated. A decreased production of red blood cells is commonly seen in acutely-ill patients. We hypothesized that CKD/ESRD patients are at higher risk of worsening anemia even with adequate hemoglobin levels on admission.

Methods: We studied 53 patients with advanced CKD or ESRD admitted to our hospital between November 2017 and January 2018. Clinical data was obtained from charts and data incorporated in the analysis included: hemoglobin (HB) on admission and upon discharge, outpatient treatment of anemia, and inpatient management of anemia such as transfusion, iron supplementation and ESA. Patients with acute bleeding during hospitalization were excluded.

Results: A total of 24 patients with HB < 10 g/dl and 29 patients with HB >10 g/dl on admission were included in our analysis. Patients with hemoglobin >10 g/dl on admission were noted to have significantly higher decrease in hemoglobin level upon discharge compared with patients with HB < 10 g/dl (mean change from baseline HB 0.9 vs -0.3, p<0.001). One third of patients with indication for ESA and no clinical contraindications for administration received EPO inpatient, while 33% of patients that were not treated with EPO received blood products.

Conclusions: Hospitalized patients with advanced CKD or ESRD are at high risk of worsening anemia despite adequate hemoglobin levels on admission. We suggest considering a closer surveillance of hemoglobin for potential administration of ESA in order to prevent worsening anemia.

SA-PO257

Improving Rates of Epoetin Alpha Administration in ESRD Patients at Two Teaching Hospitals: A Quality Improvement Initiative
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Background: Adequate management of anemia in ESRD has important clinical implications for both patients and the healthcare system at large. It improves quality of life, prevents readmissions, decreases the need for transfusions while simultaneously improving efficiency of care. Subcutaneous (SQ) Epoetin Alpha (EPO) provides a dose-sparing advantage over Intravenous (IV) EPO. In hospitals A and B, following a switch in the process of EPO administration from IV during dialysis to SQ on the general floors, we noted rates of 19.5% and 14.5% of missed EPO doses at hospitals A and B respectively. Unrefrigerated, un-administered EPO doses are discarded leading to a significant waste and worsening hemoglobin levels. The aim of this QI initiative was to understand the roots and reduce missed EPO doses to <10% over 9 months.

Methods: We utilized the PDSA performance improvement model to manage this project. A multidisciplinary team including Nephrology, Nursing, Pharmacy and IT was created. We identified the most common cause of missed doses as an inpatient dialysis schedule switch (from Monday/Wednesday/Friday to Tuesday/Thursday/Saturday or vice versa) without a coinciding change in the EPO order. Our first intervention was the creation of an EMR alert notifying nurses to administer the dose as ordered regardless of patients’ dialysis schedule and asking them to discuss with nephrology if they were to hold a dose. At month 5, we tested a second intervention: a collaborative nursing education about anemia management at Hospital B only, facilitated by a nephrologist and a nurse educator.

Results: The results of the study are summarized in Figure 1. Following the creation of an EMR alert, there was only a mild and unsustained improvement in our rates at both hospitals. After nursing education at Hospital B, we noted a sustained improvement in our rates at Hospital B but not at Hospital A.

Conclusions: While technology is an important tool providing scale and efficiency in QI initiatives, the role of targeted Nursing Education remains an effective measure to prevent waste and sustain change.

SA-PO258

24 Hydroxylase Deficiency: Contamination with Other Disorders of Vitamin D-Mediated Hypercalcemia
Sarah M. Azez, Lisa E. Vaughan, Peter Tebben, David J. Sas. Mayo Clinic, Rochester, MN.

Background: CYP24A1 gene encodes 24-hydroxylase, an enzyme that converts 25(OH)D3 (25D) and 1,25(OH)2D3 (1,25D) to inactive metabolites. Recent reports establish that loss of function mutations in CYP24A1 are associated with 24-hydroxylase deficiency (24HD), characterized by hypercalcemia, nephro lithiasis, and/or nephrocalcinosis (NC). We retrospectively compared laboratory, imaging, and clinical characteristics of patients with suspected or confirmed 24HD to other disorders of vitamin D-mediated hypercalcemia: sarcoidosis (S), lymphoma (L), and exogenous vitamin D toxicity (EVT).

Methods: Patients seen at Mayo Clinic, Rochester between 1/1/08 and 12/31/16 were further evaluated if they met biochemical criteria: serum calcium ≥ 9.6 mg/dL, PTH <30 pg/mL, and 1,25D >40 pg/mL. Patients with 24HD were then identified if they met one of the following criteria: 1) positive genetic testing or 2) 25D:24,25D ratio ≥50. Patients with diagnosis of S, L, or EVT were identified by chart review. Patients with fungal infections were also identified but excluded from analysis due to lack of systemic involvement. Data were summarized and reported using medium [IQR] for continuous variables and n(%) for categorical variables. Comparisons between disease groups were evaluated using the Fisher exact test for categorical variables and the Wilcoxon rank sum test for continuous variables.

Results: Comparison of 24HD (n=9) to all groups (n=28) revealed 24HD patients were younger at symptom onset (13.75 [1.35] vs 63 [56,79], p=0.001) and more likely to have family history (88.9% vs 20.8%, p=0.001), NC (88.9% vs 6.3%, p=0.001), lower lumbar spine Z-score (-0.50 [-0.80,0.70] vs 1.20 [0.80,2.10], p=0.011), and higher urine Ca:Cr ratio (0.24 [0.21,1.70] vs 0.17 [0.14,0.18], p=0.047).

Conclusions: Patients with 24HD have advanced age-related differences compared to other causes of vitamin D mediated hypercalcemia. 24HD should be suspected in hypercalcemic patients who present at a younger age, have a positive family history, and have nephrocalcinosis.

Funding: Private Foundation Support

SA-PO259

Severe Hypercalcemia Mitigated by Etelcalcetide in Continuous Renal Replacement Therapy
Ashita J. Tolskani, Arun Rajasekaran. University of Alabama at Birmingham, Birmingham, AL

Introduction: Secondary hyperparathyroidism (SHPT) is associated with increased bone turnover, risk of fractures, vascular calcification, and cardiovascular and all-cause mortality. We describe a critically ill ESRD patient with SHPT who developed hypercalcemia with prolonged immobilization managed with continuous renal replacement therapy (CRRT) using regional citrate anticoagulation (RCA) without calcium supplementation and treatment with intravenous etelcalcetide.

Case Description: A 51 year old lady with ESRD on hemodialysis (HD) underwent aortic and mitral valve replacement. She received maintenance HD for 10 days after cardiac surgery. Post-surgical course was complicated by hypoxic respiratory failure, mesenteric ischemia, and septic shock warranting mechanical ventilation, colectomy and vasopressor use. In the setting of SHPT with high turnover bone disease and prolonged immobilization, she developed pathologic bilateral subcapital femoral neck fractures with diffuse osteopenia 2 months after admission. She had elevated systemic ionized calcium (1.6 mmol/L), phosphorus (6.7 mg/dL), ALP (426 U/L), bone-specific ALP (90 mg/cm²), and PTH (780 pg/ml) levels. The patient was started on citrate based CRRT without the use of a calcium infusion 10 days after cardiac surgery; and was treated with intravenous etelcalcetide 5 mg thrice weekly to mitigate severe hypercalcemia. After 3 weeks, she had a reduction in systemic ionized calcium (1.1 mmol/L), phosphorus (3.5 mg/dL), ALP (316 U/L), and PTH (310 pg/ml) levels. She eventually died from worsening septic shock.

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Effect of Transition from Vitamin D2 to Vitamin D3 Supplementation on Serum 25(OH)D Levels in Patients on Chronic In-Center Hemodialysis

**Background:** Vitamin D deficiency (25(OH)D <12 ng/ml) can lead to osteomalacia in adults, and insufficiency (12 to 20 ng/ml) is associated with osteoporosis, increased falls, and possibly fractures. Clinical guidelines (KDIGO 2017) recommend correction of Vitamin D deficiency and insufficiency in all CKD 3-5D patients. Short-term pharmacokinetic studies in healthy adults have shown that Vitamin D2 (VitD2) is less effective at correcting 25(OH)D levels than Vitamin D3 (VitD3). We evaluated whether conversion from VitD2 therapy to VitD3 resulted in a meaningful change in 25(OH)D levels in hemodialysis (HD) patients.

**Methods:** Since 2006, we have directly administered 50,000 units of VitD2 monthly to all ~160 in-center dialysis patients. In June 2017, we converted to 50,000 units monthly of VitD3. We collected demographic and laboratory data from 2016 and 2017 (VitD2 dosing) and 2018-2019 (VitD3 dosing). 25(OH)D levels were measured each April at our laboratories. Assay detects both 25(OH)D2 and 25(OH)D3. Changes in 25(OH)D levels were analyzed, and relationships to demographic and other laboratory parameters were explored.

**Results:** 156 to 174 patients were included in each yearly analysis. Mean 25(OH)D levels (ng/ml) were 34.6 (2016) and 36.6 (2017) on VitD2. Levels increased to 52.9 (2018) and 53.7 (2019) on VitD3 (p<0.001). Use of VitD3 greatly reduced the proportion of patients with 25(OH)D 20-30ng/ml (29% pre; 1% post), but increased 25(OH)D levels >50 from 7% to 55%, and >80 from 0.3% to 4%. Among 96 patients present all 4 years, the results were similar (mean 35.2 on VitD2, and 55.0 on VitD3). There was no significant change in Calcium, PTH, or Alkaline Phosphatase.

**Conclusions:** Consistent with short-term studies in healthy adults, at equal doses, VitD3 led to significantly higher 25(OH)D levels than VitD2. As 25(OH)D levels >20 ng/ml are sufficient to prevent osteomalacia, our data suggest use of either 50,000 units of VitD2 monthly, or a lower dose of VitD3 (likely 20-30,000 units monthly) is sufficient to prevent Vitamin D deficiency in HD patients.

**Figure 1**

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Serum 25(OH)D Levels in Patients on Chronic In-Center Hemodialysis

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Results: Their mean age was 63.1 (±18.8) years, and median dialysis vintage was 84 (38-128) months. The distribution of patients with Ca or P levels ≤0.248 (as [Ca] ≤0.248 mg/dL and [P] ≤0.248 mg/dL, respectively) was 182 patients (47.3%). The distribution of patients with Ca or P levels ≤0.248 (as [Ca] ≤0.248 mg/dL and [P] ≤0.248 mg/dL, respectively) was 182 patients (47.3%). The distribution of patients with Ca or P levels ≤0.248 (as [Ca] ≤0.248 mg/dL and [P] ≤0.248 mg/dL, respectively) was 182 patients (47.3%). The distribution of patients with Ca or P levels ≤0.248 (as [Ca] ≤0.248 mg/dL and [P] ≤0.248 mg/dL, respectively) was 182 patients (47.3%).

Conclusions: In this study, we found that low serum vitamin D levels were associated with a high risk of mortality in patients with hemodialysis.

SA-PO264
Circadian Rhythm of Plasma Magnesium in Patients with CKD Stage 3-4 and Healthy Controls
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Background: Chronic kidney disease (CKD) is associated with vascular calcification leading to cardiovascular morbidity and mortality. Decreasing levels of plasma magnesium (Mg) are associated with increased risk of cardiovascular disease in patients with CKD, which might be amendable to Mg supplementation. Several biochemical parameters follow a circadian rhythm, which may affect the way these parameters should be measured and may be of importance for their physiological effects and interaction. The aim of this study was to identify the circadian rhythm of plasma Mg in CKD patients.

Methods: This was an investigator-initiated observational clinical trial. Subjects included were patients with CKD 3-4 without diabetes (n=10 (9 males)) and healthy controls (n=10 (5 males)). Venous blood and urine samples were collected non-fasting at 8 a.m. and every third hour during a 24-hour admission with the final collection in fasting state at 8 a.m. the following day.

Results: The baseline mean (±SD) eGFR was 27 ± 8 mL/min/1.73m² in patients with CKD and 105 ± 10 mL/min/1.73m² in healthy controls. The overall mean (±SD) plasma Mg in patients with CKD was not significantly higher than in healthy controls (1.97 ± 0.04 mmol/L versus 1.90 ± 0.07 mmol/L; p = 0.220). Cosinor analysis revealed no significant diurnal variation in plasma Mg in either subjects with CKD (p = 0.23) or healthy controls (p = 0.29). There was no significant difference between plasma Mg levels (mean ± SD) in fasting and non-fasting state in patients with CKD (fasting 0.90 ± 0.13 mmol/L and non-fasting 0.90 ± 0.06 mmol/L; p = 0.907) or healthy controls (fasting 0.84 ± 0.07 mmol/L and non-fasting 0.83 ± 0.09 mmol/L; p = 0.598).

Conclusions: Plasma Mg exhibits no diurnal variation and is not affected by fasting in patients with CKD 3-4. Evaluation of plasma magnesium levels in patients with CKD 3-4 requires no special precaution concerning the time of the day for sampling or whether the patient is in fasting state.

SA-PO265
Chemical Plausibility of the Tradeoff-in-the-Nephron Hypothesis
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Methods: Data were obtained from 500 patients with CKD (mean eGFR 29.5) and 28 controls (mean eGFR 85.9). To estimate concentrations in the CDN, we assumed fractional delivery (k) of filtrate = 0.2 in controls and 0.35 in CKD. Ca delivery = 0.1(gFR)[Ca ++ ] CDN/0.248 mg/dL (plasma ultrafilterable Ca); P delivery = urinary P excretion (Ep); and [HPO 4 ] CDN = pKa·pH + m, where m is the equilibrium constant for HPO 4 0 = 0.248 mmol/L.

Results: In CKD, regressions of [PTH] on [HPO 4 ] CDN and [1/(Ca ++ ) CDN] were significant for each patient group. [PTH] appears to be mediated by [Ca ++ ] CDN. The effect of [HPO 4 ] CDN on [PTH] appears to be mediated by [Ca ++ ] CDN.

Conclusions: SA-PO264

SA-PO266
The Importance of Biologically Active Vitamin D for Mineralization of Osteocytes After Parathyroidectomy for Renal Hyperparathyroidism
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Background: Hypomineralized matrix is a factor determining bone mineral density. Increased perilacunar hypomineralized bone area is caused by reduced mineralization by osteocytes. The importance of vitamin D in the mineralization by osteocytes was investigated in hemodialysis patients who underwent total parathyroidectomiy (PTX) with immediate autotransplantation of diffuse hyperplastic parathyroid tissue. No previous reports on this subject exist.

Methods: The study was conducted in 19 patients with renal hyperparathyroidism treated with PTX. In 15 patients, the serum calcium levels were maintained by subsequent administration of alfacalcidol (2.0 µg/day), intravenous calcium gluconate, and oral calcitriol for four weeks after PTX (Group I). This was followed in a subset of four patients in Group I by a reduced dose of 0.5 µg/day until one year following PTX; this was defined as Group II. In the remaining four patients, who were not in Group I, the serum calcium levels were maintained without subsequent administration of alfacalcidol (Group III).

Results: Transiliac bone biopsy specimens were obtained in all groups before and 3 or 4 weeks after PTX to evaluate the change of hypomineralized bone area. In addition, patients from Group II underwent a third bone biopsy one year following PTX. And we did Raman measurements from the same sections as those used for histology.

Conclusions: The maintenance of a proper dose of vitamin D is necessary for mineralization by osteocytes, which is important to increase bone mineral density after PTX for renal hyperparathyroidism. Mineral maturity and crystallinity are not expected within 3-4 weeks after PTX.

SA-PO267
Abstract Withdrawn
SA-PO268
Vitamin D Status in CKD Patients Living in the Tropics: A Cohort in Thailand
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Background: Vitamin D deficiency is a key factor of secondary hyperparathyroidism in CKD and is recommended to be evaluated in the cases found persistently elevated PTH levels. Data survey during the last decade showed vitamin D deficiency among the general Thais for 60-70% compared to 60-70% in the Eastern Asia. Data of prevalent vitamin D deficiency in Thailand is scarce, but is seriously concerned in clinical practice to balance between standard of care and healthcare budget restraint. Therefore, the study is done to evaluate vitamin D status and predictors of vitamin D deficiency in CKD patients living in Thailand.

Methods: 752 Stable CKD patients were included from CKD clinic and the outpatient section at Siriraj hospital. CKD is diagnosed based on KDIGO 2012 definition and GFR was defined as 30-60 mL/min/1.73m². Data survey during the last decade showed vitamin D deficiency among the general Thais for 60-70% compared to 60-70% in the Eastern Asia. Data of prevalent vitamin D deficiency in Thailand is scarce, but is seriously concerned in clinical practice to balance between standard of care and healthcare budget restraint. Therefore, the study is done to evaluate vitamin D status and predictors of vitamin D deficiency in CKD patients living in Thailand.

Conclusions: Data of prevalent vitamin D deficiency in Thailand is scarce, but is seriously concerned in clinical practice to balance between standard of care and healthcare budget restraint. Therefore, the study is done to evaluate vitamin D status and predictors of vitamin D deficiency in CKD patients living in Thailand.
Results: Mean age was 64.4±13.8 years old, 48% were female and 60.3% had diabetes mellitus. They were categorized to stage 1-2, 3a, 3b, 4 and 5 for 22.4, 18.7, 23.8, 24.1, and 11.0%, respectively. Prevalence of vitamin D deficiency (<20 ng/mL) and severe vitamin D deficiency (<10 ng/mL) were shown in Figure 1. Predicting factors of vitamin D deficiency in Thai CKD patients were stage 4-5 CKD 9.06 (3.64-22.58), albuminuria >1.500 mg/dL 10.62 (3.97-28.41), calcium +9.0 mg/dL 3.99 (1.54-9.45), PTH >100 pg/mL 3.82 (1.54-9.49), diabetes 3.35 (1.33-8.46), and female 2.81 (1.19-6.62).

Conclusions: Vitamin D deficiency is highly prevalent in Thai stage 4-5 CKD patients. Considerations on GFR combined with serum calcium and PTH profiles and clinical characteristics would empower cost-effectiveness of 25-hydroxyvitamin D measurement in CKD population living in the tropic area.

Figure 1 Prevalence of vitamin D deficiency in Thai stage 1-5 CKD patients

SA-PO269
1.25(OH)D Status in ESKD: Role of 25(OH)D and Residual Renal Function
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Background: Recent insights into vitamin D regulation suggest that CKD is a state of stagnant vitamin D metabolism characterized by reduced 1.25(OH)D production (mediated by CYP27B1) and catabolism. The present study aimed to clarify whether this is caused by insufficient delivery of substrate or low nephron mass. As a secondary aim we investigated seasonal variation and long term trends of vitamin D levels in patients with ESKD.

Methods: We analyzed serum levels of 1,25(OH)D3 (LC MS/MS), 25(OH)D (RIA), along with other parameters of mineral metabolism (including PTH, FGF23, sclerostin), markers of inflammation in 518 adult patients (age 54.7 ± 12.8 yrs, males 60.6%) with ESKD between April 23, 2006 and December 21, 2013. Data on residual renal function (RRF) were available in 330 patients: 115 patients were anuric (24h urine output < 100 ml) and 21 patients were anephric.

Results: Median 25(OH)D and 1.25(OH)D3 levels in the overall cohort were 35.9 [24.0 – 48.6] µg/L and 26.8 [18.2 – 36.9] ng/L, respectively. 25(OH)D levels showed seasonal variation and increased by 16% along the study period (2006-2013), most probably suggested a lower degradation of 1,25(OH)2D3 by CYP24A1 in HSF and NSF. Bone and Mineral Metabolism: Calcium, Magnesium, Kidney Stones

Conclusions: The underlying pathophysiological mechanisms for hypercalciuria as such as increased intestinal calcium absorption, reduced renal tubular reabsorption and increased bone resorption are influenced by calciotropic hormones. The levels of 1,25(OH)D3 exceed the values of controls in some but not all hypercalciureic stone formers and the expression of vitamin D receptor (VDR) remains controversial in human studies. We aimed to evaluate the serum 1,25(OH)D levels and the expression of VDR and the regulatory enzymes CYP27B1 (1α-hydroxylase) and CYP24A1, responsible for vitamin D degradation, in hypercalciuric stone formers (HSF) and compare to normocalciuric stone formers (NSF) and healthy subjects (HS).

Methods: Blood samples, 24-hour urine collection and a 3-day dietary record were obtained from 30 participants of each of the groups. The expression of VDR, CYP27B1 and CYP24A1 in monocytes were measured by flow cytometry.

Results: HSF presented a significantly higher mean urinary volume, sodium, magnesium, oxalate, uric acid, and phosphorus than NSF and HS. Mean daily calcium intake was lower in HSF versus NSF and HS (442±41 vs 594±42 and 559±41 mg, respectively, p=0.027). Ionized calcium was significantly lower in HSF than NSF (1.29±0.0 vs 1.31±0.0 mmol/L, p<0.001). Serum 1.25(OH)D3 was significantly higher, even within normal ranges, in both HSF and NSF versus HS (22.5±1.2; 22.2±1.2 vs 17.4±1.2 µg/mL, p<0.007, respectively) but serum 25(OH)D, PTH, α-Klotho and plasma FGF-23 did not differ between groups. The VDR expression was higher in both HSF and NSF versus HS (80.8±3.2; 78.7±3.3 vs 68.6±3.2%, p=0.023). Although CYP27B1 and CYP24A1 expressions were similar among all groups, the ratio of 1.25(OH)D3/CYP24A1 was higher in HSF and NSF than in HS (1.43±0.25 vs 0.56±0.10 than 0.34±0.06, p<0.000).

Conclusions: Stone-formers, regardless of urinary calcium levels, had higher VDR expression and 1.25(OH)D3 levels compared to HS. Higher 1,25(OH)D3/CYP24A1 ratio suggested a lower degradation of 1,25(OH)D3 by CYP24A1 in HSF and NSF.

SA-PO270
Expression of Vitamin D Receptor, CYP27B1 and CYP24A1 Hydroxylases, and 1,25-Dihydroxyvitamin D3 Levels In Stone Formers

Background: The underlying pathophysiological mechanisms for hypercalciuria such as increased intestinal calcium absorption, reduced renal tubular reabsorption and increased bone resorption are influenced by calciotropic hormones. The levels of 1,25(OH)D3 exceed the values of controls in some but not all hypercalciureic stone formers and the expression of vitamin D receptor (VDR) remains controversial in human studies. We aimed to evaluate the serum 1,25(OH)D levels and the expression of VDR and the regulatory enzymes CYP27B1 (1α-hydroxylase) and CYP24A1, responsible for vitamin D degradation, in hypercalciuric stone formers (HSF) and compare to normocalciuric stone formers (NSF) and healthy subjects (HS).

Methods: Blood samples, 24-hour urine collection and a 3-day dietary record were obtained from 30 participants of each of the groups. The expression of VDR, CYP27B1 and CYP24A1 in monocytes were measured by flow cytometry.

Results: HSF presented a significantly higher mean urinary volume, sodium, magnesium, oxalate, uric acid, and phosphorus than NSF and HS. Mean daily calcium intake was lower in HSF versus NSF and HS (442±41 vs 594±42 and 559±41 mg, respectively, p=0.027). Ionized calcium was significantly lower in HSF than NSF (1.29±0.0 vs 1.31±0.0 mmol/L, p<0.001). Serum 1.25(OH)D3 was significantly higher, even within normal ranges, in both HSF and NSF versus HS (22.5±1.2; 22.2±1.2 vs 17.4±1.2 µg/mL, p<0.007, respectively) but serum 25(OH)D, PTH, α-Klotho and plasma FGF-23 did not differ between groups. The VDR expression was higher in both HSF and NSF versus HS (80.8±3.2; 78.7±3.3 vs 68.6±3.2%, p=0.023). Although CYP27B1 and CYP24A1 expressions were similar among all groups, the ratio of 1.25(OH)D3/CYP24A1 was higher in HSF and NSF than in HS (1.43±0.25 vs 0.56±0.10 than 0.34±0.06, p<0.000).

Conclusions: Stone-formers, regardless of urinary calcium levels, had higher VDR expression and 1.25(OH)D3 levels compared to HS. Higher 1,25(OH)D3/CYP24A1 ratio suggested a lower degradation of 1,25(OH)D3 by CYP24A1 in HSF and NSF.
SA-PO272

Plasma Oxalate as a Predictor of Kidney Function Decline in Primary Hyperoxaluria

Background: This retrospective analysis investigated plasma oxalate (POx) as a potential predictor of end stage kidney disease (ESKD) among primary hyperoxaluria (PH) patients across varying stages of CKD.

Methods: PH patients with type 1, 2, and 3, age 2 or older, with estimated glomerular filtration rate (eGFR) and POx measures available during follow-up after PH diagnosis and prior to ESKD were identified in the RKSC PH Registry. Urinary oxalate (UOx) did not change across CKD stages 1-3, but POx increased with falling eGFR. Thus to maximize data for analysis of POx by eGFR stage, patients were further subdivided into CKD subgroups (stages 1, 2, 3a, and 3b) such that a patient started in a given CKD stage subgroup on their first eGFR observed in that range, while also continuing to remain in any prior groups. ESKD was defined as an eGFR ≤ 15 ml/min per 1.73 m² or start of dialysis or renal transplantation. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for risk of ESKD were estimated using the Cox proportional hazards model with a time-dependent covariate.

Results: There were 118 patients in the CKD1 group (9 ESKD events during follow-up), 135 in CKD 2 (29 events), 72 in CKD3a (34 events); and 45 patients in CKD 3b (31 events). During follow-up, POx Q4 was a significant predictor of ESKD compared to Q1 across CKD2 (HR 14.2, 95% CI 1.8-115), 3a (HR 13.7, 95% CI 3.0-62) and 3b stages (HR 5.2, 95% CI 1.1-25). P=0.05 for all. Within each POx quartile, ESKD rate was higher for more severe CKD stages, and within each CKD stage, ESKD rate was higher in Q4 compared to Q1-Q3, respectively.

Conclusions: Among patients with PH, higher POx concentration was a risk factor for ESKD, particularly in advanced CKD stages.

Funding: NIDDK Support, Commercial Support - OxThera, Private Foundation Support

SA-PO273

Proton Pump Inhibitors and Risk of Incident Nephrolithiasis: A Retrospective Cohort Study
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Background: Proton pump inhibitors (PPIs) have come under scrutiny given evidence of their association with various conditions including chronic kidney disease and fracture. Biochemically, the effect of PPIs and nephrolithiasis is unclear. PPIs decrease calcium gut absorption and decrease urine calcium and oxalate, which may be protective. However PPIs also decrease urine citrate which may increase stone formation. We studied the association of incident PPI use with nephrolithiasis in a large retrospective cohort.

Methods: Setting: Data were obtained from a large patient cohort from the Veteran’s Health Administration (VHA). Data including demographics, encounters, comorbidities, medications, and laboratory values were obtained through querying the VHA system. Patients with prior nephrolithiasis or PPI usage were excluded. Matched Cohort: A cohort was developed with 1:1 fixed ratio matching for PPI users and non-users based on a propensity score developed from multivariate logistic regression of the patient’s covariates. Kaplan-Meier survival analysis was used. Adjusted analysis was conducted with Cox proportional hazards model from a robust set of covariates, including demographics, comorbidities, medications, and healthcare system interaction.

Results: Of 1,065,962 patients considered, 422,153 patients met eligibility criteria. 81,654 patients had exposure to PPIs at some point during observation. Of the 81,654 PPI users, 92% were matched based on propensity score to a non-PPI user. Over 660,426 patient-years of observation, PPI-exposed individuals developed nephrolithiasis at a higher rate compared to PPI-unexposed (62.3 versus 43.1 per 10,000 patient-years, relative risk ratio 1.43 (95% CI 1.33-1.54)). Under the Cox proportional hazards model PPI usage carried a hazard ratio of 1.32 (95% CI 1.23 - 1.42).

Conclusions: In our large retrospective cohort analysis, incident PPI usage was associated with a moderately increased risk of incident nephrolithiasis.

Funding: Veterans Affairs Support

SA-PO274

Nephropathic Cystinosis: A Distinct Model of CKD-MBD
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Background: Cystinosis is a rare autosomal recessive lysosomal storage disorder. Nephropathic cystinosis (NC) presents with Fanconi syndrome and CKD. Persistent phosphate wasting is a prominent feature; however, its impact on CKD-MBD has not been described. Thus, we compare CKD-MBD in NC (n=53) vs. non-NC (n=97).

Methods: eGFR, Ca, P, PTH, 1,25DFG, FGF23, and TRP were assessed. c-Terminal FGF23 was measured by ELISA (Quadia), S-PTH and 1,25DFG by immunoassay. Subjects were grouped according to CKD stage: CKD 4 and 5 were analyzed together. Dialysis pts. were excluded. All NC patients were treated with cyssteanine, phosphate supplementation, and 1,25DFG, non-NC with 1,25DFG and binders as needed. Statistical analysis included Spearman correlations and the Mann-Whitney U test.

Results: Age and eGFR were similar between the groups (Table). In NC across all CKD stages, TRP and FGF23 were lower, and 1,25DFG higher (Figure). PTH and S-Po4 were lower in NC stage 3. In NC, FGF23 was inversely associated with eGFR (r=−0.30, p<0.05) and positively associated with S-Po4 (r=0.53, p<0.001). All hypophosphatemic NC subjects had normal FGF23 levels, independent of eGFR.

Conclusions: NC is characterized by a distinct CKD-MBD, with lower FGF23 and higher 1,25DFG.

Funding: NIDDK Support, Other NIH Support - NIDCR

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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SA-PO275

Prevalence of Kidney Stones in the United States over the Past 10 Years

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Background: Kidney stones (KS) are common in the US and cost billions of dollars on treatment. The overall prevalence of kidney stones rose from 3.2% in 1980 to 10.1% in 2014. We examined the prevalence trends of KS in subgroups of age, sex and race in the US and identify laboratory factors associated with a history of KS using National Health and Nutrition Examination Survey (NHANES) data.

Methods: We conducted a cross-sectional study among 28,209 US adults aged ≥10 years old in the NHANES from 2007 to 2016. We calculated the percent prevalence of a self-reported history of KS by using weights and standardized to the 2010 US Census population using age adjustment. We also analyzed relevant laboratory values and compared them according to history of KS.

Results: The prevalence of KS decreased from 8.8% in 2007-2008 to 8.6% in 2009-2010 and 7.2% in 2011-2012 but then increased to 9.0% in 2013-2014 and 10.2% in 2015-2016. Prevalence of KS was highest in 2015-2016 in every age range except in women aged 20-29 years. Among different races, non-Hispanic whites had the highest prevalence of KS at 12.1% for the last cycle of 2015-2016 and the trend was increasing from 2011-2016. Non-Hispanic Asians had the lowest prevalence of KS at 4.5% for the last cycle. The prevalence of KS among non-Hispanic blacks increased over the last 3 cycles from 4.2% in 2011-2012 to 5.0% in 2013-2014 and 5.7% in 2015-2016. We presented relevant laboratory values in figure 1.

Conclusions: Overall prevalence of KS has been increasing for the last 6 years but this may be random variability as the prevalence decreased then increased since 2007-2008. Men had higher prevalence of KS and Asians had the lowest prevalence. Stone formers had lower urine flow rate, eGFR, bicarbonate, phosphate, serum estrogen and testosterone while they had higher serum osmolality, creatinine, chloride and uric acid compared with non-stone formers.

SA-PO277

NOSTONE Trial: Randomized Double-Blind Placebo-Controlled Trial Assessing the Efficacy of Standard and Low-Dose Hydrochlorothiazide Treatment in the Recurrence Prevention of Calcareous Nephrolithiasis

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Background: Nephrolithiasis is a global healthcare problem with a current lifetime risk of up to 18.8% in men and 9.4% in women. Without specific treatment, 5- and 20-year recurrence rates are 40% and 75%, respectively. Given the high cost of medical treatments and surgical interventions as well as the morbidity related to symptomatic stone disease, medical prophylaxis for stone recurrence is an attractive approach. Efficacy of therapies for kidney stone prevention was tested in 11 trials in the past. However, all these trials had major methodological deficiencies. Nowadays, thiazides are widely used in the treatment of recurrent nephrolithiasis and arterial hypertension, but at significantly lower doses. In the case of recurrent nephrolithiasis, however, this practice is not supported by randomized evidence. Thus, evidence for benefits and harms of thiazides in the prevention of kidney stones remains unclear.

Methods: NOSTONE is a multicenter, randomized, placebo-controlled, double-blind, parallel-group trial with the purpose to assess the dose-response relationship for three different dosages of hydrochlorothiazide (placebo, 12.5mg, 25.0mg, 50.0mg) in kidney stone prevention. The primary outcome is the incidence of stone recurrence (a composite of symptomatic or radiologic recurrence) at 3 years, a low-dose CT will be performed at the beginning and the end of the trial. A total of 416 patients from 12 hospitals throughout Switzerland will be included in the study.

Results: NOSTONE received all necessary approvals by the end of February 2017. Recruitment started in Bern on the 9th of March 2017, all study sites are operative since June 30th 2017. As of May 30th 2019, 270 patients were randomized in the trial (regular update: www.nostone.ch). The end of recruitment is foreseen for August 2019. Baseline data concerning the study population will be available after the end of recruitment.

Conclusions: The NOSTONE study will provide critical information to physicians for the treatment of kidney stones. The impact of the results of this study will affect many patients currently treated with hydrochlorothiazide for the prevention of recurrent nephrolithiasis.

Funding: Government Support - Non-U.S.

SA-PO276

Prevalence of Kidney Stones in Patients with Enteric Disorders

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Background: Hyperoxaluria (HOx) is a serious metabolic disorder and a risk factor for kidney stone disease (KSD) and chronic kidney disease (CKD). Enteric HOx (EH) develops as a complication of increased intestinal oxalate absorption due to an underlying GI disorder (e.g., bariatric surgery, inflammatory bowel disease (IBD)). The prevalence of EH is not well described, due in part to infrequent testing for risk factors of KSD and the lack of a specific diagnostic code for EH. We sought to estimate the prevalence of EH and the distribution of underlying etiologic causes.

Methods: We developed a state-transition Markov model to estimate the current US prevalence of malabsorptive enteric disorders and the total number of stone-forming patients using data from the published literature and from a four-year claims analysis of a state history of KS by using weights and standardized to the 2010 US Census population using age adjustment. We also analyzed relevant laboratory values and compared them according to history of KS.

Results: The 2019 prevalence was determined to be 249,048 and the most frequent malabsorptive enteric conditions were Roux-en-Y gastric bypass at 62% and inflammatory bowel disease at 20%.

Conclusions: EH is associated with serious consequences, yet its prevalence is poorly understood. Based on this analysis of data across various sources, there are approximately 250,000 EH patients with kidney stone disease in the US, including those who develop CKD. Additional epidemiological research and a specific diagnostic code could further improve efforts to understand and improve the recognition of EH.

Funding: Commercial Support - Allena Pharmaceuticals

SA-PO278

A Phase 3, Randomized, Placebo-Controlled Trial of Reloxaliase in Enteric Hyperoxaluria (URIROX-1): Clinical Characteristics and Burden of Illness

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Background: Hyperoxaluria is a key risk factor for kidney stones (KS), and may lead to chronic kidney disease (CKD). Enteric hyperoxaluria (EH) results from excess gastrointestinal oxalate (Ox) absorption due to fat malabsorption. There are no approved therapies for EH; current recommendations are to reduce dietary Ox and increase calcium and fluid intake, calcium/citrate supplements, and thiazides. This phase 3 trial investigating reloxaliase, a first-in-class oral enzyme drug therapy that specifically degrades Ox within the intestinal tract, for the treatment of EH (URIROX-1) exceeded the primary outcome of the phase 2 EH.

Methods: Adults with malabsorptive conditions, UOX ≥50 mg/d and eGFR >30 ml/ min/1.73 m² were randomized to receive reloxaliase 7,500 U or placebo orally with food 3-5x/d for 28 d. The primary endpoint was percent change from baseline in 24-hour UOx collections at 1-4 d, assessed from 24-hour urine collections obtained over 4 weeks. Clinical and 24-hour UOx data were summarized overall and by enteric condition.

Results: There were 88 subjects with available data, mean age 59 years, 48% female. The two most common enteric conditions were bariatric surgery (65%) and IBD (18%).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Recent kidney stones were reported by 70% (23% having more than 5 events in the past 5 years) while 23% had no attack in the last 5 years. Mean baseline UOx was 91.5 mg/d, while 31% had UOx at 100 mg/d. Patients with short bowel syndrome (SBS) had highest 24-hr UOX, whereas more patients with IBD had recurrent stones.

**Conclusions:** Patients with EH enrolled in the URIBOX-1 trial from nephrologists and urologists were evaluated for specific metabolic abnormalities associated with recurrent kidney stones, regardless of the type of underlying enteric condition. These clinical characteristics illustrate the limitations of existing therapeutic approaches, and the opportunity for a new therapeutic approach to reduce oxalate burden on the kidneys for patients with EH.

**Funding:** Commercial Support - Alpina Pharmaceuticals, Inc.

### SA-P2079

**Mediterranean Diet Adherence and the Risk of Kidney Stones**

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**Background:** Diet plays an important role in kidney stone formation. Several individual nutrients and dietary patterns have been associated with increased or decreased risk of kidney stones, but there is limited evidence about the role of healthful dietary patterns. The objective of this study is to examine prospectively the association of adherence to the Mediterranean diet and the risk of incident kidney stones.

**Methods:** We conducted a prospective study using three different cohorts: the Health Professionals Follow-up Study (n=51,529 men), the Nurses’ Health Study I (n=121,700 women) and the Nurses’ Health Study II (n=116,430 women). We assessed diet every four years using a food frequency questionnaire and calculated the adherence to a Mediterranean diet using the alternate Mediterranean Diet Score (aMED). The score considers: a high ratio of monounsaturated to saturated fatty acids; high intakes of: fruit, vegetables, nuts, legumes and whole grains; moderate alcohol consumption; and low intakes of red and processed meats, while high intakes of red meat, refined grains and sugar-sweetened beverages are scored as low adherence.

**Results:** During more than 3 million person-years, 6,576 cases of incident kidney stones were identified. Participants with the highest aMED score (8-9) had lower BMI, lower percentage of hypertension, lower caffeine intake and higher intakes of supplements of vitamin C, calcium and total vitamin D. For participants in the highest aMED score category compared with participants in the lowest category, the risk of developing a kidney stone was between 20 and 43% lower in all the cohorts. The adjusted HR (95% CI) for the highest category of the aMED score was 0.57 (0.38, 0.85) for HPFS (p-trend=0.001), 0.71 (0.45, 1.10) for NHS I (p-trend=0.001) and 0.80 (0.45, 1.10) for NHS II (p-trend=0.003). When examining components of the score, the high intake of fruits and whole grains, and moderate alcohol consumption, were associated with lower risk of kidney stone formation in all cohorts. There was no significant effect of obesity, while high intakes of nuts and legumes were associated with a lower risk in men, but not in women.

**Conclusions:** Adherence to a Mediterranean diet is associated with a lower risk of incident kidney stones.

**Funding:** Other NIH Support - DK099410, DK9147, CA186107, CA176726, CA167552

### SA-P2080

**Effect of Hydroxycitrate (HCA) on Urinary Risk Factors for Calcium-Based Kidney Stones**

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**Background:** Potassium citrate is a mainstay of treatment to prevent calcium stones. However, it can increase urine pH and calcium phosphate (CaP) supersaturation (SS). HCA, extracted from garcinia cambogia, is a potent inhibitor of calcium oxalate (CaOx) crystal growth in vitro and may not yield HCO3. It is “generally regarded as safe” and available over the counter. We studied how HCA supplementation affects urine chemistry.

**Methods:** We enrolled 2 groups: calcium stone formers (SF) and non-stone forming (NSF) controls. Thiazides and potassium citrate were held for 2 weeks prior to study. Participants received a self-selected diet for 2 days and performed 24-hour urine collection on day 2. HCA 300 mg 3 times daily was taken orally for 7 days, and 24-hour urine was collected on day 7 while the initial, self-selected diet remained.

**Results:** 13 people, aged 26-76 years, participated. There were 6 SF and 7 NSF, combined into 1 group of 13. Patients replicated their diets well, as urine Na, volume, and creatinine were similar (data not shown). Results presented in Table. HCA increased urinary K and citrate (P<0.001 and 0.003 respectively). Mean urinary pH was unchanged (6.25 to 6.47, P=0.14), while mean urinary NH4 fell (P=0.017). 24-hour excretion of Ca and Ox did not change. SS of CaOx and CaP did not change. Serum values did not change: baseline HC03 and K were 23.5 ± 2.5 and 4.0 ± 0.2 mmol/L and 23.7 ± 1.8 and 4.4 ± 0.6 mmol/L after HCA.

**Conclusions:** Urine K concentration rose by 29 meq/day compared with an expected increase based on the label of 14 meq, suggesting the label was not accurate. Increased citrate and lower NH4 suggest some K is in the form of alkali salts or that some HCA is metabolized to bicarbonate. There was no change in CaOx or CaP SS. The lack of effect on SS may not reflect the potential ability of HCA to inhibit calcium crystallization, as it inhibits Ca crystal growth in vitro in supersaturated media.

**Funding:** Commercial Support - Lithiologic Corp

### SA-P2081

**Oxalate Degradation Rates of Oxalobacter formigenes**

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**Background:** Kidney stones commonly affect US adults. In recent years, there has been increasing interest in the human anaerobic colonic bacterium Oxalobacter formigenes because of its ability to metabolize oxalate, and its potential to protect against calcium oxalate kidney stones. Currently, there are two known groups of O. formigenes (Group 1 and Group 2) with one or two isolates from each group characterized. In our experiments, we aimed to isolate O. formigenes from subjects with primary hyperoxaluria (PH), enteric hyperoxaluria (EH) and healthy controls (HC) to compare their metabolic activities. Understanding these differences will help expand our knowledge about this important organism and its effect on oxalate homeostasis in humans.

**Methods:** We collected fecal samples from 37 patients via clinical trials at New York University Langone Medical Center and Mayo Clinic with PH, EH and HC. We cultured fecal samples in 25mM oxalate-rich selective media, then isolated O. formigenes by picking characteristic colonies from calcium oxalate agar. We identified and grouped isolates using PCR and Sanger sequencing of the oxc gene. We then tested their oxalate consumption via Oxalate Degradation Assay to compute mean oxalate degradation rates (ODR) for each group of isolates.

**Results:** We isolated 25 O. formigenes colonies from 14 subjects, with all isolates belonging to either HC (n=11) or PH (n=14) patients, and none from EH patients. Based on oxc sequences, we identified Group 1 (n=17) and Group 2 (n=5) strains, and potentially a new taxonomic group Group 3 (n=5). We were able to regroup 13 (76%) of 17 (1% (20% of Group 3 isolates) of 3 Group 1 isolates, 83% of Group 2 strains, respectively. Of the 25 strains, 11 were identified as Group 1, while HC had a mix of all three groups. Mean ODR was significantly higher in Group 1 vs Group 2 isolates (8.5 ± 3.3 vs 2.8 ± 1.9 micromole/hr, p=0.02). Group 3 isolates had intermediate ODR (5.7 ± 3.1 values). As expected, ODR was higher Group 1 isolates than Group 2 isolates, and both were higher than ODCX13 (11±1.2).

**Mean ODR between PH, EH and HC did not differ significantly.

**Conclusions:** We were able to isolate and characterize 25 colonies of O. formigenes, including a potential new group of O. formigenes. Group 1 strains appear to be more metabolically active in vitro, and were exclusively present in PH patients.

**Funding:** Private Foundation Support

### SA-P2082

**Suboptimal Screening of Primary Hyperparathyroidism Among Veterans with Urinary Stone Disease**

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**Background:** The American Association of Endocrine Surgeons recommends parathyroidectomy in stone formers with primary hyperparathyroidism to prevent recurrent stone formation, and recently recommended the initial, self-order, rates of screening for primary hyperparathyroidism among stone formers remain unknown. To address this knowledge gap, we determined the rate of parathyroid hormone (PTH) testing in a national cohort of stone formers with hypercalcemia in the Veterans Health Administration (VHA).

**Methods:** We identified stone formers as Veterans with one or more inpatient or two or more outpatient encounters for urinary stone disease (USD), or one or more stone procedures between 2008 and 2013 using the national VHA database. We excluded patients who were previously screened for hyperparathyroidism and those with an eGFR<45. We then identified and grouped patients by the highest serum calcium measurement within a 6 month period before and after initial
stone diagnosis. We then identified associated serum PTH concentrations within 9 months of initial diagnosis.

Results: We identified 140,181 stone formers who met criteria of whom 94.7% (132,787 individuals) were men. Within this cohort, 85% (119,197 individuals) had a similar baseline values of clinical data were screened out (Ratio=1:2). Chi-square test was applied. For renal indications including kidney stones and renal masses. We examined variation in mean effective dose by facility and variation in the technical parameters used for these examinations.

Results: We identified 90,459 urinary stone CT exams, 12,489 renal mass CT exams and 45,391 CT urograms. We found radiation dose varied with a threefold range in mean effective dose for urinary stone exams (49.1-13.6 mSv) and renal mass exams (12.7-41.2 mSv) and a sixfold range in mean effective dose for urograms (8.4-46.0 mSv). Adjusting for patient characteristics including size, and machine, make and model did not change these results and substantial variation in dose persisted.

Conclusions: Radiation dose varied substantially for urinary stone CT exams, renal mass CT exams and CT urograms, and these differences were not attenuated by adjusting for patient or machine factors. Doses could be substantially reduced if facilities adopted the protocols of the facilities where low dose protocols are used. This study highlights the need to adopt lower radiation dose protocols and standardize technical parameters to prevent patients from receiving unnecessarily high doses of ionizing radiation in the assessment of renal disease.

Funding: Private Foundation Support

SA-PO283

Variation in Radiation Dose of Computed Tomography Examinations Used for Renal Imaging
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Background: Computed tomography (CT) is the most commonly used imaging modality for the assessment of renal related problems (e.g. kidney stones or masses.) Patients can be exposed to higher than needed doses of ionizing radiation, a known carcinogen. The objective of this study is to examine current practice and quantify variation in radiation doses for urinary stone, renal mass, and urogram CT as a first step toward informing future quality-improvement efforts to reduce patient exposure to ionizing radiation.

Methods: We identified computed tomography examinations within the University of California San Francisco International Radiation Dose Registry which prospectively assembled CT examinations from 152 institutions in 6 countries between 2015 and 2018 for renal indications including kidney stones and renal masses. We examined variation in mean effective dose by facility and variation in the technical parameters used for these examinations.

Results: We identified 90,459 urinary stone CT exams, 12,489 renal mass CT exams and 45,391 CT urograms. We found radiation dose varied with a threefold range in mean effective dose for urinary stone exams (49.1-13.6 mSv) and renal mass exams (12.7-41.2 mSv) and a sixfold range in mean effective dose for urograms (8.4-46.0 mSv). Adjusting for patient characteristics including size, and machine, make and model did not change these results and substantial variation in dose persisted.

Conclusions: Radiation dose varied substantially for urinary stone CT exams, renal mass CT exams and CT urograms, and these differences were not attenuated by adjusting for patient or machine factors. Doses could be substantially reduced if facilities adopted the protocols of the facilities where low dose protocols are used. This study highlights the need to adopt lower radiation dose protocols and standardize technical parameters to prevent patients from receiving unnecessarily high doses of ionizing radiation in the assessment of renal disease.

Funding: Private Foundation Support

SA-PO284

The Study on Value of Bone Scan Technology in Early Diagnosis of Calciphylaxis
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Background: Current diagnostic criteria for calciphylaxis are based on ischemic necrosis and ulceration of skin and soft tissue. Nevertheless, once clinical diagnosis is confirmed, the disease progresses to the end stage with terrible prognosis. This study is aimed to investigate the early diagnostic role of bone scan technology in calciphylaxis patients undergoing dialysis, considering that this technology can reflect abnormal distribution of hydroxyapatite in extra-ossous tissue.

Methods: Analyzed clinical data of 15 hemodialysis patients with calciphylaxis diagnosed by skin biopsy who had bone scan results in Zhong Da Hospital Southeast University from Oct. 2017 to Dec. 2018. Meanwhile, non-calciphylaxis patients with the similar baseline values of clinical data were screened out (Ratio=1:2). Chi-square test was used to analyze the difference in positive rates of bone scan between two groups.

Results: General clinical data, including age, gender, dialysis time, history of diabetes and secondary hyperparathyroidism (SHPT), had no significant difference between two groups (P>0.05). In case group, 11 patients had positive result of bone scans and the positive rate was 73.3%. The positive results in calciphylaxis patients were mainly the increase in uptake or delay of clearance of radiotracer by soft tissue and the radiotracer under skin was linear or diffuse distributed. In control group, only 5 cases were positive with the positive rate about 16.7%, which was significantly lower than the positive rate in the above group. The bone scan results were confirmed by skin biopsy.

Conclusions: Bone scan has high sensitivity and specificity in the diagnosis of calciphylaxis with a wide range of uptake for radiotracers by soft tissue, it has important application value in early diagnosis of calciphylaxis.

Funding: Veterans Affairs Support, Private Foundation Support

SA-PO285

The Specificity of Histology in Calciphylaxis
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Background: Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a devastating skin lesion that occurs most commonly in end-stage renal disease (ESRD). We previously showed that many of the histologic findings considered diagnostic of CUA can be also seen in normal skin from amputations in unaffected ESRD patients, raising questions about their specificity. To address this with more appropriate control tissue, we compared affected and unaffected skin from patients with a clinical diagnosis of CUA.

Methods: Hospitalized patients were recruited by the consulting dermatologist, who then performed skin biopsies of the lesion and of normal skin on the contralateral extremity. Skin tissue was obtained at autopsy in 2 cases. Hematoxylin and eosin and von Kossa stains were examined on each specimen. Histologic findings were evaluated by a single pathologist and included small vessel calcification, small vessel thrombosis, intimal hyperplasia, extravascular calcification.

Results: Paired skin samples were obtained from 7 patients, of whom 4 were female, 5 were diabetic, 3 were receiving warfarin, 6 were receiving hemodialysis, and 1 was receiving digoxin and dialysis. Age range was 39-77. Lesions were located on the leg (4), thigh (2), and penis (1). In the latter case, control tissue was obtained from the mons pubis. The prevalence of findings in affected skin were: 5/7 (71%) small vessel calcification, 3/7 (43%) small vessel thrombosis, and 2/7 (30%) intimal hyperplasia, and 2/7 (30%) extravascular calcification. None of these findings were present in two biopsies. At least 2 findings were present in each of the other 5 specimens. A bone scan showed no abnormalities in the biopsies and only vascular calcification in the autopsy samples.

Conclusions: Based on this small study, histologic findings associated with CUA are absent in biopsies of unaffected skin from patients with suspected CUA. While small vessel calcification was noted in normal skin in the autopsy cases (possibly due to the larger sampling size), none of the other findings were present. Thus, the presence of at least 2 histologic findings appeared to be specific for CUA. Reconciling this with our previous results using amputation specimens as controls, we conclude that CUA is associated with specific histologic findings but not with any of the patients without peripheral arterial disease. However, additional cases are needed to confirm this.

Funding: Clinical Revenue Support

SA-PO286

A Novel Approach to Treat Calciphylaxis, A Deadly Disease
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Introduction: Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a rare disease mostly occurring in patients with kidney disease (CKD). It is characterized by painful, indurated and ulcerative lesions often covered by dark eschar that is very tender and leads to necrosis following calcification and occlusion of small cutaneous arterioles. Lesions may be solitary or multiple, covering several body regions. The Prognosis is generally poor. Complications, septic episodes are common and explain the high mortality rate of about 45-80% particularly in patients with ulcerative disease [1]. We report a new therapeutic approach.

Case Description: A 66-years-old woman with known CKD stage 3 secondary to diabetic nephropathy, hypertension, coronary artery disease, hyperlipidemia and bronchial asthma. There was no history of any medication allergies. The patient presented to our hospital with urinary tract infection, which was complicated with acute deterioration of her renal function approaching ESRD. Her hospital stay was complicated with appearance of multiple red indurated skin lesions of very large sizes which were progressive. They were markedly painful and required strong Opoids for pain relief. These skin lesions were rapidly progressed to deep ulcers and were requiring multiple surgical debridement’s. Skin tissue was obtained at autopsy in 2 cases. Hematoxylin and eosin and von Kossa stains were examined on each specimen. Histologic findings were evaluated by a single pathologist and included small vessel calcification, small vessel thrombosis, intimal hyperplasia and extravascular calcification. These skin lesions were markedly painful and required strong Opioids for pain relief. These skin lesions were rapidly progressed to deep ulcers and were requiring multiple surgical debridement’s. Skin tissue was obtained at autopsy in 2 cases. Hematoxylin and eosin and von Kossa stains were examined on each specimen. Histologic findings were evaluated by a single pathologist and included small vessel calcification, small vessel thrombosis, intimal hyperplasia, extravascular calcification. Histologic findings were evaluated by a single pathologist and included small vessel calcification, small vessel thrombosis, intimal hyperplasia, extravascular calcification.
Epidemiological Investigation of Calciphylaxis: Data from China

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Background: Calciphylaxis is a serious life-threatening vascular disease commonly occurred in dialysis patients. Chinese research on calciphylaxis is still in its infancy without epidemiological data. A regional epidemiological study of calciphylaxis patients was initiated at first time in China to find out its prevalence and clinical characteristics in Chinese hemodialysis patients.

Methods: The project was initiated in Aug. 2018. Stratified sampling method was used to select 28 dialysis centers in four regions of Jiangsu Province in China with an estimated sample size of 6000. Inclusion criteria: a. age ≥18 years; b. duration of dialysis ≥6 months; c. informed consent. The study used a questionnaire included general information and calciphylaxis-related symptoms.

Results: As of Apr. 30, 2019, 3790 hemodialysis patients had completed questionnaires. 77.0% of those who hadn’t heard of calciphylaxis, and another 9.2% only knew the name. Among them, 27 patients were diagnosed with calciphylaxis and unadjusted prevalence rate in hemodialysis patients was 0.71%. Of the diagnosed patients, 70.4% were male with an average age and duration of dialysis of 55.8±15.3 years and 86.0 (36.0, 144.0) months respectively. 13 patients had diabetes and 19 had secondary hyperparathyroidism (the median iPTH was 561.8 (312.9, 817.8) pg/mL). Only one used warfarin therapy. Surprisingly, 383 of 3799 (10.1%) had different types of skin lesions, including rough skin (48.3%), sensory sensitivity or loss (15.6%), diffuse rash (14.6%), calcified nodules (6.5%), painful papules (3.7%) and livedo or purpura (3.5%). Lesions were mainly in lower limbs, reaching 56.9%. 116 patients (30.3%) noticed a progressive deterioration of skin damage with potential calciphylaxis risks. Nevertheless, skin biopsy rate of these patients was only 6.3%, which affected further diagnosis.

Conclusions: This is the first epidemiological data about calciphylaxis from China. The preliminary analyses show that prevalence of calciphylaxis in Chinese hemodialysis patients is 0.71%, which seems to be lower than that from other countries due to differences in races and medication habits. In particular, we find some dialysis patients have atypical skin lesions which don’t rule out early manifestations of calciphylaxis. It’s urgent to improve clinical understanding of calciphylaxis, and multifaceted diagnostic methods will be applied for early screening.

SA-PO288
A Case-Control Study on Risk Factors of Calciphylaxis: Data from Chinese Hemodialysis Patients

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Background: Calciphylaxis (CUA) is a rare but potentially fatal disease that is commonly occurred in dialysis patients. Since there is no data based on Chinese population, the study is aimed to investigate risk factors of CUA in Chinese hemodialysis patients.

Methods: We retrospectively evaluated medical records of 20 hemodialysis patients who were newly diagnosed with CUA by skin biopsy admitted to Zhongda Hospital Southeast University from Oct.2017 to Dec.2018. Non-CUA dialysis patients with the same age and duration of dialysis were randomly selected as controls (Ratio=1:2).

Results: Most of CUA patients were male (80%) and elderly (55%), while 50% had a body mass index higher than 24. The mean time interval since start of dialysis to CUA diagnosis was 114.6±81.32 months, and the median time from appearance of skin lesion to diagnosis was 6 (2, 15) months. The incidence of hyperparathyroidism was higher in patients with CUA (80% vs 62.5%), but the differences of duration of elevated serum calcium and phosphate were not significant. Univariate logistic regression analysis indicated that male (OR 3.619, 95%CI 1.134-11.327) and male (OR 3.619, 95%CI 1.134-11.327) were independent risk factors of CUA in Chinese hemodialysis patients.

Conclusions: Calciphylaxis is a serious life-threatening vascular disease commonly occurred in dialysis patients. Since there is no data based on Chinese population, the study is aimed to investigate risk factors of CUA in Chinese hemodialysis patients. Univariate logistic regression analysis indicated that male, alkaline phosphatase (ALP) level (OR 1.005, 1.000-1.009) and each 1 mg/L increase in serum albumin level (OR 1.181, 1.041-1.340), each 1 IU/L increase in serum creatinine level (OR 1.027,12.748), each 1 point increase in score of use of vitamin D and its analogues (OR 1.027, 12.748) were independent risk factors of CUA in Chinese hemodialysis patients. Since there is no data based on Chinese population, the study is aimed to investigate risk factors of CUA in Chinese hemodialysis patients. Univariate logistic regression analysis indicated that male, alkaline phosphatase (ALP) level (OR 1.005, 1.000-1.009) and each 1 mg/L increase in serum albumin level (OR 1.181, 1.041-1.340), each 1 IU/L increase in serum creatinine level (OR 1.027,12.748), each 1 point increase in score of use of vitamin D and its analogues (OR 1.027, 12.748) were independent risk factors of CUA in Chinese hemodialysis patients.

SA-PO290
Whole-Kidney and Single-Tubule RNA Sequencing Reveal Changes of Cell Types and Signaling for Nephrogenic Diabetes Insipidus After Ureteral Obstruction

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Background: Unilateral ureteral obstruction (UUO) models in rodents are commonly employed in the study of CKD. Early stages of UUO are marked by polyaquatic impaired urinary concentrating ability, associated with loss of aquaporin-2 (AQP2) expression. Most mechanistic work in the field has focused on connecting tubule (CNT) and cortical collecting duct (CCD) features consistent with early UUO, making it difficult to discriminate ‘first cause’ events from secondary, tertiary, etc. changes in gene expression.

Methods: Preliminary whole-kidney RNA-Seq studies were performed after 0, 3, 6, and 12 hrs of UUO. Based on whole-kidney findings, cortical collecting ducts (CCDs) and cortical thick ascending limbs of Henle (cTALs) were microdissected from rats 3 hrs after UUO. Single-tubule RNA-Seq was carried out independently in 4 UUO rats versus 4 controls.

Results: Whole kidney RNA-Seq time course experiments revealed that Aqup2 and other collecting ducts markers started to decrease between 2 and 6 hrs. Decreases were seen in markers of connecting tubule (Calb1), distal convoluted tubule (Slc12a3) and thick ascending limb (Slc12a1) were also seen within 3 hours. However, there were no effects on transcripts coding for classical markers of podocytes and proximal tubules within 12 hours. Expression of renal non-epithelial cell markers showed B lymphocytes (Cd19, Cd80) rapidly increased at 3 hrs and decreased at 12 hrs followed by increased abundance of markers of monocytes (Fcer2b, Sfll), macrophages (Gata6), and chemokines (Ccl2, Ccl5, Ccl7) at 6 to 12 hrs. Several aldosterone-regulated genes showed increases in mRNA including Sgk1, Scn11a, and Tsc22d3 at 3 hrs. Single-tubule RNA-Seq data (both CCD and cTAL) showed a large number of transcripts coding for transporters and receptors that were decreased. It also revealedthat immediate early gene transcripts were increased significantly more frequently than expected from random sampling from the full pool of transcripts at 3 hrs.

Conclusions: Whole-kidney RNA-Seq results are consistent with very early effects on the distal nephron but not proximal tubule or glomerulus in terms of gene expression and provided evidence for invasion or activation of inflammatory cell types. Single-tubule RNA-Seq showed cellular signaling changes in CCD and cTAL, consistent with activation of the immediate early response.

Funding: Government Support - Non-U.S.
SA-PO291
Single-Cell Transcriptionomics of Enriched Human Intercalated Cells Exposed to Uropathogen Reveal Differential Innate Immune Signature in Intercalated Cell Subsets
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Background: We have previously shown that intercalated cells (ICs) are important for innate immunity in murine model of urinary tract infection. Little is known about their role in human innate immune function. We explored the whole genome transcriptionome after early 1 hour uropathogen vs saline exposure in enriched human intercalated cell at single cell level.

Methods: Human ICs were enriched from kidney biopsy samples using magnetic cell sorting with anti-human c-kit microbeads after removal of dead cells and CD45+ immune cells. Enriched viable ICs were exposed to saline or UPEC for 1hr. Single cells were separated on 10x single cell instrument. Single cell gel beads containing barcoded oligonucleotides and reverse transcriptase reagents were generated with the v3 single cell reagent kit. Following cell capture and cell lysis, cDNA was synthesized and amplified. Illumina sequencing library was then prepared with the amplified cDNA. The resulting library was sequenced using Illumina NovaSeq 6000. 26 bp of barcode andumi sequences and 91 bp RNA reads were generated. CellRanger 3.0.2 was utilized to process the raw sequence data generated. The R package Seurat development version 3.0.9.0 was used for the further gene expression analysis.

Results: Magnetically enriched CKit+ cells expressed higher levels of V-ATPase mRNA expression compared to CKIT- cells. 6 clusters of collecting duct cells identified including 4 alpha and 2 alpha-like clusters with variable SLCA4 (AE1) and innate gene including DEFBI (anti-microbial peptide) expression, 1 beta IC cluster (showing no innate immune gene expression) and 2 PC vs transitional IC/PC clusters (AQP2+ V-ATPase+) with distinct innate immune profile. Reactome pathway analysis predicted innate immune role for human ICs. Differential gene expression profiling significantly upregulated genes with short UPEC exposure in IC clusters included Immunoglobulin lambda constant 3 (IGL3) and adrenomedullin (ADM), an anti-microbial gene, integrin alpha E (ITGAE).

Conclusions: Innate immune function identified in murine models are conserved in human ICs. Enriched human ICs can act as model system that can be used to determine human relevance of mouse findings. Single cell analysis reveals collecting cell types/subtypes are more diverse than previously recognized.

Funding: NIDDK Support

SA-PO292
Novel Transcriptional Regulators of Tight Junction Biogenesis in Renal Collecting Ducts
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Background: The renal collecting duct is comprised of a tight epithelial barrier resulting in a strict separation of intraluminal urine and the interstitium. Disruption of this barrier leads to impaired water reabsorption and loss of adequate urine concentration ability. However, the overall transcriptional network controlling this process is only incompletely characterized. Using an integrated bioinformatics approach, we identified two transcriptional regulators (TRs), Tafap2a and Ncor1, potentially involved in this network. The transcription factor Tafap2a is a trans-regulatory factor implicated in epithelial differentiation and Tafap2a mutations have been associated with renal malformations. Ncor1 is a nuclear corepressor that assists nuclear receptors (such as thyroid hormone receptor) in the downregulation of gene expression. We hypothesize that Tafap2a and Ncor1 play a role in tight junction biogenesis and epithelial barrier formation in the CD.

Methods: Inner medullary collecting duct (IMCD3) cells were engineered to harbour CRISPR/Cas9-induced knock outs (KO) of either Tafap2a or Ncor1. Deregressed genes were identified by mRNA sequencing and confirmed with qPCR.

Results: Tafap2a and Ncor1 show predicted binding to promoters of several critical tight junction components and are highly expressed in IMCD3 cells and CD in mice. Casp9 knock-induced KO of Tafap2a and Ncor1 were confirmed with allele-specific sequencing validating frameshift mutations in the targeted areas. mRNA sequencing revealed a strong impact of Tafap2a and Ncor1 KO on the expression of important tight junction components. For example, two Claudins, Cldn4 and Cldn6, showed massive downregulation in comparison to WT clones. Interestingly, the TR grainhead-like 2 (Grhl2), which we previously identified as a critical regulator of tight junction biogenesis, was also highly downregulated in Tafap2a and Ncor1 KO clones. These findings were confirmed by qPCR. A detailed characterization of the transcriptional network is still ongoing.

Conclusions: Our data support our hypothesis that the candidates Tafap2a and Ncor1 are involved in the transcriptional network regulating tight junction biogenesis and barrier formation in the renal CD. A detailed understanding of the underlying network mechanisms controlling tight junction biogenesis might provide important insights into their potential involvement in kidney disease.

SA-PO293
A Comprehensive Transcriptome Database for Mouse Renal Tubule Segments
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Background: The mammalian renal tubule is comprised of at least 14 segments, each with distinct cell types and unique sets of transcriptomes. Recent advances in RNA-seq techniques offer the ability to profile the transcript at the level of single microdissected tubules and single-cells. To better understand the mouse renal physiology and pathophysiology, a comprehensive transcriptome database for all the mouse renal segments/cells is needed.

Methods: Here, we microdissected all 14 mouse renal tubule segments and carried out single-tube RNA-seq in each of them. These data were used to create an online database that allows for: 1) easy exploration of transcript expression; and 2) visualization of isoform distribution along the renal tubule through a genome browser, JBrowse. We also developed a flow-sorting procedure to enrich Slc12a5+ distal convoluted tubule (DCT) cells and carried out single-cell RNA-seq (10X Chromium) to study their heterogeneity.

Results: We profiled at least 3 biological samples per segment and were able to detect more than 11,000 transcripts for each mouse renal tubule segment (mean TPM >1). We identified unique patterns of protein distribution along the renal tubule, including transcription factors, metabolic enzymes, and G protein-coupled receptors. Also, we incorporated JBrowse into the database, which allows for easy and intuitive visualization of exon usage for transcripts. Our data revealed distinct segment-specific isoforms of many genes including known isoforms of ROMK (Kcnj1), Kv1, and SPAK (Stk39). This also allowed us to identify embigin (Emb) as a negative surface marker for proximal tubule cells, which was used to enrich non-proximal cell types by FACS sorting. We profiled ~2000 embigin+ cells at a median depth of ~1000 genes. Single-cell RNA-seq analysis of Emb+ CD45+ DAPI+ PTN+ Ki67+ cells indicated an enrichment of DCT cells (~1000 Slc12a5+ cells). Initial results show evidence of heterogeneity of Slc12a5+ cells separating into at least two independent clusters. Both clusters lacked AQP2 and 11β-hydroxysteroid dehydrogenase signals but a high percentage expressed ENAC subunits.

Conclusions: These data allowed us to create a resource in the form of a publicly accessible web page. They also expand our knowledge of the cell types that make up the DCT.

Funding: Government Support - Non-U.S.

SA-PO294
Identification of MAP Kinases-Regulated Proteins in Downstream Signaling Pathways of Vasopressin V2 Receptor in Kidney Collecting Duct
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Background: Vasopressin signaling mediated by G protein-coupled V2 receptor (V2R) is critical in water and electrolyte transport in the kidney collecting duct (CD) cells. Stimulation of V2R affects several downstream signaling pathways, including PKA, PKJ3/AKT, and Wnt, and Ca2+/calmodulin. MAP kinases are also involved as an apparent downstream signaling pathway of V2R, however, the roles and their substrates of MAP kinases in the vasopressin signaling are unclear.

Methods: Comprehensive substrates of MAP kinases were identified using bioinformatic analyses: 1) expression of MAP kinases were studied using database based on high-throughput profiles of transcriptome and proteome (https://hpcwebapps.cit.nih.gov/ESBL/Database/index.html); 2) MAP kinase substrates expressed in the CD were identified using multiple protein phosphorylation databases. The identified substrates were mapped on the downstream signaling of V2R. Trim28-mediated AQ2P regulation was examined using immunoblotting and immunohistochemistry.

Results: Five MAP kinases (ERK1, ERK2, ERK3, JNK2, and MAPK p38alpha) were identified as the MAP kinases expressed in kidney CD cells. From multiple protein kinase-substrates databases, 189 proteins were identified as the substrates of five MAP kinases. Among them, 51 transcription factors, 15 transcription co-regulators, 30 kinases, 4 E3 ligases and 1 deubiquitinating enzyme were classified. In particular, sequential data mining revealed that serine 595 in the tripartite motif-containing 28 (TRIM28), as the substrate of MAP kinases, was the only one phosphorylation site downregulated by vasopressin. Since TRIM28 is a transcription cofactor and also E3 ligase, we examined whether TRIM28 is a mediator of MAP kinases action on AQ2P expression. Immunofluorescent labeling of mouse and rat kidneys revealed that TRIM28 was exclusively localized in the nuclei of the tubular epithelial cells, including CD. dDAVP-induced AQ2P up-regulation was significantly attenuated in mpkCCD cells with TRIM28 knockdown.

Conclusions: We identified MAP kinase substrates of the kidney CD mapped on the downstream signaling pathways of V2R. TRIM28 was identified as a substrate of MAP kinases that involves in vasopressin-mediated signaling pathways, including regulation of AQ2P.

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SA-PO295

Phosphorylation Profile of Human AQP2 in Urine Exosome Identified by LC-MS/MS Phosphoproteomic Analysis

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Background: AQP2 water channel is the key membrane protein which determines the water permeability of collecting ducts. Multiple phosphorylation sites at the C-terminal of AQP2 are identified including S256, S261 and S264. Interestingly, the amino acid at S269 of rodent AQP2 is Thr in human AQP2. The phosphorylation of S269 in rodents has been shown to be an important signal for the apical membrane accumulation. However, the phosphorylation of T269 in human is unknown. As AQP2 is excreted into the urine by the endocytosed exosomes, human AQP2 protein is easily obtained from the urine. The purpose of this study was to examine the phosphorylation status of human AQP2 from urine exosomes.

Methods: Human urine samples of volunteers were obtained from the morning first urine. Urine exosomes were isolated by differential centrifugations and digested with trypsin in solution. Tryptic peptides were purified by MonoSpin column (GL Sciences, Tokyo, Japan) and analyzed by LC-MS/MS (Bruker Tim TOFflex). Western blot were used to detect the AQP2 phosphorylation with a usual and S256, S261, S264, and S269-phosphorylated AQP2-specific antibodies.

Results: Summation of thrice analysis identified total 185 PSMs (peptide spectrum match) of phosphorylated AQP2 at Ser and/or Thr. The most dominant form was S256 phosphorylated form (n=154), followed by S261 form (n=14). Similar numbers of phosphorylation were observed at T244 (n=6), S264 (n=4), and T269 (n=2). Western blot of human urine exosomes detected dominant S256 and S261-phosphorylations and much lower S264 and T269-phosphorylations.

Conclusions: These results indicate that the all phosphorylation sites of human AQP2 including T269 are indeed phosphorylated and S256- and S261-phosphorylations play a dominant role in its urinary exosomal excretion. The newly identified T244 phosphorylation is intriguing and worth further studies.

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SA-PO296

Three-Dimensional Visualization of the Medullary Tubular-Vascular Relationship in Adult Mouse Kidneys

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Background: A close spatial relationship between renal tubules and blood vessels in the renal medulla forms the structural basis for urine concentration, but is also the site of acute and chronic kidney injury under certain pathological circumstances. Therefore, a comprehensive understanding of the structure of this area is indispensable for nephrologists.

Methods: The tubule-vessel arrangement through whole mouse medulla was investigated using serial sections with double immunofluorescent staining for CD31 and AQP-1 or AQP-2. Subsequently, 525 tubules and 333 vessels were traced with custom-made computer software, and ultrastructurally analyzed using EM.

Results: The main findings were: 1) Descending vasa recta (DVR) and ascending vasa recta (AVR) in the center of the vascular bundle (VB) of ISOM closely accompanied each other starting at the cortex-medulla transition towards the inner medulla and gradually draining into capillaries at papilla; 2) AVR arising from capillary nets of the vas a recta (AVR) in the center of the vascular bundle (VB) of ISOM closely accompanied each other starting at the cortex-medulla transition towards the inner medulla and gradually draining into capillaries at papilla; 3) AVR accompanying with type 3 long loop nephron-descending thin limbs (SLN-DTL) mainly drained into arcuate veins, while AVR in close contact with DVR in a VB or with collecting ducts (CD) in inter-bundle regions (IBR). AVR accompanying with type 3 short loop nephron-descending thin limbs (SLN-DTL) mainly drained into arcuate veins, while AVR in close contact with type 1 and 2 SLN-DTL often drained into the lobular veins in cortex; 3) Thick ascending limbs (TAL) from the longest long loop nephron (LLN) entered into a VB, and ran mainly in parallel to CD and current to the DVR that originated from same glomeruli; 4) The number of ascending and descending tubules and vessels were almost identical; and 5) In the inner medulla, DVR became thin-walled and fenestrated, closely related to the surrounding tubules or CD.

Conclusions: The present study shows a ubiquitous phenomenon that AVR is spatially arranged with DTL and DVR as well as CD in a counter-current way throughout the whole medulla. This contributes to an efficient reabsorption of water and electrolytes in the filtrate, and makes it sensitive to the damaging factors, such as hyperoxia, hyperglycemia, cytotoxicity, etc.

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SA-PO297

Molecular Dynamics Simulations Reveal the Residues Involved in NBCe1 Ion Coordination

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Background: We have recently solved by CryoEM the near atomic (3.9 Å) structure of NBCe1-A, an electronegative Na+-CO₂ cotransporter expressed on the basolateral membrane of the proximal tubule, which plays a key role in tubular bicarbonate absorption. Although our structure and functional mutagenesis data suggest that a set of residues from TMs 3, 8, 10 and their vicinity are likely involved in ion coordination, their exact roles cannot be determined given that 3.9 Å resolution was not sufficient to detect coordinated ions.

Methods: The NBCe1 membrane domain was placed in a cubic periodic box in a POPC bilayer using the CHARMM-GUI online server. MD simulations were performed with the CHARMM36 force field and the NAMD program, and ~600 ns long MD trajectories with 2-6 fs time steps were collected and used for analysis. Ion interactions with the NBCe1 residues were quantified as contact frequency (i.e. percentage of the MD trajectory steps, in which a given ion was found at 3.5 Å from a specific protein residue). Residues exhibiting high contact frequencies with respect to Na+ and CO₂ were used for identification of the ion coordination sites.

Results: In the wild type NBCe1 protein, the Na⁺ contact frequency was highest for residues D754 and T758 (TMS) and A799 (loop prior to TM10). The CO₂ contact frequency was highest for K294 (TM13), A800 (loop prior to TM10), T801 (TM10), with less interaction at T485 (loop prior to TM3), and G486 and P487 (TM3). Mutational data supported these results. The A799V mutation found in patients with proximal RTA affecting the Na⁺ coordination site leads to significantly impaired protein-ion interactions for both Na⁺ and CO₂. Another proximal RTA causing mutation, G486R, affecting the CO₂ coordination site, demimates impaired Na⁺ protein contacts and strong interaction between R486 and CO₂ with the arginine residues positioned away from the coordination site.

Conclusions: All-atom molecular dynamics simulations of the membrane domain of NBCe1 revealed that it binds stably Na⁺ and CO₂. Na⁺ is coordinated by D754, T758, and A799. CO₂ is coordinated by K294, A800, A801, T485, G486, and P487. The proximal RTA patient mutations A799V and G486R drastically alter the coordination of Na⁺ and CO₂.

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SA-PO298

Water Loading Increases Urinary Extracellular Vesicle Size but Not Excretion Rate

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Background: Urinary extracellular vesicles (uEVs) are a promising source of kidney biomarkers, but the factors influencing uEV size and excretion rate are unclear. Here, we studied the effect of water loading on uEV size and excretion rate.

Methods: We performed a water loading test (20 ml/kg) in healthy men (n = 11) and isolated uEVs from whole urine at 6 time-points. uEVs were quantified using nanoparticle tracking analysis (NTA), a time-resolved fluorescence immunoassay that isolates CD9+ isolated uEVs from whole urine at 6 time-points. uEVs were quantified using nanoparticle tracking analysis (NTA), a time-resolved fluorescence immunoassay that isolates CD9+

Results: While EVQuant and CD9-TRFIA demonstrated that the excretion rate of uEVs was constant during water loading, NTA suggested a significant increase of 50% by the intervention (p<0.0001). Subsequently, we found on NTA that the size of uEVs generally increased (p<0.0001, Figure). This size increase was confirmed by EM (n = 4, p<0.001, Figure).

Conclusions: Water loading increases uEV size but not excretion rate. A lower urine osmolality may cause water to move into EVs. This phenomenon interferes with uEV quantification by NTA and is an important caveat in uEV studies.

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SA-PO299

Water Deprivation Shortens Primary Cilia Length in the Kidney Tubular Cells

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Background: The primary cilium, a microtubule-based cellular organelle, plays a key regulator for maintenance of cell homeostasis by sensing and transducing extracellular signals. In the kidney, the length of primary cilium links to the number of human kidney
Aquaporin 2 that is reduced in subsegments is preserved indicating maintenance of cell identity, with the exception of enhanced proliferation of kidney tubular cells in mice along with increasing urine osmolality. The kidneys derived from water-restricted mice presented low levels of acetylated-α-tubulin, EXOC5, an exocyst complex, and α-tubulin transference expression. In Madin-Darby canine kidney (MDCK) cells, high concentrations of NaCl or mannitol treatments shortened primary cilia length. This NaCl or mannitol treatment decreased the expression of acetylated-α-tubulin, EXOC5, and α-tubulin transference. Treatment of tubastatin A prevented drinking water deprivation-induced shortening of primary cilia in the mice. In addition, this HDAC6 inhibitor treatment prevented the decrease of acetylated-α-tubulin, EXOC5, and α-tubulin transference expression.

Conclusions: These findings demonstrate that the length of primary cilium in kidney tubule cells is associated with water supply and urine osmolality, suggesting that primary cilium may play an important role in body water homeostasis and regulation of urine osmolality.

SA-PO300
Inactivation of the Mitochondrial Structural Protein Opa1 in Distal Tubules and Collecting Ducts in the Mouse Causes Nephrogenic Diabetes Insipidus
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Background: Optic atrophy-1 protein (Opa1) is a nuclear-encoded mitochondrial protein localizing in the inner mitochondrial membrane, where it participates to mitochondria fusion and supports cristae folding. Mitochondria in the kidney provide energy for cell viability and function that generates ion gradients for nutrient reabsorption, electrolyte and fluid balance (Bhargava 2017). Given their essential function in aerobic metabolism, mitochondria are of interest to the pathophysiology of diabetes. To study how mitochondria fitness contributes to kidney physiology, we inactivated Opa1 gene expression in the kidney epithelium.

Methods: We generated a kidney-specific Opa1KO mouse model expressing the Cre recombinase under the kidney-specific cadherin 16 promoter (Opa1KO, for short). Mitochondria ultrastructure was analyzed by transmission electron microscopy (TEM), metabolomics analysis by NMR spectroscopy.

Results: Opa1 KO mice die within the first three months of age. Mice were housed in metabolic cages and showed progressive polydipsia and polyuria, low urinary pH, increased urinary sodium. Mitochondria ultrastructure was analyzed by transmission electron microscopy (TEM), metabolomics analysis by NMR spectroscopy.

Conclusions: Inactivation of Opa1 induces kidney enlargement and a gross impairment of renal water reabsorption, thus recapitulating the key features of nephrogenic diabetes insipidus. Further investigations will clarify the molecular mechanisms that link mitochondria dysfunction to epithelial cell proliferation, a response that seems to be under control of Opa1 knockout mice.

Funding: Private Foundation Support

SA-PO301
Induction of the Intracellular Immunomodulator Toll-Interacting Protein (Tollip) Mediates Monophosphoryl Lipid A (MPLA)-Induced Protection Against Lipopolysaccharide in Medullary Thick Ascending Limb (MTAL)
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Background: LPS inhibits HCO3- absorption in the MTAL through activation of a basolateral TLR4-MyD88-IRAK-1-ERK pathway that is upregulated by sepsis. Recently, we reported that pretreatment with the nontoxic immunomodulator MPLA prevents inhibition of HCO3- absorption by LPS through activation of a TLR4-TRIF-MKK6 pathway that prevents LPS-induced activation of IRAK-1. Here, we examined the molecular mechanism by which MPLA pretreatment suppresses IRAK-1 activation. We investigated the role of Tollip, a soluble intracellular protein that negatively regulates LPS signaling by inhibiting activation of IRAK-1 downstream of TLR4. The expression and functional significance of Tollip in renal tubules are undefined.

Methods: Results: We found that treatment with MPLA in vitro increased Tollip protein level in mouse and rat MTALs and that the increase in Tollip expression occurs within a time frame (2 h) sufficient to account for the effect of MPLA pretreatment to inhibit LPS-induced IRAK-1 activation. The MPLA-induced increase in Tollip expression was prevented by P38 inhibitors. In communoprecipitation experiments in inner stripe of medulla, we found that pretreatment with the nontoxic immunomodulator MPLA increased Tollip protein level in the MTAL and this increase was prevented by pretreatment of a P38 inhibitor. Thus, the ability of MPLA to upregulate Tollip expression in the MTAL in vitro translates to the MTAL in vivo.

Conclusions: We conclude that pretreatment with MPLA increases expression of Tollip in the MTAL through a P38-dependent pathway. Tollip, in turn, inhibits LPS-induced TLR4 signaling by suppressing activation of IRAK-1, thereby preventing downstream activation of ERK and HCO3- absorption. These results provide new evidence that MPLA induces immune reprogramming of MTAL cells that protects against LPS stimulation and that Tollip can function as an endogenous negative regulator of inflammatory TLR4-IRAK-1 signaling in renal tubule epithelial cells. Strategies targeted to manipulate Tollip expression may aid in protecting renal tubule function against infectious and inflammatory challenge.

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SA-PO302
AQP11 Deficiency Impairs Thymus Development Possibly Through Defective Fat Metabolism
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Background: Aquaporin11 (AQP11) is a superaquaporin permeable to both water and glycerol. AQP11 null mice suffer from polycystic kidneys and die within a month after birth due to uremia. Although AQP11 is expressed widely, it is most abundantly expressed in the thymus and testis. The purpose of this study is to clarify the role of AQP11 in the thymus.

Methods: Immunohistochemistry and microarray analysis with RT-qPCR.

Results: The immunohistochemical analysis revealed the AQP11 expression at the stromal and epithelial cells in the thymus medulla. Surprisingly, the size of the thymus from AQP11 null mice was much smaller than that of the wild mice by half and sometimes by 10%. The vacuolated medullary epithelial cells were observed in the thymus of AQP11 null mice with a normal cortico-medullary structure. The microarray analysis of the gene expression in the thymus was compared between AQP11 null mice and the wild mice by the annotation analysis based on the David Bioinformatics Resources 6.8(beta). We identified 1.5 or more up-regulated 66 genes which mainly participate in the PI3K/Akt signaling pathways to promote metabolism, proliferation, cell survival, growth and angiogenesis. We also found 0.5 or less down-regulated 55 genes, some of which are regulated by the peroxisome proliferator-activated receptor (PPAR) signaling pathway which is activated by fatty acids and their derivatives. RT-qPCR analysis confirmed the enhanced expression of Egrf (Epidermal Growth Factor Receptor), Iglb4 (Integrin beta-4) and Il2ra (interleukin 2 receptor alpha) and the diminished expression of AQP7, Pck1 (Phosphoenolpyruvate carboxykinase 1) and Ucp1 (Mitochondrial uncoupling protein 1). The up-regulated genes for growth signaling may support the survival of the regressed thymus while the down-regulated genes may cause deleterious effects on fat-glucose-energy metabolism in the thymus. The decreased aquaglyceroporin AQP7 in AQP11 null thymus may further compromise the glycerol accumulation leading to the thymus regression.

Conclusions: As the role of AQP's to support memory T cells through glycerol transport has been reported (Cui G et al. Cell. 161:750, 2015), such may also be working in the thymus development. AQP11 may also play an important role in the metabolic control of the thymus.

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SA-PO303
The CaSRS Signals Through CDC42, MKK6, and p38 to Inhibit SP1, a Repressor of Claudin-14 Expression
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Background: Urinary calcium (Ca2+) excretion increases in direct response to elevated plasma [Ca2+], independent of hormonal signalling, by attenuating paracellular Ca2+ reabsorption from the thick ascending limb (TAL). This occurs via sensing plasma [Ca2+] by a Ca2+ sensor, which may alter the protein expression in the kidney tubule cells. The CaSR activation via quantitative PCR, using specific primers to the different variants on cDNA derived from the inner medulla of the TAL. This increases expression of the tight junction protein Claudin-14, which blocks paracellular Ca2+ reabsorption. This pathway is inappropriately activated in some kidney stone formers, causing their disease. However, the signalling pathway between CaSR activation and increased Claudin-14 expression is unknown.

Methods: We identified the renal CLDN14 transcript variant regulated by CaSRS activation via quantitative PCR, using specific primers to the different variants on cDNA isolated from kidneys of mice treated with cinacalcet. We cloned the promoter region of this gene into a luciferase reporter construct. This region also resulted elements responsive to cinacalcet. We used this tool to delineate the signalling pathway downstream of CaSRS activation.

Results: The region 1500 bp 5’ to the 1st transcript variant when transfected in HEK293T cells contained promoter activity. Further, this region displayed more than double reporter activity in the presence of the CaSRS and cinacalcet, but not in the absence of the CaSRS. Increasing extracellular [Ca2+] similarly increased reporter activity in the presence, but not the absence, of the CaSRS. A prior microarray found increased renal MKK6 and CLDN14 expression in mice treated with cinacalcet. However, expression of MKK6 and CLDN14 was not increased after cinacalcet treatment. MKK6 can signal through JNK or p38 MAPK. Inhibition of p38 but not JNK enhanced the cinacalcet-induced reporter activity in the presence of the CaSRS.

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Underline represents presenting author.

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mediated increase in CLDN14 reporter activity. Sp1, a known downstream effector of PTH and CaSR activation, accounts for this upregulation of the reporter construct. Upstream activation of MKK6 is through CDC42, as dominant-negative CDC42 attenuated reporter activity.

**Conclusions:** CaSR activation increases CLDN14 transcription via signaling through CDC42, MKK6 and p38 to attenuate the expression of Sp1 repressor of CLDN14.

**Funding:** Government Support - Non-U.S.

**SA-PO304**

Is Claudin 16 Required for the Effect of Parathyroid Hormone (PTH) and Calcium Sensing Receptor (CaSR) on Calcium and Magnesium Reabsorption in the Cortical Thick Ascending Limb?

**Caroline Prot-Bertoxy,**1 Lucile Figueres,1 Elsa Ferriere,1 Gaëlle Brideux,1 Camille Griveau,1 Catherine Chausssain,2 Claire Bardet,2 Tilman Breiderhoff,4 Dominik Müller,4 Pascal Houillier,2,4 INSERM, UMR5138- CNRS- ERL8228, Paris, France; 3 Department of Pediatric Nephrology, Charité - Universitätsmedizin Berlin, Berlin, Germany.

**Background:** The cortical thick ascending limb of the loop of Henle (CTAL) reabsorbs 25% of the filtered calcium (Ca) and 70% of the filtered magnesium (Mg), along the paracellular pathway. The expression of claudin 16 (Cldn16) in the tight junction is required for a normal paracellular permeability and selectivity to Ca and Mg. Loss-of-function mutations of Cldn 16 in the CTAL cause familial hypomagnesemia with hypercalcuria and nephrocalcinosis (FHHNC). The CaSR has been developed as a potential therapeutic target for the treatment of PTH induced hypercalcemia and hypomagnesemia. However, the role of CaSR agonists in the CTAL has not been investigated in detail.

**Methods:** PTX and NPS2143 increased Ca reabsorption in Cldn16−/− CTAL (n=4, p=0.006; and n=3, p=0.047, respectively) and Cldn16 +/+ CTAL (n=3, n=4, p=0.006; and n=3, p=0.018, respectively). PTX significantly increased Mg reabsorption in Cldn16 +/+ CTAL (p=0.006) and Cldn16−/− CTAL (p=0.018). The effect of PTX on Mg reabsorption is currently under study.

**Conclusions:** Cldn16 is not necessary for the effect of PTH and CaSR on Ca reabsorption in the paracellular pathway in vivo. Cldn16 is not necessary for the effect of PTH on Mg reabsorption by native CTAL. Our results suggest that the current model describing the effect of PTH and CaSR on Cldn16 +/+ CTAL reabsorption is too simple. Our results constitute a proof of concept to develop new therapeutic strategies based on CaSR inhibitor and/or PTH receptor agonist for FHHNC.

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**SA-PO305**

Colocalization of Claudin-10 with Other Transport Proteins in Basolateral Infoldings of the Thick Ascending Limb.

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**Background:** The neophron is the structural and functional unit of the kidney and is composed of renal tubular segments. The thick ascending limb (TAL) of the loop of Henle is the essential segment for salt homeostasis and urinary concentration. The TAL originates from medullary and cortical nephron and share the basic transcellular transport mechanism that involves cotransport of sodium (Na+), potassium (K+) and chloride (Cl-) and paracellular pathways that contribute to the selectivity of the paracellular pathway in the TAL. The expression of claudin protein expression in the tight junctions (TJ) in the TAL. Claudin-10 has been shown to be expressed in the claudin-10 channel. Claudin-10 channel also expressed in the basolateral region of cells.

**Methods:** Freshly isolated single medullary TAL segments were treated with omeprazole (20 mg/kg bodyweight) or placebo for four weeks under normal (0.22% NaCl) or low (0.05% NaCl) dietary Mg2+ availability. Subsequently, Mg2+ homeostasis was assessed by means of serum, urine and faecal electrolyte measurements, RT-qPCR to evaluate renal and intestinal Mg2+-related genes, and gut microbiota composition was investigated by 16S rRNA gene sequencing.

**Results:** After four weeks of treatment, omeprazole significantly reduced serum Mg2+ levels in mice on a low Mg2+ diet. Renal Tppm6 expression was increased as compensation for the low Mg2+ diet in placebo-treated mice, but expression of this Mg2+-channel was not changed in the omeprazole-treated group. Moreover, these mice did not exhibit renal Mg2+ wasting. Overall, 16S rRNA gene sequencing revealed a lower gut microbial diversity in omeprazole-treated mice. Omeprazole induced a shift in microbial composition that was associated with a 5- and 2-fold increase in the abundance of Lactobacillus and Enterococcus, respectively. To examine the metabolic consequences of these microbial alterations, the colonization composition of organic acids was evaluated. Low dietary Mg2+ intake, independent of omeprazole treatment, resulted in a 10-fold increase in formate levels.

**Conclusions:** Our results imply that both omeprazole treatment and low dietary Mg2+ intake disturb the gut internal milieu and may pose a risk for the malabsorption of Mg2+ in the colon.

**Funding:** Government Support - Non-U.S.
SA-PO308
Impaired Lymphatic Vessel Function Contributes to Edema in Nephrotic Syndrome
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Background: Edema is a cardinal feature of nephrotic syndrome (NS) although the underlying mechanisms are incompletely understood. Lymphatic vessels transfer fluids, solutes, and macromolecules from the interstitial space back into the circulation. We examined the structure and function of lymphatics in the paurinum anmioncinopic (PAN) model of NS.

Methods: PAN was induced in Sprague Dawley rats, while non-injected rats served as controls (Cont). Eight days later, blood, urine, renal and mesenteric lymph, kidney and ileum were analyzed. Renal lymphatic vessels were isolated, cannulated and mounted in a perfusion chamber to assess vasoactivity.

Results: PAN caused the expected proteinuria, hypoalbuminemia, hyperlipidemia and generalized edema including in the kidney and ileum. Compared to Cont, PAN increased lymphangiogenesis, reflected by significantly increased gene expression of podoplanin (1.7-fold), VEGFR-3 (2.1-fold) and the number of lymphatic vessels. VEGF-C, the major growth factor for lymphangiogenesis was elevated (2.1-fold) and lymph contained significantly more VEGF-A (2.5-3.1-fold) in PAN vs Cont. Lymph endothelial cells (LEC) isolated from mesenteric collecting vessel showed significantly increased gene expression of VE-cadherin (2.2-fold) while ileal LECs had increased ZO-1 (2.7-fold) indicating intercellular junction transition from button to zipper type. Isolated renal collecting lymphatic vessels from PAN showed significantly increased vessel diameter (15%), deceased contraction frequency (30%), and reduced sensitivity to endothelial derived NO inhibitor (L-NAME), NO donor (sodium nitroprusside), and thromboxane A agonist (U46619).

Conclusions: Although edema-forming kidney injury increases the number of lymphatic vessels, this compensation is inadequate, and edema rather reflects impaired vessel function, e.g., reduced lymphatic vessel contractility and reabsorptive capacity that may be novel targets in edema-forming disorders.

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SA-PO309
Calcium Citrate Incorporated into Calcium Carbonate and Calcium Nanoparticles Alleviate Cellular Injury from Acidosis
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Background: Metabolic acidosis is a common complication found in patients with chronic kidney disease (CKD), and causes cellular dysfunctions, proteinuria, inflammation, oxidative stress and cell death. Current medication to treat metabolic acidosis is the supplementation of alkalizing agents such as sodium bicarbonate and sodium citrate. We proposed new nanoparticles as the adjuvant therapy to mitigate the consequences of metabolic acidosis in CKD patients.

Methods: Calcium citrate incorporated into calcium carbonate nanoparticles (CCNP) and calcium carbonate nanoparticles (CNP) were synthesized from calcium chloride and sodium citrate. A HK-2 cells cultured in DMEM with pH 7.4 (normal environment) and pH 6.5 (acidic environment) were used to study cellular toxicity by Resazurin oxidative-reduction assay, intracellular reactive oxygen species (ROS) production by 2,7-dichlorofluorescein-diacetate (DCFH-DA) test, and cell death by flow cytometry.

Conclusions: CNP and CCNP had very low cytotoxicity at the concentration up to 1 mg/mL. These results show that CNP and CCNP did not alter the extracellular pH, or extracellular and intracellular bicarbonate concentration, and they were freely uptake into the cell in normal and acidic condition. Pharmacological tests revealed that both CNP and CCNP can suppress ROS production better than sodium citrate treatment. In addition, CNP and CCNP treatment ameliorated acidosis-induced cell death and apoptosis.

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SA-PO310
Interdialytic Creatinine Rise as a Predictor of Hospital Length of Stay and Cause of Shortness of Breath in ESRD Patients
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Background: The Interdialytic Creatinine Rise (IDCR), calculated as the change in serum creatinine over time, in mg/dL/h, has been proposed as a novel marker of volume status and mortality in patients with end-stage renal-disease (ESRD). We wanted to determine if IDCR was associated with the hospital length of stay (LOS), a metric reflecting unopposing factors of hospitalization and emergency room discharge. IDCR was calculated as the difference in two serum creatinine values divided by the time between the samples. LOS and potential confounders of age, gender, race, cirrhosis, active cancer, left ventricular ejection fraction (LVEF) ≤40%, and insurance status were recorded. A Kaplan-Meier survival analysis with different variable settings was created during hospital discharge and two groups according to the cause of SOB documented in the discharge summary, as SOB due to volume excess or not. The data was analyzed using univariate analyses, multiple regression, and multiple logistic regression.

Results: IDCR is negatively associated with LOS (Spearman correlation= –0.245; p=0.003). Adjusting for the significant covariates of age, gender, race, LVEF≤40% and insurance, IDCR is negatively associated with LOS; so that for every 0.021 mg/dL/h increase in IDCR, LOS decreases by 1 day (95%CI -1.6, 0.4; p=0.002). In the subset of patients with SOB, 11 patients had SOB unrelated to volume excess and 42 patients had SOB due to volume excess, with significantly different respective IDCRs of 0.09 and 0.06 (Wilcoxon’s Rank Sum Test; p=0.018). Adjusting for the significant covariate of age, when IDCR increases by 0.03 the odds ratio of SOB being unrelated to volume excess is 2.45 (95% CI 1.23, 5.80; p=0.012).

Conclusions: Our study showed that ESRD patients with lower IDCR values due to volume overload or decreased creatinine production have increased LOS, likely due to their higher risk. In ESRD patients admitted with SOB, higher IDCR values are more likely to exclude hypervolemia as the cause of SOB.

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SA-PO313

A Role for Toll-Like Receptors and Their Endogenous Ligands in CKD-Associated Cardiovascular Disease?
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Background: Cardiovascular disease (CVD) is greatly precipitated by chronic kidney disease (CKD). Overall, there is an approximately 20-fold increase in CVD mortality among CKD patients on dialysis compared with the general population. Traditional risk factors do not account for the high cardiovascular risk in CKD and standard clinical interventions are not always effective. CKD specific factors, such as anaemia, mineral metabolism disorders and the presence of uremic toxins are believed to be partially responsible. The inflammation associated with kidney tissue damage or the dialysis process has been suggested to play a substantial role in the onset and progression of CVD, however, it has yet to be demonstrated and the mechanisms elucidated. Kidney damage has been shown to lead to the local production of Damage Associated Molecular Patterns (DAMPs) that act as endogenous ligands of TLRs. We hypothesise that the TLR DAMPs being generated during CKD reach the circulation where they engage TLRs on peripheral leukocytes and/or endothelial cells, inducing chronic vascular inflammation and dysfunction that promotes and/or accelerates CVD development.

Methods: Combination of ex vivo, in vitro and in vivo techniques

Results: A range of known TLR DAMPs were quantified in plasma from stage 5 CKD patients (n=40) at the start of PD and compared to the levels found in healthy individuals (n=30). Heat-shock protein (Hsp) 60, Hsp70, hyaluronic acid and calprotectin (S100A8/ S100A9) were found significantly elevated in CKD patients. In vitro experiments were conducted to assess the ability of each of these TLR DAMPs to affect cellular responses related to initiation and progression of atherosclerosis. (expression of adhesion molecules by endothelial cells and monocytes, production of cytokines and chemokines, phagocytosis of oxidised LDL by macrophages). In preliminary in vivo experiments, chronic kidney injury was induced by repeated administration of the nephrotoxin aristolochic acid in mice prone to CVD development (LDL receptor deficient) to confirm the findings made in vitro and ex vivo.

Conclusions: Our preliminary results reveal significantly increased levels of several known TLR DAMPs in plasma from patients with late stage CKD. In ongoing work the role that these DAMPs and their interaction with TLRs may play in initiating or worsening atherosclerosis development is being investigated.

Funding: Government Support - Non-U.S.

SA-PO314

The Effect of the Sodium-Glucose Co-Transporter-2 Inhibitor in Angiogenesis of Diabetic Cardiovascular Disease
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Background: Diabetic patients with peripheral arterial occlusive disease (PAOD) are at high risk from cardiovascular events, vascular death and ischemic ulceration. The most important and prevalent risk factor for the development of PAD is diabetes. Angiogenesis is an important part of the development of diabetic wound healing. The aim of the present study was to investigate the effects of SGLT2 inhibitor on angiogenesis in diabetic mice.

Methods: Chronic hind-limb ischaemia (15 mice) by ligation and transecting the left common femoral artery. Laser Doppler measurement of tissue blood flow to detect hind-limb blood flow. Human Endothelial progenitor cell culture were cultured in 5% CO2 at 37°C in cell growth medium. Cells from passages 4-8 were used for all experiments. MITT assay Cells were treated with variable concentration of dapagliflozin for 24 hours with hydrogen peroxide, washed with phosphate buffered solution, incubated in a conditioned medium for 1 hour with 2 µg/mL MITT, and then were lysed. Absorbance was measured at 570 nm using a spectrophotometric microplate reader (Multiskan EX, Labsystems; Helsinki, Finland). EPC migration assay was evaluated by a modified Boyden chamber assay. The magnitude of migration of late EPCs was evaluated by counting the migrated cells in six random high-power fields. EPC tube formation assay was performed with an In Vitro Angiogenesis Assay Kit(Chemicon). The average of the total area of complete tubes formed by cells was compared by using computer software, Image-Pro Plus.

Results: Dapagliflozin enhanced flow recovery in diabetic mice. Treatment of EPCs with dapagliflozin significantly increased tube formation and up-regulated impaired eNOS production and Akt action in hyperglycemic conditions.

Conclusions: SGLT-2 inhibitor improves blood flow recovery in diabetic mice with hind limb ischemia and promotes the functions of EPCs via NO-related pathways.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
immunostaining were performed to detect the levels of fibroconnectin, collagen type I, and alpha-SMA in the kidneys. Sirius red staining was performed to examine total collagen deposition in the kidney.

**Results:** Both LysM-Cre+/–/PTENf/f mice and LysM-Cre+/–/PTENf/f mice had comparable blood pressure at baseline. Angiotensin II treatment led to an increase in blood pressure that is similar between LysM-Cre+/–/PTENf/f mice and LysM-Cre+/–/PTENf/f mice. Compared with LysM-Cre+/–/PTENf/f mice, LysM-Cre+/–/PTENf/f mice developed significantly worse renal dysfunction, proteinuria, and fibrosis following angiotensin II treatment. PTEN deficiency in myeloid cells enhanced myeloid fibroblast accumulation and myofibroblast formation associated with a significant increase in total collagen deposition and extracellular matrix protein production in the kidneys in response to angiotensin II. Immunohistochemical analysis revealed that PTEN deficiency in myeloid cells augmented infiltration of F4/80 macrophages and CD3 T cells into the kidneys of angiotensin II-treated mice.

**Conclusions:** PTEN plays a crucial role in the development of hypertensive kidney inflammation and fibrosis. Trough regulation of macrophage and T cell infiltration and myeloid fibroblast accumulation.

**Funding:** NIDDK Support

**SA-PO316**

**Grain vs. Casein-Based Diet Differentially Impact Angiotensin II Hypertension (AngII-HTN) Responses in Female vs. Male Sprague Dawley Rats**

**Background:** We previously reported that the baseline renal transporter profile in females (F) is distinct from that in males (M), specifically: lower PT NHE3 activity, NaPi2, claudin 2 and AQP1, and higher DT NCC, SPAK, claudin 7 and cleaved eNac abundance in F vs. M. We reported that F and M rats respond differentially to AngII-HTN (400 ng/kg/min for 14 days) when fed casein-based diet (Envigo TD 88239, 0.74% NaCl, 2% KCl).

In F, abundance of cortical NHE3, NHE3p, NCCk2c2 and NCCp were increased, and NCC, NCCp, and cleaved eNac were unchanged, while in M, abundance of cortical NHE3, NHE3p, NCCk2c2 were unchanged and NCC, NCCp and cleaved eNac were increased (Fig A). Additionally, AngII-HTN increased proteinuria in M but not F despite similar HTN (~150 mmHg).

**Methods:** We aimed to determine if differential responses to AngII-HTN (as above) are also evident in SD rats fed grain based diet (LabDiet 5001), n=5 F and M.

**Results:** At baseline, in F fed casein (vs. grain) based diet, NHE3 and NHE3p are increased (M only), both M and F had significant decreases in abundance of medullary NHE3, NHE3p, NCCk2c2, NKA α1, and increases in cortical NCCk2c2, NCCk2c2, NCC, NCCp and cleaved eNac. Blood pressure and proteinuria were similarly increased in M and F on grain based diet.

**Conclusions:** In summary, diet impacts: 1) baseline Na transporter abundance, 2) Na transporters’ regulation during AngII-HTN, and 3) AngII-HTN provoked proteinuria. Responses to AngII-HTN are similar in grain-based diet fed F and M.

**Funding:** NIDDK Support

**SA-PO317**

**High Sodium Intake Impairs Afferent Renal Sympatho-Depressory Pathways in Rats**

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**Background:** Afferent renal nerve pathways are likely involved in the development of salt-sensitive hypertension. We recently reported that intrarenal NaCl elicited a long-lasting sympatho-depression via a neuro-humoral TRPV1-dependent and tachykinin mediated renal afferent pathway. We now wanted to test the hypothesis that high sodium intake impairs this afferent sympatho-depressory mechanism.

**Methods:** Respective groups were put on tap water, 9.9 % saline for drinking or Chow containing 8% NaCl. Cultured dorsal root ganglion neurons (DRG TH11-12.4) of rats with renal affers were investigated in current clamp mode to assess action potential generation during current injection. Rats with femoral catheters for blood pressure (BP) & heart rate (HR) assessment, drug application, a renal arterial catheter for intrarenal administration (IRA) of NaCl boli (10 % NaCl, 10 µl) or Capsaicin (CAP 3.3, 6.6, 10, 33*10-7 M, 10 µl) and a bipolar electrode for renal sympathetic nerve activity (RSNA) recordings; eventually an intravenous (iv) bolus of the NK1-receptor blocker RP67580 (10*10-3M, 15 µl) was administered. Results are means±SEM.

**Results:** In neurons from rats on 8% NaCl, but not on 0.9 % saline or controls the relation of tonic highly active neurons to less active neurons shifted towards less active units. (62% tonic neurons in the control group and 65% tonic neurons in the saline group vs. 40% tonic neurons in the high salt group, p=0.05, t-test, mean±SEM). However, cultured renal neurons from rats on 0.9% saline on or on 8% NaCl exhibited increased action potential generation during activation (controls 13.3/3.1#APs/400ms vs. 0.9% saline 19.8/2.33#APs/400ms vs. high salt diet 22.2/=4.54 APs/600ms, p=0.05, t-test, mean±SEM). 10% NaCl bolus IRA induced decreases of RSNA from baseline 4.1±0.6 µV*sec to 2.2±0.8 µV*sec impaired in rats on 8% NaCl. (Suppressed RSNA by an iv. NK1-inhibitor).

**Conclusions:** In rats on a high salt diet the number of highly active tonic neurons with regards to the number of the neurons in vitro decreased at the expense of less active phasic neurons in spite of tonic neurons producing more action potentials upon stimulation in the group on 8% NaCl. The sodium inducible long-lasting sympatho-depression via a neuro-humoral tachykinin mediated afferent renal nerve pathway was eventually impaired.

**Funding:**

**SA-PO318**

**Late-Onset Presentation of Severe Hypokalemic Hypertension Resistant to Mineralocorticoid Antagonism**

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**Introduction:** We are presenting rare case of secondary hypertension who presented with muscle cramps and severe hypokalemia treated with ENaC (epithelium sodium channel) blocker.

**Case Description:** A 45-year-old Caucasian lady was referred to clinic for management of refractory hypokalemia, uncontrolled blood pressure and metabolic alkalosis. She was complaining of intermittent muscle cramps. She was a healthy patient until 2017, when she was diagnosed with hypertension. Home medications were spironolactone 50 mg once daily, potassium chloride 20 mEq four times daily, clonidine 0.2 mg three times daily, lisinopril 20 mg once daily, amlodipine 10 mg, hydralazine 100 mg three times daily. There had been several emergency room visits for muscle cramps and uncontrolled blood pressure. Family history revealed mother died of heart attack at the age of 54 years. Father had problems of low potassium and a heart attack at a young age. Vitals revealed temperature of 98.6° F, blood pressure 143/100 mmHg, heart rate 87 bpm, respiratory rate 16 per minute breathing on room air. Examination showed no edema and no renal, abdominal or other abnormalities. Review of labs over the previous 2 months showed Na141-143, K 2.8-3.6, bicarbonate 23-27 mEq/L, BUN 6 mg/dL, creatinine 0.56 mg/dL, aldosterone 4.6 ng/dL and 5.4 ng/dL, plasma renin activity <0.6 ng/mL/hr (checked twice), random cortisol was 0.6 – 4.6 ug/dL, urine potassium 13.5 mEq/L. Renal ultrasound along with renal artery doppler, angio-ct scan of head, MRI and MRA of the head and neck revealed with in normal findings. Stopped spironolactone and started amiloride 5 mg daily. Over the next few days, blood pressure dropped to ~120-120/80-80’s. Lisinopril, hydralazine, spironolactone and potassium supplements were stopped and clonidine was weaned off. Follow up labs in one week after starting amiloride showed potassium 4.2. Thereafter patient was advised to check blood pressure twice per day and closely followed.

**Discussion:** Epidural channel blockade improved blood pressure and electrolyte abnormalities significantly suggesting either Liddle syndrome (autosomal dominant) or apparent mineralocorticoid excess (autosomal recessive) which typically presents in childhood. Our case illustrates a rare case of hypertension having at this age which is associated with hypokalemia and metabolic alkalosis that is not amenable to mineralocorticoid blockade.
**SA-PO319**

**Dietary Salt Modifies the Blood Pressure Response to Renin-Angiotensin Inhibition in Experimental CKD**

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**Background:** Salt-sensitive hypertension is a hallmark of chronic kidney disease (CKD). The role of dietary salt and the renin-angiotensin system (RAS) in the pathogenesis of salt-sensitive hypertension in CKD is incompletely understood. Our aim was to dissect the role of dietary salt and the RAS in a rat model of hypertension and CKD.

**Methods:** Sprague Dawley rats were subjected to $5\%$ nephrectomy, allowed to recover for four weeks, and subsequently subjected to one of four treatments: (1) vehicle, (2) adrenalectomy (Adx), (3) Adx + losartan (30 mg/kg/d), or (4) spironolactone (80 mg/kg/d). These interventions were performed either under normal dietary salt ($0.4\%$ NaCl) or high salt ($4\%$ NaCl) conditions. Mean arterial pressure (MAP) was measured by radiotelemetry, GFR by transcutaneous FITC-sinistrin clearance, and skin sodium (Na+) by flame photometry after dissolving skins in nitric acid and hydrogen peroxide.

**Results:** On a high salt diet, BP was resistant to RAS intervention, except for an attenuated BP rise in rats receiving sinistrone (Figure). On a normal salt diet, BP kept increasing with vehicle, but stabilized with Adx and sinistrone. Adx + losartan reduced BP remarkably. On a high salt diet, sinistrone prevented Na+ accumulation in skin. For all groups, skin Na+ correlated positively with heart weight.

**Conclusions:** High salt increasesBP in CKD in part via direct effects on the mineralocorticoid receptor. Under normal salt conditions, however, hypertension in CKD depends on the combined effects of angiotensin II and aldosterone. Dietary salt modifies the BP response to RAS interventions in CKD, and accumulates in the skin. Our observations may have both therapeutic and prognostic implications for human CKD.

**SA-PO320**

**The Effects of Sacubitril and/or Valsartan on Renal Disease Progression in Salt-Sensitive Hypertension**

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**Background:** Available medications, such as diuretics and renin-angiotensin system (RAS) blockers, are often insufficient to control the blood pressure (BP) in the salt-sensitive (SS) hypertensive subjects. Abundant data support a pathogenic role for a low level of Atrial Natriuretic Peptide (ANP) in SS hypertension; ANP is known to promote renal sodium excretion, vasodilation, and BP reduction. The goal of this project was to test if reduced BP in SS hypertension is also achieved by administration of sacubitril/valsartan.

**Results:** In SS mice fed a high fat diet (HFD) (60%) or maintained on normal diet (CTL), systolic BP was increased by approximately 3 mmHg. After 16 weeks, mice were divided into three groups for 8 more weeks with either: (i) HFD; (ii) normal diet (HFD-STOP); (iii) normal diet plus Finerenone 1 mg/kg/day in the food (HFD-STOP+FINE). Treating SS mice with Finerenone decreased systolic BP by approximately 10 mmHg in each group as compared with the respective control group.

**Conclusions:** Finerenone improves cardiovascular risk factors in SS mice. When administered as a monotherapy, Finerenone improved vascular function and renal stress indices in SS mice. Further mechanistic studies of the effects of sacubitril in the setting of SS hypertension are warranted in order to determine if pharmacological increase of circulating ANP level is a feasible therapeutic approach to further decrease the progression of the disease.

**Funding:** NIDDK Support

**SA-PO321**

**Adrenal Hyperplasia, Hormonal Disturbance, and Salt-Sensitive Hypertension in a Novel Rat Model with Glucocorticoid Resistance Syndrome**

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**Background:** Glucocorticoid resistance is often due to glucocorticoid receptor (GR) haploinsufficiency, and is characterized by partial target tissue resistance to glucocorticoids. In human, an elevation in circulating glucocorticoids may cause the development of hypertension and, in some cases, obesity and sterility.

**Methods:** So far, no animal model mimics all features observed in human generalized glucocorticoid resistance. To address the impact of GR haploinsufficiency on adrenal gland function, steroid expression and development of hypertension, we generated rats carrying a deletion within the second zinc finger of the GR, named GR$^{+/em2}$ (Ponce de Leon. A.V. et al. [Stem Cells 2014]).

**Results:** Heterozygous mutant GR$^{+/em2}$ rats showed a monolateral adrenal hyperplasia with hyperplakemia, an increase of plasmatic aldosterone ($0.47\pm 0.018$ nM vs $0.39\pm 0.019$ nM, p=0.01), plasmatic corticosterone ($576\pm 88.96$ nM vs $332\pm 75.45$ am, p=0.05; 1000 nM vs $61.41$ nM vs $615\pm 99.11$ nm, p=0.05), plasmatic 11-deoxycorticosterone ($76.6\pm 5.24$ nM vs $50.3\pm 5.97$ nm am, p=0.001; 1018.8 $\pm 4.02$ nM vs $74.6\pm 5.63$ nm, p=0.01) despite a normal activity of the 11-$\beta$-hydroxysteroid-dehydrogenase II ($GR^{+/em2}$ vs $15$, $GR^{+/em2}$ vs 8). Furthermore, GR$^{+/em2}$ mutant rats develop salt-sensitive hypertension followed by an increase of arterial stiffness, kidney weight and blood pressure. In addition, RNA-seq analysis reveals disturbances in 41 genes (21 up, 20 down regulated) implicated in e.g. adrenal gland architecture and steroid biosynthesis. We currently focus on these identified candidate genes implicated in adrenal gland function and we perform electrophysiological measurements on primary adrenal cells upon stimulation with angiotensin II and potassium chloride to determine the cell depolarization capacity in these cells.

**Conclusions:** In summary, we demonstrated that GR$^{+/em2}$ mutant rats are useful to study GR haploinsufficiency and the underlying mechanism leading to adrenal gland hyperplasia. We confirmed the role of the GR in the development of salt-sensitive hypertension. We are currently studying identified new candidate genes leading to salt-sensitive hypertension in this rat model.

**Funding:** Government Support - Non-U.S.

**SA-PO322**

**Finerenone Improves Cardiovascular Benefits After Diet Normalization in a Mouse Model of High-Fat Diet-Induced Obesity**

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**Background:** Patients with obesity exhibit high prevalence of Heart Failure with preserved Ejection Fraction (HFpEF). We hypothesized that the non-steroidal mineralocorticoid receptor (MR) antagonist Finerenone further improves cardiac function after normalization of the diet in obese mice.

**Methods:** B6D2 male mice were fed a High Fat Diet (HFD) (60%) or maintained on normal diet (CTL). After 16 weeks, obese mice were divided in 3 groups for 8 more weeks with either: i) HFD; ii) normal diet (HFD-STOP); iii) normal diet plus Finerenone 1 mg/kg/day in the food (HFD-STOP+FINE). After 16 weeks of HFD-treatment showed an increased cardiac filling pressure (LV-End-Diastolic-Pressure, LVEDP: $2.73\pm 0.16$, 4.73±0.34 mmHg, p=0.001) and impaired LV compliance (LV-End-Diastolic-Pressure-Volume-Relation, LVEDPVR: $1.19\pm 0.26$, 4.77±0.31 mmHg/RVU, p=0.001) without (5) alteration of the LV fractional shortening (LVFS) and reduced exercise ability in a stress-test on treadmill. These features are typical of HFpEF. Decreased LV Fractional Shortening developed if HFD is continued for 8 weeks more. Switching HFD to normal diet from weeks 16 to 24 improved LV compliance which was further improved by FIN (LVEDP: HFD-STOP 3.44±0.39, HFD-STOP/FINE 2.28±0.23 mmHg/RVU; p=0.05) as well as the reduction in LV fibrosis (IS-BrdU, CTL 0.21±0.02, HFD 0.47±0.12, HFD-STOP 0.28±0.03, HFD-STOP+FINE 0.23±0.02 mmHg; p<0.05). Only the FIN treatment on top of diet normalisation improved LV filling pressure (LVEDP: $2.73\pm 0.16$, 4.73±0.34, HFD-STOP/FINE 4.53±0.33, HFD-STOP+FINE 3.18±0.26 mmHg/RVU; p=0.05), Fractional Shortening, Cardiac Output, and Coronary Reserve (GR, CTL 3.7±0.72, HFD 1.00±0.33, HFD-STOP 1.19±0.25, HFD-STOP+FINE 2.78±0.67 ml/min/g; p<0.05) and total running distance. Renal function is not altered by HFD. Expression of some renal injury markers are increased and improved by HFD STOP without further additional effects of FIN.

**Conclusions:** After normalization of diet following HFD-induced obesity, Finerenone improved LV compliance, LV filling pressure, Coronary Reserve and

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.**

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exercise performance thereby indicating benefit of Finerenone in HFpEF associated to exercise capacity.

**Funding:** Commercial Support - Bayer AG, Government Support - Non-U.S.

**SA-PO323**

**Windkessel Modeling-Based Estimation of Intraluminal Pressure Using Passively Measured Renal Arterial Pressure and Flow Velocity in Humans**

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**Background:** Glomerular hyperfiltration due to a combination of failed autoregulation and progressive glomerulosclerosis is important in the pathogenesis of chronic kidney disease (CKD). Although prevention is widely recommended in current guidelines, up to now it is only possible to measure intraluminal pressure (Pglom) directly in animal models. We hypothesized that renal arterial compliance and Pglom can be estimated from proximal renal arterial measurements.

**Methods:** Pressure and flow velocity were recorded in patients with a clinical indication for either coronary or renal angiography. The data was acquired under baseline conditions and after hyperemia induced by dopamine 30 µg/kg intravenous. This was further analyzed using an adapted 3-element Windkessel model, consisting of compliance, impedance, afferent resistance and Pglom.

**Results:** We included 33 subjects with a median age of 58 years (IQR 52-65), eGFR of 85.9 mlf/min/1.73m², 31% had microalbuminuria. In 4 patients, a renal artery stenosis was found. The model predicted a mean Pglom of 47.7 ± 11.9 mmHg at baseline. After induction of hyperemia, flow increased by 90% (95%CI 66-153%) and a 172% (95%CI 181-309%) increase in renal perfusion pressure (RPP). Patients with diabetes had a significantly higher Pglom of 10.8 (95%CI 5.3-15.5) mmHg, after correction for a significant positive association with BMI (0.81, 95%CI 0.37-1.59) and renal perfusion pressure (0.40, 95%CI 0.22-0.59).

**Conclusions:** This model enables determination of parameters for the renal macro- and microcirculation using proximal pressure and flow measurements, which could be useful to identify patients at risk for CKD.

**SA-PO324**

**Indole-3-Methanol, a Dietary Constituent, Suppresses Uremic Toxicity of Indoxyl Sulfate**

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**Background:** Indoxyl sulfate (IS), a homofallic uremic toxin, mediates its vasculotoxicity in chronic kidney disease (CKD) patients through activation of the Ah receptor (i.e., a non-receptor tyrosine kinase (NRTK)). This approach, with the AHR-TF–thrombosis axis as a readout. A set of indolic compounds, including IS bioisosteres were analyzed in a three-tiered system along with validation in two human cohorts. This study employed three distinct animal models and two human cohorts to establish the role of the lead analog.

**Results:** Replacement of the sulfate moiety abrogated IS-mediated AhR-TF activation. Notably, of all the analogs, Indole-3-methanol (a.k.a. indole-3-carbinol or “I3M”) showed a dose-dependent inhibition of the AhR-TF axis and suppressed IS-induced AhR activation and carotid artery thrombosis in discrete animal models. Mechanistically, I3M reduced TF protein without downregulating its mRNA. I3M suppressed TF in cells specifically in sera from CKD patients compared to the non-CKD controls, and the extent of TF suppression correlated with their levels of IS. I3M inhibited TF in vascular smooth muscle cells in response to pre-intervention sera from subjects who had developed post-angioplasty thrombosis from a sub-endothelial of a Thrombosis in Myocardial Infarction-II trial.

**Conclusions:** This study demonstrates the importance of the IS sulfate group, and reveals I3M, as a suppressor of prothrombotic properties of IS. I3M is a naturally occurring phytochemical found in cruciferous vegetables that is a rich source of indole-based glucosinolates. These results can guide future campaigns to develop targeted therapies such as compounds against IS and plant-based diets that can be personalized to the blood IS levels in CKD patients.

**Funding:** Other NIH Support - NIH R01

**SA-PO325**

**Precision Medicine: Lanosterol Synthase Gene Polymorphisms Affect Body Na⁺ in Salt-Sensitive Hypertension**

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**Background:** For decades, it has been widely accepted that initiation of salt-induced hypertension involves a type of kidney dysfunction (natriuretic handicap) which causes salt-sensitive subjects to excrete less of a sodium load than normal subjects and to undergo abnormal increases in cardiac output, and therefore in blood pressure (BP). Our research group has reported that a Lanosterol Synthase (LSS) gene variant influences both the salt sensitivity of BP and changes in circulating Endogenous Ouabain (EO) in response to a low salt diet. Aim of the study is to explore the role of LSS genotypic variants comparing salt-sensitive (SSH) with salt-resistant (SRH) hypertensive patients for their impact on body Na⁺.

**Methods:** A large cohort (n=807) of naïve hypertensive patients (NHP) was phenotyped for salt sensitivity by giving NaCl 308 mEq 2/kg iv. Total body Na⁺ at the end of infusion (T120) and after recovery (T240) was assessed by calculating the differences between Na⁺ infused and urinary excretion.

**Results:** 516 SRH display a decrease in systolic BP (-0.63±0.2 mmHg), while in 291 SSH, SBP increases of 11.8±4.2 mmHg. Meanwhile, there was no difference in total body Na⁺ in both groups, 254.7±5.14 mEq in SRH patient and 254.0±2.03 mEq in SSH group. Moreover, LSS rs225424 AA/AC carriers retained more body Na⁺ both at T120 and T240 (255±1.52 and 255±1.6 mEq) than LSS CC wild-type carriers (256±1.72 and 251±1.6 mEq; p<0.01).

**Conclusions:** LSS gene contributes to maintaining a positive Na⁺ balance in SSH. In the precision medicine era, LSS gene may be considered as a “natriuretic handicap” gene.

**SA-PO326**

**Different Forms of Afferent Nerve Input in Cardiac and Renal Disease in Rats?**

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**Background:** Afferent nerve pathways form kidney and heart likely control sympathetetic renal nerve activity. In renal disease (anti Thy1 nephritis) the responsiveness of afferent renal nerve units was shifted from units with highly active primary neurons (tonic response pattern) to units with neurons of very low activity upon stimulation (phasic response pattern). Afferent renal nerve activity was likely decreased. Likewise, afferent vagal nerve activity in congestive heart failure (CHF) had a lower frequency at saturation than controls. Hence we wanted to test the hypothesis that in CHF the vagal afferent nerve pathway consists of a decreased number of highly active tonic sensory neurons in the nodose ganglion.

**Methods:** CHF was induced by coronary artery ligature, nephropathy by injections of an anti Thy1 antibody (OXT, 1.2mg/kg). After a respective time (CHF 21 days, nephropathy 7 days after induction) nodose ganglion neurons with cardiac vagal afferents from CHF rats or neurons form dorsal root ganglia with renal afferents from rats with nephropathy were cultured. Current clamp was used to characterize neurons as “tonic”-.
i.e., sustained action potential (AP) firing or “phasic,” i.e., <5 APs upon current injection. Electrochemical physiological parameters and AP properties were determined in neurons from animals with CHF or nephropathy.

**Results:** In CHF rats, the number of neurons with a tonic, more active response pattern from CHF animals did not differ from controls (64% vs. 70%, n.s.). However, tonic cardiac neurons in CHF rats exhibited an increased action potential amplitude compared to controls (24.4±5.0 vs. 14.7±1.8 APs/100 µs; p<0.05; mean±SEM). In nephropathy, the number of neurons with a tonic response pattern decreased significantly (43% vs. 64%, p<0.05), but there was no difference in action potential production as compared to controls.

**Conclusions:** In contrast to our hypothesis, in CHF the number of afferent neurons with a tonic response pattern was not altered, instead the active action potential production of these neurons increased increased upon stimulation. Hence, in congestive heart failure vagal afferent neurons increase their sensitivity in the presence of impaired intracardiac receptors whereas in renal disease the responsiveness of the first part of the afferent pathway is impaired as a whole

**SA-PO332**

**Afferent Peptidergic Nerve Fibers: Importance for the Salt Metabolism Beneath the Kidneys?**

Tilmann Ditting,1,2 Kristina Rodionova,1,3 Christian Ott,1 Roland E. Schnieder,1 Mario Schiffer,1 Kerstin U. Amann,1 Roland Veelken,1,2 Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; 1Paracelsus Private Medical School, Nuremberg, Germany.

**Background:** Sodium can be accumulated without commensurate water retention in the skin (non-osmotic sodium storage). Macrophages play a pivotal role in this context and their depletion can induce salt-sensitive hypertension. On the other hand renal afferent peptidergic nerves are involved. Since the skin is also densely innervated by afferent peptidergic nerves we hypothesized that high salt diet might enhance the release of neuropeptides from these nerve fibers

**Methods:** In a cross-over design, two groups of rats (n=4, each) were fed either low salt diet (LS) or high salt diet (HS) for 4 weeks and then exposed to high salt diet (HS) 8% with free access to 0.9% saline as drinking water. After 14 days a skin sample (3x3mm) of the groin area was excised, and the diet was switched for another 14 days. Then a contralateral skin sample was taken. Tissue analyzed in an organ-bath and calcium ion gene related peptide (CGRP) content in the supernatant was measured with ELISA. After two baseline measurements within 5 min, the tissue was superfused with hypertonic saline (1.5ng/g skin; *p<0.05). After diet switch the results were similar: baseline LS 1.1 ng/g skin, with HS diet the release was higher again (LS 19.7±2.1 vs. HS 29.3±1.7 ng/g skin; *p<0.05).

**Results:** Salt diet sensitized neuropeptide release from peptidergic sensory nerves in the skin. Hence peptidergic afferent nerves might be an integrated body-wide system involved in sodium handling in very different target areas like skin and kidney. Putative peptidergic mechanisms (vasoregulation, chemotaxis) remain to be determined in this respect.

**SA-PO328**

**Urineal Plasmakins Play Pathogenic Roles for the Development of Hypertension in Dhal Salt-Sensitive Rats**

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**Background:** The epithelial sodium channel (ENaC) in the renal collecting duct plays pivotal roles in the regulation of renal K+ excretion by controlling sodium and volume delivery to the distal nephron. We examined whether inhibition of the basolateral K+ channels with Ba2+ has a distinct function other than BP modulation in response to pathological stimuli.

**Methods:** In the isolated DCT by establishing the Cl-sensor contains both a chloride-sensitive YFP moiety modified from Chlomeleon. The Cl-sensor contains both a chloride-sensitive FFP moiety as well as a chloride-insensitive CFP moiety, allowing ratiometric estimation of [Cl-].

**Results:** We first measured the [Cl-]i in the isolated DCT by establishing the Cl-sensor. A chloride-sensitive fluorescent protein modified from Chloromelon. The Cl-sensor contains both a chloride-sensitive FFP moiety as well as a chloride-insensitive CFP moiety, allowing ratiometric estimation of [Cl-].

**Conclusions:** Our results indicate that the intracellular Cl- concentrations in DCT cells are low at baseline and that the depolarization decreases whereas hyperpolarization decreases the intracellular Cl- concentration. These changes in DCT voltage are associated with alteration of intracellular Cl- concentrations.

**Funding:** NIDDK Support, Private Foundation Support

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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Assessment of Sublingual Microcirculation with the GlycoCheck System: Reproducibility and Examination Conditions

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Background: The glyocalyx is an extracellular layer lining the lumen of the vascular endothelium including the glomerular capillaries. It protects the endothelium from shear stress and atherosclerosis and contributes to coagulation, immune response and micro-vascular perfusion. Degradation of the glyocalyx is a part of several renal disease processes and ultimately results in proteinuria. The GlycoCheck system is a new method to estimate the glyocalyx’s thickness in vivo from perfused boundary region (PBR) and microvascular perfusion (red blood cell (RBC)-filling) via a video camera coupled to a computer with integrated software. We evaluate reproducibility and influence of examination conditions on measurements with the GlycoCheck system.

Methods: Open-labelled randomised, controlled study including 42 healthy smokers investigating day-to-day, side-of-tongue and inter-investigator variance and influence of smoking, high calorie meal and coffee on PBR and RBC-filling at intervals from 0-180 minutes.

Results: The mean(SD) age was 24(6.1) years and 52% were male. There was no significant intra- or inter-investigator variance for PBR or RBC-filling and no for PBR for side-of-tongue. A small variance was found for day-to-day, PBR (0.012µm, p=0.007)/ RBC-filling (0.003%, p=0.005) and side-of-tongue, RBC-filling (0.025%, p=0.009). Significant influence of cigarette smoking (from 40-180 minutes), high calorie meal intake and coffee consumption was found, the latter two peaking immediately and tapering off but remained significant up to 180 minutes, highest PBR changes for the three being 0.042µm (p<0.05), 0.183µm (p<0.001) and 0.160µm (p<0.05), respectively.

Conclusions: Measurements with the GlycoCheck system have an acceptable reproducibility, even with day-to-day variability. Smoking, diet and coffee had influence on measurements of up to 180 minutes, thus abstinence is recommended at least 180 minutes before measurements. Future studies will address impact of renal disease and renal-protective intervention on glyocalyx but should standardise measurement conditions.

Funding: Private Foundation Support

Impact of Oxidative Stress on Vascular Calcification in the Setting of Coexisting CKD and Diabetes Mellitus

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Background: Vascular calcification is a crucial complication in patients with chronic kidney disease (CKD). Particularly, CKD patients with diabetes mellitus (DM) manifest severe vascular calcification but its precise mechanisms are poorly understood. It has been reported that oxidative stress plays a key role for the progression of vascular calcification. In the present study, we investigated the pathophysiological mechanisms underlying vascular calcification in the setting of coexisting CKD and DM, particularly from the perspective of oxidative stress.

Methods: Sprague-Dawley rats were randomly divided into six groups as follows: (i) control rats (control group), (ii) 5/6 nephrectomized rats (CKD group), (iii) streptozotocin (STZ) injected rats (DM group), (iv) 5/6 nephrectomized and STZ injected rats (DM+CKD group), (v) DM+CKD rats treated with insulin (DM+CKD+INS group), (vi) DM+CKD rats treated with apocynin, which is an inhibitor of NADPH oxidase (DM+CKD+APO group). All groups were fed a high phosphate diet from 11 weeks of age. At 18 weeks, the rats were sacrificed for blood and urine analysis, histopathological analysis and evaluating mRNA expressions of oxidative stress and osteoblast differentiation-related markers in the aorta.

Results: Von Kossa-positive mineralized area and calcium content of aorta were significantly increased in the DM+CKD group compared to the control, CKD and DM groups at 18 weeks. However, despite high serum glucose levels control, apocynin treatment prevented the progression of vascular calcification. The mRNA expressions of RUNX2 and ALP and the number of RUNX2-positive cells in the aorta were significantly increased in the DM+CKD group compared to the control, CKD and DM groups. Similarly, these expressions were significantly reduced by apocynin treatment. As for the assessment of oxidative stress, urinary excretion of 8-hydroxydeoxyguanosine (8-OHdG), the number of 8-OHdG-positive cells in the aorta, and the mRNA expressions of NOX4 and NADPH p2 phox were significantly decreased in the DM+CKD+APO group compared to the DM+CKD group.

Conclusions: Our results suggest that coexisting CKD and DM accelerates vascular calcification mainly by increased oxidative stress.

The Circadian Clock Provides Beneficial Effects Against the Endothelial Dysfunction to Promote Atherogenesis by Regulating Angiotensin II Generation and Vascular Endothelial Growth Factor Expression

Hideyuki Negoro.1 Harvard Medical School, The Graduate School of Project Design, Tokyo, Japan.

Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial wall. The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial wall.

Results: We estimated the prevalence, level of awareness and hypertension control in the entire cohort was 53.7%. Of those with hypertension, 70.4% were aware of their diagnosis of hypertension, 54% were on medication on medication while 32.3% had controlled blood pressure to <140/90mmHg.

Results: The prevalence of hypertension in the entire cohort was 53.7%. Of those with hypertension, 70.4% were aware of their diagnosis of hypertension, 54% were on medication on medication while 32.3% had controlled blood pressure to <140/90mmHg.

Funding: NIDDK Support, Other NIH Support - NHLBI

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Hideyuki Negoro.1 Harvard Medical School, The Graduate School of Project Design, Tokyo, Japan.

Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial wall.
structure and vascular stiffness. Chronic circadian clock disruption is also associated with dysfunction in endothelial signaling and responses. In this study, we observed that the deletion of Bmal1, a critical component of the circadian clock, can influence growth factors, such as Angiotensin II or Vascular Endothelial Growth Factor (VEGF) which play an important part in the progression of vascular diseases.

Results: Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was an increase in Angiotensin II and VEGF expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display premature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include Angiotensin II and VEGF, which are significantly elevated in Bmal1 KO mice. We also confirmed that PDK6 levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating Angiotensin II and VEGF expression. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Government Support - Non-U.S.

SA-PO336

A Novel and Reproducible Model of CKD-Induced Vascular Calcification in Mice
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Background: Vascular calcification remains a frequent complication of advanced chronic kidney disease (CKD) and a leading cause of morbidity and mortality in this population. Various animal models have been introduced to induce CKD and study the pathomechanism of vascular calcification. The most commonly used such model in rodents is 5/6 nephrectomy followed by using high phosphate diet. However, the 5/6 nephrectomy in mice is markedly challenging and results are seldom consistent.

Methods: To address this challenge, we sought to examine a novel model of vascular calcification where ten-week-old mice with DBA2 background that are prone to vascular calcification, underwent unilateral ischemia reperfusion injury (UIRI) for 25 minutes followed by complete right nephrectomy after one week. The control group underwent sham surgery and both groups were fed high phosphate diet (0.6% Ca, 0.9% P) for twelve weeks at which point mice were sacrificed for analysis.

Results: While serum creatinine did not reveal significant changes (treatment group: 0.12 ± 0.01 mg/dL vs control group: 0.13 ± 0.03 mg/dL), glomerular filtration rate measurements (GFR) were lower in the treatment groups (treatment group = 187.68 ± 31.99 mL/min vs control group = 230.99 ± 18.53 mL/min). Furthermore, proteinuria analysis on aorta of the mice demonstrated significant upregulation of osteomark markers including osteocalcin, alkaline phosphatase, and osteoblast specific transcription factor, cbfa-1.

Conclusions: Our findings suggest that UIRI followed by nephrectomy is a feasible and reproducible model of vascular calcification associated with CKD that would enable study of various transgenic mice to better understand the mechanism pathways involved in mineralization of vascular tree and targeting novel therapeutics.

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SA-PO337

Bariatric Surgery Alters Fibroblast Growth Factor 21 and the Renin Angiotensin System in Patients with Obesity
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Background: Obesity is associated with overactivation of the renin-angiotensin system (RAS). Recent studies have shown that fibroblast growth factor 21 (FGF21) presents an anti-inflammatory and anti-diabetic action. However, the effect of bariatric surgery on FGF21/RAS in morbid obesity has not been investigated in detail. In this study, we examined the relationship between circulating FGF21 and Ang II/A2E/Ang(1-7) in patients with obesity after bariatric surgery.

Methods: We prospectively enrolled obese patient who underwent bariatric surgery and age-sex matched healthy volunteers (HVs) (n=12) each. Serum FGF21, Ang II, ACE2, and Ang (1-7) levels were measured by enzyme-linked immunosorbent assay kits. We measured also FGF-21, Ang II, ACE2, and Ang (1-7) 6 months after bariatric surgery in obese patients (n=12).

Results: Ang II and ACE2 levels were significantly higher in obese patients compared with HVs, (p = 0.001, 0.001) and decreased after bariatric surgery (p = 0.002). There was no significant difference in Ang (1-7) between obese patients and HVs (p = 0.887). Although Ang (1-7) levels did not change after bariatric surgery (p = 0.480), changes in Ang (1-7) levels were positively correlated with changes in body mass index (BMI) (R² = 0.580, p = 0.048)(Fig. 1).

Conclusions: Bariatric surgery reduced the elevated systemic Ang II, FGF21 and ACE2 levels in obese patients. A decrease in BMI after bariatric surgery was associated with a reduction in Ang (1-7) levels.

Funding: Government Support - Non-U.S.

SA-PO338

Patrolling Monocyte Subsets in Patients with CKD and Coronary Heart Disease
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Background: Chronic low-grade inflammation is prevalent in Chronic Kidney Disease (CKD) patients and plays a role in the development and progression of cardiovascular diseases. Monocytes are key factors in atherosclerosis progression and can be classified into subtypes based on their profiles of LPS co-receptor CD14 and FcγRII CD16 expression. The aim of this work is to analyze circulating monocytes subsets in CKD patients with atherosclerotic coronary artery lesions undergoing coronary Artery Bypass Surgery (CABG).

Methods: A prospective Case-Control study was conducted in CABG patients. Controls were patients with non-coronary lesions undergoing valve repair heart surgery. The expression of CD14+ and CD16+ antigens were analyzed by flow cytometry in peripheral blood mononuclear cells. A sample of perivascular adipose tissue and a punch from aorta were also obtained from patients included in the study.

Results: A total of 72 CABG patients (56 males) from which 40 suffered CKD (stages 3 to 5) and 26 non-coronary surgery controls (17 males) from which 11 patient suffered CKD were included. Here, we show the flow cytometry analysis. The proportion of classical CD14+/CD16- monocytes (78.5±11% in CKD vs 75.9±12.1% in controls; p=0.3), CD14+/CD16+ (10.8±8.5% in CKD vs 12.9±7.9 in controls; p=0.64), CD14+/CD16+ (10.9±6.6 vs 11.1±5.2 %; p=0.9) was similar in CABG than in controls. CKD was associated with a depletion of the CD14+CD16+ subset (CD14+/CD16-: 76.4±12.5% in patients without CKD; n=50, vs 78.6±10.1% in CKD, n=48; p=0.4; CD14+/CD16+: 11.2±8.1% without CKD vs 11.7±8.8% in CKD; p=0.4; and CD14+/CD16+: 12.4±4.7 vs 9.7±4.5 %; p=0.026). The depletion of CD14+CD16+ monocytes showed a significant negative correlation with systolic arterial pressure (R=0.374, p=0.0001).

Conclusions: CKD and systemic arterial pressure were associated with a depletion in CD14+/CD16+ monocytes in peripheral blood of patients. Next, we plan to study the expression of adhesion molecules in the surface of the CD14+/CD16+ monocytes to determine their ability to adhere to endothelial cells.

Funding: Government Support - Non-U.S.

SA-PO339

Deficiency of the Anaphylatoxin Receptors C5aR2 and C3aR Aggravates Hypertensive Renal Injury
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Background: Complement drives the host defense against microbes and mediates inflammatory responses. In addition, recent data also support a role for complement in arterial hypertension. During the activation and amplification of the complement cascade, the anaphylatoxins C3a and C5a are released and trigger pro-inflammatory signaling

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
via their corresponding receptors. We recently described that C5a receptor 1 deficiency ameliorates hypertensive renal injury. However, the role of the second C5a receptor (C5aR2) and the C3a receptor (C3aR) in hypertension and hypertensive end organ damage remain unclear.

**Methods:** Expression of C5aR2 and C3aR on infiltrating and resident renal cells were determined using tandem reporter mice for either C5aR2 or C3aR by flow cytometry and confocal microscopy. The hypertension model of angiotensin II infusion in combination with unilateral nephrectomy and high salt diet was induced in Balb/c wildtype, C5aR2- and C3aR-deficient mice. The glomerular filtration rate (measured with tritiated inulin), albuminuria and glomerular damage were determined.

**Results:** Flow cytometric analysis of leukocytes isolated from the kidney of anaphylatoxin reporter mice showed C5aR2 expression on dendritic cells (34%), macrophages (30%) and neutrophils (14%) whereas dendritic cells are the major C3aR-expressing population (90%). C5aR2 and C3aR were also detected by confocal microscopy in the kidney only on infiltrating cells. Both anaphylatoxin receptor-deficient mice suffered from markedly increased renal injury after Ang II infusion with higher albuminuria, glomerular filtration rate and glomerular injury compared to hypertensive wildtype mice. The mortality in hypertensive C3aR-deficient mice was significantly higher than that observed in hypertensive wildtype or C5aR2-deficient mice and was associated with increased bleeding.

**Conclusions:** Our findings identify C5aR2 and C3aR expression on infiltrating (mainly monocytes/macrophages and neutrophils) but not on resident cells in the kidney. C5aR2 or C3aR deficiency was associated with strongly increased renal injury in response to arterial hypertension. Together, we propose that C5aR2 and C3aR mediate protective or homeostatic effects in hypertensive renal injury.

**Funding:** Government Support - Non-U.S.

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**SA-PO340**

Indoleamine 2,3-Dioxygenase-1, a Novel Therapeutic Target in Thrombotic Vasculitic Uremic Toxicity

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**Background:** Metabolites associated with chronic kidney disease (CKD) are highly thrombogenic. Emerging evidence validate CKD-specific mediators and defined the uremic solute aryl hydrocarbon receptor (AHR)-tissue factor (TF) axis resulting in increased thrombosis. Given the importance of tryptophan metabolites in inducing thrombosis via their corresponding receptors, we studied the role of the enzyme tryptophan dioxygenase (IDO), the rate limiting enzyme of the kynurenine pathway in CKD-mediated thrombosis.

**Methods:** Global IDO knock-out and wild type mice treated with 1-methyltryptophan (1-MT), a specific inhibitor of IDO, were used in an adenine-induced model of CKD. Plasma uremic solutes were measured by LC/MS. IDO protein and mRNA were examined in vascular smooth muscle cells (vSMCs) and in flow-loops. Prothrombotic effects of IDO were further confirmed in clinical, Dialysis Access consortium (DAC)-fistula and Thrombolysis in Myocardial Infarction (TIMI)-II.

**Results:** Compared to IDO−/− mice, IDO+/+ mice showed a significantly increased time to occlusion (TTO) in both non-CKD and CKD mice models (p<0.05). IDO−/− mice administered 1-MT in a CKD model had increased TTO compared to controls, supporting the role of IDO in thrombosis (p<0.05). Indoxyl sulfate (IS), a prothrombotic uremic solute, increased IDO expression in a dose-dependent manner in vSMCs in vitro and in vivo. IDO+ macrophages and IDO−/− vSMCs were compared in response to arterial hypertension. Together, we propose that IDO+/+ mice may serve as a monocyte/macrophage model for hypercoagulable disease (SNP, endothelium-independent vasodilator, 2/48ug/min). tPA release was measured during intra-arterial bradykinin (1000/3000ug/ml/min).

**Results:** AAV patients had a mean SD age of 55 ±13 years and 23 (72%) were male. The median (range) time from diagnosis was 4 (1-13) years and 17 (53%) were PR3+; 22 (69%) patients were prescribed a renin-angiotensin system block, and 21 (66%) were receiving ezetimibe and/or statin. Forearm blood flow increased dose-dependently during all infusions. AAV patients had reduced ACH-mediated vasodilation compared to controls (p=0.01 at peak dose, ~25% difference in area under the curve). Responses to SNP did not differ. Compared to controls, AAV patients had lower mean SD I-PA release (125±50 vs 65±52 ng/100ml/min at peak dose, p<0.001). tPA release was lower in PR3+ vs MPO+ patients (52±40 vs 90±70 ng/100ml/min, p<0.05), and in patients on maintenance immunosuppression compared to those on no immunosuppression (91±43 vs 54±50 ng/100ml/min, p=0.01), who had similar tPA release to controls.

**Conclusions:** AAV patients in long-term remission have significant endothelial dysfunction, comparable to that seen following myocardial infarction or in advanced CKD; this may partly explain their increased CVD risk. Targeting these with existing and novel therapies may improve long-term outcomes in AAV.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Online; Underline represents presenting author.

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**SA-PO342**

Lanosterol Synthase (LSS) Gene as a Predictor of Kidney Dysfunction in Hypertensive Patients

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**Background:** Hypertension (HYP) is one of the main causes of chronic kidney disease (CKD). Recently we have proposed LSS as genotype-based risk stratification to predict accelerated eGFR decay in essential HYP patients. We tried to find a confirmation of this result in an observational study on general population.

**Methods:** We extracted clinical data of a general population from HYPERGENES Consortium. We also collected genetic data for LSS polymorphism that was already demonstrated as involved in kidney damage.

**Results:** A cohort of 3137 subjects was selected. Incidence of HYP and CKD was 49.8% and 9.1% respectively. Patients with well-known no-HYP / no-angiosclerosis related CKD (as diabetes, glomerulonephritis, ADPKD), were excluded. Population was divided into 3 classes according to age. At different age, HYP status have a deep impact on eGFR. Indeed in young (< 50ys) eGFR is higher in HYP vs control (86.2±19.3 vs 82.7±16.3 ml/min; p=0.04); vice-versa in elderly (> 65ys) HYP have a reduction in eGFR (55.7±12.9 vs 71.0±12.9 ml/min; p=0.001). No direct influence of LSS polymorphism on eGFR was observed. When LSS is considered according to HYP status and age class it is possible to observe a preservation of age-associated eGFR reduction in normotensive patients (eGFR 91.4 vs 90.1 vs 81.8 ml/min for LSS risk allele); on the other side, LSS seems to enhance eGFR reduction associated with HYP status (eGFR 84.6 vs 75.6 vs 48.0 ml/min for LSS risk allele; p=0.032; fig. 1).

**Conclusions:** We confirmed on a large general population the involvement of LSS gene in enhanced eGFR loss in HYP patients. Indeed patients carrying the risk allele of this specific LSS polymorphism seem to express hyper-filtration if compared to their counterparts. When exposed to a specific pathological condition as HYP, with a further increase in eGFR in early phases, this could lead to an accelerated reduction in kidney function.

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**SA-PO341**

Mechanisms for Increased Cardiovascular Risk in Patients with ANCA Vasculitis in Long-Term Remission

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**Background:** Current treatments have improved the short-term survival of patients with ANCA-associated vasculitis (AAV), an autoimmune disease that often involves the kidneys. Long-term outcomes remain poor due to an increased risk of cardiovascular disease (CVD). AAV is defined by systemic endothelial injury but few clinical studies have robustly explored endothelial dysfunction as a contributor to CVD risk in these patients. We assessed brachial artery vasodilation and release of tissue plasminogen activator (tPA, an endogenous thrombolytic) as measures of endothelial function that predict CVD.

**Methods:** We recruited 32 AA V patients in long-term remission and 32 age- and sex-matched healthy controls into a prospective cohort study. Those with renal impairment, proteinuria, diabetes and overt CVD were excluded. Vasodilation was assessed by gold standard forearm blood flow during randomized intra-arterial infusions of acetylcholine (ACH, endothelium-dependent vasodilator, 7.5/15/30ug/min) and sodium nitroprusside (SNP, endothelium-independent vasodilator, 2/48ug/min). tPA release was measured during intra-arterial bradykinin (1000/3000ug/ml/min).

**Results:** AAV patients had a mean SD age of 55±13 years and 23 (72%) were male. The median (range) time from diagnosis was 4 (1-13) years and 17 (53%) were PR3+; 22 (69%) patients were prescribed a renin-angiotensin system block, and 21 (66%) were receiving ezetimibe and/or statin. Forearm blood flow increased dose-dependently during all infusions. AAV patients had reduced ACH-mediated vasodilation compared to controls (p=0.01 at peak dose, ~25% difference in area under the curve). Responses to SNP did not differ. Compared to controls, AAV patients had lower mean SD I-PA release (125±50 vs 65±52 ng/100ml/min at peak dose, p<0.001). tPA release was lower in PR3+ vs MPO+ patients (52±40 vs 90±70 ng/100ml/min, p<0.05), and in patients on maintenance immunosuppression compared to those on no immunosuppression (91±43 vs 54±50 ng/100ml/min, p=0.01), who had similar tPA release to controls.

**Conclusions:** AAV patients in long-term remission have significant endothelial dysfunction, comparable to that seen following myocardial infarction or in advanced CKD; this may partly explain their increased CVD risk. Targeting these with existing and novel therapies may improve long-term outcomes in AAV.

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SA-PO343
Plasma Leucine-Rich Alpha-2-Glycoprotein 1 Predicts Cardiovascular Disease Risk in ESRD
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Background: Plasma Leucine-Rich alpha-2-Glycoprotein 1 (LRG1) is an innovative biomarker for inflammation and angiogenic diseases. End-stage renal disease (ESRD) is associated with adverse outcomes including inflammation, atherosclerosis, and premature mortality. However, whether levels of plasma LRG1 correlate with the co-morbidities of ESRD patients is unknown.

Methods: Plasma LRG-1 and high-sensitivity C-reactive protein were analyzed by ELISA in samples from 169 hemodialysis patients from the Immunity in ESRD study (iESRD study). Through history taking and detailed chart reviews, baseline co-morbidities were recorded. Peripheral blood monocyte and T cell subsets were assessed by multicolor flow cytometry.

Results: In the univariate analysis, LRG1 was found to be associated with the existence of cardiovascular disease (CVD) and peripheral arterial occlusive disease (PAOD). In multivariate-adjusted logistic regression models, higher LRG1 tertile was significantly associated with PAOD (odds ratio = 3.49), CVD (odds ratio = 1.65), but not with coronary artery disease, history of myocardial infarction, or stroke after adjusting for gender, hemoglobin, diabetes, hypertension, and level of C-reactive protein. In addition, the level of LRG-1 positively correlated with IL-6 and CRP and more advanced T cell differentiation, indicating the participation of LRG1 in the progression of atherosclerosis.

Conclusions: The development of HTN in premature infants from AKI and thromboembolism is unrelated to phthalate exposure and to sodium transporter maturation. The onset of HTN for phthalate-exposed infant categories (pulmonary, medications, and CAKUT) occurs closer to an adjusted term age - more in line with activation and maturation of MR-dependent sodium transporter processes such as we reported for infants with unexplained hypertension. Phthalate exposure may be a major factor in influencing the onset of HTN amongst these categories of infant hypertension.

Diagnostic, time-course, and phthalate exposures by category for premature infants with hypertension

SA-PO345
Factors Determining Timing of Onset of Hypertension in Premature Infants
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Background: We recently demonstrated that phthalate-exposed premature infants with unexplained hypertension (HTN) had evidence of inhibition of 11-BHSD2, and secondary activation of the mineralocorticoid receptor (MR). Neither HTN nor increased sodium transporter expression occurred until an adjusted age closer to term, despite phthalate exposure weeks earlier. We tested the hypothesis that other types of HTN in premature infants might also present with a similar timeframe.

Methods: We reviewed charts of all premature infants with HTN at two tertiary-care centers during the last 8 years, excluding infants with unphthalated exposures, and single case categories: neurology and renal vein thrombosis. Analyses included HTN incidence, time-course of HTN, and phthalate exposure.

Results: 106 infants with 107 episodes of HTN were found. In both AKI and thromboembolism groups, HTN developed at an early chronological and postmenstrual age. Their phthalate exposure was small. In all other categories HTN presented near 40 weeks postmenstrual age, usually with low renin. Phthalated exposures were large in the pulmonary and medications, and moderate in the CAKUT group.

Conclusions: The development of HTN in premature infants from AKI and thromboembolism is unrelated to phthalate exposure and to sodium transporter maturation. Onset of HTN for phthalate-exposed infant categories (pulmonary, medications, and CAKUT) occurs closer to an adjusted term age - more in line with activation and maturation of MR-dependent sodium transporter processes such as we reported for infants with unexplained hypertension. Phthalate exposure may be a major factor in influencing the onset of HTN amongst these categories of infant hypertension.

Diagnostic, time-course, and phthalate exposures by category for premature infants with hypertension

SA-PO346
The Post-Stenotic Human Kidney Shows Microvascular Dropout and Remodeling
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Background: In animal models, post-stenotic kidney shows microvascular rarefaction, with loss of small outer cortical vessels correlating with limited kidney recovery after revascularization. However, whether stenotic human kidney shows microvascular loss is incompletely understood. We tested the hypothesis that Renal srtery stenosis (RAS) leads to microvascular remodeling in human kidneys.

Methods: Necropsy samples from 3 patients with obstructive RAS, & 5 discard donor kidneys (Lifesource, MN) as controls were collected after IRB approval. The renal arteries were cannulated & perfused at physiological pressure with an intravascular radiopaque contrast agent. The kidney was segmented, scanned with micro-CT at 20µm resolution, & 3D images reconstructed. Microvascular diameter & spatial density were quantified (Analyz3D). Cortical vessels were tomographically isolated to calculate tortuosity (ratio of path/linear length) as a measure of angiogenic activity & vascular immaturity.

Results: Age (55-65 yrs), sex, & body mass index were similar in both groups. Spatial density of medium & large cortical micro vessels (200-500µm in size) was significantly diminished in outer & inner cortex in Revascularization disease (RVD) compared with normal kidneys (Fig. 1A-B). RVD kidneys showed significant loss of small (<200µm) micro vessels in the outer cortex, as well as an increase in microvascular tortuosity compared with normal kidneys, suggesting remodeling & compensatory angiogenic activity.

Conclusions: The post-stenotic human kidney shows cortical microvascular loss & remodeling. These alterations may magnify deterioration of renal function & interfere with renal ability to recover upon treatment, supporting development of pro-angiogenic strategies to preserve the kidney.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Hypertension Is Associated with Podocyte Hypertrophic Stress and Detachment Among a Healthy Living Donor Cohort

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Background: HTN is a major cause of ESKD. Kidney donors are a highly selected cohort with normal renal function. Podocyte depletion is a major process by which kidney disease progression occurs. Therefore we tested the hypothesis that Mean Arterial Pressure (MAP) would be related to rate of podocyte detachment.

Methods: 87 living donors that eventually donated were utilized. Two podocyte markers (podocin,nephrin) and a distal tubular/collecting duct marker (aquaporin2) were measured from urine pellet in spot samples normalized to creatinine. UPod:CR is a marker of podocyte detachment, Podocin to Nephrin ratio (UPod:Neph) of podocyte hypertrophic stress and Podocin to Aquaporin ratio (UPod:Aqp2) to understand relation of glomerular to tubular injury. Linear regression was adjusted for donor age, BMI, eGFR before donation.

Results: No donors were on antiHTN therapy. Mean SBP was 124±13, DBP was 87±13, and preferential glomerular injury even among healthy controls cleared for donation.

Conclusions: MAP is linearly related to podocyte detachment, hypertrophic stress and preferential glomerular injury even among healthy controls cleared for donation.

Funding: NIDDK Support

SA-PO347

Hypertension and CVD: Mechanisms

SA-PO348

SNF472, a New Therapeutic Approach to Improve Outcomes in CKD Patients with Peripheral Artery Disease

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Background: Peripheral artery disease (PAD) is a common vascular disease associated with functional impairment and increased risk of cardiovascular events in Chronic Kidney Disease (CKD) patients undergoing dialysis. Poor limb salvage outcomes and high post-amputation mortality in hemodialysis (HD) patients highlight the need for earlier medical therapies. Cilostazol (SOC) use stays limited and requires caution in this population. Clinical studies demonstrate associations between arterial calcification and adverse outcomes in PAD patients. SNF472, a selective calcification inhibitor that interferes in the formation and growth of hydroxypatite, is under development for calciphylaxis. We evaluated the effects of SNF472 on limb functional recovery and blood perfusion in a rat model with Vitamin D3 (VitD)-induced arterial calcification.

Methods: Arterial calcification was induced in 32 SD rats using (VitD) by 3 consecutive daily s.c. dosing of 120 kIU/kg. Rats were divided into four groups and treated during 12 days by: vehicle s.c., vehicle p.o., SNF472 (20mg/kg/day, s.c.) or cilostazol (20mg/kg/day, p.o.). An additional group of 8 rats without VitD received vehicle only (sham). Efficacy was evaluated at day 12 and 5 days after treatment stop. Posterior limb blood perfusion was measured using Laser Doppler Imaging and limbs walking ability were evaluated by measuring Maximum Walking Distance (MWD) and Maximum Walking Time (MWT) using a treadmill. Rats were sacrificed 10 days after treatment stop, and aorta was collected for calcium analysis.

Results: VitD-induced arterial calcification was associated with decreased blood perfusion and impairment of limb walking ability (MWT and MWD) compared to sham. SNF472 reduced aorta calcification by 41% compared to vehicle. No effects of cilostazol on vascular calcification were observed. The inhibition of calcification in SNF472 treated animals was associated with significant higher limb blood perfusion compared to vehicle or Cilostazol (1.28 and 1.37-fold higher, respectively at D12: p< 0.001) and translated into significant improvement in limbs walking ability compared to vehicle (515±114 meters vs 334±187 meters, respectively: p<0.05).

Conclusions: Our results evidence that SNF472 may present a promising new therapeutic approach to treat PAD associated with high vascular calcification such as in CKD and HD patients.

Funding: Commercial Support - Sanifit Therapeutics

SA-PO349

Carbamylated Homocitrulline Is Associated with Left Ventricular Hypertrophy in CKD: Results from the CAIN Study

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Background: Carbamylated proteins arise from post-translational modifications that accelerate with renal failure, can cause molecular and cellular dysfunction, and have been strongly associated to the presence of cardiovascular disease among patients with chronic kidney disease (CKD). To-date, it is unknown whether tissue levels of carbamylated proteins are linked to specific cardiac outcomes such as left ventricular hypertrophy (LVH). We hypothesized that carbamylated protein burden in cardiac tissue is associated with LVH in dialysis patients.

Methods: We analyzed 47 left ventricular (LV) human heart tissues collected in The CAIN (Cardiac Aging in CKD) Study Cohort. LV tissues from hemodialysis (HD; n=17), hypertensive (HTN; n=10) and healthy controls (n=20) were analyzed in a 3-arm cross-sectional controlled design. All tissues underwent gross pathologic exam. Tissue
High Type VI Collagen Formation Is Independently Associated With Increased Risk of Cardiovascular Events and Mortality in the Canagliflozin Cardiovascular Assessment Study (CANVAS)

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Background: Patients with type 2 diabetes are at significantly higher risk of experiencing cardiovascular complications. It has been shown that type VI collagen (COL VI) is markedly upregulated during pathogenic processes of the heart and vasculature. The role of COL VI biomarkers has been sparsely investigated in relation to cardiovascular events. We evaluated a novel biomarker of COL VI formation as a prognostic marker for cardiovascular events and mortality in patients with type 2 diabetes from the Canagliflozin Cardiovascular Assessment Study (CANVAS).

Methods: COL VI formation was correlated with the PRO-C6 enzyme-linked immunosorbent assay (ELISA), detecting a specific fragment of COL VI released upon deposition in the extracellular matrix. PRO-C6 levels were measured in baseline plasma samples from 3531 patients from CANVAS. Results from Cox proportional hazard regression models were reported as unadjusted or adjusted for traditional risk factors age, BMI, systolic and diastolic blood pressure, duration of diabetes, LDL, cholesterol, HbA1c, egFR, and albumin/creatinine ratio.

Results: In the unadjusted analysis, levels of PRO-C6 were significantly associated with heart failure (HF), cardiovascular death (CVD), a composite of HF and CVD, and all-cause mortality. In the adjusted analysis, PRO-C6 was significantly associated with the listed outcomes (Table, all P<0.0001).

Conclusions: In conclusion, this study reveals an independent association of the COL VI biomarker PRO-C6 with cardiovascular events and mortality in the CANVAS study.

Funding: Commercial Support - Janssen Research & Development, LLC

Table: Association of PRO-C6 with heart failure (HF), cardiovascular death (CVD), HF+CVD, and all-cause mortality.

Sample size (n) | Adjusted HR (95% CI) | P Value | Sample size (n) | Adjusted HR (95% CI) | P Value
--- | --- | --- | --- | --- | ---
Heart failure (HF) | Cardiovascular death (CVD) | HF+CVD | All-cause mortality |
5351 (1275) | 1.00 (1.00-1.00) | 0.995 | 5351 (1275) | 1.00 (1.00-1.00) | 0.995 |
5351 (2401) | 1.00 (1.00-1.00) | 0.995 | 5351 (2401) | 1.00 (1.00-1.00) | 0.995 |
5351 (351) | 1.00 (1.00-1.00) | 0.995 | 5351 (351) | 1.00 (1.00-1.00) | 0.995 |

SA-P351

Deletion of the Gene for Transient Receptor Potential Canonical 1 (TRPC1) Channel Induces Diabetes and Cardiovascularopathy but Paradoxically Prevents the Cardiomyopathy from a High-Fat Diet (HFD)

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Background: TRPC1 is key in transducing Ca signal in the hypertrophic response to aortic constriction, but its natural role is unknown. Since TRPC1 and -/- mice are hyperglycemic & since untreated diabetes induces cardiomyopathy, we tested if TRPC1 deficiency creates cardiovascular phenotypes & if 45% HFD aggravates these abnormalities.

Methods: In age-matched wild type, +/- & -/- males, we measured body weights (BW), heart weights (HW) & did echocardiographic studies at ages 3, 7, 17 & 23 mon. At 7 mon, we measured blood pressure (BP) by tail cuffs & direct intraarterial readings of systolic (S) & diastolic (D) to get mean arterial BP (MABP). We studied aortic relaxation in chamber.

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SA-P352

Normalization of Matrix Metalloprotease Activity and Elastin Structure by Finerenone Reduces Arterial Stiffness in Mesenteric Resistance Arteries in a Rat Model of CVD

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Background: Both albuminuria and arterial stiffness are independent predictors of cardiovascular morbidity and mortality associated to the progression of chronic kidney disease (CKD). This association supports a potential generalized vascular dysfunction with similar pathophysiologic mechanisms linking the cardiovascular-renal axis in patients with albuminuria. We aim to explore the effect of the mineralocorticoid receptor antagonist, finerenone (FIN), on vascular mechanics and structure in 2nd branch mesenteric resistance arteries (MA) from Munich Wistar Frontler (MWF) rats, a genetic model of non-diabetic CKD.

Methods: Wistar (W) and MWF rats were randomly grouped (n=10 per group) to receive either 10 mg/kg/day FIN (W-FIN; MWF-FIN) or vehicle (W-C; MWF-C) for 4 weeks by oral gavage. Mechanical and structural properties of MA were determined by pressure myography. Elastin organization in the internal elastic lamina (IEL) was analysed by confocal microscopy based on elastin autofluorescence. Metalloproteinase activity was assayed by gelatin zymography.

Results: FIN led to a significant reduction (~40%) in MWF. The stress/strain relationship curve in MA from MWF-FIN exhibited a significant right-shift, indicative of lower intrinsic arterial stiffness. No changes were observed in structural parameters (external and internal diameter, wall thickness and area ratio). The rate of collagen formation (external and adventitial, medial and wall thickness) of MA. IEL from MWF-C animals showed significantly smaller fenestrae than W-C, without changes in total number of fenestrae. FIN significantly reduced fenestrae number in both W-FIN and MWF-FIN, and increased fenestrae area in MWF-FIN. Pro-MMP-2 activity was significantly lower in plasma samples from MWF-C rats compared with W-C rats, paralleled by higher levels of active MMP-2 and MMP-9 activities. FIN restored pro-MMP-2, MMP-2 and MMP-9 activities in MWF to control levels.

Conclusions: This study demonstrates the efficacy of FIN to ameliorate albuminuria and normalize circulating MMP activities, elastin structure and intrinsic arterial stiffness in MA from MWF rats.

Funding: Commercial Support - Bayer AG (Germany)

SA-P353

Cellular Remodeling of Cardiomyocytes: An Unappreciated Phenotype of Congenital Proximal Renal Tubular Acidosis

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Background: Proximal renal tubular acidosis is caused by mutations in SLC4A4 which encodes the electrogenic Na+/2HCO3− cotransporter NBCe1-A (predominantly renal) and a major contributor to maintenance of plasma [HCO3-] and NBCe1-B/C (predominantly non-renal and contributes to regulation of cardiomyocyte pH). Our laboratory has recently characterized a strain of Nbcce1b/c-knockout (KO) mice that maintains Nbcce1a in the kidney with widespread loss of Nbcce1b/c elsewhere, allowing for the study of Nbcce1c loss in non-renal organ systems in the setting of a normally maintained pH. To date no cardiac phenotype has been reported in pRTA patients (in fact Nbcce1b/c blockade is considered to be cardioprotective under certain circumstances)
yet studies of cardiomyocytes isolated from spontaneously-hypertensive rats, in which Nbc1b/c activity is also impaired, reveal compensatory upregulation of the electroneutral Na+/HCO3− co-transporter Nbc1 and hypertrophy. Nbc1 activity is predicted to increase a greater Na+ load than Nbc1b/c activity. This is hypothesized to affect the activity of the Na+-Ca2+ exchanger, decreasing Ca2+ extrusion, and ultimately activating Ca2+ dependent growth pathways. In the present study, we assess the hearts of Nbc1b/c-KO mice for signs of this pro-hypertrophic pathway.

Methods: Cardiac tissue from age and gender-matched C57 wild-type (WT) and KO littermates was weighed post-dissection and normalized to body weight for comparison. Cardiac tissue homogenates were prepared for RT-qPCR and western blot analysis of Nbc1 expression.

Results: KO mice had 22 ± 8% larger heart-to-body weight ratios (n=5, p<0.03). Abundance of NBCn1 transcripts was 45 ± 10% greater in the KO compared to the WT (n=3, p=0.02). Abundance of NBCn1 protein was 85 ± 17% greater in the KO compared to WT mice (n=3, p=0.05).

Conclusions: Nbc1 is upregulated both at the level of transcript and protein within cardiomyocytes of the enlarged hearts of Nbc1b/c-KO mice, consistent with the hypothesis that remodeling of acid/base transporter expression contributes to the enhanced growth of cardiac tissue.

SA-PO354
High PTH Levels Inhibit Biorhythm of Human Vascular Smooth Muscle Cells In Vitro
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Background: In normal condition, vascular smooth muscle cells have self circadian rhythm. Here we observed the influences of high levels of parathyroid hormone (PTH) on circadian genes in human aortic vascular smooth muscle cells (hASMCs) in vitro.

Methods: Human ASMCs were divided into control and (1-84)PTH(10nmol/L) group. The timing of the beginning stimulated was counted as zeitgeber time 0 (ZT0). Thereafter, cells were collected every 4 hours for a total of 28 hours. The mRNA expressions of PPARY, Bmal1, Per2 and Rev-erbs in different groups of cells at different time points were detected by quantitative polymerase chain reaction (qRT-PCR).

Results: mRNA expressions of PPARY and clock genes Bmal1, Per2 and Rev-erbs showed circadian rhythms in the control group, and peaked at ZT4, ZT12, ZT4 and ZT20 respectively. High levels of PTH could inhibit the expression amplitudes of above genes, without affecting time phases of expressions.

Conclusions: High PTH levels could inhibit biorhythm of HASMCs, its relationships with vascular circadian rhythm abnormalities need further study.

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SA-PO355
G Protein-Coupled Receptor 37L1 Is Expressed on the Nuclear Envelope
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Background: G protein-coupled receptors (GPCRs), expressed on the plasma membrane, interact with various types of ligands, which trigger a cascade of signal transduction events leading to different intracellular responses that in turn manifest in physiological changes. Some GPCRs also reside and exert signals from intracellular organelles such as the nucleus, endoplasmic reticulum, and Golgi apparatus. Recently, we reported that G protein-coupled receptor 37L1 (GPR37L1) is expressed in the apical membrane of renal proximal tubule cells (RPTCs) and participates in luminal sodium transport and blood pressure regulation by regulating the renal expression of NHE3. However, the mechanism by which GPR37L1 regulates NHE3 expression and function in the RPTC has not been studied.

Methods: We employed Tandem affinity purification using GPR37L1 tagged with biotin and streptavidin binding peptide followed by mass spectrophotometry (MS) analyses to identify the proteins interacts with GPR37L1. Subcellular location of GPR37L1 was determined by confocal fluorescence imaging and immunoblotting on the cells or the nucleus prepared from the RPTCs expressing GPR37L1 tagged with green fluorescence protein (GPR37L1-GFP).

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Results: Tandem affinity purification of GPR37L1, combined with MS analyses, revealed a strong association of GPR37L1 with mediators of nuclear importing proteins such as RAN-GTPase, importin-α, importin-β. In silico analyses of GPR37L1 amino acid sequence revealed the presence of a potential nuclear localization signal at the N-terminus. Confocal fluorescence imaging of RPTCs expressing GPR37L1-GFP showed distinct nuclear subnuclear expression consistent with the presence of histone deacetylase 2, a marker for nuclear protein, the absence of Na.K-ATPase, a marker for plasma membrane, and the absence of calnexin, a marker for endoplasmic reticulum.

Conclusions: Our results show that GPR37L1 also resides on the nuclear envelope and play a critical role in the regulation of the expression of genes responsible for maintaining normal electrolyte balance and blood pressure.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO356
Identification of X-Linked Alport Syndrome by Genetic Testing in a Girl Who Had Remained Undiagnosed After Two Kidney Biopsies Within a 10-Year Period
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Introduction: Girls with X-Linked Alport syndrome (XLAS) are reported to show slow progression of proteinuria compared to boys patients, and most of them are asymptomatic carriers. Previous reports suggest that proteinuria begins at a median age of 7 years, finally resulting in end-stage kidney disease at a median age of 65 years. However, it is well known that the rate of disease progression in girls with XLAS cannot be predicted accurately, and that the clinical phenotype shows considerable variation, even among affected girls in the same family.

Case Description: We describe a girl with XLAS who showed hematuria and proteinuria in a kindergarten urine test at the age of one year, and who was followed up regularly thereafter. Her father had undergone kidney transplantation due to end-stage kidney disease when he was in high school. At the age of 7 years, the patient underwent initial kidney biopsy. Light microscopy revealed mesangial proliferation but an immunofluorescence study revealed no IgA deposition, and electron microscopy demonstrated no basement membrane abnormalities. The patient was therefore diagnosed as having non-IgA mesangial proliferative glomerulonephritis. As her proteinuria persisted at about urine protein-creatinine ratio; 0.5 g/gCr, therapy with a cocktail of prednisolone, mizoribine, warfarin, and dipyridamole was started at the age of 8 years, and this led to a gradual decrease of the proteinuria to 0.2 g/gCr. However, from the age of 13 years, the proteinuria and creatinine increased gradually to 1.0 g/gCr and 1.0 mg/dL, respectively, so we performed a second kidney biopsy which yielded results similar to the first one. Finally, at the age of 17 years, we conducted genetic testing of both the patient and her parents. This revealed that the patient had a heterozygous missense mutation in intron 7 of the COL4A5 gene, and that her father was homozygous for the mutation.

Discussion: This girl showed relatively rapid progression of XLAS. Most girls with XLAS have no problem with ocular lesions or hearing, and those with decreased kidney function are very rare. Therefore, even today many clinical issues remain unclear, and diagnosis of XLAS in girls is sometimes very difficult without genetic testing.

SA-PO357
Spontaneous Remission of Genetic, Apparently Primary FSGS Presenting with Nephrotic Syndrome Challenges Traditional Notions of Primary and Genetic FSGS
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Introduction: Focal segmental glomerulosclerosis (FSGS) presenting with nephrotic syndrome (NS) with focal scarring lesions and diffuse foot process effacement (FPE) is considered diagnostic of primary FSGS. KDIGO guidelines advise against genetic testing in adult idiopathic variant (α-AS5521P) in TCRG6. This case variant is ultrarare, is predicted pathogenic and was previously reported in two pedigrees with FSGS with demonstrated gain of function in vitro. We continued conservative therapy and 8 months after diagnosis we has had complete remission with her UPC declining to 0.67, serum albumin improving to 4.3 and serum creatinine to 0.9 (eGFR 88).

Case Description: A 26-year-old healthy Caucasian female was referred for new onset NS. She had peripheral edema, a BP of 157/110 a urine protein creatinine ratio (UPCR) of 9.04, a serum albumin of 2.3 mg/dl and a serum creatinine of 1.2 (eGFR 62). Other serological tests were negative. A kidney biopsy showed features of primary FSGS which resolved spontaneously.

Discussion: This girl showed relatively rapid progression of NS. Most girls with NS have no problem with ocular lesions or hearing, and those with decreased kidney function are very rare. Therefore, even today many clinical issues remain unclear, and diagnosis of NS in girls is sometimes very difficult without genetic testing.

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SA-PO358

X-Linked Alport Syndrome Caused by Synonymous Mutation, p.Pro-786Pro Inducing Incomplete Aberrant Exon Skipping in COL4A5

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Introduction: X-linked Alport syndrome (XLAS) - a progressive hereditary kidney disease caused by mutations in COL4A5 gene coding type IV collagen α5 chain (α5(IV)), with the median age of developing end-stage renal failure in male XLAS patients of 25 years, and 70 or 90% of the patients had reached ESRD before the age 30 and 40 years, respectively. Additionally, patients with truncating mutations tend to show severe phenotypes.

Case Description: Two male siblings with mild phenotypes whose mother had hematuria now 43, and 34 years old; both had hematuria since childhood. Their proteinuria appeared at 33, and 20 years, respectively. The elder recently developed ESRD, and the younger is still CKD-stage III b. The younger’s kidney biopsy at 31 years of age, showed a thin glomerular basement membrane and normal α5(IV) expression. Gene analysis revealed both possessing only a novel hemizygous synonymous variant of c.2358A>G (p.Pro786Pro) in COL4A5 exon 29 among all 3 genes responsible for Alport syndrome. Further transcript analysis revealed this single base substitution caused aberrant splicing of exon 29 complete skipping which was shown both in peripheral lymphocytes and normal α5(IV) expression. Gene analysis revealed both possessing only a novel hemizygous synonymous variant of c.2358A>G (p.Pro786Pro) in COL4A5 exon 29 among all 3 genes responsible for Alport syndrome. Further transcript analysis revealed this single base substitution caused aberrant splicing of exon 29 complete skipping which was shown both in peripheral lymphocytes and urinary sediments. Exon 29 is constituted by 151bp and the skipping of this exon leads to a frameshift mutation at the transcript level and supposed to be showing severe phenotypes. However, a small amount of normally spliced transcript was also detected in the transcript from urinary sediments which might be because of incomplete aberrant splicing by the variant.

Discussion: The synonymous mutation can cause aberrant splicing in COL4A5. However, relatively mild phenotypes were led by the presence of a small amount of normally spliced transcript along with aberrant splicing. By this normal transcript, α5(IV) expression was positive on glomerulonephritis. In conclusion, synonymous mutations can have pathogenicity by causing aberrant splicing. Additionally, normal transcript production along with the aberrantly spliced transcript prevents the patients from presenting severe phenotype. Accurate genetic diagnosis would be required to elucidate the onset mechanism by synonymous variants or presentation of atypically milder phenotypes.

SA-PO359

A Novel Aquaporin 2 Insertion Mutation in a Chinese Family with Autosomal Dominant Nephrogenic Diabetes Insipidus and Chronic Renal Failure

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Introduction: Mutations in aquaporin 2 (AQP2) cause mostly autosomal recessive or rarely autosomal dominant nephrogenic diabetes insipidus (NDI). Patients with autosomal dominant NDI usually exhibit less phenotype and have mutations in the carboxy-terminal tail important intracellular routing of the AQP2. We described a family of autosomal differentiated clinically from primary FSGS and can undergo spontaneous remission. Given prognostic and therapeutic implications, we suggest that genetic testing be performed in any young adult with FSGS prior to a therapeutic trial with high dose steroids.

dominant NDI carried a novel AQP2 mutation but presented a severe phenotype, which led to early-onset renal failure.

Case Description: A 26-year-old Chinese female manifested polyuria, polydipsia, and nocturia after birth. Her family history was non-revealing. She did not have non-obstructive hydrourephrosis and never received NSAID or thiazide to treat her polyuria. Pertinent laboratory investigations showed abnormally renal function with serum creatinine 3.4 mg/dl, and hyperkalemia metabolic acidosis (chloride 115, HCO3⁻ 19 mmol/L), persistently low urine osmolality (around 50-100 mOsm/kg.H2O) and markedly increased serum von Willebrand factor and coagulation factor VIII in response to desamino-8-arginine VP (DDAVP) test. Direct sequencing of AQP2 and AQP1 gene showed two nucleotide GC insertion at c.755 of AQP2, resulting in a frameshift mutation (p.R253Dfs*82, +52 AA) and altering the amino acid sequence between R254 to A271. Of note, her one-year-old son also exhibited severe polyuria two days after birth and was found carrying the same mutation.

Discussion: We presented the first autosomal dominant NDI family with a severe phenotype, including early-onset polyuria in the neonatal period and renal failure in early adulthood. The functional experiment focusing on autosomal dominant AQP2 mutations in the C-terminal end is warranted.

SA-PO360

A Case of Classical Fabry Disease due to De Novo GLA Genetic Mutation That Showed Characteristic Findings in Both Renal and Nerve Biopsy

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Introduction: Fabry’s disease (FD) is an X-linked lysosomal storage disorder due to mutations in the alfa-galactosidase A (GLA). Most cases are related to GLA inherited mutations, cases of de novo onset occur rarely.

Case Description: A 53-year-old man has been pointed out proteinuria for 20 years, but the reason had been unclear. When he was 50 years old, he suffered from sick sinus syndrome and has been fitted pacemaker. 3 years later, serum creatinine got worse to 1.5 mg/dl and urine protein 1.5 g/gCr. Kidney biopsy was done and diagnosed as FD due to de-novo GLA mutation (R112C). Enzyme replacement therapy (ERT) using agalsidase-alfa was started and the concentration of Lyso-Gb3 went down for 2 months. But his left leg’s sensory neuropathy was obvious and nerve biopsy also showed peripheral neuropathy that could match to FD. Switching from agalsidase-alfa to agalsidase beta could lead to decrease the concentration of Lyso-Gb3.

Discussion: In Japanese FD’s patient, genetic GLA de novo mutation is rare. After starting ERT, evaluation of organ damage is necessary, and if there were any problems, switching therapy may be suggested. There are few cases which both kidney and neuro biopsy were done. These findings emphasize the importance of early diagnosis, genetic analysis, and selecting appropriate enzyme replacement therapy to prevent irreversible organ damage that occurs during the course of the disease. In conclusion, early diagnosis, evaluating organ damage, and adequate ERT may be necessary for FD’s patient to decrease the concentration of Lyso-Gb3 that would be associated with good prognosis.
Case of syphilis associated with membranous glomerulonephritis, focal segmental glomerulosclerosis, minimal change disease, and interstitial nephritis has been described in the literature. However, clinical awareness of the possibility remains crucial for timely identification and treatment.

**Case Description:**
55-year-old Caucasian male with history of hypertension presented with 1 month of diarrhea, lower extremity edema, and oliguria. Initial labs revealed a serum creatinine 9.0 mg/dL, albumin <2.0 g/dL, urine protein/creatinine ratio <2.0 g/g, and creatinine clearance of 124,000 copies and infection with hepatitis B. Kidney biopsy demonstrated chronic active TMA with features of the complement proteins C5b-9 and acute mesangial proliferation with prominent C1q deposits on immunofluorescence microscopy. The patient did not have a history of diabetes or smoking and was found to have markers positive for malignancy.

Light microscopy noted interstitial fibrosis, tubular atrophy, and globally sclerotic glomeruli. Immunofluorescence staining highlighted linear IgG accentuation. Genetic and Diagnostic Trainee Case Reports

**Discussion:**
While it cannot be shown that syphilis is responsible, clinical awareness of the possibility must be considered to avoid overlooking potentially life-threatening complications. The patient was dialysis dependent at presentation. He was initiated on antiretroviral therapy and started on eculizumab infusions every 2 weeks for treatment of HIV-associated TMA. Although his CD4 count remained low at 70, his HIV viral load became undetectable, and his hematologic parameters improved and creatinine clearance improved to 25 mL/min leading to discontinuation of dialysis after 2 months.

**Conclusion:**
In the modern era of antiretroviral therapy, TMA is a rare complication of HIV infection. Because uncontrolled HIV infection has been associated with increased complement activation, we hypothesized that HIV infection triggered dysregulation of complement activity in our patient and that treatment with eculizumab would be beneficial. Although our patient did not have a common gene mutation associated with atypical HUS, treatment with eculizumab in conjunction with ART resulted in hematologic remission as well as improvement in kidney function and discontinuation of dialysis.

**Prevention:**
Hypocupremia: Cause or Effect of Nephrotic Syndrome?

**Case Description:**
A 57-year-old Caucasian female with history of hypertension, lower extremity edema, and peripheral neuropathy was admitted to the hospital for workup after outpatient testing revealed neutropenia and severe anemia. In the setting of newly diagnosed HIV infection which was successfully treated with eculizumab.

**Discussion:**
Nephrotic syndrome is well known to cause urinary loss of several factors and trace elements. Conversely, a rare association of copper deficiency with nephrotic syndrome (NS) has been reported in the literature with possible improvement in NS with correction of deficiency. Here we report an unusual presentation of Focal Segmental Glomerulosclerosis (FSGS) with worsening peripheral neuropathy and bitemporal hemianopia.

**Prevention:**
Thrombotic Microangiopathy as the Presenting Feature of Newly Diagnosed HIV Infection Treated with Eculizumab

**Case Description:**
58-year-old Hispanic male with history of hypertension presented with 6.8 grams after normalization of copper levels. A random kidney biopsy showed FSGS. While it cannot be shown that syphilis is responsible, clinical awareness of the possibility may allow for further identification of cases in the future.

**Prevention:**
Syphilitic Nephropathy is a well-known entity which can be associated with urinary protein excretion and can be mistaken for an infection with syphilis. However, other pathophysiologic factors cannot be excluded. The diagnosis of syphilis, syphilitic involvement must be considered as an etiology in conjunction with underlying mild hypertension given lack of diabetes history. While it cannot be shown that syphilis is responsible, clinical awareness of the possibility may allow for further identification of cases in the future.

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Syphilitic Nephropathy is a well-known entity which can be associated with urinary protein excretion and can be mistaken for an infection with syphilis. However, other pathophysiologic factors cannot be excluded. The diagnosis of syphilis, syphilitic involvement must be considered as an etiology in conjunction with underlying mild hypertension given lack of diabetes history. While it cannot be shown that syphilis is responsible, clinical awareness of the possibility may allow for further identification of cases in the future.
Nephrocalcinosis Secondary to Excessive Oxalate Ingestion
Mengyao Day, Raymond C. Harris. Vanderbilt University Medical Center, Nashville, TN.

Introduction: Late-onset manifestations of urea cycle disorders may be difficult to recognize and if left untreated can lead to devastating, life threatening consequences. We present the tragic case of a young woman who presented with acute hyperoxaluric encephalopathy due to ornithine transcarbamylase (OTC) deficiency unmasked by a high protein, ketogenic diet.

Case Description: A 30-year-old male with no significant medical history presented after routine lab work at a yearly primary care visit revealed potassium 6.1 mEq/L, BUN 103 mg/dL, and creatinine 12.3 mg/dL. Corrected serum calcium was 8.2 mg/dL and 25-hydroxy vitamin D was 46.1 ng/mL. Two years prior to presentation, creatinine was 0.9 mg/dL, but had risen to 2.36 mg/dL one year prior to presentation. Four years prior to presentation, the patient had started a new diet consisting mainly of green beans, turnip greens, and brocoli. Review of previous urinalyses showed multiple instances of calcium oxalate crystals in his urine. Renal ultrasound showed decreased renal size bilaterally, as well as, bilateral non-obstructing renal calculi. CT abdomen and pelvis demonstrated bilateral nephrocalcinosis, likely secondary to hyperoxaluria in the setting of prolonged excessive dietary oxalate intake. Despite conservative medical management including initiation of a low oxalate diet, the patient did not recover renal function and became dialysis dependent.

Discussion: Once nephrocalcinosis is diagnosed, it is imperative to determine the underlying cause as to guide management. If standard laboratory testing does not reveal a cause, such as hypercalcemia or renal tubular acidosis, there should be increased suspicion for hyperoxaluria. Although secondary hyperoxaluria is most often due to fat malabsorption, a careful dietary history should also be taken to evaluate for chronic ingestion of excessive amounts of oxalate (e.g. rhubarb, spinach, green beans, etc.) or oxalate precursors (e.g. vitamin C), as highlighted by this case. In patients with secondary hyperoxaluria, dietary oxalate intake should be minimized, while calcium and fluid intake should be liberalized. If treated promptly, renal function often recovers.

SA-PO367
Fatal Hyperammonemia due to an Underlying Urea Cycle Disorder
Unmasked by a High-Protein, Ketogenic Diet
Mina Sourial,1 Maryanne Sourial,1,2 Molly Fisher.1,2 Montefiore Medical Center, Bronx, NY; 1Albert Einstein College of Medicine, Bronx, NY.

Introduction: A 30-year-old male with no significant medical history presented with altered mental status. He was an avid hiker with recent tick exposure. Two months previously, he started a ketogenic diet and was taking high dose protein shakes and anabolic mimetics to build muscle. Initial workup including computed tomography (CT) of the head, magnetic resonance imaging of the brain, electroencephalography, urinalysis, serotonin, creatinine, calcium, and fluid culture for bacterial meningitis and lactic acidosis was negative. He was found to have an ammonia level of 215 uM/L with no evidence of liver failure and undetectable alcohol level. He received one hemodialysis session but quickly deteriorated, developing seizures requiring intubation and mechanical ventilation. Repeat ammonia level worsened to 430 uM/L and repeat CT head showed diffuse cerebral edema with impending herniation. He was treated with hypertonic saline mannitol, an extraventricular drain was placed, and he was initiated on continuous-rerenal replacement therapy. Despite improvement in ammonia level to \( \leq 20 \) uM/L, the patient failed to make a meaningful neurologic recovery. Genetic testing for an underlying urea cycle disorder revealed OTC deficiency.

Discussion: Urea cycle defects result in the ability to breakdown protein and eliminate nitrogenous wastes, resulting in hyperammonemia. Symptoms vary from poor appetite, somnolence, and behavioral disturbances to rapid neurologic deterioration including seizures, coma, and death if not promptly recognized and treated. Although urea cycle disorders typically present shortly after birth, partial defects may manifest in adulthood in the context of increased catabolic stress. A high index of suspicion and rapid initiation of treatment is critical for favorable outcome. We believe our patient’s high protein diet and use of anabolic mimetics precipitated a hyperammonemia crisis in the setting of mild OTC deficiency which unfortunately proved fatal.

SA-PO368
Not All Sever Lactic Acidosis Implies an Ominous Prognosis
Nihal M. Ali, Jorge C. Castaneda. UMC, Ridgeland, MS.

Introduction: Glycogen Storage Disease (GSD) type 1, also known as Von Gierke Disease is an inherited disorder caused by deficiencies of specific enzymes in the glycogen metabolism pathway. It comprises 2 major subtypes GSD 1a (deficiency of the enzyme Glucose 6 Phosphatase) and GSD 1b (deficiency of the transporter enzyme, Glucose 6 Phosphate Translocase). GSD 1a results from mutation in G6PC gene on chromosome 17q21 that encodes G6Pase. GSD 1b results from mutations of SLC2A4 gene on chromosome 11q23.3. Incidence is 1/100,000.

Case Description: This is a 27-year-old white female who was referred to clinic due to the following complaint metabolic acidosis and proteinuria of 3. gr 24 hr. Based on chart review, she has chronic lactic acidosis between 8-12 mmol/L and subsequent GAP metabolic acidosis. In addition, she has persistent hyperuricemia, hyperglycemia and hypertriglyceridemia. She used to have hypoglycemic episodes during childhood, however she has developed chronic pancreatitis and hyperglycemia due to glycogen deposition.

Discussion: GSD leads to accumulation of Glycogen and fat in the in Liver, kidney and intestinal mucosa is the final result. Initial laboratory findings include hyperglycemia, hyperlipidemia, hypoglycemia, and hyperuricemia, respectively. Renal failure may occur from primary tubular or glomerular dysfunction. Glomerulonephritis and podocytopenias have been described previously. The main targets for the management are the prevention of acute metabolic derangements, prevention of acute and long-term complications, attainment of normal psychological development and good quality of life. The main goal of this presented case that even though lactic acidosis is usually associated with poor short-term outcomes, the knowledge of metabolic pathways will help to approximate unusual etiologies of lactic acidosis in the adult population.

SA-PO369
Pharmacologic Management with Sodium Phenyl Acetate/Sodium Benzoate with or Without Dialysis for the Treatment of Hyperammonemia: A Case Study
Zubair B. Safder Zafar,1 Kostas Papamarkakis,2 Whitney E. Besse.1,2 Yale University School of Medicine, New Haven, CT; 1Yale University, New Haven, CT.

Introduction: Hyperammonemia is an underrecognized indication for emergent renal replacement therapy in patients with inborn errors of metabolism. Duration of hyperammonemia correlates with marked neurologic consequences: permanent intellectual impairment, cerebral edema, and herniation. Dialysis decreases ammonia levels acutely, but has associated risks. Additionally, sodium phenylacetate/sodium benzoate is an FDA approved ammonia scavenger for treatment of hyperammonemia in patients with inborn errors of metabolism. There is no current study comparing the effectiveness of ammonia scavengers and dialysis for the acute management of hyperammonemia in adult patients. We present a case in which both treatments were utilized.

Case Description: The patient is a 21-year-old man with a diagnosis of pyruvate dehydrogenase deficiency type B on chronic tube feeds who presented with lethargy after one loose bowel movement. Initial workup revealed a lactate of 5mmol/L, ammonia level of 447mmol/L, and creatinine of 0.6mg/dL. On exam, the patient had no focal motor or sensory deficits but was agitated and combative. A central venous line was placed for dialysis access and he underwent 2.5 hours of hemodialysis followed by approximately 12 hours of central venovenous hemodiafiltration, in addition to IV dextrose-containing fluids. The ammonia level fell to 34mmol/L. In consultation with the Genetics service, intravenous sodium phenylacetate with sodium benzoate were started and maintained normal levels of ammonia while his home feeding regimen was adjusted. Two weeks later, the patient was readmitted to the ICU with a similar presentation and serum ammonia level of 338mmol/L. This time, sodium phenylacetate with sodium benzoate was initiated rapidly. Ammonia levels were decreased to 47mmol/L over 7 hours without requiring dialysis.

Discussion: This case highlights the potential effectiveness of sodium phenylacetate/ sodium benzoate. These ammonia scavengers combine with amino acids to form alternative products for urinary nitrogen excretion. While therapy with hemodialysis is necessary in renal function decreases, patients with normal renal function may achieve rapid resolution of hyperammonemia with volume resuscitation, feeding, and administration of sodium phenylacetate/sodium benzoate as a low risk and cost-effective treatment strategy.

SA-PO370
A Rare Cause of Resistant Hypertension
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Introduction: Resistant hypertension is defined as suboptimally controlled blood pressure despite concurrent use of three antihypertensive agents of different classes, including a diuretic. A thorough evaluation for secondary causes of hypertension is crucial to allow timely institution of treatment to limit end-organ damage and associated morbidity and mortality.

Case Description: A 66-year-old African American gentleman was referred for evaluation of uncontrolled hypertension and declining renal function. His antihypertensive regimen consisted of maximal doses of Valsartan, Verapamil ER and Clonidine. Diuretics were being held due to persistent hypokalemia despite potassium supplementation. Family history was notable for his father succumbing to renal failure of unclear etiology at age 50, his sister passing from her ESRD, and his mother having well controlled hypertension. Physical exam was otherwise unremarkable, with the patient appearing alert and oriented. The review suggested progressive decline in GFR, equating to CKD stage 3 with minimal proteinuria, with mild but persistent hypokalemia and metabolic alkalosis. An arterial blood gas confirmed chronic metabolic alkalosis. Both plasma renin activity and aldosterone were undetectable. Based on the above findings, a diagnosis of Liddle syndrome was made. Amiloride was added and the patient had a reassuring response to treatment which translated into stability of his GFR (Figure 1).
Discussion: Liddle Syndrome is a rare autosomal dominant disorder associated with a gain-of-function mutation involving the epithelial sodium channels, which mimics the manifestations of hyperaldosteronism, without a demonstrable elevation in serum aldosterone. Our case illustrates the benefits of prompt diagnosis and treatment to arrest the progression of hypertension mediated end-organ damage.

Amphotericin B, due to a relatively normal left kidney and overall clinical stability. Due to the vascular and parenchymal invasion, nephrectomy was performed with pathology consistent with invasive fungal disease with involvement of the renal pelvis. Treatment was continued with oral posaconazole for any microscopic remnants of the fungus for six weeks and did well with monitoring of CKD and diabetes.

In most cases of reported isolated renal Rhizopus, amphotericin and nephrectomy are standard of care with an azole anti-fungal used as step down therapy or therapy in which the patient does not respond to amphotericin. With utilization of both posaconazole and nephrectomy, alternative to amphotericin B, the patient was able to maintain stable residual kidney function in an infection associated with high mortality and was successfully treated for isolated mucormycosis of the rhizopus group.

Monoclonal Gammopathy of Renal Significance: Not Just a Disease of the Old
Bethany Roehm, Cindy Varga, Lesley Inker. Tufts Medical Center, Boston, MA.

Introduction: Immune-mediated glomerulopathy is a rare finding on kidney biopsy, reported in 0.6-0.1% of biopsies. It is characterized by subepithelial and subendothelial microtubules made of immunoglobulin deposits. Without clinical findings suggestive of lupus or cryoglobulinemia, monoclonal gammopathy of renal significance (MGRS) should be considered. MGRS can be caused by any B cell or plasma cell clonal proliferative disorder. Less than 2% of those diagnosed with monoclonal gammopathy of undetermined significance (MGUS) are under the age of 40 years. Of all patients with MGUS, 1.5% have MGRS.

Case Description: This is a 26 year old man who presented for evaluation of proteinuria and hematuria, found incidentally during work-up for an acute episode of diabetes and subsequently resolved. Initial UPUR and UACR were 977 mg/g and 740 mg/g, respectively. Past medical history was notable only for “ear problems” requiring Eustachian tubes as a tube. He was not on any medications or supplements. Blood pressure was 143/89, but there were no other abnormalities on physical exam. Complements, anti-dsDNA Ab, and CBC were normal. eGFR was 125 ml/min/1.73m². SPEP and UEPP were not initially done as he was deemed low risk for harboring a plasma cell dyscrasia at his age. Kidney biopsy showed immune-mediated glomerulopathy with dominant IgG kappa. SPEP and UEPP with IFE were then done and neither showed any monoclonal bands. However, urine biopsy showed rare polytypic plasma cells with a small kappa restricted plasma cell population on flow cytometry. Given his young age and the natural history of MGRS, the plan is to treat with plasma cell directed chemotherapy.

Discussion: MGRS can occur in younger patients presenting with proteinuria. When evaluating young patients with proteinuria, a broad differential should be considered. The most common causes in adults are diabetes, amyloidosis, lupus, minimal change disease, membranous nephropathy, and FSGS. We also considered IgA nephropathy and Alport’s syndrome. MGRS was low on our differential, yet kidney biopsy showed immune-mediated glomerulopathy due to MGRS despite negative SPEP and UEPP. Kidney biopsy was key in obtaining a diagnosis in our patient. It is important even in young patients not to rule out potentially treatable causes of kidney disease based on age.

A Unique Case of Malakoplaikia of the Kidney
Manognya Muttineni, Timothy A. Sutton, Elizabeth Taber-Hight, Richard N. Hellman. Indiana University School of Medicine, Indianapolis, IN; Indiana University, Zionsville, IN; Indiana University Division of Nephrology, Indianapolis, IN.

Introduction: Malakoplakia is a rare inflammatory condition that has a gross and microscopic appearance resembling xanthogranulomatous pyelonephritis but with distinctive Michaelis-Gutmann bodies on pathology. Malakoplakia can affect any organ system but genitourinary tract involvement is the most common, particularly in immunocompromised individuals. We are presenting a unique case of malakoplaikia presenting with AKI requiring dialysis and our treatment approach.

Case Description: A 40yo Caucasian female presented to a local hospital with altered mental status. She had a history of tobacco, alcohol, and cocaine abuse. There was no history of IV drug abuse or prior urinary tract infections. She was found to be in septic shock due to Escherichia coli bacteremia from a UTI that progressed to multiorgan failure requiring ventilatory support and AKI (SCR=7.2) that required renal replacement therapy. She was discharged on CAPD and bilaterally enlarged kidneys. Clinical status improved with antibiotic treatment although there was no recovery in kidney function and fevers persisted. Renal biopsy was performed revealing sheets of macrophages, cosinophils and Michaelis Gutmann bodies on EM characteristic of malakoplakia. Antibiotics were changed to ciprofloxacin and she was transferred to a tertiary care facility for further care. A multidisciplinary approach involving nephrology, urology, infectious diseases and immunology was initiated. Patient was started on methylprednisolone and consideration of bilateral nephrectomy for source control was discussed. Five weeks into the hospital course daily fever subsided and evidence of kidney recovery ensued. Ultimately, she was discharged off of dialysis with improving kidney function, prolonged course of antibiotics, and steroid taper. Six months later she is off both antibiotics and steroids with stable kidney function (SCR=1.4).

Discussion: Renal malakoplakia must be kept in mind for patients presenting with AKI and bilaterally enlarged kidneys especially in the setting of E. coli bacteremia from a urinary source. It was a challenging case given her age and nephrectomy as potential treatment options. We learned that in such cases suppressing the inflammatory process as aggressively as possible with anti-inflammatory therapy prior to kidney function. A multidisciplinary approach was very useful in avoiding surgery and coming up with treatment plan.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-P0375

Extradural Hematopoiesis Misdiagnosed as Intestinal Nephritis in a Patient with Renal Dysfunction: A Case Report
Mea Asou, Makoto Araki. Sawa Central Hospital, Sawa Central Hospital, Chino, Japan.

Introduction: Extradural hematopoiesis is widely known to occur in patients with primary myelofibrosis (PMF). Autopsy studies on individuals with PMF revealed that extradural hematopoiesis occurred in the kidneys in 35% of the cases. However, there is little awareness regarding such lesions.

Case Description: A 63-year-old man was diagnosed with PMF (Dynamic International Prognostic Scoring System: intermediate-1-risk group) with a JAK2 V617F gene mutation based on a detailed examination of persistent white blood cells (white blood cell count, >10,000/μL). An examination of the patient’s medical records revealed a correlation between leukocytosis and deterioration of renal function and urinary protein. Thus, a kidney biopsy was performed. Advanced lymphocyte invasion was recognized in the interstitial tissue, and the unifocal tubule extensively disappeared. Glomerular lesions were investigated, and only some were determined to have resulted from mesangial proliferative glomerulonephritis. Based on these findings, the pathologist diagnosed the patient with intestinal nephritis. However, because of the large number of cells with nuclear atypia in the stroma, additional immunohistochemical staining was also performed, such as glycophorin A, Nephil AS-D, Myeloperoxidase and CTM2B. As a result, invasion of three lines of immature cells, erythroblasts, megakaryocytes, and granulocytes, was identified. Renal dysfunction resulting from interstitial cellular infiltration due to extradural hematopoiesis was therefore diagnosed. Treatment with tuxolitinib was initiated after a renal biopsy. The patient’s decrease in estimated glomerular function rate stabilized, and urinary protein concentration decreased slowly.

Discussion: Although, in myeloproliferative disorders, proliferative glomerular lesions are widely considered to be renal disorders, there is little awareness regarding intestinal lesions. Extradural hematopoiesis of the kidney in PMF is not uncommon, but 40% of cases are reportedly misdiagnosed as intestinal nephritis. Because extradural hematopoiesis can be controlled by treatment with tuxolitinib, early detection is important.

SA-P0376

A Case of Membranous Nephropathy in a Child with Immune Dysregulation, Polyclonodinopathy, Enteropathy, X-Linked (IPEX) Syndrome
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Introduction: Classic IPEX syndrome is an autosomal recessive genetic disorder secondary to a mutation in the FOXP3 gene. It is characterized by enteropathy, chronic dermatitis, type 1 diabetes mellitus (T1DM), hypothyroidism, antibody mediated cytopenias, and immune dysregulation. Up to 33% of patients with IPEX syndrome have renal complications, including tubulointerstitial nephritis, focal tubular atrophy, minimal change disease, membranous glomerulopathy and irregular granular immune deposits in glomeruli/tubular basement membranes. There are fewer than 10 reported cases in the literature.

Case Description: A 3-year-old female, with a history of IPEX (known gain of function mutation in STAT3 gene), T1DM, hypothyroidism, nephrocalcinosis, and history of AKI presented with edema. Laboratory studies confirmed nephrotic syndrome: albumin of 1.6g/dL, urine protein to creatinine ratio of 33. Renal function was normal. No abnormalities found on complement, ANA, or ANCA testing; renal biopsy demonstrated subepithelial electron dense deposits consistent with membranous glomerulopathy with autoantibodies to phospholipase A2 receptor (PLA2R-positive) on biopsy stain and negative serum PLA2R. She is currently treated symptomatically with twice weekly albumin infusions in addition to intermittent IVIG. Treatment with sirolimus was initiated based on successful outcomes reported in some case reports however it did not allow for remission of nephrotic syndrome after 9 weeks of treatment. Since non-autologous stem cell transplant allows for rapid clinical improvement, the aim is for this patient to receive remission of nephrotic syndrome after 9 weeks of treatment. Since non-autologous stem cell transplant allows for rapid clinical improvement, the aim is for this patient to receive remission of nephrotic syndrome after 9 weeks of treatment. Since non-autologous stem cell transplant allows for rapid clinical improvement, the aim is for this patient to receive remission of nephrotic syndrome after 9 weeks of treatment. Since non-autologous stem cell transplant allows for rapid clinical improvement, the aim is for this patient to receive remission of nephrotic syndrome after 9 weeks of treatment.

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SA-P0377

Successful Pregnancies During Ongoing Complement Blockade in Two Patients with Complement Mediated Thrombotic Microangiopathy
Natalija Haninger-Vacariu,1 Martina M. Gagg,1 Zoltan Prohuzska,2 Christof Aigner,3 Renate Kain,1 Georg Bohmig,1 Leah C. Piggott,4 Raute Sunder-Plassmann,4 Gere Sunder-Plassmann,4 Alice Schmidt,1 Medical University of Vienna, Vienna, Austria; 2Semmelweis University, Budapest, Hungary.

Introduction: In patients with pregnancy-associated complement gene variant mediated thrombotic microangiopathy (cTMA) terminal complement blockade is used for treatment of cTMA flares during pregnancy or following delivery. Data on pregnancies of cTMA patients during ongoing eculizumab (ECU) therapy, however, are scarce.

Case Description: We report pregnancy and delivery outcomes of two cTMA patients enrolled in the Vienna TMA cohort and measured complement related proteins and ECU concentrations at regular intervals during pregnancy, thereafter, and in cord blood. The first manifestation of cTMA occurred in both patients during childhood or young adulthood and was not related to pregnancy. One patient (genetic variants in CFH, CD46, CFP, C3) had a total history of 26 cTMA flares and of two uneventful pregnancies with prophyactic plasma infusions. She started ECU at her last cTMA flare, which was continued during her third pregnancy at the age of 27 yrs. The other patient (genetic variants in CFI, CD46), 29 yrs of age at her second pregnancy, had a history of recent early abortion during long-term ECU therapy following kidney transplantation, which was performed four years after her first manifestation of cTMA. ECU plasma concentrations were maintained in the therapeutic range during both successful pregnancies and were also detectable in the cord blood. Complement related tests did not indicate alternative pathway activation during pregnancies. Kidney function and blood pressure did not change substantially in both cases. However, proteinuria increased at the end of the third trimester in both patients. Both neonates were adequate for gestational age (weight: 3720 and 3082g; head circumference: 35 and 34 cm; length: 52 and 50 cm) with vaginal delivery in week 40+3 and 37+0 of gestation, respectively. Results of complement related tests in cord blood showed deficient complement activity, with low factor and regulator levels without overactivation, which most likely reflects the situation related to age and the presence of ECU in cord blood.

Discussion: Pregnancy and delivery outcomes with ongoing ECU therapy in two genetically high-risk cTMA patients with preserved native kidney and kidney transplant function were excellent.

SA-P0378

Hypokalemic Periodic Paralysis and Hypertension in Pregnancy: A Diagnostic Challenge

Introduction: Geller syndrome is a rare autosomal dominant syndrome that causes new or worsening hypertension (HTN) during pregnancy associated with hypokalemia and metabolic alkalosis.

Case Description: We report the case of a 37-year-old Burmese female who presented at 24 weeks’ gestation with a 3-day history of progressive lower extremity weakness leading to inability to walk. Her blood pressure (BP) was elevated at 180/90. Initial labs revealed serum potassium (K) 1.6 mEq/L with ECG changes of prolonged QT interval and U waves. Initial spot urine potassium was 5.7 mEq/L and sodium 54 mEq/L. A 24-hour urine potassium was 19.8 mEq/L. Following repletion of K, both orally and intravenously, paralysis resolved. Initial diagnosis was hypokalemic periodic paralysis. She was started on nifedipine for HTN. Thyroid function was intact. Cortisol 3.4 mcg/dl (3.5-19.5 mcg/dl), renin <2.5 pg/ml (2.5-45.7 pg/ml), aldosterone <3.0ng/dl (4.0-11 ng/dl), and aldosterone/renin ratio (ARR) 3.8. Catecholamines were all normal. Moderate to severe hypokalemia recurred several times during the pregnancy, and urine K was not suppressed. BP remained high and she required addition of labetolol. She underwent cesarean delivery at 37 weeks of pregnancy due to severe pre-eclampsia.

Amiloride was started postpartum. Hypokalemia and hypertension improved.

Discussion: Low renin and high aldosterone related HTN is mainly due to excess mineralocorticoid activity. Our patient experienced worsening HTN and severe hypokalemia during pregnancy, with low renin and low aldosterone levels. The improvement of HTN and hypokalemia postpartum suggests pregnancy-specific factors. Normally, activation of mineralocorticoid receptor (MR) causes renal salt reabsorption through the epithelial sodium channel (ENaC) activity. Progestosterone binds to but does not normally activate the MR. Geller syndrome is caused by an activating mutation in the gene encoding the MR (SR101). This allows progesterone (as well as spironolactone) to function as agonist, causing increases in BP, and hypokalemia during pregnancy. Liddle’s syndrome was also considered as she responded well to amiloride. However, the age of the patient and the lack of family history argue against it. Geller syndrome is rare but should be considered in women with HTN and hypokalemia in pregnancy. Genetic testing is pending.
Nurkner Syndrome Treatment Complications
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Introduction: Nutcracker syndrome is the clinical manifestation caused by the situation that the left renal vein suffers from pressure when passing through the angle between the abdominal aorta and the superior mesenteric artery. The syndrome is characterized by hematuria, albuminuria, lumbar pain, and varicocele. Indications for surgical treatment include severe unrelenting pain, significant hematuria, renal functional impairment, and inefficacy of conservative treatment after one year.

Case Description: 29-year-old female with a past medical history of migraines presented to nephrology clinic for evaluation of fatigue, hematuria, and severe left flank pain. She previously was a healthy endurance athlete. Her left flank pain occurs daily and she describes that pain as 10/10 in severity, debilitating, and sharp. CT kidney/pelvis results with a mild narrowing of the left renal vein as it passes between the SMA and aorta and a 1.4 cm left renal cyst. Renal artery duplex subsequently performed revealed normal left renal vein proximal narrowing and midsegment dilatation suggestive of Nutcracker phenomenon. Venogram performed revealed a 6 mmHg difference between the IVC and the left renal vein confirming the diagnosis of nutcracker syndrome. Patient underwent a left renal vein to inferior vena cava bypass. Unfortunately, the bypass thrombosed and her pain returned. She is currently being considered for autotransplantation of her left kidney. Risks of autotransplantation include a high risk of left nephrectomy in this patient due to a short renal vein segment.

Discussion: Management of Nutcracker Syndrome is a challenging endeavor. Non-surgical approaches include observation, especially in patients younger than 18 years of age since increase in intra-abdominal and fibrous tissue at the SMA origin during growth releases the obstruction of the left renal vein. In addition, weight gain increases the retroperitoneal adipose tissue, which leads to change in the positioning of the left kidney with reduction of tension on the left renal vein. Surgery is definitive treatment, but does not come without risks as seen in our patient. Surgical complications include deep venous thrombosis, retroperitoneal hematoma, ileus, and renal vein thrombosis. Complications of surgery should be extensively reviewed with patients prior to surgery. In retrospect, weight gain should have been trialed in this endurance athlete prior to surgical bypass.

SA-PO380

In Vitro Fertilization (IVF): Early-Onset Preeclampsia Before 16 Weeks’ Gestation
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Introduction: Preeclampsia is a hypertensive pregnancy disorder diagnosed in women presenting with new onset hypertension and proteinuria > 20 weeks gestation. IVF has been suggested as a risk factor for preeclampsia. We describe a rare case of early onset preeclampsia ~ 20 weeks gestation conceived via IVF.

Case Description: A 38-year-old G2P0010 patient at 15w5d gestation conceived via IVF presented with headache and worsening bilateral lower extremity swelling. She was experiencing intermittent headaches and occasional foamy urine for a few weeks before presentation. No past or family history of renal disease. BP was 230/107mm Hg at presentation, UA showed >500 mg/dl protein with no hematuria, 24-hour urine protein was 18 g/day, serum creatinine 0.76 mg/dl, ALT 88 IU/L, AST 55 IU/L, Platelets 165 K/uL. Transvaginal ultrasound(U/S) confirmed stated gestational age. Renal US was unremarkable. Relevant serologies were negative. Renal biopsy (see image) showed glomerular capillary endotheliosis and new subendothelial basement membrane (BM) formation creating BM double contours consistent with preeclampsia. The patient opted for termination of pregnancy at 17w2d. BP, transaminits and proteinuria normalized after one week of pregnancy termination.

Discussion: Preeclampsia presenting before 20 weeks gestation is rare, and a case associated with IVF as a sole risk factor is unique. Other conditions like molar pregnancy, triploidy, lupus nephritis, antiphospholipid antibody syndrome, thrombotic thrombocytopaenia, acute fatty liver of pregnancy, hemolytic uremic syndrome and fetal hydrops should be excluded. Common risk factors for preeclampsia are prior preeclampsia, chronic hypertension, pre-gestational diabetes, obesity and IVF. Embryo preservation, implantation techniques and placental development with IVF have been suggested as a cause for this serious systemic hypertensive disorder. This is the first reported case of early-onset preeclampsia before 16 weeks gestation with IVF.

SA-PO381

A 64-Year-Old Woman with Raccoon Eyes After Kidney Biopsy
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Introduction: Raccoon eyes is caused by blood tracking into periorbital tissues, which are easily recognized as a symptom of basal skull fractures. However, it may be a sign of health threatening situations such as multiple myeloma, amyloidosis and so on. Here we discuss a patient with raccoon eyes after the kidney biopsy who was finally diagnosed as immunoglobulin light chain (AL) amyloidosis.

Case Description: A 64-year old woman presented to our clinic with 1-year proteinuria. Laboratory study showed Scr was 382 µmol/L and 24-hour urine protein quantification was 2.4 g. The testing for monoclonal protein by serum revealed an M-peak in the λ fraction of IgA (Fig1a). The concentrations of k and λ were 44.95 and 173 mg/L, respectively. The bone marrow cytology test was negative. Ultrasound report indicated the size of right kidney was 9.1x4.4 cm and the left one was normal. But unexpectedly, the patient showed periorbital purpura 24 hours after kidney biopsy (Fig1b). Congo red staining was positive and also showed strongly λ deposition. EM showing expansion of the mesangium by amyloid fibrils.

Discussion: AL amyloidosis is the most common type of systemic amyloidosis. Renal involvement accounts for almost 70% and most presents as clinically apparent nephritic syndrome. Sometimes it only presented with proteinuria and slowly progressive deterioration of renal function. So it is necessary to perform tissue biopsy once the patients with unknown renal failure accompany with monoclonal M protein. The vascular infiltration of amyloid fibrils in blood vessels in patients with amyloidosis can cause bilateral periorbital ecchymosis by a Valsalva maneuver or minor trauma. Here we firstly reported this rare symptom after kidney biopsy in a patient who was finally diagnosed as AL amyloidosis. During the kidney biopsy, the patient was asked to hold breath during inhalation, which mimicked Valsalva maneuver, and thus contribute to the periorbital purpura. Therefore, periorbital ecchymosis warrant more attention as an early cue of amyloidosis.
SA-PO383
Looking Beyond Tenofovir Renal Toxicity as the Cause of Bone Disease in HIV
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Introduction: Chronic kidney disease (CKD) with tubular dysfunction from tenofovir therapy in HIV disease is frequently associated with bone disease. Here we present a patient referred for evaluation of osteoporosis.

Case Description: A 48-year-old African American phenotypic female with CKD stage 3a-A3 and sub-nephrotic proteinuria, was referred for osteopenia on bone densitometry in the setting of prior history of right hand fracture with minor trauma. Her past medical history was notable for HIV/AIDS diagnosed 24 years ago, for which she was treated with Tenofovir DF/PV (TFV) including Tenofovir Disoproxil Fumarate (TDF) and protease inhibitors (PI). Upon evaluation, laboratory data showed serum creatinine of 1.5 mg/dL (eGFR 50 mL/min), low normal serum phosphorus with fractional excretion of phosphorus in the urine ~15% and glycosuria. There was mild elevation of serum alkaline phosphatase although bone alkaline phosphatase was normal. Other bone turnover markers (osteocalcin, C-Telopeptide and N-Telopeptide) were in the normal range.

Patient underwent bone biopsy with double tetracycline labeling to evaluate turnover and mineralization; histological results showed high turnover osteopenia with normal mineralization. Patient was started on anti-resorptive therapy with Alendronate.

Patient was transitioned to combination ART (dolutegravir, abacavir, lamivudine) 2 years earlier, with improvements in renal parameters. Further review of medications revealed she was being treated with estradiol for gender dysphoria (male to female transition) and had levels below low target; estradiol therapy was increased to better support hormone status and thereby mitigate bone loss.

Discussion: Although the impacts of HIV, ART with TDF and PI’s, CKD, and tubular dysfunction contribute cumulatively to long-term consequences for bone health, in this patient, hypogonadism related to transgender status was likely a major contributing factor at the time of evaluation. This report highlights that bone disease in CKD patients with HIV is multifactorial and a potentially dynamic process over time in the context of evolving risk factors. Accurate diagnosis remains critical for optimal management.

SA-PO384
Dialysis for an Adult with Maple Syrup Urine Disease
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Introduction: Maple syrup urine disease (MSUD) is a rare genetic defect in branched chain amino acid (BCAA) metabolism which, if untreated, leads to accumulation of isoleucine accompanied by significant neurologic deregulation and even death. MSUD predominantly affects children and there is little data regarding the utility of renal replacement therapy (RRT) to correct metabolic derangements in adults with MSUD.

Case Description: We present the case of a 39-year-old man who was admitted to our facility with acute encephalopathy as a consequence of decompensated MSUD secondary to acute gastrointestinal bleed (NISAAD use). He was transferred with cerebral edema attributed to an elevated leucine level of 2900 umol/L. The patient’s baseline levels of leucine, at which he had minimal symptoms, was ~1500 umol/L. Given the encephalopathy and cerebral edema, he was initially started on CVVHD with most stable status and leucine levels. Despite RRT, the patient remained symptomatic, raising the possibility his leucine levels were still elevated. He was therefore switched to intermittent hemodialysis for four hours to facilitate rapid removal of leucine, followed by resumption of CVVHD. CRRT was continued for a further 12 hours, with improvement in his leucine levels to ~800 and mental status. The patient made a full recovery and was discharged home 4 days later.

Discussion: Maple syrup urine disease is an inborn error of metabolism of BCAA, characterized by mutations in genes that result in a deficiency of the branched-chain alpha-keto acid dehydrogenase complex that is required to metabolize BCAAs. The disorder gets its name because the urine of affected infants has sweet odor. A specialized diet can prevent accumulation of BCAAs in these patients. However, any hypercatabolic state, including stressors such as infection, injury, and a failure to eat (as occurred in our patient due to his GI bleed), can lead to a metabolic derangement with a rapid increase in amino acid levels and accompanied clinical deterioration. Much of the experience in treating such patients nests in pediatric academic centers and literature, and physicians caring for adult patients have little experience with these complicated cases. Our case therefore illustrates a successful approach to managing metabolic crisis in the setting of an acute metabolic derangement in an adult patient with MSUD.

SA-PO385
Hyperbilirubinemia and Acquired Fancconi Syndrome
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Introduction: Bile cast nephropathy is characterized by renal dysfunction in the setting of severe hyperbilirubinemia. It is a rare condition that occurs as a result of direct toxicity from bile acids and from tubular obstruction by bile casts. Diagnosis requires a high degree of clinical suspicion and it should be differentiated from hepatorenal syndrome.

Case Description: A 32-year-old man with past medical history of alcoholic liver cirrhosis presented admitted for generalized jaundice and dark-colored urine. He generalized jaundice and dark-colored urine. He had a long history of alcohol consumption with a total bilirubin of >20 mg/dL and non-oliguric kidney (creatinine of 1.6 mg/dL, unknown baseline), elevated alanine transaminase (ALT) and alkaline phosphatase (ALP) levels of 140 IU/L and 350 IU/L, respectively. The patient referred for evaluation of osteoporosis.

Discussion: In this presentation, we attributed the cause of severe hyperphosphatemia and non-oliguric acute kidney injury to bile cast nephropathy. Risk of bile cast formation increases when total bilirubin levels rise above 20 mg/dL. As a majority of filtered phosphate is reabsorbed in the proximal convoluted tubule (~80%), severe hyperbilirubinemia can lead to hyperphosphatemia by way of proximal tubulopathy, more classically known as acquired Fancon ‘s syndrome. Previous case reports have reported that the degree of hyperphosphatemia is inversely correlated with bilirubinemia. As bile cast nephropathy is partially reversible, therapy should be focused on treating the cause of liver failure and correcting metabolic derangements.

SA-PO386
Euglycaemic Diabetic Ketoacidosis in Type 2 Diabetes: A Rare Complication of SGLT-2 Inhibitors
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Introduction: Diabetic ketoacidosis (DKA) is a commonly encountered condition worldwide, typically occurring in young patients with type 1 diabetes following a provoking illness. This case explores an atypical case of ketoacidosis in an elderly patient with type 2 diabetes, who was not on insulin treatment, providing a significant diagnostic challenge.

Case Description: An 81-year-old lady presented with a 48-hour history of poor oral intake, vomiting and dyspnea. Her past medical history was significant for schizophrenia and Type 2 Diabetes Mellitus. On examination she was dehydrated, but had an excellent urine output of over 1000ml/hr. Investigations revealed a raised anion gap metabolic acidosis (pH 7.08, Anion gap = 23) and ketonuria of 5.47 mmol/L. Blood glucose, lactate and renal function were within normal range and the patient denied ingestion of toxins. Chest X-ray showed evidence of pneumonia. Treatment with two litres of intravenous fluids and antibiotics did not correct the acidosis, the pH falling from an initial rise of 7.09 to 7.09 and blood glucose of 10.7 to 9.9 mmol/L (178 mg/dl). Dapagliflozin was identified in the drug history as a potential precipitant of euglycaemic diabetic ketoacidosis. Intravenous infusions of dextrose and insulin successively corrected the blood pH to 7.36 with resolution of ketonaemia over the course of twenty four hours.

Discussion: Euglycaemic diabetic ketoacidosis (eDKA) is defined as the clinical triad of a blood glucose <11.1mmol/l (<200mg/dl), raised anion gap metabolic acidosis and the presence of ketones in blood or urine. Euglycaemic DKA has similar provoking factors to DKA such as infection, fasting or surgery. This case is atypical as the patient was elderly and not on insulin treatment. The DECLARE (Dapagliflozin Effect on Cardiovascular Events) study with over 18,000 participants quoted an incidence of DKA in <0.1% of patients on this treatment. The European Medicines Agency concluded in 2016 that life-threatening and fatal cases of diabetic ketoacidosis have been reported in patients treated with SGLT-2 inhibitors. SGLT-2 inhibitors act on the proximal convoluted tubule promoting urinary sodium and glucose excretion, inhibiting glucose reabsorption. Clinicians should be mindful of this potentially life-threatening complication and consider eDKA in challenging cases of acid-base disturbance.

SA-PO387
Ectopic Adrenocorticotrophic Hormone Tumor Tumour Can Present as a Chloride-Depleted Metabolic Alkalosis
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Introduction: Metabolic alkalosis (MA) often presents with hypokalemia and is characterized by (CDMA, urine Na<15 meq/L) or CD-resistant (CRMA, urine Na>15 meq/L). CDMA is due to sustained loss of Cl, most commonly from either renal or GI losses, leading to pendrin inhibition. CRMA is most often due to direct tubular stimulation either Cl-depleted (CDMA, urine Cl<15 meq/L) or Cl-resistant (CRMA, urine Cl>15 meq/L). As a majority of filtered chloride is reabsorbed in the proximal convoluted tubule, interfering with the distal chloride and hydrogen ion secretion, the pH falls from an initial rise of 7.09 and blood glucose of 10.7 to 9.9 mmol/L (178 mg/dl). Dapagliflozin was identified in the drug history as a potential precipitant of euglycaemic diabetic ketoacidosis. Intravenous infusions of dextrose and insulin successively corrected the blood pH to 7.36 with resolution of ketonaemia over the course of twenty four hours.

Discussion: Euglycaemic diabetic ketoacidosis (eDKA) is defined as the clinical triad of a blood glucose <11.1mmol/l (<200mg/dl), raised anion gap metabolic acidosis and the presence of ketones in blood or urine. Euglycaemic DKA has similar provoking factors to DKA such as infection, fasting or surgery. This case is atypical as the patient was elderly and not on insulin treatment. The DECLARE (Dapagliflozin Effect on Cardiovascular Events) study with over 18,000 participants quoted an incidence of DKA in <0.1% of patients on this treatment. The European Medicines Agency concluded in 2016 that life-threatening and fatal cases of diabetic ketoacidosis have been reported in patients treated with SGLT-2 inhibitors. SGLT-2 inhibitors act on the proximal convoluted tubule promoting urinary sodium and glucose excretion, inhibiting glucose reabsorption. Clinicians should be mindful of this potentially life-threatening complication and consider eDKA in challenging cases of acid-base disturbance.
SA-PO388
SGLT2 Inhibitors Are a New String for Nephrologists’ Bow: Time to Be Excited yet Exercise Caution

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Introduction: Diabetic ketoacidosis (DKA) is traditionally defined as a triad of hyperglycemia, anion gap metabolic acidosis, and ketosis. On the other hand, Euglycemic DKA (EDKA), associated with blood glucose levels of ≤ 200 mg/dL is a relatively rare variant that is being recognized more in the setting of sodium glucose cotransporter 2 (SGLT2) inhibitors use. With the recent CREEDENCE trial showing that Canagliflozin (a SGLT2 inhibitor) portends better renal and cardiovascular outcomes in patients with type 2 diabetes mellitus, nephrologists need to be aware of EDKA, especially in the setting of acute kidney injury (AKI), which itself can contribute to metabolic acidosis and poor diagnostic challenge.

Case Description: A 69-year-old woman with a history of diabetes mellitus type 2, gastroparesis, hypertension and coronary artery disease presented with abdominal pain, nausea and vomiting for 3 days. She was on metformin 1000 mg twice a day, gastroparesis, hypertension and coronary artery disease presented with abdominal pain, nausea and vomiting for 3 days. She was on metformin 1000 mg twice a day. Her ketosis and renal failure resolved subsequently.

Discussion: Though initially thought to be remote use of diuretic induced CDMA, our patient’s response to Cl repletion led us to search for an alternative diagnosis. After his aldosteronism and renal limits returned low, we sent off ACTH and cortisol and found an ectopic ACTH producing tumor. His loop & thiazide diuretics had exacerbated his CMDA, but was not the sole underlying cause. At high concentrations, cortisol activates mineralocorticoid receptor in the cortex and collecting duct, leading to sodium reabsorption via ENaC and Na-K ATPase activation. This leads to Na reabsorption with H+ excretion through renal outer medullary K channels, thus causing HTN & hypokalemia. To maintain electrical neutrality, HC03 is reabsorbed and Cl is secreted into the tubular lumen via pendrin. But contrary to expected, urine Cl was low in our case which makes it an unusual presentation of hypercortisolism. Treatment strategies in these patients should focus on eliminating the primary cause if possible (decreasing tumor burden) & using medications which inhibit MR (Spironolactone) or ENaC (Amiloride).

SA-PO389
No Stone Unturned: A Case of Sjogren Syndrome Diagnosed by Recurrent Nephrolithiasis
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Introduction: The cause of nephrolithiasis is idiopathic in the majority of cases. Patients who are young, form stones recurrently, or have high stone burdens warrant more thorough investigation into an underlying cause.

Case Description: 59 year old female with past medical history of hypertension, Raynaud’s, gastric reflux, and recently diagnosed nephrolithiasis who presented with malaise, dysuria, fever, and chills after a seven day course of antibiotics for a urinary tract infection. She was evaluated in emergency department one month prior for right sided flank pain and was found to have a 4 mm obstructing stone in the proximal right ureter. This stone passed with medical expulsive therapy after which she continued to pass sandy urine sediment. On the current admission, imaging demonstrated a new 6 mm obstructing stone in the distal right ureter and a non-obstructing stone in the left renal pelvis not present a month earlier. Routine laboratory evaluation revealed a creatinine of 1.8mg/dL, non-anion gap metabolic acidosis, hypokalemia with elevated urinary potassium, and a urine pH of 6. The urine anion gap was positive and a distal renal tubular acidosis (RTA) was suspected. Further serologic testing was notable for a positive ANA (1:80), negative double stranded DNA, strongly positive anti SS-A and anti SS-B antibodies, low C3 and variable C4, hypocomplementemia, non-anion gap metabolic acidosis, lower-limb ulcerations etc. Serum ketones should be obtained in any patient with other halogens, though when measured by x-ray fluorescence spectrometry is between 3.2 to 5.6 mg/L. Significant environmental exposure is mostly limited to industrial setting. Bromine toxicity was well recognized in early twentieth century when use of bromide containing drugs was widespread. Toxic effects of bromide include neuropsychiatric disturbances, tremors, gait imbalance, rash, and dermatitis.

Case Discussion: An 82-year-old male was seen in the emergency room with sudden cognitive decline, visual hallucinations, gait disturbance and multiple falls. His medical history was significant for squamous cell cancer of head and neck and Masahein Gravis. His medication list included scheduled infusion of IVIG every four weeks and intratropoid bromide 20 mcg inhibitor two to three times daily. Notably, he was not on Pyridostigmine bromide. Physical examination was significant for blood pressure of 93/55 mm Hg, and fluctuating mental status. Serum chloride was found to be 163 mmol/L with anion gap of negative 65. Remaining serum chemistries, complete blood count, liver function tests, urinalysis, blood gas, TSH, Salicylate and Tylenol levels, B12 and cortisol levels were unremarkable. Multiple repeat labs continued to show high chloride concentration.

SA-PO390
Severe Hyponatremia Associated with Autoimmune LGI1 Encephalitis, an Underrecognized Cause of SIADH
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Introduction: SIADH is commonly caused by medications, malignancies, pain, and nausea, however autoimmune encephalitis as a cause is often underrecognized. Here we present a case of severe SIADH secondary to autoimmune LGI-1 encephalitis.

Case Description: A 79-year-old male with hypertension on hydrochlorothiazide (HCTZ) presented to the ED 2 months prior for fatigue, and was found to have hyponatremia with serum Na (sNa) of 123mmol/L. It was attributed to HCTZ, and sNa improved to 127mmol/L after its discontinuation. A month later, patient was hospitalized for left arm twitching and recurrent hyponatremia with sNa 123mmol/L, sOsma 256mmol/kg, sOsm 720omol/kg, cr 0.81mg/dL. His twitched was associated with voluntary movements, occurred 3 times a day and each lasted for 5 seconds. Workups for SIADH were unrevealing. Given the concern for symptomatic hyponatremia with arm twitching, the patient was treated with dexamethasone and 3% saline for controlled sNa correction, and discharged with sNa 137mmol/L, on salt tablets, fluid restriction, and furosemide. Neurologic symptoms had improved. Patient returned to clinic 3 weeks after discharge, and reported recurrence of left arm and hand twitching with increased frequency and severity, and now with new onset facial clenching. Labs showed normal sNa of 135mmol/L, sOsma 280mmol/kg, uOsm 681mmol/kg, Ca 9.6mg/dL. Patient was referred to Neurology Dystonia Clinic, and the diagnosis of anti-LGI1 encephalitis was confirmed with positive Leucine-rich, glioma inactivated protein IgG (LGI1) and positive Voltage gated potassium channel Ab (VGKC). He promptly treated with pulse methylprednisolone with resolution of his neurologic symptoms and hyponatremia.

Discussion: It is estimated that 60% of the patient with autoimmune LGI-1 encephalitis presented first to health care providers with hyponatremia, and yet, it is an under-recognized cause of SIADH. LGI-1 is part of the voltage-gated potassium channel complex present in the hippocampus and temporal cortex, and LGI-1 encephalitis is characterized by hyponatremia, acute or subacute cognitive impairment, fociobrachial dystonic seizures, psychiatric disturbances and epileptic seizure. If left untreated, patient would progress rapidly to end stage dementia resulting in death. However, if treated early with steroids, it has low relapse rate and good clinical outcome.

SA-PO391
Unexplained Bromide Toxicity Presenting as Hyperchloremia and Negative Anion Gap
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Introduction: Bromine is a deep red colored liquid primarily used in manufacture of chemical agents. Serum bromide concentration is difficult to quantify due to interference with other halogens, though when measured by x-ray fluorescence spectrometry is between 3.2 to 5.6 mg/L. Significant environmental exposure is mostly limited to industrial setting. Bromine toxicity was well recognized in early twentieth century when use of bromide containing drugs was widespread. Toxic effects of bromide include neuropsychiatric disturbances, tremors, gait imbalance, rash, and dermatitis.

Case Description: An 82-year-old male was seen in the emergency room with sudden cognitive decline, visual hallucinations, gait disturbance and multiple falls. His medical history was significant for squamous cell cancer of head and neck and Masahein Gravis. His medication list included scheduled infusion of IVIG every four weeks and intratropoid bromide 20 mcg inhibitor two to three times daily. Notably, he was not on Pyridostigmine bromide. Physical examination was significant for blood pressure of 93/55 mm Hg, and fluctuating mental status. Serum chloride was found to be 163 mmol/L with anion gap of negative 65. Remaining serum chemistries, complete blood count, liver function tests, urinalysis, blood gas, TSH, Salicylate and Tylenol levels, B12 and cortisol levels were unremarkable. Multiple repeat labs continued to show high chloride concentration.

Discussion: Because of interference by other halogens in routine measurements, a high bromide level can masquerade as hyperchloremia with large negative anion gap. Thus when encountered, bromism should be kept in mind.
Intoxication is the most common electrolyte disturbance in patients admitted to the hospital. We report a case of combined true- and pseudohyponatremia in a patient who was on continuous renal replacement therapy (CRRT).

Case Description: A 46-year-old female with a history of end stage renal disease (ESRD) secondary to lupus was admitted to intensive care unit with peritonitis and septic shock. The patient weighed 50 kg, with calculated Watson’s volume of 26 L. She was started on CRRT due to hemodynamic instability. Her serum sodium (Na) levels were stable around 129-130 mmol/L while on CRRT with a CRRT dailysate Na of 132 (to avoid over-correction). This was thought to be related to a hypotonic solution she was receiving (D2O for severe hyglocycmia). Overnight, the SNa was noted to drop to 122 mmol/L while she was receiving CRRT with no added hypotonic solutions administered. On call nephrology fellow was contacted urgently to establish the cause of this acute worsening of SNa. On medication review it was found that the patient received intravenous immunoglobulin (IVIG) for immune thrombocytopenia in the evening prior to the SNa of 122 mmol/L. That fact raised a suspicion of pseudohyponatremia. Further workup revealed serum Osmolarity of 281 mOsm/kg and anion gap of 1. Whole blood electrolytes were obtained and showed sodium level of 129 mEq/L.

Discussion: IVIG can cause hyponatremia by multiple mechanisms. Pseudohyponatremia results from increased percentage of protein in plasma, with a normal plasma Na concentration. IVIG therapy can also result in true hyponatremia, arising from sucrose-induced translocation of water from the intracellular compartment (ICF) to the extracellular compartment (ECF). Even in the presence of underlying true hypotenaemia, nephrologist should be cognizant of possibility of additional pseudohyponatremia. Therapeutic strategies should target whole blood Na in these situations.

Multiethnic GWAS for Idiopathic Nephrotic Syndrome in Adults and Children

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Background: Common HLA variants have been associated with steroid sensitive nephrotic syndrome (NS) in small cohort studies. We conducted a genome-wide association study (GWAS) for NS in different ethnicities, ages of onset and response to steroid therapy. Methods: We genotyped 2,639 NS cases and 16,765 genetically-matched controls. After imputation, we performed association testing using an additive model. Results: In the combined meta-analysis (2,639 cases), we discovered significant associations for the APOL1 (P=2.87x10-7, OR=1.54, 95% CI 1.19-1.99), the HLA-DQA1 locus (OR=1.43, 95% CI 1.19-1.72), and a novel locus chr1q22.2 (OR=1.34, 95% CI 1.25-1.45). After conditional analysis on the top two SNPs at APOL1 and HLA, a second independent HLA genome-wide significant signal was discovered (OR=1.36, P=2.18x10-06). Among adult onset patients (n=1,391), the strongest signals were for APOL1 (OR=3.14, P=1.82x10-05) and a novel locus on chr1q21.3 (OR=1.54, P=1.62x10-05). The HLA-DQA1 was the strongest signal overall in pediatric cases (OR=2.01, P=4.86x10-05). Interestingly, the HLA signal in Caucasians was significant also in adults (OR=1.33, P=1.20x10-04). Additional signals were found in adult and pediatric cohorts stratified by race and response to therapy. Conclusions: Our results reveal novel loci, pleiotropic risk predisposing alleles across different subphenotypes, and signals specific to race and age of onset. Specifically, we can now implicate variation in the HLA locus as a major contributor to NS also in adults. Fine-mapping of HLA in children and adults and integrating these GWAS alleles with other NS-associated genetic factors (Mendelian alleles, CNVs) holds promise in further elucidating the genetic architecture of NS. Funding: Other U.S. Government Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO396
Reverse Phenotyping After Whole-Exome Sequencing Reveals Frequent Podocytopathy Phenocopies in Steroid-Resistant Nephrotic Syndrome

Asiri
Monika
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Podocytopathy Phenocopies in Steroid-Resistant Nephrotic Syndrome
Reverse Phenotyping After Whole-Exome Sequencing Reveals Frequent SA-PO396
combination, to modify the pathogenesis of NS.

of genetic variants (residing outside of the known ‘nephrotic’ genes) working alone or in specifically enriched in likely CF disease.

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All patients affected by primary NS referred to our center between 2000 and 2018 were included in the study. Whole-exome sequencing and in silico filtering of 298 nephropathic genes were combined with reverse phenotyping performed right after genetic diagnosis in all the patients and families.

Results: A total of 111 patients (64 SRNS and 47 steroid sensitive NS, SSNS) were included in the final analysis. Not a single pathogenic variant was detected in the SSNS group. As expected, 20/64 (31.3%) SRNS patients had pathogenic variants in podocyte genes. However, 17/64 (26.6%) showed pathogenic variants in many other genes related to clinically unrecognized genetic nephropathies, i.e. in the absence of clinical signs of the underlying disorder at onset. Reverse phenotyping permitted the identification of minor clinical signs of the underlying genetic nephropathy in the patient or the family, confirming the diagnosis and explaining multi-drug resistance. Genetic patients did not experience recurrence of post-transplant NS (0/11), while NS relapsed in 40% of the others (4/10).

Conclusions: Our unique interdisciplinary workflow based on extended genetic analysis and reverse phenotyping can significantly increase the diagnostic accuracy in patients referred with the diagnosis of SSNS, avoiding mistreatment and predicting outcome in a large percentage of these patients.

SA-PO397
Genetic Identification of Two Novel Loci Associated with Steroid-Sensitive Nephrotic Syndrome

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Background: Primary idiopathic nephrotic syndrome (NS) is a typical presentation of genetic or non-genetic podocytopathies but occasionally other genetic nephropathies can present as clinically indistinguishable phenocopies. We hypothesized that such phenocopies of steroid resistant NS (SRNS) represent a relevant percentage of patients with primary NS showing frequent multi-drug resistance.

Methods: All patients affected by primary NS referred to our center between 2000 and 2018 were included in the study. Whole-exome sequencing and in silico filtering of 298 nephropathic genes were combined with reverse phenotyping performed right after genetic diagnosis in all the patients and families.

Results: A total of 111 patients (64 SRNS and 47 steroid sensitive NS, SSNS) were included in the final analysis. Not a single pathogenic variant was detected in the SSNS group. As expected, 20/64 (31.3%) SRNS patients had pathogenic variants in podocyte genes. However, 17/64 (26.6%) showed pathogenic variants in many other genes related to clinically unrecognized genetic nephropathies, i.e. in the absence of clinical signs of the underlying disorder at onset. Reverse phenotyping permitted the identification of minor clinical signs of the underlying genetic nephropathy in the patient or the family, confirming the diagnosis and explaining multi-drug resistance. Genetic patients did not experience recurrence of post-transplant NS (0/11), while NS relapsed in 40% of the others (4/10).

Conclusions: Our unique interdisciplinary workflow based on extended genetic analysis and reverse phenotyping can significantly increase the diagnostic accuracy in patients referred with the diagnosis of SSNS, avoiding mistreatment and predicting outcome in a large percentage of these patients.

SA-PO398
Genetic Variants in Basement Membrane Genes Are Enriched in Nephrotic Syndrome

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Background: Basement membranes (BM) are essential for tissue formation and function. Core components include laminins, collagens and heparin proteoglycans. Genetic defects in BM components cause a spectrum of rare human diseases, however, recent large-scale genetic studies have shown that variants in BM genes associate with more prevalent disease including diabetic nephropathy. Whilst the role of core BM components have been linked to human disease, there are more BM components and interactors that are likely to have key roles in BM assembly and regulation. We hypothesised that BM integrity is key to kidney survival and that genetic variants in a wide spectrum of BM genes associate with disease. We aimed to identify genetic differences in BM genes between patients with nephrotic syndrome (NS) and controls.

Methods: We assembled a list of 110 genes, likely to be important for BM function. The list was derived from Gene Ontology classification, proteomic analyses of extracellular matrix, and functional screens in C. elegans. We used this list to screen 133 exome sequenced Caucasian patients with paediatric onset of NS. The frequency of detected single nucleotide variations (SNVs) in the cohort was compared with the general population (gnomAD controls, European non-Finnish). Randomly selected genes were also examined and used as control genes. Chi-squared test with Yates correction (2x2 contingency tables) was used to test for differences.

Results: 25 SNVs were found to be significantly over-represented in the NS patients when compared to controls. 16 of those had the minor allele frequency (MAF) over 2x higher than in the general population. The biggest MAF differences were found in HMC1, SMC1C, LAMA5, MATN1, LAMA2 and ADAMTS16 genes. No SNVs were enriched in the control genes. Furthermore, we screened 50 genes (BM and other) known to cause NS and identified 5 candidates that caused a BM rupture phenotype in C. elegans and this frequency was approximately 20-fold higher than randomly selected genes.

Conclusions: Overall these findings support our hypothesis that BM integrity is key to long term kidney survival.

SA-PO399
Incidence of Single Heterozygous Variants in “Nephrotic” Genes in Non-Genetic Paediatric Steroid-Resistant Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) is a rare condition in childhood associated with considerable morbidity, particularly in those with early onset disease. Up to 30% of children have a monogenic cause, and research is focusing on stratifying patients at an early stage in order to ‘personalise’ their treatments. Over 70 genes have been associated with SRNS to date, most of them are autosomal recessive (AR). Exome analysis will not infrequently identify single rare heterozygous variants within AR genes that can cause uncertainty. It is often speculated that a second variant will either miss or lies within the non-coding part of the gene. There are pathogenic single nucleotide variants (SNVs) and small indels in the general population (‘carriers’ for the disease). This pilot project aims to compare the incidence of rare variants in randomly selected AR ‘nephrotic’ genes in paediatric SRNS patients with the ‘general’ population.

Methods: 133 exome sequenced Caucasian SRNS patients and the ethically matched ‘general’ population data (gnomAD, exomes) were used for the analysis. Rare (MAF<0.01) single nucleotide variants (SNVs) from the coding and splice-site regions were selected from the AR genes and their incidence was compared between the two cohorts. The data was analysed in 3 consecutive stages: 1. Rare SNVs regardless of zygosity. 2. Rare heterozygous SNVs (not found as homozygotes in any cohort). 3. Rare heterozygous SNVs + small indels, predicted to be likely pathogenic. SRNS patients with confirmed monogenic disease were excluded from this analysis.

Results: In this preliminary work we have found no statistically significant difference in the frequency of rare variants in NS genes (seen as homozygous or heterozygous (48.4% cohort / 53.1% control) / only as heterozygous (27.5% cohort / 24.6% control) /2x higher than in the general population.

Conclusions: Our preliminary findings suggest, for the case of the likely pathogenic single heterozygous variants, that these may be incidental and not indicative of a missing second hit’ within the gene.
SA-PO400

Development of a High-Throughput Screening System to Evaluate Nephrin Expression on Plasma Membrane
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Background: Nephrin is an important component of the podocyte slit diaphragm and its dysfunction leads to severe proteinuria and nephrotic syndrome. Most nephrin mutations possibly lack export to the plasma membrane as a result of abnormal folding and post-translational modification. Although normalization of nephrin trafficking is considered as a novel therapeutic target, promising agents have not yet been found, due in part to a lack of suitable screening systems for drugs that target nephrin regulation. Here, we established a high-throughput screening (HTS) system for discovery of agents that improve plasma membrane expression of nephrin.

Methods: To establish a high sensitive HTS system, we utilized split Nano-luciferase. NanoLuc-refused nephrin (HiBiT-nephrin) transgenic fibroblasts were transfected with HEK293 cell lines. Surface expression was detected by luminescence upon addition of a nonlytic reagent containing LgBT fragment and substrate. Treatment with glycosylation inhibitor (Tunicamycin) or chemical chaperone (4-PBA), as well as comparison of clinically reported mutants (15 missense mutations) evaluated the validity of this system.

Results: HiBiT-Nephrin showed remarkable RLU compared to mock (> 200-fold). In addition, the retention of nephrin phosphorylation was confirmed by western blotting. Under this condition, tunicamycin treatment significantly reduced HiBiT-nephrin RLU (< 40%). In contrast, 4-PBA treatment significantly increased RLU (> 150%). Furthermore, each of the 15 mutants of HiBiT-Nephrin showed unchanged (5) or reduced (10) expression on plasma membrane, most of which were augmented or recovered by 4-PBA treatment.

Conclusions: In this study, we succeeded in establishing a HTS system that can easily and sensitively quantify the expression of nephrin on the plasma membrane. Although the cell-based assay has limitations, this system reflected the characteristics of nephrin consistent with previous reports. With further optimization, this system will be used to screen for compounds that target nephrin.

SA-PO401

A GWAS of Congenital Anomalies of the Kidney and Urinary Tract
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Background: Congenital Anomalies of the Kidney and Urinary Tract (C AKUT) are prevalent causes of pediatric renal failure. We investigated common risk variants that may underlie this condition and increased the understanding of disease genetics.

Methods: We performed a GWAS on 2,894 children with CAKUT from 10 different centers. Genotyping was performed on the Illumina HumanOmniExpress BeadChip. We applied a false discovery rate of 0.05. Variants with an unadjusted p-value of <10-5 were included in the analysis. We performed a three-stage approach to prioritize candidate susceptibility genes in CAKUT.

Results: No genetic variants reached genome-wide significance, but a number of loci reached suggestive association thresholds (p-value < 10-8). The strongest association was with locus 12q23 (p=6.5x10-8), which contains the TWSG1, ROBO2, LAMA5 genes. These genes are involved in limb, heart, and kidney development.

Conclusions: Our preliminary GWAS identified CHD1 as a novel candidate gene, and have shown suggestive associations of variants in critical renal development genes. Integration with a subphenotype analysis may allow us to refine these loci and prioritize candidate susceptibility genes in CAKUT.

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SA-PO402

Estimation of Adenine Phosphoribosyltransferase Deficiency Prevalence Using Public Whole-Exome Sequencing Data
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Background: Adenine phosphoribosyltransferase deficiency (APRTd) is a rare, hereditary cause of recurrent kidney stones and progressive chronic kidney disease (CKD). While treatment with allopurinol or febuxostat is effective, a delay in diagnosis frequently results in adverse outcomes. The small number of reported cases in countries other than France, Iceland and Japan suggests an extremely low prevalence, although missed diagnoses may significantly affect prevalence estimates. We assessed the prevalence of APRTd based on the frequency of mutated APRT alleles in public genomic databases.

Methods: Four databases containing genome sequencing data, the Genome Aggregation Database (gnomAD, n=141,353), the NLHBI GO Exome Sequencing Project (n=65,030), the 100,000 Genomes Project (n=62,000) and the deCODE Genetics database (n=35,000) were searched for 64 reported APRT mutations and other potentially pathogenic variants. Minor allele frequencies (MAF) <0.01% were identified. The estimated prevalence of homozgyous genotypes was calculated using the Hardy-Weinberg principle.

Results: A total of 30 disease-causing mutations with MAF ≤0.01% were detected in all databases. The variants with the highest allele counts are shown in Table 1. The p.Arg98Cln mutation was found to have a heterozygous frequency of 0.4087% in the South Asian population (n=1.3 billion), yielding an estimated 17,201 homozygotes, and a heterozygous frequency of 0.03714% in the UK population (n=66 million) with an estimated 910 homozygotes. In the US, the p.Phe174 deletion had a heterozygous frequency of 0.2271% in the European-American population (n=223 million), yielding an estimated 4208 homozygotes.

Conclusions: The data suggest a greater prevalence of APRTd in the Asian, UK and US populations than is reported in the literature. Based on these findings, APRTd appears to be a seriously underrecognized cause of kidney stones and CKD.

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SA-PO403

Designing a Return of Genetic Results Workflow in Nephrology: Lessons Learned from a Pilot Study

Background: Genetic testing is an emerging tool in nephrology practice. Actionable genetic findings can be identified as part of research or clinical care. However, no best practice exists for return of results (RO) and clinical implementation of results, for renal patients.

Methods: We developed a workflow for RO of primary diagnostic and/or medically actionable (secondary) findings for adults with all-cause chronic kidney disease, who underwent exome sequencing, through participation in a biobank study.

Results: We attempted to re-contact a diverse group of 50 participants with potentially diagnostic findings. Among them, 36 were contacted and we returned actionable genetic findings to 23 individuals. We identified 6 major elements in the RO workflow for research participants: subject identification; re-contact; pre-test counseling for clinical testing; retesting for secondary validation; return of results with post-test counseling; and clinical implementation. We identified over 20 major challenges to RO, which were iteratively addressed to optimize the workflow. Some common challenges included changes of address, death, lack of insurance for clinical validation of genetic data, lack of interest in receiving actionable findings, unwillingness to contact at-risk relatives, access to genetic counseling, and lack of standardized tools for patients and physician education. Importantly, the genetic result meaningfully impacted the clinical care of all cases.

Conclusions: The lessons learned from this study provide valuable information for return of genetic result in the setting of clinical care and research for nephropathies.

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SA-PO404

Diagnostic Utility of Next-Generation Sequencing in Patients Presenting for Percutaneous Renal Biopsy

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Background: Genetic testing is fast becoming a first line of investigation in many branches of medicine. Genetic causes of kidney disease may be under-recognised and exome sequencing has been shown to detect pathogenic mutations in up to 10% of patients with CKD. We aimed to genotype a cohort of patients undergoing renal biopsy.

Methods: We recruited adult patients attending for percutaneous kidney biopsy under investigation for acute or chronic kidney disease, over an eight-year period from 2010 to 2018. Patients undergoing post-transplant renal biopsy or patients whose renal biopsy showed diabetic nephropathy or pauci-immune vasculitides were excluded. Patients underwent next generation sequencing using a specially designed Roche NimbleGen HeatSeq panel, which sequenced for 227 genes associated with kidney disease. Data was analysed using an in-house bioinformatics pipeline and variants were classified using gold-standard American College of Medical Genetics and Genomics guidelines for variant pathogenicity.

Results: We sequenced 69 patients who had undergone native renal biopsy. These included 21 patients with a histological diagnosis of IgA nephropathy, 19 with other forms of glomerular disease, 14 with interstitial nephritis, and 15 with non-specific changes on histology. We identified a pathogenic variant for Alport Syndrome (COL4A4) in a single patient (1.5%). We also identified a variant of unknown significance in CFH in the same patient, which may be contributing to the patient’s low complement levels. Additionally, we identified noteworthy variants of unknown significance in 39 patients including 12 loss-of-function variants and three truncating variants in genes previously established as contributing to renal disease.

Conclusions: Next generation sequencing may be a useful addition to renal biopsy in certain groups of patients. In an undifferentiated group of patients undergoing renal biopsy, we detected pathogenic mutations in 1.5%. This diagnostic yield may be improved when DNA is available from parents and other affected family members and with careful selection of patients sent for testing.

Funding: Private Foundation Support
Outcome of comprehensive gene panel testing in 127 renal patients

SA-PO407

Identifying New CKD Drug Targets from Genetic Analysis

Background: Identifying successful drug candidates to treat patients with Chronic Kidney Disease (CKD) is challenging due to the heterogeneity of the CKD population. As a result, no efficient treatment options to halit or reverse CKD development are today available. It’s known that the target genes associated with the clinical phenotypes are more likely to succeed in pharmaceutical development. Therefore, in an unprecedented approach to identify CKD disease drivers we have performed whole exome sequence on 3315 CKD patients and 9563 controls to search for rare mutations in CKD patients.

Methods: Collapsing analysis generated a list with 417 enriched suggestive rare mutations in CKD patients. These genes when then prioritized through a comprehensive workflow aiming to validate the hits as potential drug targets. First the genes were filtered by bioinformatics analyses with genes being ranked and selected based on their gene expression correlation to renal function and CKD stage. In addition, integrative omics analyses were performed to give information on kidney enrichment and predict renal cell type expression.

Results: The analysis leveraged 93 genes with a strong CKD correlation. In the next stage we ranked the genes based on literature supporting a link to CKD relevant biology. The 31 genes with the highest scores went into experimental in vitro and in vivo validation. Loss of function phenotypes were investigated by siRNA KD in 2D and 3D human (organoid) renal cell lines. Gain of function phenotypes were investigated by overexpression or by studying KD protection in the presence of CKD stressors. In parallel, the importance of the genes on renal function was evaluated using CRISPR knock-out of genes in zebrafish with the top ranked four genes being further processed using CRISPR knock-out mice.

Conclusions: This extensive workflow, that was processed within only one year, identified the first novel CKD drug target to have the potential to be first in class and as a result this gene entered our pipeline for drug discovery.

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SA-PO408

Unraveling the Genetic Contributions to Kidney Disease with the Kidney Genome Atlas
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Background: Focal segmental glomerulosclerosis (FSGS) is a progressive kidney disorder with limited treatment options. To discover novel drug targets for FSGS, we built the Kidney Genome Atlas (KGA), which currently contains whole-genome sequences (>30X) on 23000 individuals, including 3000 cases of FSGS, other proteinuric disorders, and diabetic nephropathy. Each patient genome is linked to longitudinal clinical records, and for a subset of 400 patients the KGA also includes matched transcriptomes from microdissected glomerular and tubulointerstitial samples. Our aim was to elucidate mechanisms of disease through genome-wide association studies (GWAS) of (1) disease severity; (2) conversion status, and (3) gene expression in cases suggestive of renal resident macrophages across species, we performed single cell RNA sequencing (scRNAseq) analysis of zebrafish medullary resident macrophages and for a subset of 400 patients the KGA also includes matched transcriptomes from microdissected tissues is a promising approach to unraveling the molecular mechanisms of kidney diseases.

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SA-PO410

More Than Half of Patients Clinically Diagnosed as Gitelman Syndrome in Adulthood Do Not Have Causal Mutations in Known Pathogenic Genes
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Background: Gitelman syndrome (GS) is an autosomal recessive kidney disorder characterized by hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis. GS is caused by loss of function mutations in SLC12A3 encoding Na+/Cl− cotransporters (NCC). Most of previous reports includes child-onset GS cases, and thus etiological profiles in adult GS have not been fully elucidated. The purpose of this study is to clarify mutation profiles of clinically diagnosed GS cases in adulthood, and to investigate the phenotypic difference between cases in which their genetic diagnoses were established or not.

Methods: A total of 84 genetically independent individuals who were referred to our institute with a clinical diagnosis of GS during 2012 to 2018 were retrospectively reviewed. Individuals who have any episodes of using loop or thiazide diuretics, or laxatives were not included. All of them received comprehensive genetic screening for known genes responsible for GS, Barter syndrome, and hypermagnesemia (SLC12A3, SLC12A1, KCNJ1, CLCNKB, REN, CLCNKA, CASR, MADD2, TRPM6, CLDN11, KCNJ10, etc.). Twenty individuals were excluded because of the following reasons; 9 with insufficient clinical information, 5 under 18 years, 2 with only single heterogeneous variant in SLC12A3, 3 with responsible mutations in CLCNKB, 1 with variants in REN. Results: Of the remaining 64 cases, 27 (42.1%) were genetically diagnosed as GS (solved cases). Thirty-seven (57.9%) did not have any responsible variants (unsolved cases). Of the remaining 31 cases, 20 (64.5%) were female (83.3% vs. 59.3%). Serum Mg was higher in unsolved cases (1.95 ± 0.47 vs. 1.67 ± 0.34, P = 0.02). There were no differences in serum K, HCO3−, FKE, urine Ca/Cr ratio between the groups. Regarding the causal mutations in SLC12A3, L588I (33.3%) and T180K (25.9%) were major, which are reported as hotspots in Japanese GS. In this study, R399C was also found in 11.1% cases.

Conclusions: More than half of the adult cases with GS phenotype were mutation-negative for known pathogenic genes. Phenotypic difference of the two was not evident other than age and serum Mg. Un solved adult cases might have novel pathogenic genes responsible for their GS phenotype.

Funding: Government Support - Non-U.S.
SA-PO411

Metabolic Profiling of Urine from Patients with Cystinuria Provides New Insight into Disease Phenotype, Associated Microbiome Effects, and Treatment Efficacy

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Background: Cystinuria is a disease of impaired absorption of cystine and dibasic amino acids (DAA) from the intestine and renal tubule leading to formation of cystine kidney stones. However, the metabolic impact of reduced amino acid absorption and excessive loss in the urine is poorly understood. We measured endogenous, gut microbiota, and xenobiotic metabolites, providing insight into consequences of the disease and its treatment.

Methods: Urinary biochemicals were assayed using LC-MS in 293 urine specimens from patients with cystinuria or control urinary phenotype. Multivariate statistical analyses were conducted to reveal statistically significant biochemical signatures of the disease and products of cystine-binding thiol drugs (CBTDs). 16s rRNA gene sequencing was performed on fecal samples from 12 wildtype (WT) and 12 cystinuric (Slc3a1 knockout; KO) mice to evaluate their gut microbial composition.

Results: Cystinuric urine samples had elevated levels of cystine-γ-glutamyl cystine disulfide (glutathione precursor), indole-3-acetic acid (microbial tryptophan metabolism), and novel conjugated forms of putrescine (microbial DAA degradation). Conversely, taurine (sulfur metabolism), indole-3-acetic acid-glucuronide, and novel urinary metabolite N-methyl piperacil acid (lysine metabolism) were reduced in cystinuric urine. Where cysteine-bound CBTDs were observed, substantial amounts of “wasted” drug were also detected as CBTD homodimers, non-cysteine disulfides, and mixed drug disulfides. The differentiation of gut microbiota-derived metabolites led us to evaluate the gut microbiota diversity and composition in a mouse model of cystinuria revealing clear beta diversity and taxa differentiation between WT and KO mice.

Conclusions: Cystinuria is associated with unique urinary metabolic profiles beyond hyperexcretion of cystine and DAA, indicating perturbed metabolic processes and potential gut microbiota effects. Study of the gut microbiome diversity and composition in a mouse model of cystinuria reveals clear beta diversity and taxa differentiation between WT and KO mice. Urinary profiles allow us to characterize the excretion profiles of CBTDs, providing insight which may be helpful to tailor treatment.

Funding: Government Support - Non-U.S.

SA-PO412

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis: Expression Pattern of Urinary Exosomal miRNAs

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Background: Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive tubulopathy caused by CLDN16 or CLDN19 genes mutations. FHHNC is characterized by urinary wasting of calcium and magnesium, nephrocalcinosis and progression to chronic kidney disease (CKD) and end-stage renal disease (ESRD). Also, some CLDN19 patients develop ocular impairment. Patients homozygous for c.59G>A; p.G20D mutation in CLDN19 (PH1) genes. Demographic, clinical, and laboratory features were compared by PH type using a Chi-square test (categorical variables) and Kruskal-Wallis test (continuous variables).

Methods: Biochemical and clinical data were obtained from patients enrolled in the Rare Kidney Stone Consortium PH registry. PH diagnosis was by molecular diagnostic testing of AGXT (PH1), GRIIPR (PH2) and HOGA1 (PH3) genes. Demographic, clinical, and laboratory features were compared by PH type using a Chi-square test (categorical variables) and Kruskal-Wallis test (continuous variables).

Results: Though they tended to be younger at onset of symptoms and diagnosis, PH3 patients were more likely to have had stones prior to diagnosis (p=0.025), a lower prevalence of nephrocalcinosis (p=0.002), and lower urine calcium, and citrate excretions than PH1 patients. (p <0.001) PH3 patients continued to experience recurrent stones throughout all decades of life. See Figure 1

Conclusions: Though more likely to have stones at presentation and higher urine calcium, nephrocalcinosis is less prevalent and kidney function better preserved in PH3 compared to PH1 and PH2. The lower Uox and higher urine citrate may contribute to preserved renal function, although the higher urine calcium may contribute to frequent stone events throughout the lifespan. The data suggest persistent stone activity throughout life in PH3 patients.

Funding: NIDDK Support

SA-PO413

Phenotypic Expression of Primary Hyperoxaluria: Comparative Features of Types 1, 2, and 3

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Background: Primary hyperoxaluria (PH) are inborn errors of metabolism that result from 3 specific hepatic enzyme deficiencies leading to hepatic overproduction of oxalate that must be excreted by the kidneys. Recurrent calcium oxalate kidney stones, nephrocalcinosis and decreased kidney function are common. PH type 3 (PH3) accounting for 10% of known PH cases was most recently described and hence the clinical expression is less defined due to small patient numbers and shorter follow-up.

Methods: Demographic and clinical data were obtained from patients enrolled in the Rare Kidney Stone Consortium PH registry. PH diagnosis was by molecular diagnostic testing of AGXT (PH1), GRIIPR (PH2) and HOGA1 (PH3) genes. Demographic, clinical, and laboratory features were compared by PH type using a Chi-square test (categorical variables) and Kruskal-Wallis test (continuous variables).

Results: Though they tended to be younger at onset of symptoms and diagnosis, PH3 patients were more likely to have had stones prior to diagnosis (p=0.025), a lower prevalence of nephrocalcinosis (p=0.002), and lower urine oxalate, and higher urine calcium and citrate excretions than PH1 patients (p <0.001) PH3 patients continued to experience recurrent stones throughout all decades of life. See Figure 1

Conclusions: Though more likely to have stones at presentation and higher urine calcium, nephrocalcinosis is less prevalent and kidney function better preserved in PH3 compared to PH1 and PH2. The lower Uox and higher urine citrate may contribute to preserved renal function, although the higher urine calcium may contribute to frequent stone events throughout the lifespan. The data suggest persistent stone activity throughout life in PH3 patients.

Funding: NIDDK Support
Interim Results from the Ongoing Phase 2 Open-Label Extension Study of Lumasiran, an Investigational RNA Interference (RNAi) Therapeutic, in Patients with Primary Hyperoxaluria Type 1 (PH1) 

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Background: PH1 is a rare genetic disorder characterized by persistent hepatic overproduction of oxalate. Oxalate crystalsizes with calcium leading to recurrent kidney stones, nephrocalcinosis, progressive renal failure, and multiorgan damage from systemic oxalosis. Lumasiran is a subcutaneously-administered investigational RNAi therapeutic specifically designed to decrease oxalate production. In Phase 1/2, lumasiran demonstrated an acceptable safety profile and clinically significant urinary oxalate (UOx) lowering in patients with PH1. Emerging data from the ongoing Phase 2 open-label extension (OLE) study will be presented.

Methods: Phase 2 OLE includes patients who completed the Phase 1/2 randomized, placebo-controlled, multicenter trial, evaluating lumasiran in patients with PH1 ≥6 years old, UOx ≥0.7 mmol/L (1.73 mmol/L/day) in eGFR <45 mL/min/1.73 m². Patients received 1 of 3 dosing regimens: 1 mg/kg or 3 mg/kg monthly x3 doses or 3 mg/kg every 3 months x2 doses. After completing Phase 1/2, all patients enrolled in OLE, starting at their original dose unless a different dose was approved prior to dosing in OLE. Endpoints include safety and change in 24-hour UOx.

Results: The Phase 1/2 study enrolled 20 patients with PH1 at 9 sites in 5 countries; mean age 14.9 years (range: 6–43), mean baseline UOx 1.69 mmol/L/1.73 m²/day (range: 0.83–2.97). As of February 2019, 18 patients were dosed in OLE for median of 870 days. After completing Phase 1/2, all patients enrolled in OLE, starting at their original dose unless a different dose was approved prior to dosing in OLE. Endpoints include safety and change in 24-hour UOx.

Conclusions: To date, lumasiran has demonstrated an acceptable safety profile and clinically significant reduction in UOx in patients with PH1. A Phase 3 program evaluating efficacy and safety of lumasiran in patients with PH1 is ongoing.

Funding: Commercial Support - Sanofi Genzyme

SA-PO411

SA-PO416

Methyl-CG Erosion Define Core Pathways in the Progression of Diabetic Nephropathy 

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Background: To apply systems level understanding of the role of DNA methylation, it is important to distinguish the essential sequence elements involved in regulating gene expression. This becomes a particularly challenging task for diabetic kidney disease (DKD) when reliable epigenetic markers such as DNA methylation are limited. While genome-wide methylation studies are typically performed using BeadChip array technology, this approach does not provide sufficient coverage to construct an integrated epigenetic regulatory network. Therefore, an important goal in diabetic nephropathy is considered a combination of polygenic and multifactorial disorder. To address this knowledge gap, we examined DNA methylation using massive parallel sequencing to describe an ERN using methylation changes from multi-centre diabetes registries.

Methods: DNA methylation sequencing was used to define an epigenetic regulatory network in the Finnish Diabetic Nephropathy (FinnDiane) discovery cohort. DNA methylation changes were also assessed using independent replication cohorts from Hong Kong and Thailand. Methylation mediated gene regulation using primary human renal and vascular endothelial cells confirm functional methylation-dependent CTGF and PDZB2 regulation of gene expression.

Results: Differential methylated regions (DMRs) in leukocytes are associated with DKD progression and integrative methylation analyses reveal 494 differentially methylated genes (DMGs) that intersect with CTGF binding sites (181 genes with increased- and 313 genes with reduced- methylation). Integration of DNA methylation and CTGF/PDZB2 profiles confirm the major pathways associated with insulin receptor signalling, lipid metabolism and integrin cell interactions with the progression of DKD.

Conclusions: The progression of nephropathy in T1D remains unexplained, using multi-centre registries combined with functional studies using primary human renal cells we identify methylation indices and specifically erosion on core genes that functionally regulate pathways describing an epigenetic regulatory network.

Funding: Government Support - Non-U.S.

SA-PO417

SA-PO418

Targeted Next-Generation Sequencing of Nephropathy Genes in Non-Diabetic and Diabetic Kidney Disease Patients Facilitates Clinical Diagnoses 

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Background: For patients with concomitant diabetes and chronic kidney disease (CKD), diabetes is often assumed to be the underlying cause of their kidney disease. Without histopathological evidence, however, it’s unclear if such patients have diabetic
kidney disease (DKD), nondiabetic kidney disease (NDKD), or concurrent DKD and NDKD. To examine the utility of targeted next-generation sequencing (NGS) in facilitating clinical diagnoses in CKD, we coupled this technology with a custom nephropathy gene panel to determine the genetic cause of CKD in NDKD and DKD patients from the Utah Kidney Study.

Results: Targeted NGS of 345 nephropathy genes was performed in 186 patients (87 NDKD and 99 DKD). Identified variants were prioritized by predicted effect on protein function, frequency (minor allele frequency (MAF) < 0.1%), and a CADDD-based mutation significance cutoff (MSC) at the 95% confidence interval for ClinVar. After applying a MAF filter and MSC impact score cutoff, retaining only variants marked as highly likely to be deleterious, we identified 563 rare, functional variants, 113 of which are novel. These included 509 non-synonymous, 20 nonsense, 24 frameshift, and 10 splicing variants. No enrichment of these variants was observed in NDKD patients when compared to DKD patients (p=0.55); there was, however, a trend of non-significant excess of novel rare variants in the NDKD cohort (p=0.15). An excess of rare variants was identified in the NDKD cohort in several genes, including COL4A5 and PKD2. Conversely, variants in DYNDC1H1, APPTB, NEK8, and ACE were enriched in the DKD cohort. Interestingly, variants PKHD1 and CUBN were nearly equally distributed between the two cohorts.

Conclusions: We identified many rare and novel variants in known nephropathy genes in both NDKD and DKD patients. Our findings suggest that many DKD patients likely have concomitant diabetes and non-diabetic CKD that can be attributed to a genetic cause. Our study suggests that targeted NGS may prove useful as a diagnostic tool to enable an accurate molecular CKD diagnosis, particularly in patients whose underlying CKD cause is incorrectly attributed to their diabetes.

Funding: Private Foundation Support

SA-PO419
Effects of the GLUT1 A-2841T Polymorphism on Proteinuria in CKD Patients Prior to the Onset of ESRD

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Background: The potential role of selected Glucose transporter 1 (GLUT1) single nucleotide polymorphisms (SNPs) in the pathogenesis of diabetic kidney disease has previously been published in human studies, with certain polymorphisms conferring a higher risk of nephropathy. We studied the effects of the GLUT1 A-2841T SNP in the promoter region on proteinuria in chronic kidney disease (CKD) patients prior to onset of their end-stage renal disease (ESRD).

Methods: This was a prospective cohort study of 127 ESRD patients whose GLUT1 A-2841T genotype was determined from their blood specimen and classified as: AA, AT or TT with the T polymorphism present in none, one or both alleles, respectively. Proteinuria was assessed by the highest protein to creatinine ratio within the 6-month period prior to ESRD onset, provided there was no sign of acute kidney injury. Covariates collected were patient age, race/ethnicity, gender, ESRD cause and date of onset as documented by their chronic dialysis unit, left ventricular ejection fraction <40%, smoking status, and presence of coronary/peripheral arterial disease. The gene analysis was performed by the UF Center for Biotechnology. Protein to creatinine ratio results were available in 78 patients. ESRD causes were categorized as type 2 or 1 diabetes mellitus, hypertension, polycystic kidney disease, glomerulonephritis or primary nephrotic syndromes, and other.

Results: The distribution of genotypes does not vary among the ESRD causes (p=0.54), but differs among the race/ethnicities (p=0.0002), with the TT genotype present in 50/4/8, 7.7% (8/104), 10% (1/10) and 40% (2/5) of Hispanic, black, white and American Indian/other patients, respectively. Adjusting for the ESRD cause, the TT genotype is associated with 5.73 g/g more proteinuria than AA (95%CI 2.9, 8.5; p<0.0001). The AT genotype is associated with 0.71 g/g more proteinuria than AA, but the results are not significant.

Conclusions: Proteinuria in CKD patients tends to increase with a single A to T allele change at the -2841 position of the GLUT1 gene and becomes very significant with A to T changes in both alleles, with the results applicable to all ESRD causes.

Funding: Commercial Support - Dialysis Clinic, Inc.

SA-PO420
Contribution of SLC22A12 on Hypouricemia and Its Clinical Significance for Screening Purposes

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Background: Renal hypouricemia (RHUC) is a rare inherited disorder strongly associated with genetic mutations of renal transporters genes. Despite its adverse complications (e.g. increased risk of kidney failure and nephrolithiasis), differentiating between inherited renal hypouricemia and transient hyperuricemic status is challenging. Here, we aimed to identify genetic variants in hypouricemia patients using whole-exome sequencing (WES) and assess the feasibility for genetic diagnosis in primary screening.

Methods: We selected a cohort of 31 patients with extreme hypouricemia (<13 mg/dl) from Korean urban cohort of 179,381 subjects; selection criteria included 1) abstinence from alcohol or smoking and 2) an absence of underlying conditions (i.e., hypertension, diabetes and taking anti-hypertensive medication). WES and corresponding downstream analyses were performed for discovery of coding variants causal for hypouricemia. Two known causal variants within SLC22A12 (p.Trp258* and p.Arg90His) were identified, we then directly genotyped the 2 SLC22A12 variants in independent 50 hypouricemia subjects to assess the diagnostic utility of these two causal variants.

Results: For the discovery cohort who had undergone WES, 27 of 31 (87.1%) individuals harbored missense or nonsense variants in either the homozygous or compound heterozygous state in SLC22A12. 24 of 31 (77.4%) subjects were shown to have at least 1 copy of the truncating p.Trp258* and/or p.Arg90His. Four novel variants in SLC22A12, p.Asn136Lys, p.Trh225Lys, p.Arg284Gln, and p.Glu429Lys were discovered and were predicted to cause uric acid transport defects by molecular dynamics. Individuals (n=50) from an independent cohort were directly genotyped for the two SLC22A12 variants and p.Arg90His variants, 47 of 50 cases (94%) were explained by only these two variants.

Conclusions: This is the first study to show the value of genetic diagnostic screening for hypouricemia in the clinical setting. Screening of just two ethnic-specific variants in SLC22A12 and p.Arg90His variants can explain almost all cases in Korean patients with hypouricemia. Early genetic identification of constitutive hypouricemia may prevent acute kidney injury by avoidance of dehydration and excessive exercise.

Funding: Government Support - Non-U.S.

SA-PO421
Long-Term Renal Outcomes with Migalastat in Patients with Fabry Disease: Results from Phase 3 Trials

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Background: Fabry disease is a multisystem disorder of which nephropathy is an important feature, with untreated male patients experiencing a decline in glomerular filtration rate (GFR) of up to 12.2 mL/min/1.73 m² per year. Here, we assessed long-term changes in renal function in patients with Fabry disease and amenable mutations who were treated with migalastat in the phase 3 FACETS (NCT00925301) and ATTRACT (NCT01218659) trials.

Methods: In FACETS, enzyme replacement therapy (ERT)-naïve patients were randomized to 6 mo of double-blind migalastat 150 mg every other day (QD) or placebo, followed by an additional 18 mo of migalastat. In ATTRACT, patients receiving ERT were randomly assigned to 18 mo of migalastat 150 mg QD or continued ERT, followed by an additional 12 mo of migalastat. Patients could continue migalastat in separate long-term extension trials. Renal outcomes were evaluated using the beginning of treatment as the baseline, and were analyzed by sex, baseline eGFR, QD-vs-QOD, and baseline 24-h urine protein.

Results: Overall, mean (range) duration of migalastat exposure was 4.4 (0.1-7.8) years. Mean (SD) baseline eGFRQD (mL/min/1.73 m²) was 93.1 (24.6) in FACETS and 49.9 (20.4) in ATTRACTS. Annualized rates of change in eGFRQD, by baseline variables are shown in the table.

Conclusions: Data suggest that patients who received long-term treatment with migalastat experienced a rate of eGFR decline comparable to published data with ERT. In addition, starting treatment early may prevent irreversible renal progression.

Funding: Commercial Support - Amicus Therapeutics

SA-PO422
Evaluation of Renal Biomarkers for Fabry Disease Patients with and Without Enzyme Replacement Therapy

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Background: Renal follow-up is an important part of clinical monitoring in patients with Fabry disease (FD) with the aim of avoiding renal failure. Despite its limitations, creatinine is still the most used biomarker. While new renal biomarkers are described, their effectiveness has not yet been fully evaluated for FD. This study aimed to compare renal biomarkers generally and rarely used in the evaluation of FD patients receiving or not enzyme replacement therapy (ERT).

Methods: The usual biomarkers for renal monitoring (microalbuminuria, proteinuria and creatinine) and the proposed biomarkers (cystatin C, beta-2-microglobulin (B2M), NGAL) were quantified in blood and/or urine samples of 40 patients with FD, 39 controls without renal disease paired by age and sex and 38 controls with renal disease undergoing hemodialysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

[Underline represents presenting author.]
Results: In FD group, 32.5% are men with mean age of 41 years old and mean age of 41 years old. There was a statistically significant difference (p=0.05) for proteinuria and microalbuminuria in isolated urine samples and, in results for both plasma and serum samples for cystatin C,NGAL,B2M, creatinine and GFR. All analytical parameters evaluated, including ROC curve, sensitivity, specificity and accuracy indicated B2M as the best biomarker for proteinuria and microalbuminuria. Results of NGAL and urinary creatinine do not indicate good predictors of renal impairment. Although 72.5% patients were receiving ERT, similar results were found when comparing individuals with and without ERT with controls, suggesting that the treatment does not have significant influences on the evaluated parameters. When comparing the results of FD receiving or not ERT with the control volunteers without kidney disease, there was a significant statistical difference for the results of NGAL, microalbuminuria and proteinuria. Microalbuminuria and proteinuria are widely accepted as one of the evidences for starting ERT in FD patients. Since NGAL has already been described as a potential biomarker of inflammation, it might help to explain the higher results of this biomarker in FD patients compared to control groups.

Conclusions: Considering the biomarkers proposed, serum B2M was the best renal biomarker for renal follow-up in FD patients, followed by cystatin C. Moreover, TR-E does not seem to have influences on biomarkers results.

SA-PO423

Family Screening Among CKD Patients with Fabry Disease: A Very Important and Undertaken Task

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Background: Introduction: Fabry disease is a chronic, progressive and multi-systemic hereditary condition, related to a Xq22 mutation in X chromosome, which results in deficiency of acid alpha-galactosidase, hence reduced capacity of globotriaosylceramide (Globotriaosylceramide, GLA) degradation. GLA accumulates in lysosomes throughout virtually every organ, thus causing considerable morbidity and mortality. Objective: Evaluate the prevalence of Fabry disease, as well as its signs and symptoms, among relatives of chronic kidney disease (CKD) patients diagnosed with Fabry disease during a previously conducted study. Methods: Clinical and epidemiological analysis of Fabry disease in dialysis centers in Brazil – the Brazil Fabry Kidney project'.

Methods: Transversal study, interviewing the relatives of patients and performed blood tests for both GL3 dosage and genetic testing. Results: Among the 214 interviewed relatives, 115 (9.47%) were given the diagnosis of Fabry disease, with a predominance of women (66.10%). The most prevalent comorbidities were rheumatologic conditions and systemic hypertension (1.7% each), followed by heart, neurological and cerebrovascular disease, and depression, in 0.9% of individuals. Intolerance to physical exercise and tiredness were observed in 1.7%, followed by periodical fever, intolerance to heat or cold, diffuse pain, burn sensation or numbness in hands and feet, reduced or absent sweating, as well as abdominal pain after meals, in 0.9%.

Conclusions: Family screening of Fabry disease is highly indicated, since we found a prevalence of 9.47% of relatives of CKD patients with this condition, remarkably with a 66.1% predominance of women, which contrasts with previous reports.

SA-PO424

Natural Killer Subsets in Patients with Fabry Disease

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Background: Fabry Disease (FD) is a storage disorder which affects mostly kidney, kardio and serebrovascular systems. The lysosome, whose function is impaired in FD and systemic hereditary condition, related to a Xq22 mutation in X chromosome, which results in deficiency of acid alpha-galactosidase, hence reduced capacity of globotriaosylceramide (Globotriaosylceramide, GLA) degradation. GLA accumulates in lysosomes throughout virtually every organ, thus causing considerable morbidity and mortality. Objective: Evaluate the prevalence of Fabry disease, as well as its signs and symptoms, among relatives of chronic kidney disease (CKD) patients diagnosed with Fabry disease during a previously conducted study. Methods: Clinical and epidemiological analysis of Fabry disease in dialysis centers in Brazil – the Brazil Fabry Kidney project'.

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Conclusions: Family screening of Fabry disease is highly indicated, since we found a prevalence of 9.47% of relatives of CKD patients with this condition, remarkably with a 66.1% predominance of women, which contrasts with previous reports.

SA-PO425

Tunneling Nanotubes Shuttle Lysosomes with Low-Level α-Galactosidase A from Non-Fabry to Fabry Podocytes In Vitro

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Background: Fabry disease is an X-linked disease; however, females can suffer from serious complications. Biopsy studies are suggestive of no effective cross-correction between non-Fabry and Fabry podocytes. We aimed to examine if there is any level of cross-correction between these cells in vitro.

Results: Using a stable line of podocytes (FD-ko) containing lysosomes and α-Gal-A activity in Fabry podocytes but was lower than intracellular WT, respectively. While there was almost no α-Gal-A activity in no-CGG-LA-ko podocytes, this was present in FD-ko cells, albeit being 6 fold less than WT podocytes. There was no detectable α-Gal-A mRNA or enzyme activity in the media. A cultural assay showed similarly reduced cellular proliferation in both CC-GGLA-ko and no-CGG-LA-ko podocytes compared to CC-WT or no-CG-WT podocytes. IF staining showed tunneling nanotubules (TNs) containing lysosomes were running between FD-ko and WT cells.

Conclusions: Our data suggest that there is small transfer of GLA-mRNA and α-Gal-A protein from non-Fabry to Fabry podocytes through TNs. This low level cross-correction led to small increase in α-Gal-A activity in Fabry podocytes but was not enough to improve survival of these cells. It will be important to demonstrate if this phenomenon exists in vivo and between other cells. These studies may lead to novel treatment options for females with Fabry disease.

Funding: Commercial Support - Sanofi

SA-PO426

Think, Rethink, Diagnose: Dent Disease Type 1

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Background: Dent’s disease type 1(Dent1) is a rare X-linked tubulopathy with no cure at the present time. It affects mainly males and is characterized by low-molecular-weight proteinuria(LMPW), hypercalciuria, nephrolithiasis, nephrocalcinosis and progressive renal failure. There’s a broad phenotypic variability unrelated to the different mutations. LMWP is routinely tested so that it may go unnoticed results to misdiagnosis. The prevalence of Dent1 is unknown. The geographic dispersion and the lack of common registries make epidemiologic studies difficult. We aim to evaluate the Spanish Dent1 cohort and assess its genetic and clinical characterization.

Methods: We identified 18 patients with genetic confirmation of Dent1 diagnosed in 9 different hospitals in Spain. Only two individuals belonged to the same family; the rest to different families.

Results: Genetic analysis revealed 17 different mutations in CLCN5 gene in the 18 patients. The median age of diagnosis was 15 months [IQR,11–108] and the main sign leading to diagnosis was proteinuria (40%). All patients had proteinuria measured by protein/creatinine ratio(pCOR), median 1600mg/g [IQR,715-1665] and LMWP. During follow-up, 40% of patients presented with nephrocalcinosis and 11% with lithiasis. Mean creatinine at diagnosis was 0.3740,18mg/dl and estimated glomerular filtration rate(eGFR) 140.5±59 ml/min. After follow-up, median 6 years [IQR,3-12.25]) creatinine was 1.24±0.9 mg/dl and eGFR 88±44 ml/min. No patients required renal replacement therapy (Table 1).

Conclusions: One should suspect Dent1 in males with a history of lithiasis, nephrocalcinosis or bone disease. Although LMWP is the hallmark of Dent1, many

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Poster/Saturday

Underline represents presenting author.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Patients with Fabry disease (n=15)</th>
<th>Mean±SD or Median (IQR)</th>
<th>P value</th>
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<td>34.92±12.00</td>
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<td>Body mass (kg)</td>
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<td>78±10</td>
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<td>Glucose (mmol/L)</td>
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<td>eGFR (ml/min)</td>
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<td>Uric acid (mg/dl)</td>
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<td>Albumin (g/L)</td>
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patients show albuminuria. LMWP should be tested in young males with albuminuria and no other sign/symptom of nephrotic syndrome. Common registries are important.

**Funding:** Private Foundation Support

SA-PO427

RNA Sequencing Profile of Circular RNAs in Mouse Kidney During Aging

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**Background:** Kidney aging is an important clinical problem, not only because normal aging reduces renal function but also because of the high frequency of ESRD, renal cancer, and renal failure in elderly people. At the present time, the molecular basis of renal aging is not clearly known. For example, the abundance and function of circular RNAs (circRNAs) in other disease have been reported, but their alterations in the biology of renal aging remain elusive.

**Methods:** Renal Specimens were collected from 3-month-old and 24-month-old C57BL/6 mice. Total RNA was extracted using Trizol reagent following the manufacturer's procedure. circRNA expression was performed using secondary Sequencing. Quantitative real-time reverse-transcription polymerase chain reaction (qRT-PCR) was used to quantify the expression of circRNAs.

**Results:** A total of 134 distinct circRNA candidates were detected. Among them, we defined the statistical criteria for selecting aberrant-expressed circRNA using a p-value of < 0.05 with a fold change of ≥ 2.0 or < 0.5. A total of 86 circRNA were upregulated, and 48 circRNA were downregulated significantly in the 24-month-old tissues. Furthermore, an association of the circRNA-miRNA-mRNA was investigated, showing that 17 dysregulated circRNA were downregulated significantly in the 24-month-old tissues. Furthermore, an association of the circRNA-miRNA-mRNA was investigated, showing that 17 dysregulated circRNA were downregulated significantly in the 24-month-old tissues. Furthermore, an association of the circRNA-miRNA-mRNA was investigated, showing that 17 dysregulated 3-month-old by qRT-PCR, indicating that circRNA6456 may delay renal senescence in mice.

**Conclusions:** This observational study demonstrated dysregulation of circRNA in age-related kidneys, which may have an impact on development of potential biomarkers in aging.

**Funding:** Government Support - Non-U.S.

SA-PO428

Amniotic Fluid Stem Cells Ameliorate Experimental Acute Renal Failure via Induction of Autophagy and Inhibition of Apoptosis

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**Background:** Amniotic fluid stem cells (AFSC) have been shown to contribute in renal repair after Acute Renal Failure (ARF), however, the mechanism responsible for its renoreprotective effects still remains unclear. Therefore, in the present study we evaluated the therapeutic efficacy of AFSC and investigated the underlying mechanisms responsible for its renoprotective effect.

**Methods:** To study the therapeutic potential of AFSC, ARF was induced in rats by a single dose of cisplatin. Five days after cisplatin injection, AFSC or normal saline were injected intravenously. On day 3 and 7 post-therapy, blood biochemical parameters, histopathological changes, apoptosis and expression of pro-apoptotic, anti-apoptotic and autophagy-related proteins in renal tissues were studied in both groups of rats. Furthermore, to confirm whether the protective effects of AFSC on cisplatin-induced apoptosis are dependent on autophagy, chloroquine, an autophagy inhibitor, was administered intraperitoneally.

**Results:** Administration of AFSC in rats with ARF, resulted in improvement of renal function and attenuation of renal damage as reflected by decreased blood urea nitrogen and serum creatinine levels and alleviation in tubular cell apoptosis as assessed by lower Bax/Bcl2 ratio and decreased levels of pro-apoptotic proteins viz. PUMA, Bax, cleaved caspase-3 and cleaved caspase-9 as compared to saline-treated group. Furthermore, in the AFSC-treated group as compared to saline-treated group, there was increased activation of autophagy as evident by increased expression of LC3-II, ATG5, ATG7, Beclin1 and Bax/Bcl2 ratio and decreased levels of pro-apoptotic proteins viz. PUMA, Bax, cleaved caspase-3 and cleaved caspase-9 as compared to saline-treated group. Furthermore, in the AFSC-treated group as compared to saline-treated group, there was increased activation of autophagy as evident by increased expression of LC3-II, ATG5, ATG7, Beclin1 and phospho-AMPK levels with a concomitant decrease in phospho-p70S6K and p62 expression levels. Chloroquine administration led to significant reduction in the anti-apoptotic effects of the AFSC which further aggravated the deterioration in renal structure and function caused by cisplatin.

**Conclusions:** This study suggests that induction of autophagy is essential for the renoprotective effects of AFSC against cisplatin-induced apoptosis. Collectively, our results show that AFSC ameliorate cisplatin-induced ARF through induction of autophagy and inhibition of apoptosis.

**Funding:** Government Support - Non-U.S.

SA-PO429

Engineered Bone Marrow Stem Cell Sheets Ameliorate Renal Fibrosis in a Chronic Glomerulonephritic Rat Model

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**Background:** Although mesenchymal stem cell (MSC)-based regenerative therapy is currently being developed for treatment of kidney diseases, it is ineffective due to a few functional cells present at the target tissue. Thus, we developed an MSC-engineered cell sheet technology using the temperature-responsive cell culture surfaces to release cultured MSCs in a patient living condition. We hypothesized that this technology will improve MSC transplantation efficiency and therapeutically reduce kidney disease.

**Methods:** Three experimental groups included normal, untreated disease control but received sham surgery, and allogeneic bone marrow-derived MSC-sheets treated disease rats. The chronic glomerulonephritis was induced by two doses of anti-Thy 1.1 antibody (OX-7) in rats. The MSC-sheets were prepared and transplanted as patches onto the surface of the two kidneys of each rat in the treated group at 24h after the first injection of OX-7.

**Results:** At 4 weeks, retention of the transplanted MSC-sheets was confirmed and animals with MSC-sheets showed significant reductions in proteinuria, glomerular staining for periodic acid-Schiff positive materials, collagen III and fibronectin, and in renal TGFβ1, PAI-1, collagen I and fibronectin mRNA and protein levels. Treatment also altered renal overexpression of KIM-1 and NGAL mRNA and reversed disease induced reduction of WT-1, podocin and nephrin mRNAs. Furthermore, treatment enhanced regenerative gene expression, and IL-10, Bcl-2, and HO-1 mRNA levels but reduced TSP-1 levels, NF-κB and NADPH oxidase production in the kidney, which were consistent with the reduction of glomerular macrophage cell infiltration and glomerular and tubular cell apoptosis.

**Conclusions:** These observations strongly support our hypothesis that MSC-sheets facilitated MSC transplantation and effectively retarded progressive renal fibrosis through paracrine or autocrine signaling involving cellular inflammation, oxidative stress, apoptosis and regeneration.

SA-PO430

Gene-Modified Urine-Derived Stem Cells Home to the Ischemic Kidney

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**Background:** Acute kidney injury is a major cause of morbidity and mortality, with only half of those diagnosed surviving three months. The current therapies for acute kidney injury are supportive rather than regenerative. We sought to evaluate if human urine-derived stem cells were able to migrate to the kidney following ischemia/reperfusion injury in mice.

**Methods:** Urine is a practical and painless source of cells for gene and cell therapy applications. Urine-derived stem cells are adult human cells of renal origin that propagate in tissue culture in media containing growth factors on gelatin-coated plates. We have isolated, expanded, transfected, and tracked these cells following injection into live NSG immunocompromised mice in order to assess their potential for regenerative gene and cell therapies.

**Results:** FACS characterization revealed that they expressed the characteristic marker panel (CD44, CD73, CD90, & CD146 + / CD31, CD34, & CD45 -). They differentiated in tissue culture in media containing growth factors on gelatin-coated plates. We have isolated, expanded, transfected, and tracked these cells following injection into live NSG immunocompromised mice in order to assess their potential for regenerative gene and cell therapies.

**Results:** FACS characterization revealed that they expressed the characteristic marker panel (CD44, CD73, CD90, & CD146 + / CD31, CD34, & CD45 -). They differentiated in tissue culture in media containing growth factors on gelatin-coated plates. We have isolated, expanded, transfected, and tracked these cells following injection into live NSG immunocompromised mice in order to assess their potential for regenerative gene and cell therapies.

**Funding:** Government Support - Non-U.S.
imaging gantry for quantitative tomographic optical live animal imaging. We found luciferase signal localized within 2 hours post-injection to the injured kidney with lower levels in the spleen.

**Conclusions:** Urine-derived stem cells represent an easily isolated, clinically relevant cell type that can be manipulated with non-viral genetic tools. We have found that the cells quickly migrate from their injection site to injured tissues. Next we will assess functional correction following injection of urine-derived stem cells into mouse models of acute kidney injury.

**Funding:** NIDDK Support, Veterans Affairs Support, Private Foundation Support

**SA-PO431**

Bone Marrow Mesenchymal Stem Cells-Derived Exosomes Reduce Pericyte Transition by Inhibiting Core Fucosylation

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**Background:** Renal interstitial fibrosis is the last common pathway to progression to end-stage renal disease. Myofibroblasts are a key event in renal interstitial fibrosis, and pericyte transition is one of the major sources of myofibroblasts. Our previous study found that CF (core fucosylation) mediated by FUT8 (α1,6-fucosyltransferase) could regulate the "fibrotic signaling pathway" such that TGFβ-Smad pathway inhibition in renal interstitial fibrosis. MSCs (Mesenchymal stem cells) can alleviate renal interstitial fibrosis and are potential therapeutic targets; however, the mechanism is still unclear. The exosomes are an extracellular vesicle secreted by MSCs, and can transmit functional substances such as microRNAs and proteins through membrane ligand-cell receptor interaction. It was found that exosomes could regulate damage repair, but the mechanism is also unclear.

**Methods:** Primary culture of pericytes to establish a TGFβ1-stimulated pericyte transition model. After cell modeling, they were co-cultured with transwell upper MSCs, exosomes, CM, and CM for exosomes removal. Morphological changes of pericytes were observed by light microscopy. The levels of αSMA and LCA were observed by immunofluorescence. The levels of αSMA and FUT8 were observed by Western blot. The level of FUT8 was observed by HPLC (High Performance Liquid Chromatography).

**Results:** TGF-β1 stimulated pericytes to form spindle-shaped myofibroblasts, and the expression of αSMA, LCA and FUT8 increased. TGF-β1 induced pericyte transition activity increased. MSCs have an inhibitory effect, CM and exosomes have similar inhibitory effects, while CM for exosomes removal is ineffective. RT-PCR, immunofluorescence and Western blot confirmed that FUT8 was successfully transfected into pericytes. After FUT8 transfection, the degree of spindle-shaped myofibroblasts increased, and the expression of αSMA, LCA and FUT8 increased, the inhibition by MSCs,exosomes and CM was significantly weakened.

**Conclusions:** MSCs-derived exosomes reduce pericyte transition by inhibiting CF Funding: Clinical Revenues Support

**SA-PO432**

Human Mesenchymal Stem Cells Modulate High Glucose-Induced Inflammatory Responses of Renal Proximal Tubular Cell Monolayers and Their Cross-Talk with Macrophages

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**Background:** Renal proximal tubular epithelial cells (RPTEC) are dysfunctional in diabetic kidney disease (DKD). Mesenchymal stem cells (MSCs) have been shown to modulate DKD pathogenesis. Having previously observed that solute products of human MSC suppress high glucose (HG)-induced inflammatory responses of RPTEC/TERT1 stable monolayers, we aimed here to characterize the modulatory effect of MSC indirect co-culture on the transcriptional profile of RPTEC monolayers and to further explore the influence of MSC on RPTEC/Macrophage crosstalk.

**Methods:** Human RPTEC/TERT1 cells were cultured for 12 days to generate stable confluent monolayers. Normal medium or medium supplemented with 25mM D-Glucose (HG) or 25mM D-Mannitol (MAN) were applied for a further 5 days. Human bone marrow MSC were co-cultured 1:10 with RPTEC monolayers for the final 2 days in a trans-well system. RNA Sequencing, qRT-PCR and ELISA were performed on resulting samples. Conditioned Media from HG- and MAN-exposed RPTEC/MSC co-cultures were applied to monocyte-derived human macrophages under HG and MAN conditions.

**Results:** Bioinformatics analysis of RNA-sequencing data confirmed a predominant effect of HG on inflammation-related mediators and biological processes/KEGG pathways in RPTEC/TERT1 stable monolayers as well as the anti-inflammatory effect of HG on TGFβ and inflammation-related pathways, indicating HG-stimulated pathway activity increases. MSCs have an inhibitory effect, CM and exosomes have similar inhibitory effects, while CM for exosomes removal is ineffective. RT-PCR, qRT-PCR, ELISA, and Western blot analysis showed HG-induced gene upregulation within the TNF-signalling, cytokine-cytokine receptor interaction and NOD-like receptor signalling. These gene expression signatures were modulated toward control expression by MSC co-culture. The HG-induced increase in RPTEC monolayer expression of transcripts for multiple cytokines (IL-1α, IL-6, IL-8, TNFα, MCP-1) and for S100A13 as well as their counter-regulation by MSCs were confirmed by qRT-PCR and ELISA. Conditioned medium from HG-exposed RPTEC/MSC transwell co-cultures attenuated secretion of inflammatory mediators (IL-8, TNFα, MCP-1) by macrophages compared to medium from unstimulated RPTEC alone.

**Conclusions:** Stable RPTEC monolayers demonstrate a delayed pro-inflammatory response to HG that is attenuated by close proximity to human MSC. In DKD, this MSC effect may potentiate to modulate hyperglycaemia-associated RPTEC/macroage cross-talk - a key pathogenic mechanism of chronic interstitial inflammation.

**SA-PO433**

Mesenchymal Stem Cells Cultured in IFN-γ-Containing Medium Ameliorate Experimental Renal Fibrosis

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**Background:** Mesenchymal stem cells (MSCs) have been reported to promote regeneration of damaged tissues and suppress fibrosis. However, the clinical use of MSCs was reported to enhance the paracrine activities of MSCs. In this study, we investigated the effect of MSCs cultured in IFN-γ-containing medium on inflammation and fibrosis using unilateral ureteral obstruction (U/UO) and ischemia-reperfusion injury (IRI) models.

**Methods:** After 4 days following unilaterial ureteral obstruction, we injected rat MSCs (3×10⁶ cells/rat) cultured in 10% FBS-containing DMEM (mMSCs) or IFN-γ-containing medium (IFN-γ mMSCs), or PBS only (Control) through the rat tail vein. In addition, we injected rats after an IRI operation through the abdominal aorta with PBS, rMSCs, or IFN-γ mMSCs (5×10⁶ cells/rat). Next, we investigated the effect of IFN-γ on human MSC (hMSC)-conditioned medium (CM) on TGFβ1-induced fibrotic changes by western blotting. As an anti-inflammatory mediator, we analyzed CM from IFN-γ hMSCs by an enzyme-linked immunosorbent assay.

**Results:** Immunohistochemical staining revealed that IFN-γ mMSCs strongly ameliorated interstitial fibrosis. IFN-γ mMSCs also attenuated renal inflammation and fibrosis more significantly than mMSCs in IRI models. IFN-γ mMSCs-CM decreased the expression of phosphorylated Smad2 and Smad3 compared with hMSCs-CM without IFN-γ stimulation. We found that prostaglandin E2 (PGE2) expression was significantly increased in IFN-γ mMSCs-CM. Knockdown of prostaglandin E synthase (PTGES), which is a synthetic enzyme of PGE2, weakened the anti-fibrotic effect of IFN-γ MSCs in IRI models.

**Conclusions:** Our findings indicate that IFN-γ potentiates the anti-fibrosis and anti-inflammatory activities of MSCs and administration of MSCs cultured in IFN-γ-containing medium has the potential to be a useful strategy to prevent the progression of renal fibrosis.

**SA-PO434**

Hypoxia Preconditioning Modifies Mesenchymal Stem Cell Senescence and Epigenetic Mechanisms in Experimental Atherosclerotic Renal Artery Stenosis

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**Background:** Atherosclerotic Renal Artery Stenosis (ARAS) is a contributor for hypertensive nephropathy (HJN). Autologous mesenchymal stem cells (MSCs) is a promising therapy for ischemic nephropathy in patients with ARAS. However, MSCs from older ARAS patients are associated with impaired function, senescence, and DNA damage, possibly due to epigenetic mechanisms. Hypoxia preconditioning (HPC) exhibits beneficial effects on cellular proliferation, differentiation, as well as gene and protein expression. We hypothesized that HPC could influence MSC function, senescence and epigenetic mechanisms by modulating chromatin-modifying enzymes.

**Methods:** MSCs harvested from subcutaneous abdominal fat tissue of healthy (N=5) or ARAS (N=8) pigs were cultured under normoxia(20%) or hypoxia(5%) until 70-80% confluence. MSC function was measured by migration and proliferation assays, as well as cytokine levels in conditioned media. MSC senescence was evaluated by SA-β-gal activity and epigenetic markers, including HDAC activity and DNA hydroxymethylation using dot blot analysis.

**Results:** MSCs cultured under HPC had higher migratory and proliferative capacity as well as increased VEGF and IGF levels than normoxia-cultured MSCs(Figure). Under basal conditions, dot blot analysis showed lower DNA hydroxymethylation in ARAS. During HPC, MSC HDAC activity increased whereas DNA hydroxymethylation decreased, suggesting broad epigenetic changes. Furthermore, SA-β-gal activity fell, indicating lower senescence burden on HPC-MSCs.

**Conclusions:** HPC mitigates autologous MSC dysfunction, decreased MSC senescence and DNA hydroxymethylation in ARAS pigs. Future studies are needed to
determine the effect of HPC in MSCs of patients with other vascular nepathies to optimize the potential use of autologous MSC therapy in this population.

Funding: NIDDK, Support, Private Foundation Support

SA-PO435
Hypoxia-Preconditioned Mesenchymal Stem Cells Prevent AKI to CKD Transition
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Background: Several studies have reported that mesenchymal stem cells (MSCs) promote regeneration of injured tissue via their paracrine activities, which are enhanced by hypoxic preconditioning. In this study, we examined the therapeutic efficacy of hypoxia preconditioned MSCs for preventing acute kidney injury (AKI) to chronic kidney disease (CKD) transition in rat models of ischemia/reperfusion injury (IRI).

Methods: We injected rats through the abdominal aorta with hypoxia-preconditioned rat MSCs (1%O2, mMSCs) or rat MSCs under normoxic conditions (21%O2, nMSCs). We also administered hypoxia-preconditioned human MSCs (1%O2, hMSCs) via the same procedure. In addition, we analyzed the conditioned medium from 1%O2 hMSCs using ELISA kit and identified the humoral factor involved in anti-fibrotic abilities of MSCs.

Results: The administration of 1%O2, nMSCs attenuated renal fibrosis induced by IRI more significantly than that of 21%O2, nMSCs. 1%O2, mMSCs also attenuated renal fibrosis and the anti-fibrotic effects of hypoxia-preconditioned MSCs were almost equivalent in bone marrow MSCs derived from rat and human. We also found that MSCs derived from rat and human were both observed in the kidney at day 21 post-IRI. Moreover, using flow cytometry, we confirmed that hypoxic preconditioning did not change the HLA expression of MSCs. These results suggest that 1%O2, hMSCs have low immunogenicity and may be a good candidate for allogeneic transplantation cell therapy. We also found that hypoxic preconditioning enhanced vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) secretion from MSCs. VEGF knockdown in 1% O2 hMSCs by siRNA attenuated HGF secretion and the inhibition of TGF-β1 induced fibrotic changes in HK-2 cells. It also weakened the suppression of renal fibrosis by 1% O2, hMSCs in IRI models.

Conclusions: Our results indicate that hypoxia-preconditioned MSCs may be useful as an autologous transplantation cell therapy for preventing the progression of AKI to CKD.

SA-PO436
Metformin Improves Dysfunction of Mesenchymal Stem Cells Associated with CKD via Protection from Senescence
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Background: Mesenchymal stem cells (MSC) are promising source of cell-based regenerative therapy; however, adequate cell functionality is a critical factor for the success of autotransplantation. We previously reported a functional incompetence of CKD (chronic kidney disease) MSC.

Methods: In this study, we investigated the effects of metformin on CKD-associated cellular senescence using MSC isolated from sham operated and subtotal nephrectomized mice and further explored the protective role of metformin-treated CKD MSC in renal progression using unilateral ureteral obstruction (UUO) model and in vitro co-culture system.

Results: When compared to normal MSC, MSC isolated from CKD mice displayed reduced proliferation and early senescence as determined by enlarged cell morphology, increased oxidative stress, accumulation of DNA damage response marker p53 binding protein 1 (53BP1), phospho p53, p16INK4a, and b-gal expression, and decreased cyclin-dependent kinase 4 (CDK4) and cyclin D. CKD MSC exhibited activation of NFκB resulting in expression of senescence-associated secretory phenotype (SASP) factors such as MCP-1, TNF-α, IL-6, and IL-1β compared to normal MSC. All of these changes were significantly prevented by metformin treatment. In vivo, metformin-treated CKD MSC attenuated ASCN inflammation and fibrosis in UUO kidney as compared to CKD MSC. Co-culture of LPS-treated HK2 cells with normal MSC almost completely rescued LPS-induced tubular expression of MCP-1 and TNF-α. Of note, metformin-treated CKD MSC markedly decreased tubular expression of MCP-1 and TNF-α when compared to CKD MSC suggesting paracrine action of CKD MSC enhanced by metformin treatment.

Conclusions: Taken together, our data suggest that metformin prevents cellular senescence of CKD MSC and improves their renoprotective effects.

Funding: Government Support - Non-U.S.

SA-PO437
Extracellular Vesicles from Human Bone Marrow Mesenchymal Stem Cells Repair Organ Damages Caused by Cadmium Poisoning in a Medaka Model
Tomoko Obara, University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Background: Treatment modalities for kidney disease caused by heavy metals, such as cadmium (Cd), are limited. Often, chronic, long-term environmental exposure to heavy metal is not recognized in the early stages; therefore, chelation therapy is not an effective option. Extracellular vesicles (EVs) derived from stem cells have been demonstrated to reduce disease pathology in both acute and chronic kidney disease models.

Methods: To test the ability of EVs derived from human bone marrow mesenchymal stem cells (hBM-MSCs) to treat Cd damage, we generated a Cd-exposed medaka model that we treated with EVs.

Results: This model develops heavy metal-induced cell damage of various organs and tissues, and shows decreased survival. Intravenous injection of highly purified EVs from hBM-MSCs repaired the damage to kidney proximal tubules apical and basolateral membranes, and mitochondria, glomerulus podocytes, repaired bone deformation caused by Cd, and enhanced survival.

Conclusions: Our system serves as a model with which to study age- and sex-dependent cell injuries of organs caused by various agents and diseases. The effects of EVs on the tissue repair process, as shown in our Cd-exposed medaka model, may open up new broad avenues for interventional strategies.

Funding: Private Foundation Support

SA-PO438
Extracellular Vesicles of Adipose-Derived Stem Cells from Obese Patients Drive ROS-Dependent Premature Senescence in Renal Tubular Cells
Ting Luo, Yu Meng, The First Affiliated Hospital of Jinan University, Jinan University, Guangzhou, China.

Background: Premature tubular cell senescence is characteristic of obesity-associated renal injury. Extracellular vesicles from adipose-derived stem cells (ADSC-EVs) are highly abundant, while their role in obesity-associated disorders remain unclear. We hypothesized that ADSC-EVs from obese patients were involved in renal tubular cell senescence, possibly via a ROS-dependent pathway.

Methods: ADSCs were isolated from the omental adopts from patients with morbid obesity and healthy volunteers (n=7 each). ADSC-EVs were co-cultured with HK-2 cells. The level of cellular senescence was assessed as senescence-associated β-galactosidase (SA-β-gal) activity using fluorescent quantitative detection, target gene expression using RT-PCR or western blot analysis, and reactive oxygen species (ROS) generation using CMH2DCFDA staining. The next-generation mRNA sequencing was performed on ADSC-EVs to predict the enriched biological process (DAVID 6.8).

Results: Compared with the control, ADSC-EVs from obesity induced upregulation of SA-β-gal activity, p16(INK4a), TGF-β1 and α-SMA in HK-2 cells. The mRNA levels of IL-1β, IL-6, and TNF-α also increased (Figure). Totally 56 up-regulated genes were found in ADSC-EVs from the obese compare to the control, and enriched the ROS-related biological processes (Figure). ADSC-EVs from obese patients could induce ROS formation in HK-2 cells. Conversely, ROS inhibitor N-acetylcyesteine prevented the premature tubular cell senescence induced by ADSC-EVs from obese patients (Figure).

Conclusions: These findings suggest that EVs from the ex vivo ADSCs of obese patients induce premature tubular cell senescence through a ROS-mediated mechanism. Targeting ADSC-EV shedding may provide opportunities to limit the dysfunction of renal tubular cell post-obesity.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-PO439
Systematic Implantation of Dedifferentiated Fat Cells (DFAT) Ameliorated the Monoclonal Antibody 1-22-3-Induced Glomerulonephritis with Stimulation of TSG-6
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Background: Implantation of mesenchymal stem cells has recently been reported to repair tissue injuries through anti-inflammatory and immunosuppressive effects. We established dedifferentiated fat cells that show identical characteristics to MSCs.

Methods: We examined the effects of 10^6 of DFAT cells infused through renal artery or tail vein on monoclonal antibody 1-22-3-induced glomerulonephritis and adriamycin-stimulated rats. Also, we implanted DFAT cells with TSG-6 siRNA through tail vein.

Results: Although DFAT cells transfused into blood circulation through the tail vein were trapped mainly in lungs without reaching the kidneys, implantation of DFAT cells reduced proteinuria, renal dysfunction and renal degeneration by the immunosuppressive effects of TSG-6. Thus DFAT cells will be a suitable cell source for the treatment of immunological progressive renal diseases.

Conclusions: DFATs-EVs ameliorate obesity-induced renal tubular injury by activating SPI, Klotho and rescue senescence, thereby prevent the renal premature aging in obesity. DFATs-EVs might be a natural nano-biomaterial for senescence-related diseases therapy.

Funding: Government Support - Non-U.S.

SA-PO440
The Extracellular Vesicles from Adipose Tissue-Derived Mesenchymal Stem Cells Attenuate the Renal Sclerosis via SPI/Klotho Pathway in Obesity
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Background: Patients with obesity have a high risk of chronic renal disease and premature aging of the kidney has been proved as a major contributor. The extracellular vesicles from adipose tissue-dedifferentiated mesenchymal stem cells (ADSCs-EVs) have therapeutic potential in many diseases. We aimed to investigate whether ADSCs-EVs could rejuvenate the senescent renal tubular cells in Obesity.

Methods: ADSCs-EVs were isolated from the subcutaneous adipose tissues from healthy volunteers (n=6). The murine model with obesity was obtained after 8 weeks of the obese diet. ADSCs-EVs were injected to the obese mice in vivo and co-cultured with primary renal tubular cells from the obese mice in vitro. The level of senescence was assessed as P16, P21 with histological analysis and western blot. Next-generation mRNA sequencing (RNAseq) was performed to predict the key transcription factor. The expression of SPI and Klotho were analyzed by PCR in cells.

Results: ADSCs-EVs treatment could rescue the obesity-induced senescence of renal tubular cells in vivo and in vitro. The expression of Klotho restored and the P16 was significantly ameliorated. Further study revealed the levels of SPI and the Klotho were synergetically elevated after ADSCs-EVs treatment (Figure). RNA-seq identified five aging-associated genes upregulated after EVs treatment (fold change >2, p<0.05). The pathway analysis showed TGF-β and ERK pathway could play a crucial role in ADSCs-EVs mediated rejuvenation through up-regulating transcription factor SPI (Figure).

Conclusions: ADSCs-EVs ameliorate obesity-induced renal tubular injury by activating SPI, Klotho and rescue senescence, thereby prevent the renal premature aging in obesity. ADSCs-EVs might be a natural nano-biomaterial for senescence-related diseases therapy.
Development and Regenerative Medicine

SA-PO442

Cell Sheet Therapy to Suppress Renal Vascular Injury and Fibrosis in Rat Unilateral Ureteral Obstruction and Ischemia-Reperfusion Injury Models

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Background: CKD is a growing and unsolved problem and a new strategy to suppress renal fibrosis is required. In CKD, lack of vasoprotective factors such as VEGF and HGF causes renal vascular injury and subsequent progressive fibrosis. Recently, many researchers reported that administration of vasoprotective factors or the cells producing those factors suppressed vascular injury and fibrosis in preclinical studies. However, the therapeutic effects were limited due to their short half-life in circulation or low retention of the transplanted cells in the kidneys. To solve this problem, we applied cell sheet technology for kidney diseases. We aimed to suppress renal vascular injury and fibrosis by long-term and direct supply of vasoprotective factors secreted form cell sheets.

Methods: Using a temperature responsive culture dish, HGF transgenic mesothelial cell sheet (HGF-tg MC sheet) and rat bone marrow derived mesenchymal stromal cell sheets (MSC sheet) were prepared. In rat UUO or IRI models, the renal capsule was removed and cell sheets were transplanted onto the kidney surface. We analyzed the behavior of the transplanted cells (immunostaining, in vivo imaging system), morphology of the kidney/reinal microvascular density/ renal artery blood flow rate (US, CT), and renal fibrosis. The effects were compared between those in receiving intravenous administration of HGF protein or MSCs.

Results: Transplantation of HGF-tg MC sheets significantly protected microvascular density, maintained renal artery blood flow, and suppressed renal fibrosis compared with intravenous administration of HGF protein. Transplantation of MSC sheets showed superior survival of the donor cells in the kidney compared with intravenous administration of MSCs, resulted in strong suppression of renal fibrosis and protection of microvascular density in the whole kidney.

Conclusions: Transplantation of cell sheets onto the kidney surface ameliorated renal vascular injury and suppressed renal fibrosis in UUO and IRI by long-term and direct supply of vasoprotective factors secreted from grafted cells. Renal treatment with cell sheets would be a promising strategy.

Funding: Commercial Support - CellSeed, Inc., Government Support - Non-U.S.

SA-PO443

Kidney Podocytes Generate Autonomous Calcium Transients That Regulate Glomerular Capillary Tuft Formation

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Background: Podocytes are critical to maintaining the glomerular filtration barrier; mutations in nephrin syndrome genes lead to defects in barrier function and can affect podocyte calcium signaling. The role of calcium signaling during podocyte development in vivo remains unknown however.

Methods: Using the genetically encoded biosensor GCaMP6s expressed in zebrafish podocytes we quantified intracellular calcium dynamics in differentiating podocytes in vitro.

Results: Immature podocytes (2.5 days post fertilization (dpf)) generate calcium transients that correlate with cell motility and podocyte interactions with forming glomerular capillaries. Calcium transients persist until 4 dpf and are absent when glomerular barrier formation is complete. Calcium transients are not affected by deficiencies in heartbeat (tnnt2 morphant), endothelium (cloche mutant) or endoderm (sox32 morphant), suggesting they may be generated cell autonomously. Dissociated, intact GCaMP6s-expressing glomeruli in short term in vitro culture continue to exhibit calcium transients similar to in vivo podocytes, indicating the transients are autonomously generated. Inhibitors of SERCA or IP3 receptor calcium-release channels block calcium transients, while lanthanum and medium EGTA are ineffective, indicating the source of calcium is podocyte ER stores. Blocking calcium release impacts glomerular shape and cell organization; suggesting further that calcium signaling guides glomerular morphogenesis.

Conclusions: Our results establish cell autonomous calcium signaling as a prominent feature of podocyte differentiation and present a model to decipher mechanisms leading to proper glomerular morphogenesis.

Funding: NIDDK Support

SA-PO444

Whole-Genome Bisulfite Sequencing Identifies Key Roles for Dnmt3a and Dnmt3b in Renal Tubular Cell Development


Background: Cytosine methylation is an epigenetic mark that can stably repress gene expression. De novo DNA methyltransferases 3a (Dnmt3a) and 3b (Dnmt3b) play key roles in establishing cell type specific methylation patterns. However, their roles in kidney development are poorly understood.

Methods: We generated mice with genetic deletion Dnmt3a and Dnmt3b in nephron progenitor cells using Siz22 and tubule cell specific cells using the Kspf Kspf Dnmt3a3b and Kspf Kspf Dnmt3a3b, DKO). Next generation sequencing techniques, such as reduced representation bisulfite sequencing (RRBS), whole genome bisulfite sequencing (WGBS) and RNA sequencing (RNA-seq) were performed on whole kidney samples and on isolated and sorted renal tubule cells from 3-week-old mice. We induced kidney disease by foal acid injection at 8 weeks of age.

Results: Compared with littermate controls, no obvious developmental defect was identified in Kspf and Siz22 Dnmt3a3b and Dnmt3b double knock-out mice. RRBS data showed significant methylation changes in both DKO mice consistent with Dnmt3a3b role in establishing de novo methylation pattern. More hypo-methylated regions (Hypo-DMR) were identified in Siz22 DKO mice, suggesting the key role of Dnmt3a3b in cell type specific methylation in development. To explore the genome wide effect of Dnmt3a3b and WGBS was performed on isolated Kspf positive renal tubule epithelial cells. Remarkable decreased in cytosine methylation was observed at genome wide level, especially affecting fetal enhancers which gain methylation in normal development. Refine enrichment analysis showed the significant enrichment of hypo-methylated regions in binding sites of kidney developmental transcription factors including Siz2. Despite the broad changes in cytosine methylation, the effect of Dnmt3a3b loss on gene expression was less pronounced. DKO mice showed no differences when compared to control following kidney injury.

Conclusions: Our results indicate Dnmt3a3b is necessary for de novo methylation of enhancers which are active in fetal kidney and closed in adult kidney. Despite the significant methylation changes on enhancer regions, the effect of de novo methylation on gene expression regulation and phenotype was less pronounced.

Funding: Government Support - Non-U.S.

SA-PO445

Essential Roles of Testosterone in Male Kidney Maturation and Repair After Injury

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Background: The newborn kidneys are structurally and functionally immature. They mature after birth to adapt to extra-uterine life, yet the comprehensive changes of the kidney have not been defined. We investigated the structural and functional changes in the kidney after weaning and examined the effect of testosterone in this maturation process in male mice.

Methods: We performed phenotypic analysis of mouse kidneys utilizing a combination of histological analysis, bulk transcriptome analysis, charged metabolite analysis by CE-TOFMS and brush border membrane vesicles LC-MS/MS analysis.

Results: Bulk transcriptome analysis of postnatal 3 and 8 week male kidneys showed the gene sets enriched in 8w included those associated with metabolic process and transport in proximal tubule, and structural analysis revealed proximal tubule elongation and hypertrophy in 8 weeks. Most differentially expressed genes (DEGs) identified above were induced between postnatal day 28 and 40, a period of testosterone surge, and were closely correlated with DEGs between adult male and female kidneys. These structural and gene expression changes during maturation were mostly canceled by castration before testosterone surge. Proximal tubules expressed androgen receptor, and some gene expression changes were confirmed in cultured proximal tubules stimulated with testosterone. Consistent results with DEGs were also confirmed at protein levels and related metabolites in vivo. For instance, induction of cystine transporter SLC7A13 expression as well as the increase in cystine and cysteine-glutathione disulfide-Divalent in all patients were confirmed in this period. Fatty acid b-oxidation enzymes were also increased during this period. Some of the down-regulated genes across puberty were reactivated after injury and returned back with repair.

Conclusions: Proximal tubules are the main site of maturation after weaning and acquire the ability to absorb and metabolize a variety of filtered substances and increase energy metabolism, which were mainly driven by testosterone.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Ectopic Proximal Tubules Formation and Kidney Fibrosis

Bingjue Li, Jianghua Chen, Hong Jiang.
Orleans, LA; Ihor V. Y osypiv, Morphogenesis by Regulating V-ATPase Activity and Autophagy in UB Tulane University, New Orleans, LA; 2Tulane Medical School, New Orleans, LA; 3Southwest Baptist University, Bolivar, MO.

Background: Targeted ablation of the PRR in the UB lineage in Hoxb7(−/−) PRR(lox/−) (PRRUB−/−) mice causes severe defects in UB branching, leading to decreased nephron endowment and renal hypoplasia. Since PRR is an accessory subunit of the vacuolar proton pump V-ATPase, we investigated the role of V-ATPase and autophagy in PRR-induced UB branching in mice.

Methods: UB cells were FACS-isolated from Hoxb7(−/−) PRR(lox/−) (PRRUB−/−) and control (PRR(−/−)) littersmates at birth (P0). V-ATPase subunit expression in isolated cells was determined by microarray and validated by real-time RT-PCR. PRR knockdown in immortalized UB cells (iUBc) was achieved with adenovirus-driven shPRR. Effect of PRR knockdown on cell pH and V-ATPase activity was determined by staining with Lysotracker (a lysosomal pH marker) and from measurements of Na+-independent cell pH recovery rates after intracellular acidification with a NH4Cl pulse.

Results: Expression of V-ATPase subunits Atp6ap2 (PRR), V0a4, V0b, V1b1 and V1g1 was reduced in PRRUB−/− compared to PRR(−/−) UB cells. shPRR decreased mRNA levels of PRR by 80-90% and of kidney-specific c4 V-ATPase subunit by 50% compared to control scrambled control PRR (scPRR) virus in iUBc. shPRR decreased lysotracker fluorescence in iUBc compared to scPRR (p<0.001). Intracellular pH (pHi) measurements (by BCECF fluorescence) indicated slower recovery from acid loads in shPRR-treated cells due to reduced V-ATPase activity. Immunofluorescence of key autophagy protein LAMP2 was increased in the UB of PRRUB−/− compared to PRR(−/−) kidneys on E14.5, consistent with autophagic defects in UB cells in PRR−/− kidneys.

Conclusions: PRR knockdown decreases expression of c4 subunit of V-ATPase and suppresses V-ATPase activity in iUB cells in vitro, resulting in decalcification of intracellular vesicles. We propose that endogenous UB PRR regulates normal UB branching morphogenesis through stimulation of V-ATPase activity, control of lysosomal pH and appropriate autophagic flux in UB cells.

Embryonic Stage Adalim/Notch Pathway Excessive Activation Promotes Ectopic Proximal Tubules Formation and Kidney Fibrosis

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Background: Chronic kidney disease (CKD) is an outstanding public health problem. It is important to elucidate the pathogenesis of CKD and researches on kidney development become a breakthrough. Studies have verified that Notch pathway plays a significant role in kidney development, it is widely believed that Notch promote the formation of proximal tubules. In addition to its role in kidney development, Notch was also found to be involved in kidney fibrosis. Here using prenatal chlorpyrifos (CPF) exposure mouse model we make a further study on the role of Notch in kidney development and fibrosis.

Methods: CPF 5mg/kg/d was administrated by subcutaneous injection in CPF-treated pregnant mice from gestation day 7.5-11.5 while the controls were injected with vehicle. At E12.5, E14.5, E16.5 and E18.5 days, RT-qPCR, western blot, IF and IHC showed decreased. mRNA and protein levels were verified by RT-qPCR, WB, IF and IHC. IF and IHC showed the increasement of proximal tubules. Experiments of offspring mice kidneys showed abnormal embryonic kidney phenotypes persisted in adult kidneys. Activation of Notch also led to impaired kidney function and more severe renal fibrosis.

Conclusions: Excessive activation of Adalim/Notch pathway caused the depletion of SIX2 NPC and ectopic proximal tubules formation and aggravate kidney fibrosis.

Embryonic Stage Unilateral Ureteral Obstruction Mice

Dae Eun Choi, Wonjung Choi, Da bi Kim, Eunji Kim, Tae Woong Hwang, Kwajin Kim, Ki Ryang Na, Kang Wook Lee, Jin young Jeong, Yoon-Kyung Chang. Nephrology, Chungnam National University, Daejeon, Republic of Korea; 2Department of Medical Science, Chungnam national university, Daejeon, Republic of Korea; 3The Catholic University of Asia, Daejeon, Republic of Korea.

Background: Toxicodendron vernicifluumis used as a traditional herbal medicine in Asia. The physiological properties and antioxidative effects of Toxicodendron vernicifluum extract (TV) have been demonstrated in several experimental studies. The physiological properties and antioxidative effects of Toxicodendron vernicifluum extract (TV) have been demonstrated in several experimental studies. This study evaluated the possible renoprotective effects of TV on UUO induced tubular damage, as well as the mechanism through which it exerts antioxidative and antiapoptotic effects against UUO induced cell death.

Methods: Male Sprague-Dawley rats weighing 180–200 g each were assigned to one of two groups. The first group (UUO+TV) of rats drank TV for 2 weeks after surgery. The second group (UUO) of rats drank water for 2 weeks. Three days later, a morphologic evaluation of renal injury was conducted using hematoxylin and eosin and TUNEL staining. The renal protein expression of PCNA, caspase3, Nr2, catalase, and phosphorylated p38 as markers of autophagy was determined by immunoblotting.

Results: Obstruction injury caused marked apoptosis and oxidative stress in the UUO group. It also increased the level of phosphorylated p38 and decreased the level of PCNA, suggesting delayed recovery from damage. The number of TUNEL positive cells, which were detected based on DNA fragmentation, was increased in the UUO group. It also increased the level of phosphorylated p38 and decreased the level of PCNA, suggesting delayed recovery from damage. Moreover, a comparison with the UUO group revealed that TV significantly enhanced the regulation of autophagy and autophagic flux.

Conclusions: Taken together, our findings suggest that the induction of autophagy protects against UUO induced apoptotic damage via ROS and a p38 regulated pathway in this in vivo model.

Funding: Clinical Research Support
hypothesis and hyperplasia during homeostasis. We then exposed the cells to PBS and histones (stressing ischemia/ injury) followed by a return to normal culture conditions (mimicking reperfusion), to test for the compounds pro-regenerative effects. Electric cell impedance sensing and selective progenitor cell expansion were used to monitor effects on wound healing and target cell response, respectively. Only those compounds that proved pro-regenerative in human and murine cells alike were tested in a mouse model of unilateral IRI.

Results: We identified RKL-1447 and SB-525334 in vitro/ ex vivo, and tested both substances in male C57BL/6J, 8-10 weeks of age, at 10 mg/kg every 2nd day for a duration of 3 weeks, starting from day 3 after IRI. Both molecules reduced intrarenal mRNA markers of injury, inflammation, and fibrosis. A corresponding trend towards less parenchymal loss and fibrosis was observed in histology.

Conclusions: We were able to show, that an appropriate setup of in vitro and ex vivo experiments using meaningful biological material is suitable for (a) efficiently screening of compound libraries, (b) significantly reducing animal numbers used and (c) predicting outcome in vivo.

Funding: Government Support - Non-U.S.

SA-PO450

Rapid and Efficient Method to Generate Donor Vectors for Homology-Directed Repair Mediated Genome Editing

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Background: Stem cell-derived kidney organoids are a powerful, tractable tool with numerous potential applications, including the investigation of complex processes underlying human kidney development. To further develop organoids as an embryologic model, it will be essential to generate genetic tools such as fluorescent reporters and lineage tracing systems, which have proven instrumental in rodent studies. With the emergence of CRISPR/Cas9 gene editing via homology directed repair (HDR) is becoming more common in pluripotent stem cells. However, construction of donor vectors that contain gene-specific homology regions remains a time-consuming and often costly endeavor. Thus, we simplified this process through the creation of a modular system to allow rapid and efficient cloning of homology arms into HDR donor vectors.

Methods: We designed and synthesized a plasmid with numerous features and cassettes that are easily interchangeable. These include fluorescent reporters, antibiotic resistance genes and an HSV-TK for use in negative selection. The genes for selection were contained in a floxed cassette to allow easy cre-mediated removal following successful integration. Gene-specific homology arms were created using high fidelity PCR, and final donor vectors were assembled using HiFi Cloning.

Results: To facilitate simultaneous dual and triple knock-in alleles, we used restricted cloning to generate a repertoire of vectors that pair different combinations of reporter and antibiotic resistance genes. The PCR primers designed to amplify the homology arms from genomic DNA of the cell lines of interest also contained sequences of overlap with the sites of insertion on the vector. Thus, in one step using HiFi cloning, we were able to assemble both homology arms into the double-digested vector. This process, including PCR of homology arms, cloning, and sequence validation, can be completed within one week at minimal cost.

Conclusions: Through creation of this vector collection and application of HiFi cloning, we have successfully devised an efficient, streamlined process for cloning donor vectors for use in HDR-mediated gene editing. Given the modular design, these plasmids can also be adapted to permit knock-in of any DNA of interest. This approach is now broadly applicable for editing of any cell line, including human pluripotent stem cells and hPSC-derived kidney organoids.

Funding: NIDDK Support, Other NIH Support - NCATS

SA-PO451

Defects in the Exocyst-Cilia Machinery Results in Disease Development in the Kidney and Heart

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Background: Patients with polycystic kidney disease such as ADPKD and Joubert syndrome have elevated risk for bicuspid aortic valve disease (BAV). Non-syndromic BAV affects 1% of the population and often leads to aortic stenosis and the need for surgery. We have previously shown a link between these disorders and defects of organelles called primary cilia. Primary cilia are immotile projections of microtubules that act as signaling hubs for numerous pathways. We previously demonstrated in the kidneys that primary cilia are built by a highly-conserved octameric protein-traffic complex, known as the exocyst. These studies leveraged the expression of the central exocyst protein, EXOC5. Knockdown of EXOC5 in MDCK cells inhibited ciliogenesis and, conversely, EXOC5 overexpression resulted in longer cilia.

Methods: We performed two human GWAS studies, generated two exoc5-/- zebrafish knockout lines and two conditional Exoc5 mouse knockout lines. Phenotypes were characterized through immunohistochemistry, 3D reconstructions, confocal microscopy, and echocardiography.

Results: GWAS identified the exocyst as being near SNPs most associated with BAV. Next we noted that at three days post fertilization, exoc5-/- zebrafish embryos had cardiac edema and outflow tract stenosis. This phenotype was rescued in a dose dependent manner by injection of human EXOC5 mRNA at the one cell stage; however, the rescue was significantly reduced with injection of a targeting mutation in the highly-conserved EXOC5 VxPs ciliary targetting sequence. These findings prompted us to examine the cardiac phenotype following Exoc5 deletion in mice. We previously reported altered ciliogenesis and nephrogenesis in Exo5-/- mice when bred with a kidney-specific Cre. To examine the heart, we bred these mice with endocardial-specific Nurr1-Cre; and later endothelial-specific Tie2-Cre, lines. This resulted in mice with highly- penetrant BAV and aortic valve calcification. Echocardiography also revealed aortic valve stenosis and increased aortic root diameter similar to what is seen in BAV patients. There was also evidence of significant cilia disruption, and conditional homozgyous mutants were embryonic lethal by E15.5, likely due to cardiac defects.

Conclusions: These data for the first time link cilia, BAV, and the exocyst, and explain the clinical association of cardiac valve abnormalities with PKD.

Funding: NIDDK Support, Other NIH Support - National Heart, Lung, and Blood Institute, Veterans Affairs Support, Private Foundation Support

SA-PO452

Metabolic Syndrome (MetS) Upregulates the Tumour Necrosis Factor Alpha (TNF-α) Transcriptome and Proteome in Swine Adipose Tissue-Derived Mesenchymal Stem Cells (MSC)

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Background: MSC have intrinsic reparative properties, & may serve as an exogenous therapeutic intervention in patients with chronic kidney disease (CKD). This microenvironment of MetS induces fat tissue inflammation, with upregulation of TNFα. MetS may also alter the transcriptome and proteome of adipose tissue-derived MSC, which might affect their reparative potency. We hypothesized that MetS upregulates MSC mRNA and proteins of the TNFα pathway.

Methods: Domestic pigs were fed a 16-week Lean or MetS diet (n=4 each), and MetS upregulated the TNFα pathway genes revealed 13 mRNAs & 4 proteins upregulated in MetS compared to lean MSCs (fold change>1.4, p<0.05) (Fig. 1, A & B). Ureguplated mRNAs and proteins were mostly involved in TNFα-1 receptor pathway. A similar pattern was observed in upregulated proteins, except for Traf2 involved in TNFα-2 receptor pathway. MetS induced changes in MSC TNFα signaling were associated with nuclear translocation of NF-κB(Fig 1, C).

Conclusions: MetS upregulates the TNFα transcriptome & proteome in swine adipose tissue-derived MSC, leading to activation of NF-κB and inflammatory signaling. Hence, the MetS milieu may affect reparative function of endogenous MSC & limit their use as an exogenous regenerative therapy. Targeting the TNFα pathway might be a novel strategy to restore MSC expression patterns, & in turn function, and permit their use in situations with MetS & CKD.

Funding: NIDDK Support, Other NIH Support - NCATS

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SA-PO453
Isolation of Primary Cell Types from the Human Kidney Cortex
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Background: In vitro studies can help elucidate kidney pathophysiology and nephrotoxicity. Cell lines and primary animal cells can be poor representatives of human cell biology. Primary human renal cells are essential tools for studying such mechanisms. Herein we describe isolation of primary cell types from the cortex of whole human kidneys.

Methods: Podocytes, Proximal Tubule Cells (PT), Mesangial, and Glomerular Endothelial Cells were isolated from non-transplantable human kidneys donated for research. The kidney cortex is surgically separated from the medulla, the tissue is minced, glomeruli are separated, and further digested using a collagenase based enzymatic blend to obtain a heterogeneous single cell suspension. Cells are cultured and expanded in specialized media to enrich for the target cell populations. Homogenous cell isolates for a proximal tubules (CD10/CD13) b. mesangial cells (PDGFβRb) c. glomerular endothelial cells (CD31) d. podocytes (neprhin) are isolated by immunomagnetic sorting. Proximal tubular cells, mesangial cells and glomerular endothelial cells further expanded in specific media before undergoing a second round of selection to ensure purity. Podocytes are not expanded to avoid de-differentiation. Characterization of the isolated populations is performed by immunofluorescence and flow cytometry for cell-specific proteins.

Results: We successfully obtained pure human proximal tubular cells, podocytes, mesangial cells and glomerular endothelial cells using the outlined methodology. Each population was assessed for viability, attachment, proliferative ability. Purity and cell-specific marker expression were assessed by flow cytometry and flow cytometry; PT: AQ1, cytokeratin, Na/K-ATPase, and ENT1; Mesangial: PDGFβRb, CD206, and Vimentin, GEC: EDH3, Ve Cadherin, and CD31; Podocytes: WT1, Synaptopodin, and Podocin. Proximal Tubular cells retained activity demonstrated by enzymatic GGT assay.

Conclusions: We have developed and optimized a streamlined method for isolating target populations from the human kidney. Our process yields highly pure homogeneous cell populations that can proliferate in vitro and express population specific surface markers. Furthermore, isolated proximal tubule cells retained functionality and can be used in transporter assays.

Funding: Commercial Support - Parent company, Promethera Biosciences, partially funding the Novabiosis division. Additional funding comes from revenue generation of life science products.

SA-PO454
Renovascular Disease Induces Mitochondrial Damage and Impairs the Reparative Capacity of Swine Scattered Tubular-Like Cells
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Background: Scattered tubular-like cells (STC) contribute to repair neighboring injured renal tubular cells. Mitochondria mediate STC biology and function, but might be injured by the ambient milieu. We hypothesized that the microenvironment induced by the ischemic and metabolic components of renovascular disease (RVD) impairs STC mitochondrial structure and function in swine, which can be attenuated with mitoprotection.

Methods: CD24+/CD133+ STCs were quantified in pig kidneys after 16 weeks of metabolic syndrome (MetS) or Lean diet with or without renal artery stenosis (RAS) (n=6 each). Pig STC were isolated and characterized, and mitochondrial structure and membrane potential were assessed in cells untreated or incubated with the mitoprotective drug elamipretide (ELAM, 1nM for 6hrs). STC protective effects were assessed in-vitro by their capacity to improve viability of injured pig tubular epithelial (PK1) cells.

Results: The percentage of STC was higher in MetS+RAS-STC compared to Lean (Fig. A). STC isolated from Lean+RAS and MetS+RAS pigs showed decreased mitochondrial matrix density and membrane potential, which were both restored by mitoprotection (Fig. B). Furthermore, mitoprotection improved the capacity of MetS+RAS-STC to repair injured tubular cells in-vitro (Fig. C).

Conclusions: RVD in swine is associated with a higher percentage of STC, which was predominantly affected by MetS. Ischemia induces structural and functional alterations in STC mitochondria, which can be attenuated by mitoprotection. These observations suggest a key role for mitochondria in the renal reparative capacity of STC.

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SA-PO455
Mild AKI in a Murine Polymicrobial Sepsis Model and Its Value for Preclinical Testing of Human Cell Therapies
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Background: Even mild AKI greatly worsens the prognosis of sepsis. Allogeneic mesenchymal stem cells (allo-MSC) have potential therapeutic value in sepsis-associated (SA-AKI) but their optimal administration is undetermined. Improved analysis of human MSC effects in pre-clinical models of SA-AKI could improve future clinical trial design. We aimed to develop a model of mild SA-AKI in which to test a human allo-MSC cell product.

Methods: Cecal ligation and puncture (CLP) or Sham surgery with frequent post-procedural monitoring were performed in male C57BL/6 mice. Blood was sampled at 24, 48 and 72 hrs and kidney tissue collected at 72 hrs. Antibody-selected human umbilical cord (UC)-MSC were injected IV at 106 cells/animal 4 hours post-CLP. Plasma and renal tubular neutrophil gelatinase associated lipocalin (NGAL) were quantified by ELISA and IHC. Renal lymphoid and myeloid cells were quantified by multi-color flow cytometry of collagenase/DNase-digested kidney.

Results: CLP was associated with 10-15% body weight loss and low (10%) mortality by 72 hrs. Plasma liver enzymes were mildly increased in CLP vs Sham but BUN and creatinine were not raised. Plasma (p)NGAL was markedly increased in CLP versus Sham animals (p<0.001), peaking at 24 hrs and remaining elevated at 48 & 72 hrs. NGAL staining intensity in renal tubular epithelial cells strongly discriminated between CLP and Sham at 72 hrs (Mean score 2.6±1.2 vs. 0.0±0.0, p=0.0003) and correlated with pNGAL. Intra-renal immune cell profiling indicated that SA-AKI was associated with proportionately reduced T-cells, increased neutrophils and a complex modulation of MHC II+ mononuclear phagocytes (MP). A single administration of UC-MSC (compared to saline) resulted in less body weight loss (6.8±3.7% vs. 10.0±5.2%, p<0.05), trends toward lower pNGAL and renal NGAL staining intensity and reversal of SA-AKI-associated alterations to intra-renal T-cells, neutrophils and MP.

Conclusions: Mouse CLP with frequent post-procedural monitoring resulted in mild SA-AKI best detected by pNGAL, renal tubular NGAL staining intensity and altered

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SA-PO456 Intrarenal Hh Signalling Mediates Fibrosis in Aged and Injured Kidneys

Abstract: While specific functions of extracellular vesicles (EVs) have been discovered in many fields of biology and medicine, very little is known about their role paired to young serum factors to ‘young’ levels, and show reduced fibrotic phenotype, revert five serum factors to ‘young’ levels, and show reduced fibrotic transcription factor promotes a pro-inflammatory macrophage phenotype. Irf5 expression in resident macrophages, and reduced the severity of cystic disease. In addition, IRF5 treatment significantly reduced macrophage numbers, oligonucleotide (ASO) in 1K Pkd1 mice. IRF5 treatment significantly reduced macrophage numbers, oligonucleotide (ASO) in 1K Pkd1 mice. IRF5 treatment significantly reduced macrophage numbers, oligonucleotide (ASO) in 1K Pkd1 mice. The Hh pathway therefore plays a crucial role in the regulation of kidney growth in health and disease. Furthermore, our data show that genetic strain influences the subtype of infiltrating macrophage and its contribution to disease progression. In these studies, we assess the importance of macrophage-derived Hh signalling and downstream transduction in controlling renal fibrosis.

Methods: In order to determine the cellular origin of the ACPSVs, we performed RNA sequencing on the separated vesicle fraction. We identified several genes that are enriched in the ACPSVs, including genes involved in vesicle biogenesis and trafficking. Additionally, we performed qRT-PCR and immunohistochemistry to confirm the presence of ACPSV markers in renal tissue.

Results: We found that the ACPSVs are shed into the urine of both young and old mice. These vesicles are enriched in genes involved in vesicle biogenesis and trafficking, indicating that they may play a role in the regulation of renal fibrosis.

Conclusions: Our results suggest that ACPSVs may play a crucial role in the regulation of renal fibrosis. Further studies are needed to determine the mechanisms by which these vesicles contribute to renal fibrosis.
cyst formation and their relationship with cystic disease caused by mutations in proteins associated with cell damage-associated molecular motifs. Inflammasome assembly results when cells are exposed to extracellular danger signals such as silica, LPS, or ATP, which induce the activation of the inflammasome. Two inflammasomes have been identified: NLRP3 and AIM2. Inflammasomes can be activated by various stimuli, including infectious agents, tissue damage, and immune cell activation.

Results: Our data indicate that induction of inflammasome dysfunction (Pld2 mutation) in juvenile mice results in more severe cysts 21 days post induction compared to mice lacking both Pld2 and Pld1 (Pld1−/−;Pld2−/−). In both Pld2 and Pld1, analysis of flow cytometry data indicate that the number of CD206+ resident macrophages is directly correlated with the severity of cystic disease with juvenile-induced Pld2 deficient mice having the greatest number of CD206+ resident macrophages. Further, we show that treatment of Pkd1 p.R3277C (RC) model, strain matched wildtypes (WT), and Pkd1 Δ/Δ (Δ) mice were treated during an early stage of disease with adenine (2.5% in the chow), and the control group received standard chow. Mice were examined at PN43. Caspase-1 (Casp1) was knocked out in the Pdk1ΔC/Δ mice (Pdk1ΔC−/−;Casp1Δ/Δ). The effects on cystic kidney disease in Pdk1ΔC/Δ and Pdk1ΔC−/−;Casp1Δ/Δ mice were assessed at 6 months of age.

Mouse models of ADPKD: Elevated expression of these components was found in the jck and Pdk1ΔC/Δ mice and human ADPKD kidneys (NLRP3, NLRP1, Mev1, Casp1, Il1β, NLRP3, IL1β, NLRP5, IL10, AMP, ASC1, IL1β, NLRP3, IL1β in ADPKD). Adenine consumption promoted elevated 2K-TBW and cystic index in jck; Metas-Casp1 knockout lowered 2K-TBW (Pdk1ΔC/Δ = −2.2 ± 0.4, Pdk1ΔC−/−;Casp1Δ/Δ = 1.8 ± 0.15, p=0.01; compared with WT=1.2 ± 0.13) and cystic index in Pdk1ΔC−/−;Casp1Δ/Δ mice.

Conclusions: These preclinical studies identify Caspase1 as a promoter of PKD progression and a potential therapeutic target for cystic disease.

Funding: NIDDK Support, Commercial Support - Resilio Therapeutics, LLC

SA-PO463

Autosomal Dominant Polycystic Kidney Disease Shows a Tumor-Like Microenvironment

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Background: Polycystic kidney disease (PKD) is an inherited genetic disorder characterized by progressive growth of cysts in the kidneys. Despite not being a cancer, PKD shares many features with tumors. For instance, recent studies suggest a role of immune cells in PKD progression. Tumor-modifying infiltrating cells function to create a tumor-like microenvironment (TME) that could alter main PKD drivers, and the effect of opportunistic immune-driven processes on disease progression in PKD mice remains elusive. The goal of this study was to characterize the renal tissue microenvironment of PKD mice and to determine the presence of a tumor-like microenvironment (T-LME).

Methods: We have characterized the renal tissue microenvironment of a Pdk1ΔC−/−;Casp1Δ/Δ inducible and the Pkd1ΔC−/−;KspCre ADPKD mouse models. We have analyzed the presence of infiltrating immune cells and CAFs, and the state of the Ecm through histological analysis and quantitative Real-Time-PCR. In addition, we have performed an in situ quantification employing an F4/80 detection algorithm.

Results: We have detected a statistically significant increased level of CD45+ leukocytes in the ADPKD kidneys compared to the controls. In contrast, B and T populations could not be detected in late PKD models. Macrophages, activated myofibroblasts (potentially corresponding to CAFs), and extensive fibrosis in the kidneys of the ADPKD affected mice could be detected. In particular, while M1-macrophages (expressing Nos2) did not significantly change between the PKD kidneys and the controls, M2-macrophages (expressing Arg1) were found significantly increased in the kidneys of PKD mice compared to controls.

Conclusions: Our analysis on the kidneys of the ADPKD mouse models reveals the presence of a tumor-like microenvironment (T-LME), which could promote disease progression. The analysis of the crosstalk among the different components of the microenvironment might provide important insights into disease progression in PKD.

SA-PO464

Peptides Derived from the Stalk Region of Polycystin 1 Function as Ligands to Activate Signaling by the C-Terminal Fragment and to Ameliorate Cystogenesis

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Background: Polycystin-1 (PC1) modulates G protein signaling by as yet unknown regulatory mechanisms. Like the adhesion class of GPCRs, PC1 undergoes autocatalyzed cleavage at a GPS motif, which generates a large extracellular, C-terminal fragment (CTF) that is membrane-embedded, C-terminal fragment (CTF) of 11 transmembrane domains preceded by an N-terminal extracellular stalk of 25 residues. We previously reported that CTF-mediated signaling to an Nfat reporter is dependent on the presence of the stalk and is reduced by specific amino acid substitutions within its stalk-like microenvironment (T-LME), which could promote disease progression. The analysis of the crosstalk among the different components of the microenvironment might provide important insights into disease progression in PKD.

Results: All of the stalk region (P7-P21) enhanced signaling from CTF to the Nfat reporter, albeit to varying degrees, possibly due to differences in peptide structure. Peptides P7, P9, P13, P15 and P17 significantly reduced the cystic index of treated embryonic kidneys to different extents (e.g., −25% for P7 to −90% for P17), while P11 had no ameliorative effect. Treatment with P19 or P21 prevented kidney growth and decreased kidney survival. A mutant peptide containing a ADPKD-associated missense mutation was also detrimental in organ culture unlike its wild type parental peptide.

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Conclusions: These results support an Adhesion GPCR-like, stalk-dependent mechanism for CaMK4 in regulating a physiological and disease-relevant role for this mechanism in renal tubulogenesis, and suggest a novel therapeutic avenue for ADPKD.

Funding: Other U.S. Government Support, Private Foundation Support

SA-PO465
RNA Helicase p68 Inhibits Pkd1 Transcription and Promotes Cyst Growth in ADPKD
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations of PKD1 and PKD2, resulting in progressive deterioration of kidney function due to the formation of cysts. Expression of PKD1 is high in the fetal kidney, which is essential for kidney development, and then is reduced after nephron formation has completed. However, the transcriptional regulation of PKD1 remains elusive. In this study, we investigate the roles and underlying mechanisms of p68, a DEAD box RNA helicase, in regulating Pkd1 gene expression.

Methods: To understand the role of p68 in ADPKD, we examined the expression of p68 and its regulation in Pkd1 mutant renal epithelial cells and ADPKD patient kidneys by qRT-PCR, Western blot and immunostaining/immunohistochemistry, and investigated how p68 regulates cystic cell proliferation, oxidative stress and renal fibrosis. To investigate if and how p68 regulates the transcriptional and post-transcriptional processing of the Pkd1 gene, we performed co-IP and Chip assays in renal epithelial cells with and without knockdown of p68.

Results: We found that p68 was upregulated in Pkd1 mutant renal epithelial cells compared to that in wild type control cells as examined by Western blot and qRT-PCR analysis. The level of p68 was also increased in cyst lining epithelial cells in kidneys from Pkd1 mutant mice and ADPKD patients. Knockdown of p68 increased Pkd1 gene transcription, whereas upregulation of p68 decreased Pkd1 transcription, which involved 1) activation of p68 with c-Src and Doshia to form a ternary complex on the promoter of the Pkd1 gene, and 2) increased p68 mediated microRNA 182 (miR182). Inhibition of miR182 increased Pkd1 mRNA and protein levels. In addition, we found that oxidative stress decreased Pkd1 expression in a p68-dependent manner. We further found that p68 regulated cystic epithelial cell proliferation via the activation of ERK, mTOR and Bcl signaling, and regulated renal fibrosis via TGFβ1 signaling.

Conclusions: This is the first study to show that one of the RNA helicases, p68, inhibits the transcription of the Pkd1 gene and promotes cystic renal cell proliferation and the expression of factors that contribute to cystic disease. Together, these data suggest that regulating p68 expression might be a potential therapeutic strategy for ADPKD treatment.

Funding: NIDDK Support

SA-PO466
The Consequences of Decreased Cap-Dependent Translation in Polycystic Kidney Disease
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Background: Autosomal Dominant polycystic kidney disease (ADPKD) is the most common life-threatening hereditary disease, characterized by cyst formation and growth. Unchecked proliferation of cyst epithelial cells is a major contributor to cyst growth. At the nexus of regulating proliferation is the 4E-BP1 pathway, a crucial mechanism for translation, decrease proliferation, and reduce cyst expansion.

Methods: 22 renal biopsies, and 10 brokens kidney by Western blot analysis. The effect of KN-93, a CaMK4 inhibitor, on mTOR signaling was evaluated in ADPKD cells. To determine if CaMK4 regulation of mTOR was dependent on the LKB1/AMPK pathway, we tested KN-93 on renal cells with an inducible knockout of Lkb1, pcy/mice, a well-characterized PKD model, received 10 mg/kg KN-93 every day for one week to determine the effect of CaMK4 on mTOR signaling.

Results: CaMK4 levels were 2.5-fold higher in human ADPKD cells compared to NIH3T3 cells. No effect of CaMK4 levels were also observed in the C57BL/6 Pkd1 F113A mouse model. We found no effect of CaMK4 levels on the ADPKD cell proliferation. CaMK4 inhibition with CaMK4 decreased renal levels of P-S6 in pcy/mice.

Conclusions: CaMK4 promotes mTOR signaling in PKD kidneys and may be a potential target to reduce mTOR-dependent cell proliferation and cyst growth.

Funding: NIDDK Support, Private Foundation Support

SA-PO467
Elevated Calcium/Calmodulin-Dependent Protein Kinase IV (CaMKIV) Promotes mTOR-Dependent Cell Proliferation in ADPKD
Yan Zhang, Emily A. Daniel, Yuqiao Dai, Gail Reif, Darren P. Wallace. University of Kansas Medical Center, Kansas City, KS.

Background: Mammalian target of rapamycin (mTOR), a central integration area for pathways involved in cell growth and proliferation, is abnormally activated in cyst-lining cells in ADPKD. mTOR inhibition reduces cell proliferation and PKD progression in rodent; however, the therapeutic value of targeting mTOR with rapalogs in ADPKD patients remains unclear due to dose-limiting side effects. The development of new therapies requires a better understanding of pathways responsible for aberrant mTOR activation in cystic epithelial cells. Calcium/calmodulin-dependent kinase type IV (CaM4) stimulates mTOR signaling in various cell types including hepatic cancer cells and immune cells; however, the role of CaM4 on mTOR signaling and cyst growth in PKD has not been examined.

Methods: CaM4 levels were measured in primary ADPKD and normal human kidney (NHB) cells, and in Pkd112/12 (slow onset), Pkd112/12 (rapid onset) and normal mouse kidneys by Western blot analysis. The effect of KN-93, a CaMK4 inhibitor, on mTOR signaling was evaluated in ADPKD cells. To determine if CaM4 regulation of mTOR was dependent on the LKB1/AMPK pathway, we tested KN-93 on renal cells with an inducible knockout of Lkb1, pcy/mice, a well-characterized PKD model, received 10 mg/kg KN-93 every day for one week to determine the effect of CaM4 inhibition on renal mTOR signaling.

Results: CaM4 levels were 2.5-fold higher in human ADPKD cells compared to NIH3T3 cells. No effect of CaM4 levels were also observed in the C57BL/6 Pkd1 F113A mouse model. We found no effect of CaM4 levels on the ADPKD cell proliferation. CaM4 inhibition with KN-93 decreased renal levels of P-S6 in pcy/mice.

Conclusions: CaM4 promotes mTOR signaling in PKD kidneys and may be a potential target to reduce mTOR-dependent cell proliferation and cyst growth.

Funding: NIDDK Support, Private Foundation Support

SA-PO468
Polycystin 1 Regulates Cilia Length and Cyst Formation by Controlling Centrosomal ARHGAP35-Dependent Rhoa Activation
Andrew J. Streets,1 Philipp P. Prosseda,2 Maya Boudiffa,1 Albert C. Ong,1 Kidney Genetics Group University of Sheffield, Sheffield, United Kingdom; 2Stanford University, Palo Alto, CA.

Background: Mutations in PKD1 encoding for PC1 account for most patients with ADPKD but it is still unclear how these result in the highly complex cellular phenotype of ADPKD. It had been reported that primary cilium length is normal in ADPKD cells implying an abnormality in function (flow-dependent signalling); however this hypothesis has been recently challenged. Unexpectedly, we observed consistently shorter cilium in patient-derived PKD1 cystic cells compared to normal tubular cells and its correction by cytochalasin-D, an inhibitor of actin polymerisation.

Methods: Rhoa activity (GST pulldown) and its localisation (Rhoa biosensor) were determined in ciliated cells; siRNA knockdown of reported centrosomal ARHGAPs identified from ciliome and centrosome databases and their effect on cilia length; and immune cells; however, the role of CaMK4 on mTOR signaling and cyst growth in PKD patients remains unclear due to dose-limiting side effects. The development of new therapies requires a better understanding of pathways responsible for aberrant mTOR activation in cystic epithelial cells. Calcium/calmodulin-dependent kinase type IV (CaM4) stimulates mTOR signaling in various cell types including hepatic cancer cells and immune cells; however, the role of CaM4 on mTOR signaling and cyst growth in PKD has not been examined.

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Methods: Rhoa activity (GST pulldown) and its localisation (Rhoa biosensor) were determined in ciliated cells; siRNA knockdown of reported centrosomal ARHGAPs identified from ciliome and centrosome databases and their effect on cilia length; PKD1 null human tubular cells were generated by CrispR/Cas9 mutagenesis; BioID proximity assay using a centrosome targeting sequence (PACT) to confirm centrosomal localisation of ARHGAPs; effect of a selective ROCK inhibitor (hydroxyfasudil) in a Pkd1 mouse model.

Results: We confirmed that primary cilium are shorter in vivo (human ADPKD and mouse Pkd1 kidneys) and in PKD1 null CrispR cells. In ciliated cells, increased Rhoa (but not Cdc42 or Rac1) activation was observed in PKD1 cystic cells with a localised increase at the cilia base. Cilia length could be normalised by Rho kinase (ROCK) inhibitors or expression of dominant negative Rhoa (but not Cdc42 or Rac1). Knockdown of several centrosomal ARHGAPs (5, 29, 35) resulted in shorter cilium but only ARHGAP35 centrosomal localisation was reduced in the absence of PKD1. Specific binding of ARHGAP3 to the PCl C-terminal domain was shown by co-IP. Finally, we demonstrate that selective ROCK inhibition reduced cyst growth in vitro (PKD1 human cystic cells) and in vivo (Pkd1 mouse).

Conclusions: PC1 appears to regulate centrosomal Rhoa activity through the recruitment or stabilisation of ARHGAP35. Mutations in PKD1 lead to shorter cilium due to increased RhoA and ROCK activity. Interestingly a recently reported ARHGAP35 hypomorphic mouse develops shorter cilium and glomerular cysts. Inhibition of ROCK normalised cilia length and reduced cyst expansion suggesting that the Rho/ROCK pathway is a potential new axis to develop therapies to inhibit cilium initiation in ADPKD.

Funding: Government Support - Non-U.S.
Genetic Reduction of Cilium Length by Targeting Pitx8 Impedes Kidney and Liver Cyst Formation in Autosomal Polycystic Kidney Disease Mouse Models

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Background: Mutations in polycystin-1 (PC1) and -2 (PC2, products of the PKD1 and PKD2 genes, cause autosomal dominant polycystic kidney disease (ADPKD). They localize to the primary cilium; however, their ciliary function is in dispute. The loss of either the cilia or PC1 or PC2 causes cyst in orthologous mouse models. Cystogenesis is inhibited in the absence of both cilia and PC1 or PC2. How the cilia and PC1 or PC2 interact to regulate cystogenesis is still unknown. The role of intracellular transport proteins in PKD1-deficient mouse is also unknown.

Methods: In this study we used human and mouse kidney tissues to study the correlation between cilia length and cyst formation. We developed Pkd1 and Pkd2 single and double knockouts with Ift88 to thoroughly investigate the correlation between cilia length and cystogenesis in mice and to identify downstream signaling targets.

Results: 1) We report, for the first time that cilia length is elongated in human ADPKD kidneys. 2) We found similar elongation in Pkd1 and Pkd2 knockout mice following polycystin inactivation. 3) We show that inactivating the intracellular transport protein Ift88 in Pkd1-deficient mice and Pkd2-deficient mice shortens the elongated cilia, impedes kidney and liver cystogenesis and reduces cell proliferation. 4) Multi-stage in vivo analysis of signaling pathways revealed a novel early, and sustained activator in disease onset and progression in Pkd2 single knockout (SKO) which is rescued in Pkd2 and Ift88 double knock out (DKO) mouse kidneys. 5) On the other hand, ERK pathway was activated in the SKO but no rescue was observed in the DKO mouse kidneys.

Conclusions: Our findings advocate an essential role of polycystins in the structure and function of the primary cilium and implicate a novel target as a key inducer of cystogenesis downstream of the primary cilium. These data suggest that modulating cilia length and/or its associated signaling events may offer novel therapeutic approaches for ADPKD.

Funding: NIDDK Support, Private Foundation Support

SA-PO470

SMYD3: A Novel Regulator of Cystogenesis and Ciliogenesis in ADPKD

Ewoud Agborsong,1 Xia Zhou,1 Xiaogang Li.2 University of Kansas Medical Center; Kansas City, KS; Mayo Clinic, Rochester, MN.

Background: Deregulation of lysine methylation signaling has emerged as a common aetiologic factor in disease pathogenesis, such as cancers. We found that the lysine methyltransferase, SMYD3, is upregulated in ADPKD, a genetic and “ciliopathy” disease characterized by renal cyst formation and ciliogenesis defects. However, if and how SMYD3 regulates cyst formation and its relationship to ciliogenesis remains elusive.

Methods: We investigate the role of Smyd3 on renal cystogenesis by knockout of Smyd3 in Pkd1 conditional knockout mouse kidneys, and investigate if Smyd3 regulates ciliogenesis in mMCD3 and RCTE cells with and without knockdown of Smyd3 and in primary renal cells isolated from Smyd3 Ifi16:Ksp-Cre mouse kidneys. We determine the effect of Smyd3 on the localization of proteins on the basal body and cilary axoneme by immunofluorescence.

Results: 1. We found that knockdown of Smyd3 delayed cyst growth as seen by decreased cystic index, kidney weight (KW)/body weight (BW) ratios, blood urea nitrogen (BUN) levels, and cyst lining epithelial cell proliferation in Pkd1 mutant mice (all P < 0.05). We further found that knockdown of Smyd3 decreased the activity of STAT3 and β-Catenin. In in vitro, we found that SMYD3 interacted with CDK2, a direct regulator of the cell cycle, and knockdown of Smyd3 decreased the phosphorylation of CDK2 in Pkd1 mutant mouse kidneys. We further found that Smyd3 is localized on the centrosome and basal body and silencing or knockout of Smyd3 inhibits primary cilia assembly in renal cells. Smyd3 is localized with centriolar distal appendage proteins, Cep164, Cdc3 and Ofd1, and interacts with Ofd1, Ift88 and TTBK2 proteins, known to play an essential role in ciliogenesis. Depletion of Smyd3 increased the recruitment of IRI140, but decreased the recruitment of Rab8 and Cep164 to the cilary axoneme. Last, knockdown of Smyd3 regulates the expression of key distal appendage and trafficking related proteins at the transcript and protein levels.

Conclusions: Smyd3 regulates cystic renal epithelial cell proliferation via STAT3, β-catenin and CDK2 signaling to promote cystogenesis, and regulates ciliogenesis by activating trafficking of proteins, controlling the trafficking of proteins in and out of the cilium. The interactions between Smyd3 and its novel binding partners provide novel mechanisms of Smyd3 in regulating cystogenesis and ciliogenesis in ADPKD.

Funding: NIDDK Support

SA-PO471

Protein Phosphatase 1 Alpha Interacts with Polycystin-1 and Regulates Polycystin-1 Targeting to Primary Cilium

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease, which is caused by mutations in PKD1 or PKD2 genes. However, how mutations in these two genes lead to ADPKD remains partially understood. Recent studies have indicated that defective cilary trafficking of polycystin-1 (PC1, encoded by PKD1 and PKD2, respectively) underlies the pathogenesis of a subgroup of ADPKD cases. We have recently identified a novel ciliary targeting sequence (CTS) in the C-terminus of PC1. We found that this CTS interacts with protein phosphatase 1-a (PP1a), a ubiquitously expressed phosphatase in the PPP family. Shortening of PC1 mRNA mediated knockdown of PPIa in IMCD3 cells results in reduced PC1 ciliary localization and elongated cilium without affecting GSS cleavage or protein maturation of PC1. Nevertheless, the precise mechanism under which PPIa regulates ciliary targeting of PC1 is still obscure.

Methods: Four PC1 constructs with phosphomimic or phosphodeficient mutations were transfected into IMCD3 cells and co-stained with cilia marker. HA-tagged PC1 and flag-tagged PPIa were co-transfected into IMCD3 cells and then stained to detect the subcellular localization of PPIa/PC1 complex. PC1 and 2 were co-transfected into PC1 knockdown cells and then the ciliary targeting efficiency of PC1 was analyzed.

Results: Ciliary localization of all the four PC1 mutations was not affected compared with wild type control. PPIa and PC1 do not co-localize on the primary cilium but in the cytosol. Overexpression of PC1 is able to rescue the ciliary targeting defect of PC1 in PPIa knock downed cells.

Conclusions: Preliminary results suggest PPIa bind with PC1 in the cytosol and regulates PC1 trafficking. This regulation is probably not caused by PPIa mediated PC1 dephosphorylation. PPIa might function in this process via modifying PC1, a prerequisite for PC1 targeting to cilia. Further investigation is required to delineate the exact role of PPIa in PC1 trafficking.

SA-PO472

Pannexin-1 Mediates Fluid Shear Stress-Sensitive Purinergic Signaling in Renal Cyst Growth in Polycystic Kidney Disease

Eric Verschuren,1 Juan pablo Rigalli,2 Charlotte Castenmiller,2 René J. Bindels,1 Dorien J. Peters,1 Francisco J. Arjona,1 Joost Hoenderop.1

1Massachusetts General Hospital, Charlestown, MA; 2Brigham and Women’s Hospital, Boston, MA.

Background: Tubular ATP release is regulated by mechanical stress of fluid shear stress (FSS), but the molecular mechanism mediating this process is poorly understood. Extracellular ATP is implicated in polycystic kidney disease (PKD), where polycystin-1/polycystin-2 (PC1/PC2) is dysfunctional. In health, PC1/PC2 functions as a mechanosensor in the proximal renal tubule. In PKD, where urinary ATP levels are elevated, presents pannexin-1 as a new therapeutic target.

Methods: To model mechanical stress of FSS, we used a microfluidic device, the vancomycin-1 (mDCT15) mouse kidney cell line was grown on the microfluidic device, to measure the trans-epithelial fluid flow as a function of the pressure difference across the cell layer.

Results: Isolated mDCT15 cells were subjected to FSS and observed a decreased ATP release. Further, inhibition of mTORC1 amplified this FSS-modulated ATP release. ATP levels were reduced in vancomycin-1 (mDCT15) cells subjected to FSS as observed an increased ATP release. Further, inhibition of mTORC1 reduced the ATP release under variable urinary flow. PKD models, using inducible kidney-specific Pitx1 knock out mice (iKsp-Pitx1cre) and a transgenic mouse with translation blocking the ortholog of human PKD2 (Pkd2), were employed to study in vivo the relevance of the mechanisms disclosed in vitro.

Conclusions: Our results suggest that renal vancomycin-1 channels mediate ATP release from epithelial cells towards the tubular lumen. The redundancy of this mechanism in PKD, where urinary ATP levels are elevated, presents vancomycin-1 as a new therapeutic target to prevent cyst growth in PKD.

Funding: Government Support - Non-U.S.

SA-PO473

Trans-Epithelial Fluid Pumping Performance of Renal Epithelial Cells and the Mechanistic Basis of Polycystic Kidney Disease

Mohammad ikbal Choudhury,1,2 Feng Qian,1,3 Owen M. Woodward,1 Sean X. Sun.1,3 Sean Sun Group1 Johns Hopkins University, Baltimore, MD; 2Institute for NanoBiotechnology, Baltimore, MD; 3University of Maryland School of Medicine, Baltimore, MD.

Background: The epithelial cells lining nephrons in kidneys are highly efficient fluid reabsorption and secretion units. Imbalance in the trans-epithelial fluid flow leads to various renal diseases including polycystic kidney disease, which is stimulated by mutations of numerous fluid-filled cysts in the renal tubules. Surprisingly, no work has been done so far to quantify the fluid pumping performance of renal epithelial cells in a physiologically relevant setup. To make progress, we developed a microfluidic kidney pump (MFKP) device, to measure the trans-epithelial fluid flow as a function of the hydrostatic pressure gradient generated by cells.

Methods: MFKP mimics a tubular segment of the nephron as it has two microfluidic channels separated by a porous membrane. A microcapillary connected to the basal side acts a sensor to measure both the trans-epithelial fluid flow (J) with a resolution of 0.31 ul. and corresponding hydrostatic pressure gradient (AP) with a resolution of 10 Pa. This

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
setup was placed inside the incubator and fluid flow in the microcapillary was recorded using videography. Jp was the flow at AP – BP and Jg was the stall pressure when J = 0.

Results: Here we report that normal human cells pump fluid from apical to basal side with Jg in the range of 10 µL/min/cm² and APg of 250 Pa. Interestingly the PKD cystic cells pump fluid in the reverse direction (basal to apical) with Jg of 5 µL/min/cm² and APg of -300 Pa. Fluid flow in the reverse direction was abolished by 1 µM Tolagaptan caused a decrease in both Jg and APg. The developed pressure gradient translates to a force of 50-100 nanoNewtons per cell, which can potentially expand the cyst lumen. In both normal and PKD cells, the trans-epithelial fluid flux (Jp) and the PPCs are modulated by mechanical (fluid shear stress), chemical (arginine vasopressin) and apical hypo-osmotic perturbations.

Conclusions: Our combined results offer insights into kidney fluidic pumping action and ADPKD cyst formation. To our knowledge this is the first demonstration of a decrease in secretory fluid flow and hydrostatic pressure gradient by PKD cells in response to a Tolagaptan treatment. Our results demonstrate that secretory and absorptive functions of epithelia can generate significant mechanical forces, and maybe a general phenomenon in tubular morphogenesis in other contexts.

Funding: NIDDK Support

SA-PO474
Defective Glomerulotubular Balance (GTB) in PKD2 Mutant and Conditional Pkd2 Knockout Mice Before Renal Cyst Formation
Zhaopeng Du,1 Xin Tian,2 Ming Ma,2 Alan M. Weinstein,2 Stefan Somlo,2 Tong Wang.2 C. M. & C. Physiology, Yale University, New Haven, CT; 2Nephrology, Yale University, New Haven, CT; 2Physiology and Biophysics, Weill Medical College of Cornell University, New York, NY.

Background: PC2 (Pkd2) is a nonselective calcium permeable cation channel belonging to the polycystin family, at the apical membrane, functions as a Ca²⁺ channel in the ER. Previous studies showed Pkd2 mutation or knockout resulted in an absence of IP3 receptor mediated calcium release from the ER. We have reported that blocking IP3 receptor abolished the Na⁺ and Cl⁻ transport in mouse proximal tubules. We investigated whether Pkd2 has a physiological function in response to flow-mediated PT transport.

Methods: The flow-mediated Na⁺ and Cl⁻ transport were studied by microperefusion of proximal tubules in vitro in WT, Pkd2−/− and Pkd2 conditional KO (Pkd2fl/fl; Pax8rtTA TetOCre) mice. The KO mice were induced with doxycycline from 4-6 weeks of age and used at 20 weeks of age.

Results: When perfusion was increased from 5 to 20 nL/min, Jp and Jg increased 48% and Jg doubled in WT. In contrast, the flow-stimulated component of Jp and Jg could not be detected, and that of Jg was significantly reduced in both Pkd2−/− and the Pkd2 mice, similar to the effect of the IP3 receptor antagonist (2-APB).

Conclusions: These results indicate that Pkd2 is necessary for normal flow-mediated PT transport, and support the hypothesis that impaired GTB may contribute to renal cyst formation.

Funding: NIDDK Support

SA-PO475
Effect of Axial Flow on Sodium and Bicarbonate Absorption in PTs of WT and Pkd2 Mutant Mice

Effect of Axial Flow on Sodium and Bicarbonate Absorption in PTs of WT and Pkd2 Mutant Mice

<table>
<thead>
<tr>
<th>Flow rate</th>
<th>Jp (µmol/min/cm²)</th>
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<td>Pkd2−/−</td>
<td>5</td>
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* P<0.05 compared from low flow rate; TP<0.05 compared with WT at the same flow rate.

SA-PO476
ATP Release into Renal Cysts Via Pannexin-1/P2X7 Channels Decreases ENaC Activity

ATP Release into Renal Cysts Via Pannexin-1/P2X7 Channels Decreases ENaC Activity

ENaC Activity

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SA-PO477
Novel PC2 Regulation of Ezrin in Renal Epithelia Reveals Insight into ADPKD Cystogenesis
Eyrn E. Dixon, Carmen C. Leitch, Norann A. Zaghoul, Paul A. Welling, Owen M. Woodward. University of Maryland School of Medicine, Baltimore, MD.

Background: Ezrin plays the role of master scaffold of the apical compartment in epithelial cells and is critical in regulation of polarity, cytoskeleton organization, and protein trafficking. Ezrin regulation and the downstream consequences of its disruption have not been elucidated. Investigation into the initiating events of cystogenesis in autosomal dominant polycystic kidney disease (ADPKD) revealed a dramatic change in ezrin, following loss of polycystin-2 (PC2). ADPKD is caused by loss of function mutations in PKD1 and PKD2, which encode for transmembrane proteins PC1 and PC2, respectively.

Methods: Using an inducible Cre system (Pkd2fl/fl Pax8rtTA TetOCre), PC2 loss in a three dimensional renal epithelial model resulted in decreased ezrin abundance. Ezrin accumulation in vivo model (Pkd2fl/fl Pax8rtTA TetOCre) of rapid cystogenesis exhibits significant changes in ezrin at the apical membrane of renal tubules after a short induction period of five days, and before the manifestation of cysts. Human ADPKD tissue also confirms changes in the structure of the apical compartment in emergent cystic cells, which correlated with significant alterations in the localization and abundance of ezrin in comparison to controls. A potential regulatory relationship between PC2 and ezrin is supported by experiments that demonstrated PC2 and ezrin interact in an overexpression system and share a similar phosphostimulable binding profile in a lipid context. Based on this novel regulatory relationship between PC2 and ezrin, as well as the antecedent loss of ezrin to cyst formation, human ezrin was overexpressed in the pkd2 morpholino pronephric cyst model of zebrafish. Increased expression of ezrin abolished the formation of pronephric cysts.

Results: The interaction profile of PC2 and ezrin, disruption of ezrin in pkd2 inducible in vitro and in vivo model systems, changes in ADPKD patient tissue, and rescue of pronephric cysts in the pkd2 MO suggest there is a significant role of ezrin in renal cystogenesis.

Conclusions: Understanding the relationship of a master scaffold, ezrin, with PC2 in renal epithelial cells will help elucidate the mechanism of ADPKD cystogenesis and define important downstream pathways necessary for epithelial functions.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO478
ADAM10-MMP14 Complex Regulates Adherens Junction Integrity at Renal Cystogenesis in Autosomal Dominant Polycystic Kidney Disease
Frank Xu,1 Tianqing Kong,2 Tzongshi Lu.1 1Brigham and Women’s Hospital, Harvard Medical School, Natick, MA; 2Brigham and Women’s Hospital, Boston, MA.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common life-threatening genetic kidney disease and currently do not have relevant therapeutic methods, which eventually results in end-stage renal disease. We previously reported ADPKD is associated with mutations in polycystins, alterations in cell-cell junctions, and disruption of cell polarity in renal epithelial cells. Moreover, our data indicated that Gli1 promotes the cystogenesis of kidney cells, and the inhibition of ADAM10 can block the cystogenesis in renal cells through the preservation of E-Cadherin. In addition, studies also indicate that Matrix metalloproteinase-14 (MMP14) promotes cystogenesis, which is blocked by its inhibitors. However, mechanisms of ADAM10 and MMP14 regulated cystogenesis in ADPKD are not fully understood. In this study, we investigate these two major sheddases association and their roles in renal cystogenesis.

Methods: Immunoprecipitation, immunostaining and 3-dimensional (3D) cell culture technologies are used to analyze the interaction between metalloproteinase ADAM10 and MMP14 in Madin-Darby Canine Kidney (MDCK) cells.

Results: Our data showed that ADAM10 and MMP14 associated at hemopxin domain of MMP14 to form a complex, and activation of MMP14 is required for ADAM10 in shedding of E-Cadherin. The enzyme-inactive mutant MMP14A24A (Glu240 to Ala) or the deletion of the catalytic domain of MMP14 (MMP14 CAT) significantly decreases the shedding activity of ADAM10. In addition, ectopic expression of MMP14 increases the proliferation of MDCK cells, alters the cell-cell adhesion and promotes the cystogenesis of renal epithelial cells in our 3D cell model. Our results also show that knockdown of MMP14 decreases the cleavage of E-Cadherin by ADAM10, and knockdown of ADAM10 enhances the activation of proMMP2 by MMP14. Furthermore, ectopic expression of the MMP14E240A mutant promotes inhibition of cystogenesis in our 3D epithelial cell models.

Conclusions: Our study shows for the first time that ADAM10 form a unique, stable complex at hemopxin domain of MMP14, and the ADAM10-MMP14 complex play a pivotal role in regulating E-cadherin sheddase activity at cell-cell junctional protein and cystogenesis in renal epithelial cells. Our data provide a potential therapeutic target in ADPKD through the modulation of ADAM10-MMP14 complex.

Funding: Private Foundation Support

SA-PO479
Persistent Upregulation of Homologous Recombination Repair Signalling in Cyst epithelial Cells in Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Jennifer Zhang,1 Sayanthooran Saravananbavan,1 Alexandra Munt,1 Irene Sangadi,1 Arnaud Weng,1 Peter C. Harris,1 David Harris,1 Yiping Wang,1 Gopi Ramalingam,2,3 Westmead Institute for Medical Research, The University of Sydney, Westmead, NSW, Australia; 2Department of Renal Medicine, Westmead Hospital, Westmead, NSW, Australia; 3Mayo Clinic, Rochester, MN.

Background: In ADPKD, homologous recombination (HR) of the Pkd1 allele in response to DNA damage might explain the postnatal reduction in gene dose and triggering of focal kidney cyst formation. In this study, the hypothesis that HR signaling is increased in ADPKD and correlates with kidney cyst formation, was investigated.

Methods: Markers of HR (H2AX, γH2AX, phosphorylated H2AX) were assessed by immunostaining and Western blotting in kidneys from Pkd1+/− and Pkd1−/− mice (both ages 12 months) and SD rats. Quantitation of Pkd1−/− H2AX expression in adult kidneys was compared to respective controls. Further, amino acids availability for ROS production was deprived from glucose, p-eIF2α-mutant cells were compared to controls. p-eIF2α-activator of the integrated stress response (ISR) sitting at the intercross of metabolic and glutamine contribution to the TCA cycle. Here, we explore ASNS as an ER-bound protein that triggers the ISR, which is responsive to amino acids availability for ROS production. This was supported by increased GSH (reduced glutathione) levels in p-eIF2α-mutant cells compared to respective controls.

Results: In vitro, p-eIF2α increased 1.6-fold (p<0.01) in MCT (12%), SC (36%), MC (37%) and LC (45%)

Conclusions: Kidney cyst-lining epithelial cells exhibit DNA damage and the persistent upregulation of HR signalling which correlates with cyst size. These data suggest that low-dose inhibition of HR pathways using sub-lethal dose of ATR or ATM inhibitors could be used to selectively target kidney cyst growth.

Funding: Government Support - Non-U.S.

SA-PO480
Loss of Mitochondrial Transcription TFAM in Renal Tubular Epithelial Cells Is Associated with Cyst Development
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Background: Mitochondrial dysfunction plays an important role in the pathogenesis of kidney diseases. However, mechanisms of mitochondrial disorders, indicating that mitochondrial dysfunction can initiate and promote kidney disease.

Methods: In the kidney, mitochondria (mito) are highly abundant in renal tubular epithelial cells due to their high energy demands. In order to gain insights into function during renal pathogenesis, we inactivated the gene encoding mt transcription factor A (TFAM) in Six2-expressing progenitor cells, resulting in TFAM function loss in all nephron segments except collecting ducts; mutant mice are from hereof referred to as Six2-Tfam−/−. TFAM is required for mt DNA replication and gene transcription and is thus essential for the maintenance of mt mass and function.

Results: We found that Six2-Tfam−/− mice developed severe renal cystic disease and died by postnatal day (P) 30 from renal failure (76.0 ± 3.46 mg/dl for mutants vs. 22.0 ± 2.0 mg/dl BUN for control; n=4 and n=3, respectively; p<0.0001). Although nephropathy was not affected (normal morphology at P0), the expression of proximal and distal renal differentiation markers was severely reduced by P7. Furthermore, Six2-Tfam−/− mice were characterized by significant changes in mt morphology [EM and structured illumination microscopy (SIM)], as well as alterations in cellular energy metabolism; increase in glycolysis and decrease in oxygen consumption in isolated proximal tubule epithelial cells using Seahorse XF-24 instrument. To investigate TFAM in autosomal dominant polycystic kidney disease (ADPKD), we examined two mouse models of ADPKD: ROSA26.CreERT.Pkd1RC/RC and Cyst+−/− mice as well as human nephronyctosis tissues by immunohistochemistry and RNA in situ hybridization. We observed that TFAM as well as TFAM-regulated mt genes were significantly downregulated in cyst-lining epithelial cells in both mouse and human PKD tissues. Consistent with reduced TFAM expression was a decrease in mt volume in cyst-lining epithelial cells compared to non-cystic tubular epithelium using SIM.

Conclusions: Taken together, our data establish that loss of TFAM is associated with the development of polycystic renal disease providing strong rationale for developing strategies that target mt function for ADPKD therapy.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO481
Investigating the Centrality of the Asparagine Synthetase Enzyme in the Metabolic Reprogramming and Glutamine Usage in ADPKD
Christine Podrini, Marco Chiariavalli, Alessandra Boletta. San Raffaele Scientific Institute, Milan, Italy.

Background: We showed that metabolic alterations in the TCA cycle and increased glutaminolysis interlinked with asparagine metabolism are important features of ADPKD (Podrini et al. Commun Biol, 2018). Tracing studies with labelled [15C5,15N2] glutamine showed that Pkd1−/− cells increased glutamine uptake and N-labeled asparagine, indicating a central role for asparagine synthetase (ASNS). Indeed, siAsns in vitro abrogated glutamine contribution to the TCA cycle. Here, we explore ASNS as an ER-bound protein activator of the integrated stress response (ISR) sitting at the intercross of metabolic and glutaminolysis pathways. Further, amino acids availability for ROS production was deprived from glucose, p-eIF2α-mutant cells were compared to controls. Further, amino acids availability for ROS production was significantly decreased, suggesting that eIF2α/ATF4 axis might be responsive to amino acid deprivation. Moreover, downregulation of Asns in Pkd1−/− mutant cells causes cell death and rescues the accumulation of metabolites of the TCA cycle, suggesting a potential dual role for ASNS in glutaminolysis and cross-talk with ROS production. To validate ASNS as a therapeutic target, we have designed specifically the silencing of ASNS by LNA GompR. Initial testing in vitro was done in Pkd1−/− mutant cells on five different GompR. The most effective is currently being tested in vivo in an inducible Pkd1 KO mouse model.

Conclusions: Our data raises the possibility that asparagine metabolism interlinked with the ISR might offer a novel therapeutic intervention in PKD.

Funding: Government Support - Non-U.S.
Investigating the Role of Peroxisomal Metabolism in Polycystic Kidney Disease
Takeshi Terabavshii, Luis F. Menezes, Fang Zhou, Gregory G. Germino. NIDDK, National Institutes of Health, Bethesda, MD.

Background: Our group recently reported impaired fatty acid oxidation and abnormal mitochondria in Pkd1 mutants. However, how these phenomena contribute to cystogenesis in ADPKD is unclear. Peroxisomes interact with mitochondria physically and functionally, and congenital peroxisomal biogenesis disorders cause developmental and metabolic phenotypes including renal cysts and aberrant mitochondria. Given the features observed in both PKD and the peroxisome diseases, we hypothesized PKD1 might affect peroxisomal function thereby altering mitochondrial behavior. Our results suggest that peroxisome dysfunction is not responsible for the fatty acid oxidation defect observed in Pkd1 mutants. On the other hand, further study will be required to figure out the role of the observed reduction of fatty acids levels in vivo.

Funding: NIDDK Support

Evidence for Genetic Compensation for Cilia Membrane Delivery Defects in cep290/NPH6 Mutants
Magdalena Cardenas-Rodriguez,1 Iain A. Drummond.1,2 Massachusetts General Hospital, Charlestown, MA; 2Harvard Medical School, Boston, MA.

Background: Apical cilia move fluid and participate in sensing the extracellular environment. Cilia dysfunction or "ciliopathy" results from disruptions in cilia structure and functionally, and congenital peroxisome biogenesis disorders cause developmental and metabolic phenotypes including renal cysts and aberrant mitochondria. In the labeled behenic acid. Lastly, comprehensive analyzes of long-chain/very long-chain fatty acids were performed by MS of cystic kidneys of Phk103, Ksp-Cre mice. Results: There was no significant difference in peroxisomal abundance in control and Pkd1+/− cells [peroxisome number per cell: 9678±4114 WT 49.0±3.2 MUT 43.0±1.8 (p=0.4), 12111±1215 WT 30.4±0.9 MUT 25.9±3.8 (p=0.2)]. GFP-SKL was equally well-recruited into peroxisomes in WT and MUT cells, suggesting peroxisome biogenesis is not defective. Exogenously expressed P1 CTT exclusively localized to mitochondria. In the labeled behenic study, peroxisome β-oxidation was not significantly different in Pkd1−/− cells [n=3 each cell line pair (each with 3–5 replicates), 89.6±6.7 vs 84.2±7.6% (p=0.3)]. In the kidney tissues, total levels of fatty acids (C10−C24) were lower in Pkd1 mutant mice (control vs MUT: n=12, 104.6±27.7 vs 83.9±7.1 mg/mg, p=0.35), while the ratio of C24:0/C22:0, used as a readout of peroxisome disorder was not changed in the mutant mice (0.56±0.11 vs 0.58±0.11, p=0.5).

Conclusions: These data suggest that peroxisome dysfunction is not responsible for the fatty acid oxidation defect observed in Pkd1 mutants. On the other hand, further study will be required to figure out the role of the observed reduction of fatty acids levels in vivo.

Funding: NIDDK Support

Fibrocytisin Is Central to Cellulor Control of Adhesion Forces and Epithelial Polarity

Background: Mutations of the Phk1 gene cause autosomal recessive polycystic kidney disease (ARPKD). Phk1 encodes fibrocytisin/polyactin (FPC), a ciliary type I membrane protein of largely uncharacterized function, suggested to affect adhesion signaling of cells. Contributions of altered epithelial cell adhesion and contractility to the disease process of ARPKD are elusive. Here, we study how loss of FPC (function) modulates epithelial cell response to adhesion stimuli and contractile force distribution leading to defective control of epithelial polarity.

Methods: To address FPC function in cells with renal collecting duct characteristics, we study Phk1-silenced Madin-Darby canine kidney cells (MDCKII) and human urinary collecting duct cells. By transducing with FPC-deficient cells, we studied the effect of FPC deficiency on adhesion signals, impaired epithelial morphology and by implication homeostasis, which are presumably related to progressive epithelial defects in ARPKD. Epithelial cell-based models with selective genetic alterations allow a better molecular understanding and furthermore may provide means to test pharmacological correction of epithelial defects in PKD.

Background: Human ARPKD (MIM 263200) results from mutations in Pkhd1, but mouse Phk1 models express limited or no renal cystic disease. The protein product, FPC, undergoes a Notch-like processing with regulated membrane release and nuclear translocation of the intracellular C-terminal domain (FPC-CTD). We have previously shown that c-Myc is overexpressed in human ARPKD and mouse Cyp1α1 cystic kidneys, but not in Phk1−/−, Phk1−/−; or Phk1−/−;kidneys (ASNS 2018). Trdel (2016) demonstrated that the CTD plays a dual role—transcription is increased in mouse, through Myc-mediated mechanisms and a feed-forward regulatory Pklr–Myc loop. The current in vitro study was designed to compare MYC/Myc regulation in human and mouse FPC-CTD in collecting duct cell lines.

Methods: We generated immortalized normal human (HSTERT) and mouse (mTERT) kidney collecting duct cell lines; V5-tagged hFPC-CTD and V5-tagged mFPC-CTD constructs; and luciferase constructs of the P1 promoter for human MYC and mouse Myc. Luciferase reporter assays were performed as previously described (Wu, 2013).

Results: Sequence analysis revealed 74% identity between the human MYC and mouse Myc P1 promoters and 55% identity between hFPC-CTD and mFPC-CTD. Luciferase assays demonstrated that FPC-CTD activates MYC and Myc promoter activity in both human and mouse collecting duct cell lines. Conclusions: These data strongly suggest that FPC-CTD activates MYC expression in both human and mouse collecting duct cells. Paradoxically, we have previously shown that loss of FPC-CTD leads to cystogenesis and c-Myc overexpression in human ARPKD kidneys, but not in mouse Phk1 models. We speculate that in renal collecting duct cells, FPC may function at the P1 promoter to modulate expression of MYC, which is modulated by species-specific mechanisms. In the mouse, we propose that in normal collecting duct cells, FPC-CTD function at the P1 promoter is constrained by mouse-specific mechanisms. Current efforts are focused on ex vivo studies in mouse metanephros to test this model.

Funding: Private Foundation Support

Intrahepatic Bile Duct Morphogenesis in Phk11 Mutant Mice
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Background: ARPKD is a complex disease caused by mutations in the PKHD1 gene (encoding the Fibrocytisin/Polyductin protein, or FPC). The predominant clinical manifestations are enlarged echogenic kidneys with distal tubule dilatation and cysts in the biliary tract with congenital hepatic fibrosis. The pathognomonic liver defect in ARPKD is the bile duct epithelial hyperplasia which is characterized by increased numbers of tortuous, irregular bile ducts within the portal tract and fibrosis. In mice, as in humans, the biliary tract development is initiated by the induction of bili-potential hepatoblasts adjacent to the portal vein mesenchyme expressing Sox9 that eventually will form the primitive ductal structures (PDS) by recruiting Sox9+ HNF4α− cells from the surrounding parenchyma that will mature into symmetric structures with all the cells Sox9+ HNF4α−. From around E17 onwards, in a process termed ductal plate remodeling, these dilatations become surrounded by portal mesenchyme to eventually give rise to mature (intrahepatic biliary ducts). To date, few studies have characterized the DPM

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associated with ARPKD in either humans or mouse models and the precise cellular defect remains undefined.

Methods: To gain insights into the mechanism altered during the development of the DPM we harvested livers from homozygous \( \text{Pkhd1} \)-/- mice, the control littermates and pregnant females injected with rapamycin (IP, 1 mg/kg every other day) was injected to pregnant females between E15.5 and E18.5, and performed H&E staining. To understand the effect on kidney development we isolated biliary duct cells using anti-EpCAM+ (cholangiocytes specific marker) coated magnetic beads from homozygous mutants and control littersmates at E15.5 and P0, and performed RNA sequencing (RNA-seq).

Conclusions: Tubular damage and cyst formation in TS correlate with increased cell proliferation and c-Myc expression, as well as modifications of specific molecular and biochemical pathways.

Funding: Government Support - Non-U.S.

SA-PO489

Pattern of Urinary Inflammatory Markers in Longstanding Type 1 Diabetes with and Without Diabetic Kidney Disease: Results from the Canadian Study of Longevity in Type 1 Diabetes

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Background: Diabetic kidney disease (DKD) contributes to significant mortality and morbidity in type 1 diabetes (T1D). Inflammation is a contributing factor to the pathogenesis of DKD, even during its early stages. Urinary inflammatory markers have been used to determine distinct urinary secretion phenotypes in different stages of DKD in T1D. The nature of urinary inflammatory markers in longstanding T1D is, however, unclear. The objective was to study changes in urine inflammatory markers within the normal range of albuminuria in longstanding T1D, and to quantify the differential urinary excretion of inflammatory markers in participants with DKD versus those without DKD (resistors).

Methods: A 42-plex human urinary inflammatory markers was analyzed from participants of Canadian study of longevity in T1D of more than 50 years duration (n=74) and compared to age and sex matched comparators (n =73). Normalalbuminuric T1D participants (n=44) were categorized into tertiles of albumin:creatinine ratio (<0.5, 0.5-1.2, 1.2-2 mg/mmol). T1D subjects were grouped as those with and without DKD (n=25 vs n=49).

Results: A stepwise increase was observed in 27 of 42 urine inflammatory markers across tertiles of normalalbuminuria. Urinary inflammatory marker excretion was lower in both DKD and DKD-resistors vs. controls. When comparing participants with DKD vs. DKD-resistors, IL-6, a potent inflammatory cytokine, was significantly different, with higher urinary excretion in DKD versus resistors (0.24±0.25 vs 0.13±0.16, P=0.03). Conclusion: Urinary excretion of inflammatory markers increases with the degree of albuminuria within the normal range in participants with longstanding T1D. This is consistent with our previous observation in an adolescent T1D cohort with shorter disease duration. Lower urine inflammatory marker excretion in longstanding T1D versus comparators may represent as yet unidentified protective factors in these long-term survivors in spite of DKD status, and needs further exploration. DKD participants had higher urinary excretion of IL-6 compared to resistors, highlighting a possible role of inflammation in DKD risk.

SA-PO490

Tim-3 Aggravates Podocyte Injury in Diabetic Nephropathy by Promoting Macrophage Activation via the NF-κB Pathway

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Background: Macrophage-mediated inflammation plays a significant role in the development and progression of diabetic nephropathy (DN). However, the underlying mechanism remains unclear. Here we suggest that T cell immunoglobulin and mucin domain-3 (Tim-3) has complicated roles in regulating macrophage activation, but its roles in the progression of DN are still completely unknown.

Methods: We downregulated Tim-3 expression in kidney (intrarenal injection of Tim-3 siRNA expressing lentivirus or global Tim-3 knockout mice) and induced DN by streptozotocin (STZ). We analyzed the degree of renal injury, especially the podocyte injury induced by activated macrophages in vitro and in vivo. Then, we transferred different bone marrow derived macrophages (BMs) into STZ-induced Tim-3 knockdown mice and determine the effects of BMs on the development of DN.

Results: First, we found that Tim-3 expression on renal macrophages was increased in patients with DN and in two diabetic mouse models, i.e. STZ-induced diabetic mice and db/db mice, and positively correlated with renal dysfunction of DN patients. Tim-3 deficiency ameliorated renal damage in STZ-induced diabetes with concurrent increase in protein levels of Nephrt and WT1. Similar effects were observed in mice with Tim-3 knockdown diabetic mice. Second, adoptive transfer of Tim-3-expressing macrophages,
but not Tim-3 knockout macrophages, accelerated diabetic renal injury in DN mice, suggesting a key role for Tim-3 on macrophages in the development of DN. Furthermore, we found NF-kB activation and TNF-α expression were upregulated by Tim-3 in diabetic kidneys, and podocyte injury was associated with the Tim-3-mediated activation of the NF-kB/TNF-α signaling pathway in DN macrophages both in vitro and in vivo.

Results: These results suggest that Tim-3 functions as a key regulator in renal inflammatory processes and serves as a potential therapeutic target for renal injury in DN.

Funding: Other NIH Support - National Natural Science Foundation of China (No. 81670660), Government Support - Non-U.S.

SA-PO491
Prolyl Hydroxylase Domain Inhibitor Protects Against Metabolic Disorder-Related Kidney Disease by Suppressing Monocyte Chemotact-tractant Protein 1 Expression in Mesangial Cells
Mai Sugahara,1 Shinji Tanaka,1 Yu Ishimoto,2 Kenji Fuku,1,2 Akira Shimizu,3 Reiko Imaji,3 Toshimasa Yamauchi,1 Takashi Kadokawa,2 Masaoori Nagakuki,1 Tetsuhiko Tanaka1 Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan; JT CPRI, Osaka, Japan; 1Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan; 2Department of Diabetes and Metabolic Diseases, The University of Tokyo Graduate School of Medicine, Tokyo, Japan.

Background: We previously showed that administration of a prolyl hydroxylation domain (PHD) inhibitor, enarodustat, improved glucose/lipid metabolism and restored adiponectin levels in BTBR ob/ob mice. It also reduced albuminuria and ameliorated glomerular endothelial and mesangial damage (TH-PO450, ASN Kidney Week 2016). To elucidate the mechanism of renoprotection, we performed transcriptome analysis of isolated glomeruli and in vitro experiments using murine mesangial cells.

Methods: Four-week-old male BTBR ob/ob mice were divided into vehicle and enarodustat groups. Enarodustat (0.005% in feed) was administered from 4 weeks of age until euthanasia at 22 weeks. cDNA samples from isolated glomeruli were hybridized using Agilent SurePrint G3 Mouse GE Microarray 8x60K ver. 2.0. SV40 MES 13 cells were stimulated by palmitate with either enarodustat or AdipoRon (adiponectin receptor agonist).

Results: Enarodustat-treated mice tended to exhibit lower blood glucose (HbA1c: 8.9±3.0 vs 8.2±2.0, p = 0.060) and significantly lower total cholesterol levels (260±26 vs 164±17 mg/dL, p = 0.019) with comparable intake. Plasma adiponectin was increased in enarodustat-treated mice (6.7±6.6 vs 9.8±8.0 μg/mL, p = 0.014). Enarodustat significantly decreased albuminuria (5.9±1.3 vs 2.3±0.5 mg/mgCr, p = 0.017) without affecting GFR. Electron microscopic examination revealed amelioration of glomerular epithelial and endothelial damage in enarodustat-treated mice. Transcriptome analysis of isolated glomeruli revealed reduced expression of monocyte chemotactant protein 1 (MCP-1) in enarodustat-treated mice. Urinary MCP-1 was decreased in enarodustat-treated mice (317±62 vs 173±25 μg/mgCr, p = 0.006), accompanied by reduced glomerular macrophage infiltration (2.7±0.5 vs 1.1±0.2, p = 0.006). In vitro experiments demonstrated that both enarodustat and AdipoRon suppressed palmitate-induced MCP-1 production in mesangial cells. Enarodustat’s suppressive effect was abolished when HIF-1α was knocked down by siRNA.

Conclusions: Enarodustat conferred renoprotection through both indirect and direct pathways: improvement in glucose/lipid metabolism and suppression of MCP-1 production in mesangial cells via HIF-1α activation.

Funding: Commercial Support - Japan Tobacco Inc., Government Support - Non-U.S.

SA-PO492
Effects of Triptolide on Macrophage Function and Phenotype by Modulating Autophagy
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Background: Macrophage infiltration process including capacity of adhesion migration and phenotype transformation are key points in diabetic nephropathy (DN). Triptolide (TP), a classical Chinese medicine, can alleviate macrophage infiltration effectively in renal inflammatory diseases. However, the relationships between autophagy and Triptolide are unknown. This study aims to investigate whether Triptolide affects macrophage function and phenotype through modulating autophagy.

Methods: RAW264.7 cells were divided into normal (NC) and high glucose treatment groups (HG). Triptolide (10.0ng/mL) was added to respective groups after 4 hours of cell incubated. Western blot and immunofluorescence staining were used to detect the expression of M1 macrophage marker (iNOS, TNF-α), M2 macrophage markers (MR, Arg-1) and autophagy markers (LC3, Beclin-1 and p62). The capacity of macrophage adhesion and migration with and without Triptolide treatment were assessed.

Results: Our study showed that macrophage infiltration was inhibited by HG, which results revealed a decrease expression of LC3 and Beclin-1, but increase expression of P62. Subsequently, the numbers of macrophage adhesion and migration were increased (P<0.05). HG induces M1 activation with increase expression of iNOS and TNF-α and inhibits M2 transformation (with increase expression of MR and Arg-1)(P<0.05). However, TP recovers macrophage autophagy level that inhibited by HG (with increase expression of LC3 and Beclin-1, whereas a reduction expression of P62), which lead to inhibition of macrophage adhesion and migration under HG (P<0.05). In addition, TP inhibits M1 macrophage transformation (with decrease expression of iNOS and TNF-α while induces M2 macrophage activation (with increase expression of MR and Arg-1) (P<0.10).

Conclusions: HG induces classical activation of M1 macrophages and promotes macrophage adhesion and migration, which is associated with decreased autophagy level. TP promotes M2 macrophage transformation under HG through reducing expression of inflammatory factors, thereby affect macrophage adhesion and migration, which is related to the recovery of autophagy.

Funding: Government Support - Non-U.S.

SA-PO493
Decay Accelerating Factor (DAF), a Local Complement Inhibitor, Protects from Streptozotocin (STZ)-Induced Diabetic Nephropathy (DN)
Chiara Cantarella,1 Sofia Andrihetto,2,1 Susan Hartzell,1 Chiara Guglielm,1 Enrico Fiaccardor,1 Gianluigi Zaza,2 Paolo Cravedi.1 Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY; 1University of Verona, Verona, Italy; 2Dipartimento di Medicina e Chirurgia, Università di Parma, Parma, Italy.

Background: Glomerular deposition of complement components has been described in individuals with DN. Whether altered expression of DAF on podocytes mediates complement deposition in DN and affects disease severity is unknown.

Methods: We injected STZ (50 mg/kg, ip) into male WT and germfree DAF−/− BALB/c mice and in B6 DAF68−/− crossed to podocin Cre-transgens (the B6 strain is resistant to STZ nephropathy). We serially measured urine albumin/creatinine ratio (ACR) and at 20 weeks we quantified histological injury and stained sections for C3b.

Results: STZ-induced nephropathy was associated with C3b deposition (Fig. 1A). In BALB/c mice, STZ caused more severe proteinuria in DAF−/− than in WT animals (Fig. 1B), a finding associated with more severe histological changes (Fig. 1C). Newly developed DAF68−/−podocin-Cre68−/− animals lacking DAF conditionally in podocytes showed albuminuria and histological changes of DN, while DAF68−/−podocin-Cre68−/− did not develop the disease (Fig. 1D-E). DAF-deficiency-induced proteinuria correlated with glomerular staining for C3b (Fig. 1F), mechanistically implicating DAF-dependent restraint on complement activation in the disease process.

Conclusions: Podocyte-expressed DAF mediates resistance to STZ-induced glomerular injury in B6 mice. In the absence of DAF, STZ-induced kidney injury is propagated by local deposition of complement. These data provide the rationale for further studying a role of DAF-complement in human diabetic nephropathy.

Funding: NIDDK Support

Figure 1. A) C3b deposition in the glomeruli of BALB/c mice at 20 weeks after vehicle or STZ injection. B) Serial ACR in WT and DAF−/− BALB/c mice injected with STZ. C) H&E staining of kidney tissue of the same mice at 20 wks after STZ injection. D) Serial ACR in DAF68−/− podocin-Cre68−/− and Cre68−/− WT B6 mice injected with STZ. E) Renal histology of the same mice at 20 wks after STZ injection. H&E (top) or C3b (bottom) staining. *P<0.05 vs. controls at the same time-point.

SA-PO494
The Contact Pathway of Coagulation and Complement Activation Participates in the Progression of CKD in Obese Diabetic Rats
Katherine J. Kelly.1,2 Jesus H. Dominguez.1 Indiana University, Indianapolis, IN; 1Medicine, Roudebush VA Medical Center, Indianapolis, IN.

Background: Diabetic nephropathy is the leading cause of end stage renal disease. Obese diabetic ZS rats become nephrotic at age 12 weeks and develop advanced chronic renal failure (CKD), the hallmark of human diabetic nephropathy, by 24 weeks. We have proposed that episodes of ischemic acute kidney injury (AKI) are key in the progression of CKD. We have also found that, in AKI, disorders of innate and inflammation prevent furosem and promote ongoing ischemia, leading to loss of functional tissue and fibrosis. We hypothesize that activation of the contact pathway of intrinsic coagulation with complement activation is involved in the development of CKD.

Methods: Male lean (L) and obese, diabetic ZS rats were subjected to sham surgery (DS) or bilateral renal ischemia (DI) at 10 weeks of age (total n=24). The rats

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Underline represents presenting author.
were terminated at 28 weeks of age. Renal function and structure were assessed and comprehensive genetic sequencing was performed.

**Results:** The nephrinopathy in the diabetic rats postchisemia was characterized by renal failure, the sin que non of human disease. The relevant renal transcripts (table) included activation of the contact pathway with increases in F9, 10, 12 and 13 as well as fibrinogen chains A, B, G, platelet mRNA p1g1B, F2R, FP4 and C.

**Conclusions:** This rat renal transcript profile strongly points to a persistent disorder of renal coagulation and immunity consistent with activation of renal contact pathway. This pathway is a critical juncture of coagulation and inflammation and has multiple therapeutic targets opportunities for diabetic nephropathy.

**Funding:** Veterans Affairs Support, Post-Grant Foundation Support

### Coagulation Contact Pathway

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SA-PO495

**Transcriptional Inhibitory Peptides of NFkB and JAK/STAT Pathways Improve Renal Damage in BTBR ob/ob Model**

Lucas Opana-Rios,1,2 Ana Plaza,1 Yennifer Sanchez,1 Daniel Carpio,1 Maria A. Droguett,1 Jesus Egidio,1 Carmen Gomez-Guerrero,2 Sergio A. Mezzano,1

**Unidad de Nefrología, Universidad Austral de Chile, Valdivia, Chile; 2Renal, Vascular and Diabetes Research Lab, IIS-Fundación Jiménez Díaz – Universidad Autónoma y Spanish Biomedical Research Centre in Diabetes and Associated Metabolic Disorders (CIBERDEM), Madrid, Spain.**

**Background:** Diabetic nephropathy (DN) is the leading cause of chronic kidney disease and despite improvements in glycemic and blood pressure control by RAAS inhibitors, end-stage renal disease still remains a growing issue. Chronic inflammation plays a key role in the DN progression, but the underlying mechanisms are largely unknown. Therapeutic modulation of inflammation can be assessed by targeting soluble cytokines, their receptors or the involved cell signaling. In the BTBR ob/ob mice, a model of progressive DN that recapitulates the lesions seen in human DN, we have examined and compared the modulation of NFkB and JAK/STAT, two major inflammatory signaling pathways involved in the pathogenesis of DN. To do that we have employed inhibitory peptides targeting key domains of regulatory proteins such as Nemo-Binding Domain of IKK complex (NBD peptide) and the kinase-inhibitory region of SOCS1 (MiS1 peptidomimetics), which respectively prevent the nuclear translocation of p65 and STAT1/3 transcription factors.

**Methods:** Six-weeks old BTBR ob/ob mice were given intraperitoneal injections of active peptides (NBD, 6 and 10 µg), inactive mutant peptides (10 µg), respectively) and vehicle for 7 weeks (n=6-8/group). At the end of the study, animals were sacrificed to obtain blood, urine and kidney tissue samples for further analysis.

**Results:** *In vivo* and *ex vivo* imaging revealed efficient peptide delivery and rapid systemic biodistribution, with selective renal metabolism in BTBR ob/ob mice. Although both active peptides significantly reduced albuminuria (ACR) in diabetic mice, a greater effect was observed with MiS1 (decrease 57% with 2 µg and 66% with 4 µg vs vehicle). Both NBD and MiS1 treatment improved glomerular and tubulointerstitial injury (49% with NBD and 48% with MiS1 vs vehicle) and increased the number of podocytes (46% with NBD and 55% with MiS1 vs vehicle), without changes in metabolic parameters (glycemia and lipid profile) and body weight. Additionally, high dose of MiS1 significantly reduced renal weight in compared to controls.

**Conclusions:** Transcriptional inhibitory peptides NBD and MiS1 significantly improve albuminuria and alleviates DN in ob/ob mice, being the inhibition of JAK/STAT pathway more effective in achieving these objectives.

**Funding:** Government Support - Non-U.S.

### SA-PO496

**TNF-α Inhibition Protects Against Renal Tubulointerstitial Injury Associated with Suppressing NLRP3 Inflammation in Diabetic Rats**

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**Background:** Tubular injury exerts a pivotal role in the development of diabetic nephropathy (DN), but current therapies used to treat DN do not control tubular injury. This study was conducted to investigate whether TNF-α inhibition protected against tubular injury in diabetic rats and examine the associated mechanisms.

**Methods:** Kidney biopsy tissues, taken from twelve patients with DN and five control subjects, were analyzed. STZ-induced diabetic rats were treated with a TNF-α inhibitor (Humira) for twelve weeks. Renal function, albuminuria, histological injury, renal TNF-α mRNA, and NLRP3 inflammation as assessed.

**Results:** Diabetic patients with tubulointerstitial injury presented with higher renal tubular expression of TNF-α mRNA and NLRP3 inflammation. TNF-α inhibition reduced albuminuria, glomerular injury, and tubular injury in STZ-induced diabetic rats. Importantly, TNF-α inhibition significantly reduced NLRP3 inflammation in tubules. Moreover, TNF-α inhibition decreased expression of tubular IL-6 and IL-17A, which could activate NLRP3 inflammasome.

**Conclusions:** TNF-α inhibitor can protect against tubulointerstitial injury associated with suppressing NLRP3 inflammation in diabetic rats.

**Funding:** Other NIH Support - HL116264, HL125409, and HL121233

### SA-PO497

**Comparison of Nrf2-Inducing Compounds on Renal Tubule Cell Responses Associated with Diabetes**

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**Background:** The transcription factor Nrf2 regulates cell stress responses. Though many reports suggest the therapeutic potential of Nrf2 inducing compounds in models of kidney disease, use of these agents in clinical settings is limited. Our lab found disparate effects of two Nrf2 inducing compounds, Dimethyl fumarate (DMF) and Protandim (a dietary supplement with no previously reported findings in renal cells), on renal tubule cell morphology and actin cytoskeleton. Due to varying interactions with the Nrf2 inhibitor, Keap1, and ultimately Nrf2 target gene induction, this study tested the hypothesis that DMF and Protandim differently regulate renal tubule cell responses associated with disease.

**Methods:** Human renal proximal tubule cells were treated with 5μg/ml Protandim or 10μM DMF, before or after culture in high glucose (HG; 25mM) concentrations to mimic diabetes. Cell viability was examined via MTT Assay (reduction of (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (MTT) viability and fibroblast secreted via fibroblast immunoblot of cell culture medium, and cell structural proteins (E-Cadherin and α/β tubulin) analyzed via Immunofluorescent staining.

**Results** analyzed by two-way ANOVA with post hoc.

**Results:** Culture in HG for 24h increased MTT reduction. When cells were treated with inducers for an additional 24h after culture in HG, DMF reversed the effects of HG on MTT reduction. When cells were instead pre-treated with inducers for 24h prior to culture in HG for an additional 24h, DMF again tended to reverse the effects of HG on MTT reduction. Prior treatment with DMF or Protandim prior to culture in HG showed a trend (*P=0.07*) of lowering HG-induced fibroblast production. Importantly, treatment with inducers after HG conditions exhibited the same trend with Protandim but an opposing trend with DMF. Expression of E-cadherin decreased with DMF and protein distribution was more punctate, while α/β tubulin expression and/or polymerization increased with Protandim.

**Conclusions:** Protandim and DMF differentially regulate renal tubule cell matrix protein secretion and cell structural protein expression and distribution, responses known to be altered with diabetes. The differential effects of Nrf2 inducers on renal cells may lead to different outcomes if/when used for treatment of kidney diseases.

**Funding:** NIDDK Support

### SA-PO498

**Serpin1/Antithrombin III Protects Against Diabetic Nephropathy**

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**Background:** Antithrombin III (ATIII), encoded by the gene Serpin1, is a serine protease inhibitor in the coagulation cascade and exhibits significant anti-inflammatory properties. Inflammation contributes to the development of diabetic nephropathy. The aim of this study was to investigate the effect of Serpin1/ATIII on diabetic nephropathy.

**Methods:** ATIII activity was analyzed in patients with diabetic nephropathy. Kidney injury and inflammation were evaluated in streptozotocin (STZ)-treated Serpin1 heterozygous knockout (Serpin1+/−) rats and in db/db mice treated with adeno-associated virus (AAV) Serpin1+/− gene. The effects of ATIII on tubulointerstitial activity and podocytes treated with high glucose were also examined in vitro.

**Results:** Diabetic patients with lower ATIII activities had a significantly higher incidence of macroalbuminuria and microalbuminuria (n=328, P<0.05). Albuminuria with STZ-treated in STZ-treated Serpin1+/− rats compared with STZ-treated wild-type littermates 8 weeks after diabetes induction (albuminuria 76.1±17.1mg/24hr in Serpin1+/− rats vs 26.6±4.7mg/24hr in wild-type controls, n=6, P=0.05). Serpin1 heterozygous knockout significantly exacerbated renal infiltration of macrophages and increased renal NF-kB activity and IL-6 and MCP-1 mRNA abundance in rats with STZ-induced diabetes. Serpin1 overexpression in db/db mice reduced albuminuria (273±42.7±7mg/24hr in db/db mice treated with AAV-Serpin1 vs 430±92±6.8mg/24hr db/db mice treated with AAV-control, n=6, P<0.05) and attenuated renal infiltration of macrophages and decreased renal NF-kB activity and IL-6 and MCP-1 abundance. Treatment with high glucose (25mM) significantly increased NF-kB activation and IL-6 abundance in macrophages and podocytes in vitro. Treatment with ATIII protein attenuated these effects of high glucose.

**Conclusions:** In conclusion, Serpin1/ATIII reduces inflammation and attenuates diabetic nephropathy.

**Funding:** Other NIH Support - HL116264, HL125409, and HL121233
SA-PO499

Immunosenescence in Type 2 Diabetic Patients with Chronic Renal Disease
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Background: Immunosenescence is an important challenge for an aging population. It is known that patients with end-stage renal disease suffer from immunosenescence and premature T cell aging but whether such changes occur in diabetic patients with less severe chronic renal disease is unclear.

Methods: 832 patients with type 2 diabetes with different levels of renal function were recruited in this study. Immunosenescence was analyzed by staining peripheral blood with two immunophenotyping panels and analyzed by multicolor flow cytometry.

Results: Out of all the 832 participants, there were 171 patients with stage 3 CKD and 46 patients with 4/5 CKD. Compared to patients with eGFR<60 ml/min, patients with more severe CKD showed progressively decreased CD3+ T cell and CD4+ and CD8+ T cell, but not monocyte numbers. In addition, immunosenescence, as defined by various phenotypic markers, showed significant upregulation in both stage 3 and stage 4/5 patients. However, immunosenescence was not associated with proteinuria level nor worse glucose control. In age and sex adjusted regression models, stage 3 CKD patients already exhibited significantly elevated percentages of CD28-, CD127- and CD57+ cells among CD8+ T cells when compared to patients with eGFR<60 ml/min. In addition, stage 3 CKD patients exhibited depressed HLA-DR and Cx3CR1 expression in specific monocyte subpopulations.

Conclusions: Level of immunosenescence is not significantly associated with proteinuria nor glucose control in type 2 diabetes patients. Both T cell and monocyte compartment exhibit characteristics of immunosenescence during renal function decline, starting from stage 3 CKD.

SA-PO500

Targeted Transgenic Expression of Catalase to Mitochondria Reduces Reactive Oxygen Species and Ameliorates Diabetic Nephropathy in BTBR ob/ob Mice
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Background: Diabetes induced mitochondrial dysfunction from increased generation of reactive oxygen species (ROS) is pathogenic for diabetic complications including diabetic nephropathy. Catalase is a major scavenger of ROS and protects tissue damage from oxidative stress. To explore pathogenic mechanisms and to test a targeted ROS reduction strategy for treating DN, we created diabetic BTBR ob/ob mice with inducible transgenic human catalase expressed only in mitochondria (mCAT) to determine the efficacy of reducing mitochondrial ROS in a murine model of DN.

Methods: Transgenic Rosa 26 mice containing loxp-stop-loxp-mCAT and tamoxifen-inducible Cre mice (B6.D2-ROSA26Sortm1(Sor)Tyj/J) were backcrossed into the BTBR mouse strain. The heterozygous ob/+ mice of each strain were crossed to obtain ob/ob double transgenic mice. At 16 weeks of age, the mCAT gene expression was induced by oral administration of tamoxifen and the induced mice were referred as mCAT ob/ob.

The double transgenic mice without tamoxifen treatment were used as control group (Rosa ob/ob). Fasting glucose levels were monitored and timed (6 hour) urine samples were collected at weeks of 18 and 24. At the end of the study (24wks), mice were sacrificed and blood and organs harvested.

Results: Both mCAT ob/ob and Rosa ob/ob were hyperglycemic (499.2 vs 566.7mg/dl) and obese. mCAT ob/ob mice with inducible transgenic human catalase expressed only in mitochondria (mCAT) to determine the efficacy of reducing mitochondrial ROS in a murine model of DN.

Conclusions: Reduction of ROS specifically in mitochondria by targeted expression of catalase to mitochondria reduces diabetic nephropathy.

SA-PO502

CD248 Modulates Unfolded Protein Response in Diabetic Nephropathy
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Background: Diabetic nephropathy (DN) is a major cause of end-stage renal disease and a growing public health burden. Recently DN has been linked with maladaptive unfolded protein response (UPR) and sterile inflammation, but the underlying mechanism triggering the glucose induced maladaptive UPR and sterile inflammation remain poorly defined. We focused on CD248, a type 1 transmembrane glycoprotein expressed by pericytes, such as glomerular mesangial cells and tubulointerstitial fibroblasts whose expression correlates with renal fibrosis development. Hence, aim of our study is to investigate the role of CD248 in regulating UPR and sterile inflammation in DN.

Methods: C57Bl/6 (WT) mice and CD248-/- mice were used for the study. Diabetes was induced using streptozotocin (STZ) and samples were obtained after 26 weeks. Albuminuria (UACR), PAS staining and WT-1 immunostaining of kidney sections were examined for circulating spexin level using commercially available ELISA kit. Serum samples from patients who were diagnosed as type 2 diabetes were examined for spexin level using commercially available ELISA kit (Spexin/neuropeptide Q(NPQ)). Serum and renal expression of spexin was examined in experimental mice models; 1) normal control, 2) db/db mice, 3) fat chow diet induced obese and diabetic patients. Recent study has shown that spexin mRNA was significantly detected in human kidney tissue. Therefore, we investigated the expression of spexin in diabetic kidney disease in clinical and experimental model.

Methods: Serum samples from patients who were diagnosed as type 2 diabetes were examined for circulating spexin level using commercially available ELISA kit (Spexin/neuropeptide Q(NPQ)). Serum and renal expression of spexin was examined in experimental mice models; 1) normal control, 2) db/db mice, 3) fat chow diet induced obese mice and 4) non-diabetic UUO-induced mice.

Conclusions: Collectively, lysyl oxidase-like 4 may regulate the acetylation/deacetylation of mitochondrial proteins and protects mitochondrial respiration and function in diabetic kidney tube.

Funding: Government Support - Non-U.S.

SA-PO503

Spexin: Is It Another Bystander or a New Biomarker in Diabetic Kidney Disease?
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Background: Spexin is a highly conserved active neuropeptide that has been recently identified in the involvement of controlling appetite and energy balance. Although few is known regarding to the role of spexin, spexin level was noted to be significantly lower in obese and diabetic patients. Recent study has shown that spexin mRNA was significantly detected in human kidney tissue. Therefore, we investigated the expression of spexin in diabetic kidney disease in clinical and experimental model.

Methods: Serum samples from patients who were diagnosed as type 2 diabetes were examined for circulating spexin level using commercially available ELISA kit (Spexin/neuropeptide Q(NPQ)). Serum and renal expression of spexin was examined in experimental mice models; 1) normal control, 2) db/db mice, 3) fat chow diet induced obese mice and 4) non-diabetic UUO-induced mice.

Conclusions: Collectively, lysyl oxidase-like 4 may regulate the acetylation/deacetylation of mitochondrial proteins and protects mitochondrial respiration and function in diabetic kidney tube.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Results: Total 89 diabetic patients participated in the study. The circulating spexin levels were significantly increased in patients on dialysis (both peritoneal and renal) compared to patients with estimated GFR ≥60 ml/min/1.73m². In diabetic patients with chronic kidney disease stage 1 to 3, spexin level was significantly increased in patients with overt proteinuria (urine protein to creatinine ratio). There was significant correlation between overt proteinuria, however no correlations were observed in healthy gender, BMI, blood glucose, lipid profiles and HOMA-IR or estimated GFR with serum spexin level. Spexin was detectable in serum and kidney tissue of murine models. In experimental mice of obese type 2 diabetes (db/db), serum spexin level was significantly increased, whereas its expression was not significantly different compared to normal and obstructed kidney control.

Conclusions: The spexin expression in the kidney from experimental mice and circulating spexin level in diabetic patients may indicate that spexin may be a biomarker of diabetic kidney disease. However, further study is needed to elucidate the specific role and mechanism of spexin in metabolic kidney disease.

SA-PO504

Hyperinsulinemia Contributes to High-Fat-Induced Kidney Injury in Mice

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Background: The mechanism of obesity-induced kidney injury is not well understood. We hypothesized that hyperinsulinemia activates kidney proximal tubular epithelial insulin receptor (IR) and contributes to obesity-induced kidney injury in high fat diet (HFD) mice.

Methods: We generated kidney proximal tubule IR knock out (KPTIRKO) mice by crossing IR lox mice with Sglt2-Cre mice. We administered normal fat diet (NFD) or high fat diet (HFD) to 5-8 months old male Control and KPTIRKO mice for 4 months (n=10, 3 batches) and evaluated changes in albuminuria, blood pressure (BP), renal matrix proteins, signaling pathways and intraglomerular GPT.

Results: KPTIRKO mice grew normally. In KPTIRKO mice renal cortical IR expression was decreased by more than 60% although it was unchanged in other tissues. Serum insulin, creatinine, urinary albumin to creatinine ratio (ACR) and renal cortical IGF-1 receptor expression in KPTIRKO mice were similar to Controls. On HFD, food consumption, increase in body weight and serum cholesterol were similar in Control and KPTIRKO mice. HFD increased the following in Control mice: renal cortical content of tyrosine phosphorylated IR indicating IR activation, matrix proteins laminin, fibronectin and collagen I, urinary and renal cortical KIM-1 content, urinary ACR, systolic BP, these changes were significantlyameliorated in HFD-fed KPTIRKO mice (p<0.05-0.001). HFD activated renal cortical IR-Akt axis in Control but not KPTIRKO mice. HFD increased serum insulin and C-peptide levels in Control but not in KPTIRKO mice. To explore if improved glucose tolerance was the reason for lack of hyperinsulinemia in KPTIRKO mice on HFD, GGT was done. KPTIRKO mice on NFD had lower fasting glucose and improved glucose tolerance; however, glucose intolerance was similar in Controls and KPTIRKO mice on HFD.

Conclusions: HFD-induced hyperinsulinemia activates renal cortical IR and contributes to kidney injury manifesting as albuminuria, elevated BP, and matrix protein accumulation in male mice. These results provide a mechanistic explanation for obesity-induced kidney injury. The finding of lack of hyperinsulinemia in HFD fed KPTIRKO mice needs further investigation.

Funding: Veterans Affairs Support

SA-PO505

Deletion of Peroxisome-Proliferator-Activated Receptor δ in Mice Promotes High-Fat-Diet-Induced Renal Injury

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Background: Peroxisome-proliferator-activated receptor δ (PPARδ), the least studied member of the PPAR group in the nuclear receptor superfamily, plays a crucial role in cellular metabolic functions and other physiological processes. Recent evidence highlights the therapeutic potential of PPARδ agonists in obesity, dyslipidemia, diabetes resistance/type 2 diabetes. However, little is known about PPARδ in the pathogenesis of obesity related renal injury. It is reported that PPARδ gene is a primary target of 1α,25-dihydroxyvitamin D3 (calcitriol), the aim of this study is to investigate the effects of calcitriol on the role of PPARδ in HFD-induced renal injury.

Methods: Diet-induced obese (DIO) mice were generated on PPARδ KO, age-matched PPARδ wildtype (WT) littermates at the 6 weeks of age and were fed with high-fat-diet (HFD) for 12 weeks. In addition, 12 weeks after HFD feeding, mice were treated with 1α, 25-dihydroxyvitamin D3 (calcitriol) or vehicle by intraperitoneal injection at the dosage of 100 ng/kg three times a week for 4 weeks. The effects of calcitriol on the role of

PPARδ in HFD-induced renal injury were evaluated by real-time quantitative polymerase-chain reaction (RT-PCR), immunohistochemistry (IHC) of renal Slc12a8. Further, we measured serum and urinary NAD+ metabolites at 24 weeks of age. We performed immunohistochemistry (IHC) of renal Slc12a8. Further, we measured serum and urinary NAD+ metabolites at 24 weeks of age. We evaluated renal NAD+ loss by calculating uric acid NAD+ to creatinine ratio (NAD+/Cr). NMR resonation was evaluated by the calculation of the fractional excretion of NAD+ (FeNAD).

Results: Serum NAD+ concentration of NAD+ decreased in ddb mice as compared to that in ddb mice at the age of 8 weeks, although that of NMM was not different. Urate NAD+/Cr ratios were higher in ddb mice than in ddb mice, suggesting an increased renal loss of NAD+ in ddb mice. IHC revealed weak staining of Slc12a8 in the glomerulus and proximal tubules, while strong staining in the distal tubules. Slc12a8 expression was higher in ddb mice than in ddb mice. Further, the expression of Slc12a8 was detected mostly on the basolateral side in ddb mice, it was expressed on both apical and basolateral side in ddb mice. These findings suggested the increased translocation of Slc12a8 towards apical side of distal tubular cells in DN. Consistently, FeNMM was lower in ddb mice than in ddb mice, indicating increased retention of NAD+ at the tubules in ddb mice.

Conclusions: Novel NMR transporter, Slc12a8 was dominantly expressed in the distal tubules. In DNR, Slc12a8 translocation to apical side was enhanced, which can be the compulsory mechanism for NAD+ loss in diabetic mice.

SA-PO507

Molecular Mechanism of Regulatory Effect of Vitamin D Receptor on Mitophagy of Proximal Tubular Epithelial Cells in Diabetic Nephropathy

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Background: Vitamin D receptor (VDR) is a kind of nuclear transcription factor, which is widely expressed in proximal tubular epithelial cells (PTECs). Our previous study found that VDR has anti-inflammatory and anti-fibrotic effects. Given the previous evidence that the expression of VDR decreased in PTECs of DN patients and VDR can regulate the mitophagy, how VDR contribute to the development of renal tubulointerstitial fibrosis in diabetic nephropathy is not entirely clear. In this study, we tend to investigate the regulatory effect of VDR on mitophagy dysfunction in diabetic nephropathy and its molecular mechanism.

Methods: VDR-knockout mice in C57BL/6 background were generated and streptozotocin (STZ)-induced diabetic mice were used in these experiments. Mitophagy in renal proximal tubules was observed by electron microscope, and the pathological changes of the kidneys were delineated by periodic acid–Schiff (PAS) staining. Immunohistochemistry and Western blotting were performed to identify the expression of VDR, Collagen 1, Fibrogen, α-SMA, TGF-β, Drp1, mitofusin 2, Pink1 and Bnip3. These findings suggested the increased translocation of Slc12a8 towards apical side of distal tubular cells in DN. Consistently, FeNMM was lower in ddb mice than in ddb mice, indicating increased retention of NAD+ at the tubules in ddb mice.

Results: 1. The blood glucose of the mice was significantly increased in the first week after the injection of STZ. 16 weeks after STZ injection, PAS staining revealed the glomerularmesangial and renal tubular injury of diabetic mice, suggesting that STZ-induced diabetic mice were generated successfully. 2. The accumulation of collagen in glomeruli had significantly increased in the STZ-induced mice. The expression of Collagen 1, Fibrogen and α-SMA in wild-type diabetic mice was lower than that in VDR-KO diabetic mice, thus confirming the anti-fibrotic effect of VDR in the pathogenesis of DN. In the diabetic model induced by STZ, there is severer mitophagy dysfunction in VDR-KO mouse than that in the wild type diabetic mouse, which indicates that VDR may regulate the mitophagy in diabetic nephropathy.

Conclusions: VDR can control the renal fibrosis and the progression of diabetes by regulating the mitophagy. VDR overexpression may act as a new target for the prevention and treatment of DN.

Funding: Government Support - Non-U.S.
SA-POS08

Activation of Vitamin D Receptor Attenuates High Glucose-Induced Cellular Injury Partially Dependent on CYP2J5 in Murine Renal Tubule Epithelial Cell

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Background: Vitamin D receptor (VDR), have renoprotection effect against diabetic nephropathy (DN). Paricalcitol is a VDR activator. Epoxygenoxygenated products of cytochrome P450 (CYP) protect against diabetes and DN. Our objective is to investigate whether activation of vitamin D receptor protect nephropathy partially dependent on CYP2J5 in murine renal tubule epithelial cell.

Methods: Adult male wile type (WT) and VDR-/- mice were used. STZ-induced diabetic nephropathy model was established and paricalcitol was injected. 12 weeks after the STZ injection, mice were sacrificed. Kidneys were collected for histology and immunohistochemistry staining.

Results: 1. STZ, VDR-/-,VDR-/-+STZ mice tubulointerstitial injury were more severe than WT, the expression of CYP2J5 and VDR decreased. But STZ mice treated with paricalcitol had attenuated tubulointerstitial injury and increased CYP2J5 and VDR expression levels.

Conclusions: Activation of VDR attenuates high glucose-induced cellular injury partially dependent on CYP2J5 in murine renal tubule epithelial cells and paricalcitol represent a potential therapy for DN.

SA-POS09

The Potential Therapeutic Effect of Active Vitamin D Supplementation in Preventing Initiation and Progression of Diabetic Nephropathy in a Diabetic Mice Model

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Background: Diabetic nephropathy (DN) is characterized by morphological changes in podocytes and proximal tubule cells (PCT), and are characterized by hypertrophy, albuminuria, glomerular sclerosis to ESRD. DN mice suffer from an active vitronectin receptor expression in podocytathy and PCT injury. We hypothesize that supplementation of active vitamin D paricalcitol (P) to DN mice may slow the development & progression of DN.

Methods: Renal injury in diabetic mice with and without P treatment (TX), and control mice were investigated. After 12 weeks of P treatment, PCT were harvested. The kidney biopsies were subjected to PAS & H&E staining of: vitamin D receptor (VDR) expression, villi, nephron, podocin and fibronectin proteins. We used 4 groups of mice: (1) CON-wild type (2) DM group after DM induction with STZ was treated with vehicle for 12 weeks (3) DM/P after STZ group - diabetic mice treated with P before the onset of DN, and one week after DM induction, i.p. 3 times a W for 12 wks, (4) DM/P group - 3 weeks after diabetes induction, the mice were treated with P i.p. 3 times a W for 12 wks.

Results: 1. VDR expression increased in DM/P after STZ (1.08±0.13) compared with DM group (0.59±0.13). 2. Renal villin expression of DM mice was significantly decreased (0.53±0.09) compared with control mice (1.14±0.05, p<0.001), but P TX before and after the onset of DN (DM/P and DM/P after STZ) restored villin nephron levels to normal (1.0±0.2). 3. P TX (DM/P and DM/P after STZ) decreased fibronectin expression. 4. Nephron expression levels were decreased in DM group (0.5±0.11) compared with control group (1.03±0.07). 5. Nephron expression was restored in DM mice compared with control mice. P TX restore podocin expression in DM/P after STZ.

Conclusions: 1. Significant protective effect of Paricalcitol treatment in preventing the initiation and progression of DN in STZ-induced diabetic mouse model. 2. Increasing the expression of VDR and restoration of nephrin-podocine proteins with decreasing fibronectin, prevent the progression of DN 3. Our findings can be proposed as a new approach to deal with proteinuria in clinical patients using vitamin D supplementation in early stages of DN.

Funding: Government Support - Non-U.S.

SA-POS10

Downregulation of EHHADH and Tubular Dysfunction in Diabetic Nephropathy

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Background: The pathophysiology of diabetic nephropathy (DN) is not well understood. In previous studies, we analyzed renal cortical tissue from the db/db/eNOS-/- murine model by RNA-seq, identified altered novel genes with human orthologs, and assessed mRNA expression of these genes in human DN versus control. Ehahdd was downregulated in human DN. Ehahdd encodes for a peroxisomal protein that catalyzes the conversion of stearoyl CoA to 2-enoyl CoA which are intermediates in the peroxisomal beta-oxidation pathway (PBO), which is responsible for oxidizing long-chain and complex fatty acids. We investigated the potential role of Ehahdd in DN.

Methods: Biopsies with mild (n=20), moderate (n=19), or severe (n=20) DN were compared. Immunohistochemical staining for Ehahdd protein expression and localization were scored and compared to morphological lesions, clinical data, and follow-up. Multiplex analyses examined the relationship of Ehahdd and KIM1 expression. Subcellular localization of Ehahdd and peroxisom membrane protein ABCD3 was analyzed via super-resolution microscopy (SIM). Ehahdd mRNA expression was analyzed by high-glucose assay of cultured human proximal tubular cells (PTC) was assessed by qPCR.

Results: In normal controls, Ehahdd protein was strongly expressed in tubular epithelium and was significantly reduced in moderate and severe DN groups versus control. Downregulation of tubular Ehahdd significantly correlated with increased mRNA expression of KIM1 (r=0.587, p<0.0001), increased serum creatinine (r=0.488, p<0.0001), and increased UPCR (r=0.327, p<0.005). Ehahdd expression correlated positively with renal survival (p=0.054). Ehahdd exhibited complementary expression with KIM1 with no co-localization in tubules. SIM analyses of Ehahdd and ABCD3 indicated that tubular downregulation of Ehahdd in DN precedes loss of peroxisomal membranes. Ehahdd transcription was significantly downregulated in PTC under high-glucose conditions.

Conclusions: Ehahdd downregulation is associated with tubular injury and worse renal survival in human diabetic nephropathy. We postulate that the dysmetabolism caused by downregulated EHADH and PBO pathways increased levels of complex lipid products in PTC, possibly contributing to progression and tubulointerstitial fibrosis.

Funding: Other NIH Support - R24 Grant

SA-POS11

Cell Proliferation of Proximal Tubular Epithelia Leads to Renal Hypertrophy in Early Diabetic Nephropathy

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Background: The initial phenotypes of diabetic nephropathy are renal hypertrophy accompanying an increase in GFR, resulting in an increase in glucose reabsorption at proximal tubules. However, the detailed morphological changes and underlying mechanisms are not fully understood.

Methods: To investigate the proximal tubule-specific phenotypes in type 2 diabetic mice, we generated transgenic db/db mice carrying tamoxifen-inducible proximal tubule-specific tdTomato reporter genes (SCL34A1CreER266tdTom). We isolated tubular epithelial cells by FACS from mice in which the proximal tubular epithelium was exclusively labeled by tdTomato, and evaluated the tubule-specific molecular mechanisms of the development of diabetic nephropathy. To assess the proliferation of tubular epithelial cells, we also performed lineage tracing analysis of single-labeled proximal tubular epithelial cells in db/db mice by low-dose tamoxifen injection.

Results: Histological analysis of 18-week-old diabetic mouse kidneys revealed expansion of the renal cortex and enlargement of the cross-sectional area in each tubule. The protein/DNA ratio, a marker of cellular hypertrophy, was not increased in FACS-isolated tubular epithelial cells from the diabetic mouse kidney. qPCR analysis revealed that SGLT2 and GLUT2 expression in isolated tubular epithelial cells was not increased in diabetic mice. Lastly, lineage tracing analysis of single-labeled proximal tubular epithelial cells revealed significant clonal expansion of the labeled epithelium in db/db mice, suggesting increased cell proliferation during the observational period.

Conclusions: Our study using a proximal tubule-specific reporter demonstrated that cell proliferation, rather than cellular hypertrophy, plays a role in the enlargement of the tubular lumen and subsequent kidney hypertrophy in early diabetic nephropathy. This suggests an increase in cell proliferation, rather than cellular hypertrophy, in diabetic conditions is due to the expansion of proximal tubular epithelial cells, which predominantly express SGLT2, and not to the overexpression of SGLT2 in individual cells.

SA-POS12

VEGFR2 Blockade Improves Renal Damage in the Experimental Model of Diabetic Nephropathy

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Background: Chronic inflammation is the main feature of progressive kidney disease, including Diabetic Nephropathy (DN). Among the potential therapeutic targets of renal damage induced by diabetes, a pathogenic role for Gremlin has been described. Recent Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
studies in our group have described that Gremlins activate the vascular endothelial growth factor-2 receptor (VEGFR2) associated with renal inflammation. The animal model of BTBR ob/ob has been widely used for the study of DN, since it develops histological characteristics that resemble the human DN. In these mice, Gremlin expression increases at week 8 and remains elevated until week 20 of life. This model offers an opportunity to study the mechanisms that could lead to more specific therapies that lead to the regression of the DN. Our aim was to evaluate the role of VEGFR2 blockade in the progression of the DN in the BTBR ob/ob model.

**Methods:** In this animal model, VEGFR2 was blocked with the pharmacological inhibitor SU5416. The inhibitor was administered to mice of 15 weeks of life, 3 times a week for 5 weeks and then sacrificed (0.1 mg per mouse, i.p.). The parameters of weight and glycemia, the ratio of Albumin/Creatinine (ACR) in urine, glomerular and tubulointerstitial damage at the microscopic and ultrastructural level, as well as inflammatory and podocyte damage markers by real-time PCR and IHC were evaluated in non-diabetic, diabetic and diabetic SU5416-treated groups. (n=6-8 animals per group).

**Results:** VEGFR2 blockade improved the ACR during all period of study compared to diabetic group. At glomerular level, SU5416-treated mice showed lower cellularity and lower mesangial matrix expansion and decreased thickening of the glomerular basement membrane. Also, in the tubulointerstitial compartment, the inflammatory infiltrate decreased and some foci of tubular atrophy were observed. In response to VEGFR2 blockade, there was a downregulation in the kidney damage markers (KIM1 and Ngal), in podocyte markers WT-1, Nphp1 and Nphp2 and in the pro-inflammatory factors MCP-1, Rantes, IL-17A and IL-6. However, Gremlins levels were not affected. Decreased inflammatory infiltrating cells in SU5416-treated mice was histologically observed.

**Conclusions:** These results show that the Gremlin/VEGFR2 axis would be involved in kidney damage mediated by diabetes and could be a new therapeutic target for ND.

**Funding:** Other NIH Support - Proyecto Fondecyt Regular 116-0465.

**SA-PO514**

**Function of Protein X as a Novel Regulator of NADPH Oxidase 4 in Diabetic Nephropathy**

**Sae ron Lee, Yun soo Bae. Ewha Womans University, Seoul, Republic of Korea.**

**Background:** Several lines of evidence indicate that NADPH oxidase (Nox)-derived excessive reactive oxygen species (ROS) play important role in diabetes complications such as diabetic nephropathy. It has been reprinted that Nox4 isozyme is major source of superoxide anion in diabetic kidney, the isozyme, is known to be constitutively active, but its activity is associated with diabetic nephropathy. We recently identified a novel regulator of Nox4, PX which interacts and activates Nox4. Here, we show that association of Nox4 with PX is involved in chronic kidney disease.

**Methods:** Eight-week-old male wild type (WT), PX KO, Nox4 KO mice were subjected into the development of type I diabetes by injection of streptozotocin (STZ). Kidney tissues of the mice were analyzed with histological analyses, PAS-staining and collagen with immunohistochemistry (IHC) staining. Oxidative stress was assessed with urinary 8-isoprostane. Furthermore, renal functions were investigated by measurement of urinary albumin excretion and creatinine clearance rate (CCR).

**Results:** Mesangial expansion as a marker of glomerulosclerosis was reduced in PX KO and Nox4 KO mice. Albumin to creatinine ratio (ACR), urinary albumin excretion, and blood urea nitrogen (BUN) of protein X KO and Nox4 KO mice markedly decreased, compared to diabetic WT. Extracellular matrix (ECM) including collagen type I, type IV, TGFB-1 and α-SMA were significantly reduced in PX KO and Nox4 KO mice. Levels of H2O2 and urinary 8-isoprostane were suppressed in PX KO and Nox4 KO mice, compared to diabetic WT. To investigate clinical significance of PX-induced H2O2 generation, we evaluated the level of PX expression in type II diabetic patients. Interestingly, significantly elevated levels of PX were seen in type II diabetic patients. It strongly suggests that PX is involved in renal damage in type II diabetic patients.

**Conclusions:** In conclusion, PX as a Nox regulator plays important role in progression of diabetic nephropathy.

**Funding:** Government Support - Non-U.S.
Methods: Six-week-old diabetic DBA/In2Akita and their controls were treated with or without 3% supplementation via drinking water or min osmotic pump for twelve weeks. Results: Plasma and kidney HA levels were significantly reduced by 25% (p<0.05) and 65% (p<0.05) in In2Akita; respectively compared to control mice. Vehicle-treated In2Akita mice showed significant increases in urine albumin excretion (UAER) (p<0.01), renal function changes (score: 1.5 vs. 0.25), glomerular macrophage recruitment (p<0.01), inflammatory KC-GRO/CXCL1 (p<0.0005), and urinary TBA (p<0.0001); a marker of oxidative stress, along with reduction in kidney nitrate and nitrile levels (p<0.01) compared to non-diabetic controls. HA supplementation by either drinking water or 3% osmotic pumps for 12 weeks in In2Akita mice significantly reduced UAER (p<0.05), renal histological changes (score: 0.625 and 0.375), glomerular macrophage recruitment (p<0.05), KC-GRO/CXCL1 (p<0.0005), and urinary TBA (p<0.05), along with significant increase in kidney nitrate and nitrile levels (p<0.05) compared to vehicle-treated In2Akita mice.

Conclusions: These data demonstrate that L-homoarginine supplementation attenuates specific features of diabetic nephropathy in mice and could be a potential new therapeutic tool for treating diabetic patients.

Funding: NIDDK Support

SA-PO517

Parkin Accelerates Tubular Cell Senescence Through GATA4/GAS1 in Diabetic Nephropathy

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Background: Accelerated senescence of renal tubular epithelial cell (RTEC) plays a fundamental role in the pathogenesis of diabetic nephropathy (DN). Gene mutation of Parkin, a ubiquitin ligase, can accelerate neuron degeneration in familial aging-related diseases. We investigated the role of Parkin in accelerating senescence of RTEC and its mechanism.

Methods: 149 cases of patients with DN diagnosed by renal biopsy were recruited in our study. 32 normal kidney samples were obtained from renal carcinoma as control. Renal Parkin expression was detected by immunohistochemistry. In vivo, we used C57BL/6 Parkin−/− knockout mice, Parkin overexpression mice and wild-type controls with or without streptozotocin-induced diabetes over 5 months of follow-up. In vitro, mouse primary RTEC were exposed to high glucose (HG) for 48h. Moreover, co-immunoprecipitation and ubiquitination experiments were applied to evaluate the relationship of GATA4 with Parkin.

Results: Expression of Parkin was gradually decreased with development of DN. The expression of wild-type PARKIN in renal biopsy samples of DN patients and mouse tubular cells. Furthermore, Parkin ubiquinated GATA4 in vivo and in vitro. Parkin KO/stz mice showed significantly higher plasma BUN, SCR and urinary NAG than those in wild-type STZ mice. The degree of renal interstitial fibrosis in the STZ−/− Parkin overexpression group was significantly lower than that in STZ mice. The proportion of P16-positive renal tubular cells showed significantly higher plasma BUN, SCR and urinary NAG than those in wild-type STZ STZ mice. The degree of renal interstitial fibrosis in the STZ−/− Parkin overexpression group was significantly lower than that in STZ mice. The proportion of P16-positive renal tubular cells showed significantly higher plasma BUN, SCR and urinary NAG than those in wild-type STZ.

Conclusions: Parkin inhibits RTEC senescence in diabetic nephropathy by inhibiting GATA4/GAS1 pathway. Parkin is a potential anti-senescence factor in the development of diabetic nephropathy.

Funding: Government Support - Non-U.S.

SA-PO518

Tubular Secretory Clearance Is Associated with Whole-Body Insulin Clearance

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Background: The kidneys eliminate insulin via glomerular filtration plus tubular reabsorption and by extraction from the basolateral surface of proximal tubule cells. The relative contributions of each mechanism are incompletely understood. We tested associations of proximal tubular secretory clearances and estimated glomerular filtration rate (eGFR) with whole-body insulin clearance.

Methods: The Study of Glucose and Insulin in Renal Disease performed the hyperinsulinemic-euglycemic clamp in 57 non-diabetic persons with CKD (eGFR <60 mL/min 1.73m2) and 35 T1D patients without kidney disease (T1D). We defined insulin clearance as the intravenous insulin infusion rate divided by the steady-state plasma insulin concentration. We measured plasma and 24-hour urine concentrations of 7 tubular secretory solutes using targeted liquid chromatography-tandem mass spectrometry. We estimated renal insulin clearance using the CKD Epidemiology Collaboration equation.

Results: Mean age was 63 ± 13 years and mean insulin clearance was 924 ± 228 mL/min. After adjustment for demographics and body composition, lower eGFR and lower kidney clearances of 3 solutes were associated with lower insulin clearance accounting for multiple comparisons (Table). Lower kidney clearances of sucalaryglycine and xanthosine remained associated with lower insulin clearance after further adjustment for eGFR.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

Model 1: Adjusted for age, sex, Black race, fat mass, fat free mass, and log (albumin excretion rate).

Model 2: Model 1 + log(eGFR).

*pDifference in insulin clearance (mL/min) per 20% lower kidney function.

**Statistical significance after accounting for multiple comparisons (Bonferroni adjustment).

SA-PO519

Effects of RAAS Activation on Intrarenal Inflammation and Intrarenal Hemodynamics: Results from the Canadian Study of Longevity in Type 1 Diabetes

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Background: Inflammation and pro-fibrotic pathways are implicated in the pathogenesis of diabetic kidney disease (DKD) and are activated by chronic hyperglycemia and renin-angiotensin aldosterone system (RAAS) stimulation. We defined RAAS activation at the renal tissue level leading to inflammation even after 50 years of diabetes duration (n=74) and compared to age and sex matched adult controls without diabetes (n=73). Renal hemodynamic function was measured using inulin and p-aminohippurate (PAH). Changes in urinary inflammatory marker excretion post angiotensin II (AngII) infusion were compared between comparators, and TID participants with and without DKD (resistors). Renal hemodynamic function was correlated with urinary inflammatory markers independent of A1c, TID duration, and systolic blood pressure.

Results: The renal hemodynamic response to AngII in this cohort has been previously published, with an attenuated response in DKD vs. DKD resistors and controls, likely signifying high baseline RAAS activation. Conversely, in this analysis, RAAS activation stimulated a significant increase in the urinary excretion of 31 inflammatory markers in both DKD and DKD resistors, compared to adults without diabetes (p<0.05). There were no differences in inflammatory marker excretion between participants with DKD and resistors. Inulin, p-aminohippurate correlated with urinary excretion of proinflammatory markers (IL-18, IP-10, and RANTES), growth factor receptors (PDGF-AA & VEGFAA), and chemokines (Eotaxin & MCP-1).

Conclusions: RAAS activation was associated with increased markers of intrarenal inflammation in TID participants with and without DKD, suggesting a consistent role for RAAS activation at the renal tissue level leading to inflammation even after long-standing TID.
SA-PO520

ManNAc Improves Nephropathy but Worsens Hyperglycemia in Diabetic Rats by Inducing O-GlcNAcylation
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Background: The sialylation inducing compound N-acetyl Mannosamine (ManNAc) improved renal function in Nephrotic syndrome rats model (Clement LC et al Nature Medicine Jan 2011). We compared the overall efficacy and side effect profile of ManNAc with another sialylation inducing compound GDT01 in diabetic rats.

Methods: MMannAc study: 5 month old ZDF male rats (n = 5 rats / group) were treated for 5 months with tap water or ManNAc in drinking water. Changes in proteinuria, BUN, creatinine, hyperglycemia and histology were assessed. GDT01 study: 5 month old male ZSF1 rats (n = 6 rats / group) were treated with plain tap water or GDT01 over a period of 7 months. Same parameters as above were assessed. Muscle protein content of the diabetogenic sugar O-GlcNAc was assessed using 1D and 2D gel Western blots for both studies. O-GlcNAcylation occurs at the same amino acid residues as O-glycosylation and phosphorylation.

Results: ManNAc reduces proteinuria in ZDF rats significantly (P<0.05, P=0.01) when compared to water control group. The blood glucose level in ManNAc treated animals was also significantly (P<0.05) increased. GDT01 treated rats showed a significant reduction in proteinuria (P<0.05 to P<0.01) without any increase in blood glucose levels. Analysis of BUN and creatinine levels showed no significant changes in the ManNAc study. In GDT01 study, the GDT01 treated group in the GDT01 treated group showed a significant (P<0.05, P<0.01) reduction in renal histology compared to water controls. Assessment of O-GlcNAc showed increased levels in skeletal muscle in ManNAc treated rats, but no change in GDT01 treated rats. This suggests that shifting of ManNAc into O-GlcNAc induces diabetic changes, that negate otherwise potentially beneficial effects in treating diabetic nephropathy. It is likely that this phenomenon is noted also in non-diabetic rats, suggesting “diabetes like” side effect profile in the absence of diabetes.

Conclusions: The sialic acid precursor ManNAc is diabetogenic and should be avoided as a sialylation inducing agent. GDT01 improves diabetic CKD without being diabetogenic, and remains the preferred sialylation inducing agent

SA-PO521

Urinary I. Type Fatty Acid Binding Protein Reflects the Degree of Renal Hypoxia in Spontaneously Diabetic Torii Fatty Rats
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Background: Tubulointerstitial damage is known to be strongly associated with renal prognosis in diabetic kidney disease (DKD). Because renal hypoxia is an aggravated factor for the tubulointerstitial damage, urinary marker which is capable of detecting the renal hypoxia, is useful for monitoring the DKD. The aim of this study is to reveal the correlation between urinary liver-type fatty acid binding protein (L-FABP) and renal hypoxia using novel model of type 2 diabetes with obesity.

Methods: Male spontaneously diabetic torii (SDT) fatty rats (n = 6) were used as an animal model of type 2 diabetes with obesity. Age- and sex-matched Sprague–Dawley rats (SD) were used as control group. Blood glucose levels were measured at 8, 12, 16 and 24 weeks of age. Urine samples, serum and kidney tissues were obtained at 24 weeks of age. Microvascular blood flow index (BFI) in renal cortex was measured using diffuse correlation spectroscopy (DCS) before removing the kidney at 24 weeks of age.

Results: Obesity, hyperglycemia and hypertension were observed in the SDT fatty rats. Mild glomerular hypertrophy and sclerosis, moderate interstitial infiltration and fibrosis, and accumulation of renal oxidative protein were significantly observed in the SDT fatty rats compared to the SD rats. While frequency of peritubular endothelial cells and phango- endothelial nitric oxide synthase levels were similar between the SDT fatty rats and the SD rats, the degrees of renal hypoxia-inducible factor-1a expression significantly increased and renal vascular endothelial growth factor expression levels did not increase in the SDT fatty rats compared to the SD rats. Urinary L-FABP levels in the SDT fatty rats were significantly higher and renal microvascular BFI's in the SDT fatty rats was significantly lower compared to the SD rats. The levels of urinary L-FABP were significantly positively correlated with renal HIF-1a expression levels and were negatively correlated with renal microvascular BFI's.

Conclusions: Urinary L-FABP levels reflected the degree of renal hypoxia in DKD of type 2 diabetic animal model. In clinical practice, urinary L-FABP may be useful for monitoring DKD in type 2 diabetic patients as a renal hypoxia marker.
Methods: We investigated intrarenal expression of VEGF and LRG1 in a mouse model of Diabetic Nephropathy (db/db mice) by immunohistochemistry and a laser capture microdissection method, and compared the changes in expression at 16 and 24 weeks of age to evaluate their association with diabetic nephropathy development.

Results: At 16 weeks, diabetic db/db mice exhibited glomerular hypertrophy with abnormal angiogenesis characterized by endothelial cell proliferation, which was concomitant with an increase in LRG1 expression of glomerular endothelial cells. However, glomerular VEGF expression was not increased at this early stage. At 24 weeks, the features of early diabetic nephropathy in db/db mice had developed further, along with further enhanced glomerular LRG1 expression. At this late stage, glomerular VEGF and fibrosis related-gene expression was also significantly increased compared with nondiabetic db/m mice.

Conclusions: These results suggest that LRG1 plays a pivotal role in the initial development of diabetic nephropathy by promoting abnormal angiogenesis, thereby suggesting that LRG1 is a potential preempptive therapeutic target of diabetic nephropathy.

SA-PO525

Deletion of Endothelial Nitric Oxide Synthase in BTBR ob/ob Mice Enhances Mesangiolysis and Worsens Diabetic Nephropathy

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Background: Leptin receptor deficient db/db mice with endothelial nitric oxide synthase (eNOS) deficiency and leptin deficient BTBR ob/ob mice have been useful models of moderately advanced diabetic nephropathy (DN). eNOS is essential for maintaining integrity and health of endothelial cells and podocytes. We postulated eNOS deficiency in BTBR ob/ob mice would exacerbate the severity of DN, allowing testing of whether intact eNOS is essential or not to enable regression of DN with leptin replacement.

Methods: CRISP/Cas9 was used to delete eNOS in BTBR ob +/- heterozygous mice. The resultant BTBR ob +/- eNOS-/- mice were crossed to obtain BTBR ob/ob eNOS-/- homozygous mice (eNOS ob/ob), and control BTBR wt eNOS-/- mice (eNOS ob/ob). At 16 weeks, fasting glucose levels and timed (6 hour) urine samples were collected. The mice were then euthanized, and blood, urine and tissue samples collected.

Results: eNOS ob/ob mice exhibited robust hyperglycemia (517.5 mg/dl) and a marked increase in urine albumin/creatinine ratio (ACR) (791.9 vs 172.3 mg/mg in eNOS ob/ob, p < 0.01). Podocyte density decreased in eNOS ob/ob compared to treated mice (90.5 vs 149.8 pod/sx10^6 um^2, p < 0.01). In addition, significantly higher amounts of urinary 8OHdG (a DNA/RNA marker of oxidative stress) were detected in eNOS ob/ob mice than in control mice (511.2 vs 35.9 ng/mg creatinine, p < 0.05). Podocyte density decreased in eNOS ob/ob compared to treated mice (90.5 vs 149.8 pod/sx10^6 um^2, p < 0.01). In addition, significantly higher amounts of urinary 8OHdG (a DNA/RNA marker of oxidative stress) were detected in eNOS ob/ob mice than in control mice (511.2 vs 35.9 ng/mg creatinine, p < 0.05).

Conclusions: ATG5 protein expression was decreased in DM patients, with and without complications (0.66 ± 0.06 A.U in DM patients (n=30) p<0.01), 0.62 ± 0.06 A.U in DM (n=30) p<0.001), 0.67 ± 0.05 A.U in DR patients (n=30) p<0.01), compared with the healthy control 0.97 ± 0.04 A.U. 2. A 2.5-fold decrease in the percentage of ATG5-stained areas in the PCT of DN mice (4.4 ± 1.08% compared with W.T mice (10.87 ± 1.01%). 3. The expression of Arg5 gene between the groups by qRT-PCR analyses: in the DN (0.0069 ± 0.0005) and DR patients (0.0069 ± 0.0004) was down regulated at the mRNA levels, compared with healthy controls (0.0083 ± 0.0008). 4. Decreased LC3-II levels in DM patients (0.50 ± 0.04 A.U (n=18) p< 0.001) DN patients (0.44 ± 0.05 A.U, (n=19) p< 0.001) and DR patients (0.43 ± 0.05 A.U (n=18) p< 0.001) compared with the healthy control (0.81 ± 0.05 A.U (n=19). 5. The renal LC3-II protein expression was found to be greatly decreased in the tubules of DN mice when compared with W.T mice.

Conclusions: 1. ATG5, as well as its downstream collaborator LC3-II, are down-regulated in DN & DR patients, which contributes to deficiencies in autophagy process. 2. Impairment of this process can lead to accumulation of abnormal proteins and molecules that can lead to the development and progression of DN & DR. 3. Therapeutic potential of ATG5 modulations as a novel treatment strategy for DN/DR patients through the autophagy mechanism may serve as a goal in the development of drugs for diabetic complications.

 Funding: Government Support - Non-U.S.

SA-PO527

Semicarbazide-Sensitive Amine Oxidase (SSAO) Inhibition Ameliorates Albuminuria and Glomerulosclerosis but Does Not Significantly Improve Tubulointerstitial Fibrosis in Diabetic Nephropathy

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Background: SSAO is an enzyme known for its dual function in mediating inflammation and reactive oxygen species production. However, the role of SSAO inhibitors in chronic kidney disease is unclear. We aimed to determine the effectiveness of a SSAO inhibitor (PX54728A) as an antiinflammatory agent using a diabetic model of chronic kidney fibrosis.

Methods: A streptozotocin-induced diabetic model in male eNOS-/- mice on a C57BL/6 background. Diabetic mice were treated with SSAOIs for 24 weeks and outcomes compared with untreated diabetic mice and telmisartan treated animals as a comparator of current standard of care.

Results: Albuminuria, the extracellular matrix marker fibronectin, inflammatory marker expression of CD45 and oxidative stress, assessed by nitrotyrosine staining, were lower in diabetic mice treated with SSAOIs compared with untreated diabetic mice. Glomerulosclerosis was reduced to a greater extent by SSAOIs compared to telmisartan.

Conclusions: The effect of SSAO inhibition in diabetic mice resulted in a significant reduction in inflammation, oxidative stress, glomerulosclerosis and albuminuria in untreated diabetic mice. However, the effect of SSAOIs was less obvious in the tubulointerstitial compartment than in the glomeruli. Therefore, SSAOIs may be a potential target for diabetic glomerulosclerosis.

SA-PO526

Low Expression of Autophagy-Related Protein 5 (ATG5) Leads to Suppression of Autophagy in Patients with Diabetic Nephropathy and Retinopathy

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Background: Autophagy is a catabolic mechanism that involves lysosomal-dependent degradation of unnecessary or dysfunctional intracellular components, plays role in diabetic nephropathy (DN) and retinopathy (DR). ATG5 is one of the most important participants in the autophagy mechanism. Our study’s aim was to investigate if abundant expression of ATG5 proteins Arg5 gene is associated with DN or DR.

Methods: The study included 120 human participants in 4 groups – Healthy, diabetic (DM), DN and DR; 10 mice in 2 groups – healthy and DN. Western blot analyses of ATG5 and its downstream collaborator LC3-II were performed on human white blood cell lysates and murine renal lysates. Immunohistochemical analysis was performed on mice renal tissues. qRT-PCR analysis of ATG5 was performed on total mRNA isolated from human WBC.

Results: 1. ATG5 protein expression was decreased in DM patients, with and without complications (0.66 ± 0.06 A.U in DM patients (n=30) p<0.01), 0.62 ± 0.06 A.U in DN (n=30) p<0.001), 0.67 ± 0.05 A.U in DR patients (n=30) p<0.01), compared with the healthy control 0.97 ± 0.04 A.U. 2. A 2.5-fold decrease in the percentage of ATG5-stained areas in the PCT of DN mice (4.4 ± 1.08% compared with W.T mice (10.87 ± 1.01%). 3. The expression of Arg5 gene between the groups by qRT-PCR analyses: in the DN (0.0069 ± 0.0005) and DR patients (0.0069 ± 0.0004) was down regulated at the mRNA levels, compared with healthy controls (0.0083 ± 0.0008). 4. Decreased LC3-II levels in DM patients (0.50 ± 0.04 A.U (n=18) p< 0.001) DN patients (0.44 ± 0.05 A.U, (n=19) p< 0.001) and DR patients (0.43 ± 0.05 A.U (n=18) p< 0.001) compared with the healthy control (0.81 ± 0.05 A.U (n=19). 5. The renal LC3-II protein expression was found to be greatly decreased in the tubules of DN mice when compared with W.T mice.

Conclusions: ATG5, as well as its downstream collaborator LC3-II, are down-regulated in DN & DR patients, which contributes to deficiencies in autophagy process. 2. Impairment of this process can lead to accumulation of abnormal proteins and molecules that can lead to the development and progression of DN & DR. 3. Therapeutic potential of ATG5 modulations as a novel treatment strategy for DN/DR patients through the autophagy mechanism may serve as a goal in the development of drugs for diabetic complications.

Funding: Government Support - Non-U.S.
Chloride Channel Accessory 1 (CLCA1)-TMEM16A-Chloride Current Axis: A Novel Kidney Injury Pathway in Aging and Diabetes

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Background: CLCA1 activates TMEM16A, a Ca2+-dependent chloride channel. RNA Seq showed increased expression of CLCA1 in renal cortex of old vs. young mice. We have reported that renal changes in aging and diabetes are associated with deficient generation of hydrogen sulfide (H2S) (Lee, 2012, Lee, 2018). We studied role of CLCA1 in kidney injury in aging and diabetes.

Methods: We employed young and aging mice (n=10 per group). We also studied aging mice treated with (n=20) or without sodium hydrosulfide (NaHS) (n=14), a source of H2S. Diabetic db/db mice with littersmate controls (n=3 per group) were studied after being treated with or without NaHS. We overexpressed human CLCA1 (hCLCA1) in proximal tubular epithelial MCT cells.

Results: In aging mice renal CLCA1 expression was increased but not TMEM16A in association with mTORC1 activation, senescence associated secretory phenotype (SASP, consisting of increase in p53, p21, p16, IL-1 and IL-6), albuminuria and fibrosis; these changes were ameliorated by NaHS. In MCT cells, NaHS individually abolished these changes. In diabetic mice renal cortical expression of SASP, consisting of increase in p53, p21, p16, IL-1 and IL-6), albuminuria and fibrosis; these changes were ameliorated by NaHS and TMEM16A inhibitor. In association with mTORC1 activation, senescence associated secretory phenotype (SASP, consisting of increase in p53, p21, p16, IL-1 and IL-6), albuminuria and fibrosis; these changes were ameliorated by NaHS and TMEM16A inhibitor. We demonstrated that allogeneic, ip administered “Neo-Islets” (NIs), aggregates of cultured islet cells (ICs) and immune- and cyto-protective Adipose Derived Stem Cells (ASCs), reestablished durable normoglycemia through oralenatal engraftment and splenic and omental upregulation of Tregs, in autoimmune T1DM NOD mice without immunosuppressive agents (SCTM 2017;6:1631). Comparably euglycemia was achieved with dogs- or human-derived NIs in STZ-diabetic NOD/SCID mice. Here we update our report on an FDA supervised study using NI therapy in diabetic pet dogs.

Methods: Insulin dependent, diabetic pet dogs were included; 8 enrolled; 6 treated, and 4 followed for a 6 mos. Pre-treatment serum samples were tested for islet autoantibodies. Comorbidities and blood glucose levels were treated. Allogeneic NIs were given once ip (2.5x10e5/kg bw). No encapsulation or antirejection agents were used. Blood glucose levels, insulin need and antibody responses were monitored.

Results: Prior to treatment 3 dogs had islet autoantibodies indicating autoimmunity. NIs appear to engraft, redifferentiate and physiologically produce insulin, and are neither rejected by auto- nor allo-immune attacks, as evidenced by (i) an absent IgG response to the administered NIs, and (ii) progressively, durably (a 12 mos) and improved glyceremic control, achieved with an up to 50% reduction in daily insulin need paralleled by a fall in serum glucose (See Figure). No adverse events attributable to therapy have been observed to date. While no dog has achieved insulin independence, preclinical results using human NIs indicate that redosing could accomplish this.

Conclusions: Allogeneic NI therapy is feasible, safe, and durably effective. We conclude that this therapy has significant translational relevance for dog and human T1DM.

Funding: Commercial Support - SymbioCellTech, LLC.

Poster/Saturday

SA-PO528

Allogeneic “Neo-Islets” Composed of Adipose-Derived Stem and Islet Cells Durably Reduce Diabetic Pet Dogs’ Insulin Needs Without Requiring Immunosuppression (INAD 012-776)

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Background: We demonstrated that allogeneic, ip administered “Neo-Islets” (NIs), aggregates of cultured islet cells (ICs) and immune- and cyto-protective Adipose Derived Stem Cells (ASCs), reestablished durable normoglycemia through oralenatal engraftment and splenic and omental upregulation of Tregs, in autoimmune T1DM NOD mice without immunosuppressive agents (SCTM 2017;6:1631). Comparably euglycemia was achieved with dogs- or human-derived NIs in STZ-diabetic NOD/SCID mice. Here we update our report on an FDA supervised study using NI therapy in diabetic pet dogs.

Methods: Insulin dependent, diabetic pet dogs were included; 8 enrolled; 6 treated, and 4 followed for a 6 mos. Pre-treatment serum samples were tested for islet autoantibodies. Comorbidities and blood glucose levels were treated. Allogeneic NIs were given once ip (2.5x10e5/kg bw). No encapsulation or antirejection agents were used. Blood glucose levels, insulin need and antibody responses were monitored.

Results: Prior to treatment 3 dogs had islet autoantibodies indicating autoimmunity. NIs appear to engraft, redifferentiate and physiologically produce insulin, and are neither rejected by auto- nor allo-immune attacks, as evidenced by (i) an absent IgG response to the administered NIs, and (ii) progressively, durably (a 12 mos) and improved glyceremic control, achieved with an up to 50% reduction in daily insulin need paralleled by a fall in serum glucose (See Figure). No adverse events attributable to therapy have been observed to date. While no dog has achieved insulin independence, preclinical results using human NIs indicate that redosing could accomplish this.

Conclusions: Allogeneic NI therapy is feasible, safe, and durably effective. We conclude that this therapy has significant translational relevance for dog and human T1DM.

Funding: Commercial Support - SymbioCellTech, LLC.

Poster/Saturday

SA-PO531

Hyperglycemia Reduced DUSP4 Expression Leads to JNK MAPK Activation, Increased NOX4 Expression, and Insulin Resistance in Podocytes and Diabetic Nephropathy

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Background: Podocyte dysfunction is an early event in the development of diabetic nephropathy (DN) with multiple causes including insulin resistance and increased oxidative stress (ROS via NOX4) which lead to the activation of p38 and JNK MAPK pathways. Previous study has shown that JNK activation leads to sert incorporated 370 (ser370) phosphorylation of IRS1 (inhibitory phosphorylation) in insulin-resistant ob/ob mouse. Our laboratory recently reported a decrease in the expression of DUSP4, a dual specificity phosphatase known to inhibit the MAPKs, which was associated with elevated JNK activation and NOX4 expression in podocytes exposed to high glucose. Thus, we hypothesized that hyperglycemia-induced DUSP4 expression reduction leads to insulin resistance in podocytes and DN via JNK activation and NOX4 expression.

Methods: Cultured podocytes were exposed to normal (5.6 mM) or high (HG; 25 mM) levels of glucose for 5 days. Therefore, on day 60, mice were redosed and followed as detailed above. This second dose of normalized both blood glucose levels and GTTs.

Conclusions: We conclude that these data support the planned redosing of dogs whose need for insulin has been reduced but not eliminated through allogeneic NI treatment, as initial allogeneic treatment of these dogs failed to elicit an immune response. We expect that doing so may lead to insulin independence, i.e., in analogy to islet transplant recipients who require several doses of islets but who are, however, treated with anti-rejection drugs.

Funding: Commercial Support - SymbioCellTech, LLC.

Poster/Saturday
Diverseity of Biopsy-Proven Kidney Diseases in Japanese Patients with Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD), including diabetic nephropathy (DN), is the leading cause of chronic kidney disease worldwide including Japan. However, there is also increasing recognized diagnosis of non-diabetic renal diseases (NDRD) in diabetic patients, which may influence in the different treatments and outcomes. This study reported the spectrum and clinical characteristics of NDRD and NDRD superimposed DN in Japanese diabetic population.

Methods: Clinical data of the diabetic patients with aged ≥ 18 years undergone kidney biopsy in Kochi Medical School hospital during 2001-2017 were collected. These data including the and laboratory data together with renal biopsy pathological findings.

Results: The 165 from 872 patients were recruited in this study; 108 cases were male (60.4%). The mean age was 61.1±1.1 years, and the median serum creatinine was 1.86 mg/dL (0.96-2.76). The 48 cases (29.0%) were diagnosed NDRD, while 50 cases (30.3%) were diagnosed NDRD superimposed DN. The rest of the patients were diagnosed isolated diabetic nephropathy; DN (40.6%). IgA nephropathy was either the most prevalent glomerular disease in NDRD (39.5%) and NDRD superimposed DN (34.0%). The second and third kidney biopsy findings in NDRD were lupus nephritis (18.7%), membranous nephropathy (12.5%), respectively. In NDRD superimposed DN, membranous nephropathy (18.0%), and ANCA associated vasculitis (14.0%) were the second and third pathological findings. The serum creatinine levels were higher in DN than in NDRD and NDRD superimposed DN (2.47±0.57 mg/dL, 1.25 mg/dL, and 1.63 mg/dL, respectively). Nephrotic syndrome was more common in NDRD superimposed DN, following DN and NDRD (38.0%, 37.5%, and 31.2%, respectively, p<0.05). Moreover, the quantity of proteinuria was found to be higher in DN and NDRD superimposed DN than in NDRD (4.0, 3.2, and 2.8 g/gCr, respectively, p<0.05).

Conclusions: This study disclosed the diversity and prevalence of NDRD that was diagnosed in almost 60% of DKD in Japanese diabetic patients. Presence of nephrotic syndrome was the more suggestive diagnosis of DN or NDRD superimposed DN. Kidney biopsy is the important means for the definite diagnosis and the proper treatment of glomerular disease in diabetic patients.

Synergistic Effects of Glomerular Lesion and Interstitial Lesion on Increased Proteinuria But Not on Renal Prognosis
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Background: Diabetic kidney disease (DKD), a recently proposed concept, is associated with various proteinuria level and heterogeneous renal prognosis; however, the identification of patients with DKD or NDRD was rarely examined by renal biopsy. We have biopsy-proven diabetic nephropathy (DN) cohort including many patients with relatively mild proteinuria. That encouraged us to examine the association between histological findings and proteinuria level and renal prognosis in DKD.

Methods: This is a longitudinal study of 396 adults with biopsy-proven DN from 1981 to 2014. Predictors were renal pathological findings. DN was evaluated by two renal pathologists according to 13 histological findings (9 glomerular lesions, 2 tubulointerstitial lesions and 2 vascular lesions). Cross-sectional association with proteinuria level was examined with multivariable general linear model and two-way analyses of covariate and variance, and longitudinal association with renal prognosis was examined with Cox regression model.

Results: Median proteinuria level was 0.5 g/day (25th and 75th percentile: 0.2 and 2.6 g/day) at the time of renal biopsy. During mean follow-up of 9.9 years, 99 patients reached end-stage kidney disease (ESKD). Among thirteen histological findings, nodular lesion (NL) and interstitial fibrosis and tubular atrophy (IFTA) were significant predictors for proteinuria levels after adjustment for clinical risk factors. Among patients with NL or >25% IFTA, 31% of patients had only IFTA and 20% had only NL. NL and IFTA had a synergistic effect on increased proteinuria after adjustment with clinical parameters (p for interaction=0.07). Cox regression analysis showed NL and IFTA were significantly associated with a development of ESKD but there was not a synergetic effect on renal prognosis between these two factors (p for interaction=0.94).

Conclusions: These data suggest the fluctuation in the balance between glomerular and interstitial damages could interpret various degrees of proteinuria and heterogeneous renal prognosis in DKD.
SA-PO536

Implications of Solidified Glomerulosclerosis and Extracapillary Hypercellularity in Chinese Patients with Type 2 Diabetes and Diabetic Nephropathy
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Background: This study was aimed to determine nephropathologic markers for time to end-stage renal disease (ESRD) in Chinese patients with type 2 diabetes and diabetic nephropathy (DN).

Methods: This retrospective cohort study recruited 322 Chinese type 2 diabetic patients from 2003 to 2017 with biopsy-proven diabetic nephropathy who received follow-up over 12 months. All kidney biopsy specimens were fully assessed under a uniform scale. Competing risk models with death as the competing risk was used to estimate the subdistribution hazard ratios (SHRs) for ESRD.

Results: During a median follow-up of 26.0 months, 144 (44.7%) patients progressed to ESRD and 17 (5.3%) patients died before entering ESRD. Global glomerulosclerosis was further separated into three categories: solidified glomerulosclerosis (Figure 1 A-B), ischemic obsolete glomerulosclerosis (Figure 1 C-D) and not otherwise specified glomerulosclerosis (Figure 1 E-H). Pathological parameters in Renal Pathology Society system were associated with ESRD in univariate analysis but failed to predict ESRD in multivariable models. After adjusting for parameters of demographics, baseline kidney functions, nutritional status, and medications in the multivariable model, solidified glomerulosclerosis and extracapillary hypercellularity (SHR, 1.77; 95% CI, 1.11-2.80; and SHR, 2.48; 95% CI, 1.58-3.90, respectively) were identified as risk factors for ESRD. Moreover, patients in RPS class III with a higher proportion of solidified glomerulosclerosis had a lower 5-year renal survival rate than class IV.

Conclusions: In Chinese type 2 diabetic patients with DN, solidified glomerulosclerosis and EXHIC were prognostic indicators for ESRD. Solidified glomerulosclerosis contributed partly to the worse renal outcome of patients in class III.

Funding: Government Support - Non-U.S.

SA-PO537

Association Between Renal Fibrosis and Early Renal Decline in Type 2 Diabetes
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Background: The association between fibrosis and early progressive renal decline in diabetes is unclear. Recently, MMP-7 (Matrilysin) and WFDC2 (WAP four-disulfide core domain protein 2) were postulated to be markers of renal fibrosis. We hypothesized that the effect of fibrosis index on eGFR decline, multivariable logistic regression was applied for determining the association between the tubulointerstitial plasmocyte infiltration and the clinical impact.

Methods: This nested case-controls study was selected from among patients participating in the 2nd Joslin Kidney Study with T2D, CKD stage 1 and 2, and normo- or microalbuminuria at enrollment. Patients were followed for 6-12 years. The primary outcome was eGFR decline defined as eGFR slope ≥5 mL/min/1.73m²/year. We developed the fibrosis index by integrating serum and urinary MMP-7 and plasma WFDC2 into a predictive probability model of renal decline using logistic regression, after verifying that these markers were not highly correlated between each other. To estimate the effect of fibrosis index on eGFR decline, multivariable logistic regression was applied adjusting for eGFR, ACR, plasma TNF-R1, plasma KIM-1, and urinary EGF/MCP-1 ratio at baseline. The markers included in our model were based on our previous prediction model (Nowak et al. Kidney Int 2018).

Results: One hundred sixty patients were enrolled. Median age was 57.5, 43.1% were women, 75.6% were Caucasian, median HbA1c was 7.7%, and median duration of diabetes was 10.0 years. eGFR and ACR at baseline were 97.0 mL/min/1.73m² and 24.1 mg/g, respectively. One hundred patients experienced eGFR decline, and 60 were non-decliners. In comparison with non-decliners, the group of eGFR decline at baseline had elevated plasma TNF-R1, KIM-1, WFDC2, serum and urinary MMP-7, whereas urinary EGFR/MCP-1 ratio was decreased. Quartile change of the fibrosis index was significantly associated with eGFR decline [odds ratio (OR) 2.04; 95% confidence interval (CI) 1.38-3.03] and was consistent with patients with microalbuminuria (OR 5.18; 95% CI 2.00-13.41) and microalbuminuria (OR 2.33; 95% CI 1.38-3.96). The effects of the fibrosis index on eGFR decline were robust across sex, HbA1c duration of diabetes, and use of renin-angiotensin system inhibitors in subgroup analyses.

Conclusions: Renal fibrosis is associated with early progressive renal decline in type 2 diabetes, even in patients without albuminuria.

Funding: NIDDK Support, Private Foundation Support

SA-PO538

Effects of Tubulointerstitial Plasmocyte Infiltration on Hard Clinical Renal Outcomes in Subjects with Diabetic Kidney Disease
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Background: Identification of the tubulointerstitial inflammatory features has the potential to the prediction of renal prognosis of diabetic kidney disease (DKD); however, the influence of plasmocyte infiltration on the DKD is unclear. This study was conducted to determine the association between the tubulointerstitial plasmocyte infiltration and DKD in a cohort of Chinese patients with type 2 diabetes mellitus (T2DM).

Methods: We enrolled 226 adult patients with biopsy-proven DKD for a follow-up time more than 12 months. Tubulointerstitial plasmocyte cells in kidney biopsy tissues were detected by immunohistochemistry and immunofluorescence. The patients then were divided into two groups based on tubulointerstitial plasmocyte infiltration: plasmocyte group (n=171) and non-plasmocyte group (n=109). Hard renal outcome was defined as end stage renal disease (ESRD). A comparison of the baseline features and renal prognosis between the two groups was performed.

Results: The accumulation of tubulointerstitial plasma cells was found to be related with more serious anemia, heavy proteinuria, renal function decline, and more serious glomerular, interstitial and arterial lesions. During the follow up (12-85 months), 42.5% (96) of patients developed ESRD. Patients in plasmocyte group exhibited a high percentage of incident ESRD (53%) than those (31.2%) in non-plasmocyte group (p=0.05). A Cox regression showed that the plasmocyte infiltration had a significant effect on the renal endpoint (HR, 1.969; 95%CI, 1.292-3.000), though it was not an independent risk factor.

Conclusions: As one of contributors to the renal inflammatory response, the tubulointerstitial infiltration of plasmocyte was associated with severity of glomerular, interstitial, and arterial lesions as well as DKD hard clinical renal outcome.

Funding: Government Support - Non-U.S.

SA-PO539

Impact on Kidney Function with Focal and Segmental Glomerulosclerosis (Tip) in Patients with Diabetic Nephropathy
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Background: Type 2 Diabetes Mellitus is the first cause of end stage kidney disease (ESKD). Focal and Segmental Glomerulosclerosis (FSG) is the most common glomerulopathy in western world. Tip variant is the most common glomerulopathy associated with Diabetic Nephropathy (DN). By now, only mathematical and experimental models tried to explain the association between DN and FSG (tip) without including the clinical impact and the prognosis of these patients. This study is the first in Mexico which evaluates this combination and the clinical impact.

Methods: Retrospective cohort with patients over 18 years with renal biopsy who at that moment, didn’t had ESKD. We did descriptive and analytic statistics and a survival analysis with Kaplan Meier. We considered as primary outcome, the need of dialysis, lowering glomerular filtration rate (GFR) -90% of basal value and/or doubling the basal serum creatinine.

Results: 41 patients included, 64% (26) male, 73% (30) had hypertension at the moment of the biopsy, 83% (34) had nephrotic syndrome, the chronic changes score (CCS) were moderate or severe in >90% of patients. The age was 51±13, follow up of 18±12 months, the initial proteinuria was 8.8±4.3 gr/24h in the group without FSG and 8.3±5.7 gr/24h in the other group. The proteinuria at 6 months after the biopsy was different between groups (p=0.03). The group without FSG had worse GFR, but with no difference in the analysis of the primary outcome, (Figure 1).

Conclusions: There was no difference between groups in the primary outcome, but we observe some clinical differences. The CCS did evaluate better the outcomes than the histologic changes in both groups. Maybe further studies with more patients, could find a difference in the impact of FSG on kidney function proposed in our study.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Blood eosinophil counts (0.22 × 10^9/L vs. 0.43 × 10^9/L, p<0.001), higher HbA1c (7.5 vs. 7.7, p=0.003), higher proteinuria (7.5 ± 4.8 vs. 5.4 ± 6.5 mg/dL, p<0.004), more prevalence of hematuria (82.4% vs. 43.9%, p<0.001), higher blood eosinophil counts (0.22 ± 10^9/L vs. 0.16 ± 10^9/L, p=0.001), severer tubulointerstitial injury including tubular injury (p=0.004), interstitial inflammation (p=0.004), tubular atrophy (p=0.007) and interstitial fibrosis (p=0.020). IEA was associated with worse renal prognosis (HR 2.42, p<0.001). Consistently, use of corticosteroids (mg/kg/day) was associated with renal survival (HR 1.166, p=0.024). Patients with IEA were more likely to be treated with steroids (IEA vs. non-IEA: 47.1% vs. 14.7%, p=0.001) but did not show renal benefit.

Conclusions: It suggested that both blood and renal infiltrated eosinophils were prevalent in DN and associated with severity of DN. But IEA in renal pathology showed better fit in correlation with renal prognosis. Treatment with steroid/immunosuppressant showed no significant improvement regarding renal prognosis.

Funding: Government Support - Non-U.S.

SA-POS541
The Feasibility and Safety of Obtaining Research Kidney Biopsy Cores in Patients with Diabetes: An Interim Analysis of the TRIDENT Study
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Background: Obtaining additional kidney tissue for research is essential for advancing the understanding and treatment of kidney disease. The Transforming Research in Diabetic Nephropathy (TRIDENT) Study is a multi-center, longitudinal, observational cohort study for adults with diabetes who are undergoing a clinically indicated kidney biopsy, and requires an additional research biopsy core. We present an interim analysis of the feasibility and safety of obtaining research kidney biopsy cores in the TRIDENT study.

Methods: The TRIDENT database was analyzed for data acquired as of May 1, 2019. Data on adverse events (AEs) were obtained for cases where a research core was successfully obtained and a central pathologist confirmed the histologic diagnosis (N=134). Clinical and demographic data was obtained at the enrollment visit, which occurred within 6 days of biopsy. We defined AEs as hematuria >5cm, gross hematuria, and prolonged hospital stay. Serious AEs included unplanned blood transfusion, transfer to an intensive care unit (ICU), respiratory distress requiring intubation or vascular surgery intervention to halt bleeding.

Results: As of May 1, 2019, 160 patients were consented and underwent kidney biopsy at 15 centers, with a research biopsy core successfully obtained in 134 cases (89%). Diabetic glomerulosclerosis was found in 110 (82%) of cases. Patients had a mean age of 54.7 (SD 12.6) years, with 45% female, 32% African American race and 34% Hispanic ethnicity. The mean serum creatinine was 2.9 (SD 1.9) mg/dL. A 16-gauge needle was used in 96 (72%) of biopsies and the mean number of biopsy passes was 3.6 (SD 1.0). Serious AEs occurred in 4 patients (3%): blood transfusion in 2 (1.5%), post-biopsy aspiration leading to respiratory failure and prolonged hospitalization in 1 (0.7%) and ICU observation in 1 (0.7%). Post-biopsy hemotma >5 cm was noted in 7 (5.2%), 2 developed transient gross hematuria (1.5%) and 5 (3.7%) patients required a prolonged hospital stay.

Conclusions: This interim analysis of the TRIDENT study suggests that obtaining tissue for research purposes in adults with diabetes undergoing clinical kidney biopsies is feasible and is associated with an acceptable complication rate.

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SA-POS542
Incidence in Kidney Failure from Diabetes Among Native Americans, 2000-2016
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Background: Diabetes-related end-stage renal disease (ESRD-D) among Native Americans (NAs) declined from 1996 to 2013. We assessed recent data to determine if the rates have continued to decline.

Methods: From the US Renal Data System, we obtained the number of NA adults and adults of other races (whites, blacks, Asians, Native Hawaiians/Pacific Islanders, and others) aged ≥18 years with newly treated ESRD-D (with diabetes listed as primary cause of ESRD) between 2000 and 2016. ESRD-D rates by age and sex were calculated using general population estimates from the US Census and age-adjusted based on the 2000 US standard population. Jointpoint regression was used to assess trends and estimate the annual percentage change (APC).

Results: From 2000 to 2016, the number of US adults starting ESRD-D therapy increased slightly from 2000 to 2006 (from 19.7 to 20.7, APC= -0.6%, p=0.04), decreased from 2006 to 2012 (20.7 to 19.1, APC= -1.1%, p=0.007), and again increased from 2012 to 2016 (19.1 to 20.3, APC=1.5%, p=0.009). By age group, ESRD-D rates showed no change for NAs aged 18-44 (from 7.7 in 2000 to 7.6 in 2016), declined for NAs aged 45-64 (from 108.3 in 2000 to 95.2 in 2013, APC=-5.8%, p<0.001) and 65-74 (from 231.2 in 2000 to 88.6 in 2012, APC=-7.6%, p<0.001) and then leveled off, and declined throughout the period for NAs aged ≥75 (119.3 to 61.9, APC=-4.2%, p<0.001).

Conclusions: From 2000 to 2016, ESRD-D continued to decline in NAs aged ≥75 years but, after an initial decline, has leveled off in more recent years in NAs aged 45-74 years. During the period, the disparity gap between NAs and other races was reduced more than 2-fold. Continued efforts might be considered to sustain and improve ESRD-D trends in NAs.

Funding: Government Support - Non-U.S.

SA-POS543
Genetic Determinants of CKD Progression Among Individuals with Diabetes: The Million Veteran Program
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Background: The rate of CKD progression among individuals with diabetes varies widely and is incompletely explained by known risk factors. While the genetic determinants of cross-sectional eGFR have been identified, only one small analysis of longitudinal change in eGFR among individuals with CKD has been conducted.

Methods: We performed a genome-wide association study of the relative rate of decline in estimated glomerular filtration rate (eGFR, % decline/year) among individuals with CKD and diabetes participating in the Million Veteran Program. Our study included participants...
with genetic data available from the MVP second data release, with 351,510 participants from whom 91,523 individuals had type 2 diabetes. Analyses were stratified by race.

Results: There were 28,368 individuals with CKD and diabetes. 21% (n=5904) were of non-hispanic black race /ethnicity. Mean (SD) eGFR at baseline was 51.1 (±8.1) ml/min/1.73m² and median relative kidney function decline was 0.5%/year. Trans-ethnic meta-analysis uncovered 6 SNPs from only one region significantly associated with decline in kidney function. The SNP with the strongest association, rs6047460, lies 45kb upstream of UGT2A1; every additional minor allele was associated with a 1%/year faster decline in eGFR (p=1.1 x 10^-10). Among blacks, we were able to replicate one of four previously identified SNPs, rs161356141, which lies between SIZ1D8B and NRG3 (p=0.03). Among whites, we were able to replicate 2 of 11 SNPs previously associated with incident CKD, rs12917707 (near UM0D, p=6x10^-4) and rs7805747 (intronic for UGT1A1, p=9x10^-6).

Conclusions: Our data suggest that while there is genetic basis for diabetic kidney disease progression, the discovery of the genetic variants involved has been difficult. The etiologic heterogeneity of the phenotype could preclude true associations from being detected.

Funding: Veterans Affairs Support

SA-PO544
Poor Renal and Cardiovascular Outcomes in Patients with Biopsy-Proven Diabetic Nephropathy
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Background: Despite high level of mortality related to cardiovascular disease (CVD) in diabetic patients with renal injury, few studies have compared cardiovascular characteristics and outcomes between patients with diabetic nephropathy (DN) and non-diabetic renal disease (NDRD).

Methods: A total of 370 T2DM patients with renal biopsy was assigned to one of three groups (DN, NDRD, and NDRD with underlying EN). Echocardiography and Doppler ultrasound were performed to evaluate left ventricle hypertrophy (LVH) and peripheral atherosclerosis disease (PAD). Renal and cardiovascular survival rates were compared between the DN and NDRD groups by Kaplan-Meier analysis (median follow-up, 29 months). Risk factors for renal and cardiovascular events were identified by Cox proportional hazards model.

Results: DN patients were more vulnerable to developing LVH than NDRD patients (37.3% vs 6.8%, P < 0.001). PAD was more severe in DN group, with thicker intima-media and more atherosclerotic plaques (P < 0.001). Poorer renal (log Rank X² = 22.089, P < 0.001) and cardiovascular (log Rank X² = 9.346, P = 0.002) prognosis were seen in DN group. Low estimated glomerular filtration rate at baseline was associated with renal events (HR = 0.962 [0.942-0.983], P = 0.001), while elevated levels of glycosylated hemoglobin A1c (HR = 1.599 [1.256-2.635], P = 0.041) and postprandial blood glucose (HR = 1.321 [1.072-1.626], P = 0.009) were identified as risk factors for cardiovascular events.

Conclusions: Patients with DN had more severe CVD along with poorer renal and cardiovascular prognosis than those with NDRD.

Funding: Government Support - Non-U.S.

SA-PO545
Association of Urinary Acidification Function with the Progression of Diabetic Kidney Disease in Patients with Type 2 Diabetes
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Background: Although diabetic kidney disease (DKD) has been considered as a glomerulosclerotic disease in the past few decades, growing evidence demonstrated that tubular damage is indispensable in its pathogenesis and progression. This study was designed to investigate the association of urinary acidification dysfunction with the progression of DKD in type 2 diabetic patients.

Methods: Here we measured the urinary acidification function from 80 participants with renal biopsy-proven DKD. The different kinds of renal tubular transportation dysfunction were analyzed by urinary acidification function, including the dysfunction of bicarbonate reabsorption, titratable acid secretion, and ammonium secretion. In addition, patients were followed up for 17 (interquartile range, 11-32) months to evaluate the effect of urinary acidification dysfunction in the progression of DKD.

Results: The dysfunction of ammonium secretion was the most common, accounting for 53.75%. The more proteinuria excretion and the lower glomerular filtration rate (GFR) were observed in the urinary titratable acid secretion disorder group than the normal group, and the same results were obtained for ammonium secretion disorder. Urine titratable acid was positively correlated with eGFR whereas it was inversely correlated with proteinuria, serum creatinine and BUN. Moreover, 24h urine protein, serum creatinine, BUN and cystatin C increased from DKD stage I to stage IV, whereas the eGFR and urine titratable acid decreased in the same way. Furthermore, Kaplan-Meier analysis and Cox regression showed that the dysfunction of titratable acid secretion was an independent risk factor of DKD progression.

Conclusions: The dysfunction of titratable acid secretion is a potential biomarker for the severity of proteinuria, eGFR and glomerular lesions in patients with DKD. Moreover, the titratable acid secretion disorder is an independent risk factor of the DKD progression.

Funding: Government Support - Non-U.S.
SA-PO548
Diabetic Retinopathy and Progression of Diabetic Kidney Disease in Asians
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Background: Diabetic kidney disease (DKD) and diabetic retinopathy (DR) share similar risk factors and pathogenic mechanisms. We examined the prospective relationship between DR and incidence and progression of DKD in a multi-ethnic Asian population in Singapore.

Methods: We analysed data from 2981 Chinese, Malay and Indian adults with diabetes aged 17–90 years who attended annual screening visits (3–6 visits) at primary care clinics from 2010–2015 as part of the Singapore Integrated DR Screening Program (SIDRP). DR (n=297) was assessed from retinal photographs graded using a standard protocol and defined as presence of mild/moderate/severe DR. Incident DKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2; and diabetes mellitus, 18.8%. In the test dataset, the accuracy of DL was 0.95, which was higher than those of multivariate logistic regression models (0.84) and support vector machine models (0.84). Then, various patterns of characteristics of a 60-year-male patient were evaluated. The predicted risk of the outcome is shown in heat maps (Figure 1), and various patterns are observed. A basic pattern (e.g., CKD severity category) shows high risks in categories of low eGFR and high proteinuria. And, the nephrosclerosis-like pattern shows higher risks at low eGFR than at high proteinuria levels. Moreover, DKD shows a mix pattern, which suggests that DKD patients are a heterogenous population.

Conclusions: We developed a new exhaustice risk-prediction system using DL model and found different patterns of kidney disease progression based on patient characteristics. This model may be useful for identifying patients at an increased risk of DKD progression for early treatment.
Background: Trichlemamine-N-Oxide (TMAO) is suggested as an independent gut microbiota derived risk marker for several diseases. We investigated associations between plasma TMAO concentrations and all-cause mortality, cardiovascular disease (CVD) and deterioration in renal function in individuals with type 2 diabetes and microalbuminuria.

Methods: Plasma TMAO was measured at baseline in 311 individuals with type 2 diabetes and microalbuminuria. All-cause mortality and CVD (fatal and non-fatal) were tracked from national registers. Yearly p-creatinine was measured after baseline in 166 of the participants, the renal endpoint was defined as eGFR-decline of >30%. Associations between TMAO and events were analyzed using Cox regression models. Adjusted models included age, sex, HbA1c, systolic blood pressure, urine albumin excretion rate and eGFR.

Results: Baseline mean (SD) age was 57.2 (8.2) years, 75% were male and median [IQR] of TMAO was 5.87 [3.79-9.04] µM. TMAO was negatively associated with eGFR at baseline (R2 = 0.05, p = 0.0001). Follow-up was up to 21.8 years for all-cause mortality and CVD events (median 6.8 years and 6 years) and for renal events up to 5.8 years (median 4.6 years). eGFR was recorded 106 events and 41 1266 CVD events and 41 1268 renal events. Higher plasma TMAO concentrations were associated with renal events in unadjusted analyses (p = 0.03), but not after adjustment (p = 0.17). TMAO was not associated with mortality (unadjusted p = 0.53; adjusted p = 0.87) or CVD events (unadjusted p = 0.14; adjusted p = 0.24).

Conclusions: In individuals with type 2 diabetes and microalbuminuria, plasma TMAO was negatively correlated with eGFR at baseline. Moreover, higher plasma TMAO was in unadjusted analysis associated with renal events, but not after adjustment. Plasma TMAO was not associated with mortality and CVD events.

Funding: Private Foundation Support

SA-PO552
Visit-to-Visit Variability of Albuminuria and eGFR as Risk Markers for Renal Complications, Cardiovascular Events, and Mortality in Type 1 Diabetes

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Background: Clinicians strive towards obtaining stable and reliable measures for monitoring risk of diabetic complications. The impact of visit-to-visit variability (VVV) of albuminuria (ALB) and eGFR needs further clarification. We investigated VVV in ALB and eGFR as risk markers of renal complications, cardiovascular events (CVE), and mortality in subjects with type 1 diabetes (T1D).

Methods: 1077 individuals with T1D a range of albuminuria were included. VVV was calculated using the standard deviation (SD) of the residuals in individual linear regression models, calculated using all measures of ALB or eGFR from 1998-2016. Data on end-stage renal disease (ESRD), CVE, and mortality were gathered through national registers. eGFR and ALB was traced through laboratory records from ambulatory care. Endpoints were ESRD (cKD stage 5, dialysis or transplantation), eGFR-decline a 30%, CVE (cardiac death, myocardial infarction, stroke and arterial interventions) and mortality. Hazard ratios (HR) were calculated using Cox models and are presented per doubling of VVV. Adjusted included sex, age, total cholesterol, HbA1c, systolic blood pressure, body mass index, smoking, 24h ALB, eGFR, and the intercept and slope of the respective linear models.

Results: Median follow-up ranged from 6.1-13.4 years for ALB and 6.8-16.2 years for eGFR, depending on endpoint. Subjects had a mean (SD) age and diabetes duration of 47 (13) and 27 (13) years, respectively, at baseline. Depending on availability of data, 848-1077 subjects were included in the respective models. Adjusted HR (95% CI) p for ALB VVV were 1.68 (1.38-2.05, p<0.001), 1.34 (1.25-1.44, p<0.001), 1.12 (1.04-1.20, p=0.002) and 1.10 (1.01-1.19, p=0.029) for development of ESRD, eGFR decline a 30%, CVE and mortality, respectively. Adjusted HR (95% CI) p for eGFR VVV were 1.79 (1.29-2.45, p=0.001), 2.02 (1.68-2.43, p<0.001), 0.96 (0.83-1.08, p=0.091) and 0.93 (0.79-1.11, p=0.424) respectively.

Conclusions: The demonstration an independent association between long term VVV in ALB and eGFR and development of renal complications, addressing stabilisation of VV and reduction of endpoints, were warranted.
Results: A total of 7,587 T2DM patients were included. Sixty-four percent were female. The mean age was 63 ±11 years old. The prevalence of MAU was presented by percentage and 95% confidence interval (CI): CKD stage G1 32% (30–34); stage G2 34% (32–35); stage G3a 41% (39–44); stage G3b 47% (43–50); stage G4 70% (63–77); and stage G5 73% (60–82) (Figure 1). The multivariate analysis identified the odds ratio (OR) of time-average systolic blood pressure (adjusted OR; 95% CI, P-value) as an independent risk factor for MAU presence. After adjusting for age, gender, body mass index, occupation, provinces, religions, categories of cholesterol, and % glycosylated hemoglobin, the resulting levels were 1.12; 0.94–1.32; 0.20 (<120 mm Hg group), reference group (120–140 mm Hg group), 1.21; 1.07–1.36; 0.003 (140–160 mm Hg group), and 1.45; 1.21–1.75; <0.0001 (>160 mm Hg group).

Conclusions: Several factors demonstrated independent correlations with MAU in Asian populations. Higher time-average systolic blood pressure was associated with MAU, which may lead to further target organ damage in T2DM. MAU has also been observed to be much more prevalent in later CKD stages.

Funding: Government Support - Non-U.S.

SA-PO557
The Association Between Vitamin D Level and Microvascular Complications in Persons with Type 2 Diabetes
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Background: The objective of this study is to examine the association between vitamin D level and presence of microvascular complications in persons with type 2 diabetes.

Methods: Cross-sectional study including 789 persons with type 2 diabetes followed at Steno Diabetes Center Copenhagen with information on plasma concentration of vitamin D and relevant clinical data. Peripheral neuropathy was defined as bilaterally decreased sensibility of vibration and minimum one symptom.

Results: The cohort included 378 persons with normal albuminuria (NA) (mean (SD) age 63.7 (11.5) years), 260 with moderately increased albuminuria (MA) (mean age 68.3 (10.9) years) and 148 with severely increased albuminuria (SA) (mean age 67.2 (11.0) years). The overall prevalence of vitamin D deficiency (<25 nmol/L) and severe deficiency (<25 nmol/L) was 19.3% and 6.6%, respectively. In persons with NA, MA and SA, the mean (SD) vitamin D level was 78.1 (35.7), 75.7 (33.6) and 65.2 (35.0) nmol/L, respectively. There was no difference between the NA and MA group (p=0.41), but the difference between the NA and SA group was significant both unadjusted (p=0.0002) and after adjustment for age, sex, seasonal variation, HbA1c, smoking, BMI, systolic BP and eGFR (p=0.005). In linear regression analysis, vitamin D level was negatively associated with albuminuria unadjusted and after adjustment (both p<0.0001). When stratified into CKD stage 1 to 5, including 254, 309, 195, 20 and 11 persons, respectively, the mean (SD) vitamin D level was 70.3 (34.5), 78.6 (33.9), 74.2 (36.7), 81.5 (43.7) and 67.4 (25.9) nmol/L in stage 1 to 5. There was no difference between groups (p=0.25). The mean (SD) vitamin D level was 81.4 (41.2) nmol/L in persons with proliferative retinopathy (n=48) and 75.3 (35.0) nmol/L in persons without (n=62) (p=0.25). In persons with peripheral neuropathy (n=153), the mean (SD) vitamin D level was 74.3 (34.4) nmol/L and 74.7 (35.4) nmol/L in persons without (n=470) (p=0.91).

Conclusions: Among persons with type 2 diabetes, persons with severely increased albuminuria had a lower vitamin D level; moreover, an inverse relationship between vitamin D level and albuminuria was demonstrated. Interestingly, no association between vitamin D level and CKD stage, proliferative retinopathy or peripheral neuropathy was observed.

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The Target Glycated Albumin Level May Differ According to Dialysis Patients’ Nutritional Status and Use of Hypoglycemic Agents: A 3-Year Nationwide Cohort Study

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Background: We previously reported a J-shaped association between glycated albumin (GA) and mortality in diabetic patients on dialysis. However, it remains unclear what GA level is associated with the cause-specific mortality among patients taking or not taking hypoglycemic agents and among those with or without malnutrition.

Methods: We examined 40,417 diabetic patients on maintenance hemodialysis in a cohort studied by the Japanese Society for Dialysis Therapy (female, 30.8%; mean age, 67.3±11.2 years; mean dialysis duration, 5.4±4.6 years) and followed up for 3 years from 2013-2016. GLIM criteria were used to assess malnutrition. Patients on PD, who had history of kidney transplantation, or who did not have data of baseline GA or hypoglycemic agent use were excluded. We used Cox regression to calculate adjusted hazard ratios (HRs) and 95% confidence limits (95% CL) for 3-year mortality after adjusting for 18 potential confounders. Subdistribution hazard ratios (SHRs) were used to explore cause-specific mortality.

Results: Using GA levels of 15.9–17.2% as the reference, patients not taking hypoglycemic agents in the lowest GA deciles (≤15.8%) had slightly worse mortality (HR 1.10 [0.94–1.30]), mainly due to increased deaths from cancer (SHR 1.64 [0.99–2.68]), which was not observed in those patients taking hypoglycemic agents. Malnourished patients using hypoglycemic agents in the lowest GA deciles had slightly lower mortality (HR 1.05 [0.75–1.46]), mainly due to increased deaths due to infections (SHR 1.31 [1.07–2.44]). In addition, their lowest mortality was observed at a GA level of around 21.5%, which was higher than that seen in other patients.

Conclusions: These data suggest that GA levels may differ according to patients’ hypoglycemic agent use, nutritional status, and cancer status. Target GA levels in malnourished patients may be higher than in other diabetic patients, and a very low GA level in dialysis patients not taking hypoglycemic agents may be associated with an increased risk of mortality.

Funding: Private Foundation Support

Predictors of CKD Progression, Mortality, and Cardiovascular Outcomes in Patients with and without Diabetes

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Background: Diabetes and CKD are a growing burden for health systems, both in the US and internationally. Diabetes is thought to be responsible for approximately half of all end-stage renal disease (ESRD) cases. Also, the number of people with diabetes and CKD has increased dramatically along with the increase in diabetes itself. The role of albuminuria in CKD progression and cardiovascular (CV) outcomes is still underappreciated. This study examines CKD progression and CV outcomes in a contemporary real-world setting.

Methods: This retrospective cohort study used administrative data in Henry Ford Health System. eGFR lab results were used to identify patients with stage 2-4 CKD (index date) from 2006-2016 and followed through 2018. A second eGFR >90 days from index date excluded acute kidney injury. Patients with a history of renal transplant, death within 30 days of index date, or progression to ESRD within 6 months of index date were excluded. Logistic regression models were used to identify factors associated with ESRD and occurrence of a composite of myocardial infarction (MI), stroke, and all-cause mortality within 5 years of follow-up.

Results: The final cohort consisted of 29,303 patients. The population was 45% male, 38% African American (AA), 48% white, and had a mean age of 61 years. At baseline, 72% of patients had stage 2 CKD and 64% had type 2 diabetes (T2D). At 5 yrs of follow-up, ESRD occurred in 3.8%, heart failure (HF) in 17.6%, and the composite outcome in 17.5% (MI 5.8%, stroke 5.0%, all-cause mortality 9.4%). In the ESRD regression model, male gender, AA race, baseline eGFR, and diabetes were associated with high risk, and older age with lower risk. For the composite outcome, male gender, AA race, older age, T2D, and baseline eGFR were all associated with greater risk. In additional models examining the subset of patients with UACR (48% of patients), elevated UACR became the strongest predictor, with a 4-fold increased risk for both ESRD and the composite outcome.

Conclusions: There was a moderate risk of progression to ESRD, but a significant risk of CV composite and HF outcomes over a 5-yr period. Traditional factors (e.g., male gender, increasing age) were observed, but albuminuria was further identified as a strong independent risk factor.

Funding: Commercial Support - AstraZeneca

Modifiable Factors Associated with Health-Related Quality of Life in Patients with Diabetic Kidney Disease

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Background: Poor health-related quality of life (HRQOL) is associated with increased cardiovascular risk and mortality in patients with kidney disease. Therefore, it is critical to identify potential modifiable clinical factors contributing to poor HRQOL. This study examined clinical factors associated with poor HRQOL in patients with diabetic kidney disease (DKD) focusing on depression, anxiety, sleep quality, and physical activity.

Methods: Between April 2017 and March 2018, 141 adult (≥18 years) with DKD were recruited in single tertiary hospital. HRQOL was assessed at baseline with the Short Form 36 (SF – 36) Health Survey Questionnaire. Poor HRQOL was defined as baseline scores below the median value. Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS). Sleep quality and physical activity were measured using Korean version of the Pittsburgh Sleep Quality Index (PSQI-K) and Short form of Global Physical Activity Questionnaire (GPAQ) respectively.

Results: The age was 65 [57-72] years old, and 73% (n=103) of participants were men. Prevalence of anxiety and depression were 17% (n=24) and 21% (n=30) respectively. Forty-eight (34%) subjects corresponded to poor sleepers and 40 (28%) subjects showed low physical activity. SF-36 scores were decreased with advanced CKD stages (stage 3, 79 [71-82]; stage 4, 71 [56-82]; stage 5, 70 [57-82]; p = 0.029 for trend). Anxiety, depression, and poor sleep quality were negatively correlated with SF-36 scores (p < 0.05). eGFR and physical activity were positively correlated with HRQOL (p < 0.05). Analyses performed on the linear scale showed no significant mediation effect of potential confounders on the association between HRQOL and the studied factors.

Conclusions: In patients with DKD, depression was a major determinant of poor HRQOL among the modifiable clinical factors such as anxiety, sleep and physical activity. Active surveillance of depression and psychosocial intervention should be considered to improve the well-being of these patients.

Characterization of Extracellular Vesicles Derived from Human Amniotic Fluid Stem Cells (hAFSC-EVs) and Their Therapeutic Effect in Alport Syndrome

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Background: Alport Syndrome (AS) is an inherited disease characterized by a loss of glomeruli cells and kidney function. Based on our previous results that EVs from AFSC modulated glomerular crosstalk, we proposed that hAFSC-EVs might represent a new therapeutic approach to treat AS. In light of clinical translation, we characterized hAFSC-EVs as potential therapeutic agents, investigated their ability to modulate glomerular crosstalk, the mTOR pathway, and TGF-β pathways involved in collagen deposition remodeling, in addition to downstream targets involved in tissue homeostasis, the mTOR pathway, and TGF-β pathways. When injected in vivo into AS mice, biodistribution studies showed hAFSC-EVs localized in the kidney, corrected proteinuria and prolonged the life-span of treated mice. No side effects (including teratoma) were noted in the treated mice. RNA-seq of glomeruli obtained from treated AS mice showed similar gene expression patterns to WT, by cluster analysis. Our data indicated that hAFSC-EVs highly modulated multiple pathways involved in collagen deposition remodeling, in addition to downstream targets of VEGF, FGF, TNF, angiostatin and preserved glomerular cells structure and function.

Conclusions: Our protocol for hAFSC-EVs derivation is reproducible and allows derivation of EVs with the same identity (specific cargo of proteins and miRNAs), purity (absence of contaminants) and potency (present therapeutic effect in AS). hAFSC-EVs modulated signaling pathways that are central to maintaining glomerular homeostasis and preserved glomeruli structure with improved kidney function. This suggests the possibility of using hAFSC-EVs as a new therapeutic option for treating AS in humans.

Funding: Private Foundation Support
Macula Densa mTOR Signaling Regulates Renin Cell and Glomerular Endothelial Remodeling

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Background: Macula densa (MD) cells are critical regulators of glomerular filtration rate, renal blood flow and renin release via paracrine signaling that involves MD MAP kinases ERK1/2 and p38, and the MD-specific enzymes COX2 and nNOS. The mTOR complex is known to act as a central mediator, integrating the downstream effects of several cell signaling pathways to promote cell growth and protein synthesis. The present study aimed to examine the role of mTOR signaling in regulating MD cell function and its effect on glomerular tissue remodeling.

Methods: An MD-specific genetic mouse model for upregulated mTOR signaling was developed by crossing nNOS Cre mice and with a truncated form of TSC2 that upon tamoxifen induction results in mTOR gain-of-function in MD cells (MD-mTOR+). Changes in expression of MD molecular players controlling renin release (ERK1/2, COX2, nNOS) and in renal galectoinein labeling for renin granules and on immunoblots. MD-mTOR+ mice featured significantly increased number of Meis2+ glomerular endothelial cells as well as CD34+ endothelial precursor cells with the highest density close to the MD.

Results: In summary, upregulation of MD-mTOR signaling has robust effects on both the traditional MD cell functions (renin control), and their newly emerging role in long-term glomerular tissue remodeling. Since MD-mTOR signaling significantly alters the glomerular architecture, it may be targeted to develop future therapeutic strategies for end-stage kidney disease.

Funding: NIDDK, Support, Private Foundation Support

SA-PO565

Anti-KITLG Therapy in Renal Injury
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Background: Activation of TGFβ signaling promotes organ fibrosis. KIT/KITLG signaling regulates inflammation and fibrosis in humans and animal models and cross-talks with CD33+ CD14+ macrophages, kidney injury and fibrosis. However, the role of KITLG in the kidney is not well understood.

Methods: Ten-day old TGBF1-TG mice were treated biweekly with a monoclonal antibody against KITLG (aKITLG) (n=17) or control-lgf (IgG) (n=15) and euthanized after two weeks. Six wild-type mice were used as non-treated controls.

Results: Severe IgG mice had significantly higher pKITLG and mesangial index and lower podocyte density compared to mild IgG mice (p<0.01). pKITLG levels significantly correlated to podocyte density (inversely) and mesangial index (positively) (p<0.05). aKITLG mice had no change in body weight and trended towards improved survival. aKITLG mice demonstrated significantly reduced fibrosis and mesangial index (p<0.05) and a trend towards improved podocyte density compared with IgG mice. Expression of extracellular matrix genes Col3a1 and Col6a1 was significantly reduced in kidney cortex of aKITLG vs IgG mice (p<0.05). IPA identified several candidate signaling pathways altered by aKITLG.

Conclusions: Our findings that pKITLG increased with severity and aKITLG alleviated podocyte injury and ameliorated kidney fibrosis support KITLG therapy as a candidate intervention for fibrotic kidney disease. Studies examining human biofluids and aKITLG therapy in other mouse models of kidney injury are ongoing.

Funding: NIDDK Support

Inhibition of Human Antigen R Reduces Glomerular Injury in Experimental Glomerulonephritis
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Background: Recent identification of a mRNA-binding protein (human antigen R (Hr)) that regulates mRNA turnover and translation of numerous genes involved in innate immune response, inflammation, fibrosis and oncogenic signaling and is abnormally elevated in varied kidney diseases offers a novel target for the treatment of renal fibrosis. Thus, we hypothesized that therapy with a selective inhibition of Hr function with a small molecule, KHS, would reduce inflammation and profibrotic factors thereby improving glomerulosclerosis.

Methods: Three experimental groups included normal, untreated disease control, and KHS-treated nephritic rats. Disease was induced in rats with monoclonal anti-thy 1.1 antibody. KHS was given via daily intraperitoneal injection from day 1 after disease induction for the dose of 50mg/kg/day.

Results: At day 6, animals treated with KHS showed significant reductions in proteinuria, podocyte injury determined by ameliorated podocyte loss and glomerular podocin expression, glomerular staining for periodic acid-Schiff positive material (41%), and collagen types 1 and 3 staining in collagen and fibronectin mRNA levels and protein production. Treatment with KHS also reduced disease-induced increases in

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renal TGF-β1 and PAI-1 mRNA levels and protein levels. Additionally, a marked increase in renin gene expression was observed in MGF-induced glomerulonephritis observed in disease control group was largely reversed by treatment with KH3.

Conclusions: These observations strongly support our hypothesis that inhibition of HμR with KH3 has therapeutic potential for reversing glomerulosclerosis by inhibiting inflammatory cell infiltration, decreasing local NADPH oxidase-mediated oxidative stress, and TGF-β1 and PAI-1’s expression and action.

SA-PO567
D-Site Binding Protein Regulates Cell Proliferation Through Mediating Cell Cycle Progression in Rat Mesangial Cells
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Background: Over proliferation of glomerular mesangial cells (MCs) disturbs mesangial homeostasis and leads to renal damage in mesangio proliferative glomerulonephritis. It is documented that transcriptional factors may be involved in the proliferation of MCs. This study aims to identify the key transcriptional factor that prevents the MCs from over proliferation and to clarify its regulatory mechanism.

Methods: Glomeruli were isolated from rats subjected to anti-Thy-1 antibody or phosphate buffered saline. Total RNA was extracted and subjected to microarray analysis. Lenti viral transfection and siRNA transfection were used to obtain D-site binding protein (DBP)-over expressed and DBP-knockdown rat primary MCs, respectively. The cell proliferative capacity was measured by 5-Ethynyl-2-deoxyuridine (Edu) assay. Flow cytometry was conducted for cell cycle analysis. Histology, immunohistochemistry, and western blot analysis were performed to detect the expression of selected gene and cell cycle regulators.

Results: The cell cycle pathway was the most enriched pathway in the anti-Thy-1N model, and the DBP ranked first in the cluster of transcription factors, which was markedly decreased accompanied by an over proliferation of MCs in anti-Thy-1N model rats. The knockdown of DBP significantly promoted the proliferation of primary rat MCs, whereas the DBP over expression inhibited the MCs’ proliferative capacity in vitro, compared to that of the control cells. DBP arrested G1/S-phase transition by inhibiting the expression of p21, p27 and inducing the Cyclin D1 expression in MCs.

Conclusions: DBP effectively inhibits the proliferation of MCs through G1/S phase arrest, and the decrease of DBP may induce mesangial over proliferation in the anti-Thy-1N model.

SA-PO568
Integrin β6 Knockout Ameliorates Glomerular Sclerosis Sensitization to Podocyte-Specific Injury
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Background: We previously showed that even mild tubulointerstitial injury sensitized glomeruli to subsequent podocyte-specific injury. We also showed that tubulointerstitial fibrosis in DBP-/- mice was ameliorated in MGF-S by 2.8-fold vs controls, led to 2.3-fold increased glucose uptake and PKC activation, resulting in 2.4-fold excess Fibronectin (FN) and 1.7-fold excess glucose uptake. Transgenic overexpression of MGF in mouse glomerular MC’s in vivo by 2.7-fold vs controls, led to 2.3-fold increased glucose uptake and PKC activation, resulting in 2.4-fold excess Fibronectin (FN) and 1.7-fold excess glucose uptake. Transgenic overexpression of MGF expression at both 18 and 26 weeks of Type 2 diabetes mellitus in db/db mice vs db/+ and WT, with less decrease in renin mRNA and protein levels. Additionally, a marked increase in urinary sodium excretion, compared to normal salt, vs Glomerular Diseases: Fibrosis, Extracellular Matrix.

Methods: Wild type (WT) or β6-/- mice were mated with NEP25 mice which express β6-/- mice. Integrin β6 was expressed on some tubular epithelial cells, including macula densa, but not on glomerular tufs, and activates latent TGFβ. We aimed to investigate whether β6-/- mice had ameliorated sensitization to glomerular injury induced by initial tubular injury, and possible mechanisms of β6 in tubuloglomerular crosstalk.

Results: In wild-type (WT) or β6-/- mice, there was a clear decrease in both β6-/- mice as compared to controls and the role of MC glucose uptake and PKC in this process. Mice overexpressing MGF in glomerular MC were produced to determine its role in glomerulosclerosis (GS).

Conclusions: IHC for glomerular proteins using specific antibodies, with 0-4+ scoring. A sequential tubular-glomerular injury model was performed by inducing acute tubular injury by aristolochic acid injection at wk 0, followed by podocyte injury by LMB2 injection at wk 8, when tubular injury had functionally recovered. Uninephrectomy was performed at wk 9 and mice sacrificed at wk 12. Effects of β6 on tubuloglomerular feedback were assessed by adding high salt from wk 6 to subgroups.

Results: KIM-1 expression in tubules was decreased in β6-/- at wk 8 after tubular injury but with only numerically reduced interstitial fibrosis (Sirius red morphometry). However, even this minor tubulointerstitial protection by β6 deficiency resulted in a marked effect on glomerular sensitization to podocyte injury. β6-/- mice had less albuminuria and glomerulosclerosis with more preserved GFR and WT1 cells vs WT, with less TGFβ activation. Further, WT subgroups treated with high salt had greater increase in urinary sodium excretion, compared to normal salt, vs β6-/- mice. High salt increased calculated single-nephron GFR (SNGFR) in β6-/- but not in WT, with less decrease in renin mRNA and protein in β6-/- NKRCC2 activity (measured by OXSR1 and VAMP2 expression), adenosine formation enzyme (ecto-5'-nucleotidase) and AII adenosine receptor were lower in high salt exposed β6-/- vs WT.

Conclusions: We conclude that integrin β6 show very mild amelioration of acute tubulointerstitial protection vs WT and show markedly less glomerular sensitization to subsequent podocyte-specific injury, which is contributed to by blunted tubuloglomerular feedback. We postulate that β6 may, in addition to effects on tubulointerstitial injury, also modulate macula densa function.

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SA-PO571

Glomerular Diseases: Fibrosis, Extracellular Matrix

Kidney Biopsy in Initial Presentation of Markedly Reduced Kidney Function: Is It Safe? Will It Make a Difference?

Background: One of the dilemmas faced by nephrologists is a patient presenting for medical attention with a rapidly declining glomerular filtration rate (GFR) and less abnormal findings on routine laboratory tests. The dilemma lies in the indication for performing a kidney biopsy. It is often difficult to decide if a kidney biopsy should be performed to make a diagnosis or rule out treatable conditions.

Methods: We performed a retrospective review of all the kidney biopsies performed over a 4-year period (2017-2020) in our institution. The indications for performing a kidney biopsy were recorded.

Results: A total of 53 kidney biopsies were performed. The indications for performing a kidney biopsy were divided into two categories: diagnostic and prognostic. Diagnostic indications included suspected glomerular disease, suspected tubulointerstitial disease, and suspected dysplastic kidneys. Prognostic indications included high-risk patients with a history of malignancy, patients with end-stage renal disease, and patients with suspected genetic diseases.

Conclusions: Kidney biopsy can be performed safely in patients with markedly reduced kidney function. However, the decision to perform a biopsy should be made carefully considering the patient's clinical history, laboratory results, and the results of other diagnostic tests.

SA-PO572

Kidney Biopsy in Initial Presentation of Markedly Reduced Kidney Function: Is It Safe? Will It Make a Difference?

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identified caspase 9 as a kidney disease risk gene. Caspase 9 is an initiator caspase in the apoptotic pathway, which was found in many cells. Here we analyzed the role of caspase9 in kidney disease development.

Methods: We used a Bayesian colocalization method to integrate kidney eQTL data from 151 healthy individuals of European descent with CKD GWAS. We complemented our coexpression analyses with publicly available kidney eQTL data from the APOL1 transgenic mouse model but not in the UO induced kidney fibrosis model, the expression of cleaved Caspase9 was increased. Caspase9 heterozygous mice appeared healthy without renal abnormalities. In the folic acid induce kidney injury model, not only the expression of cleaved Caspase9, but other effector caspases such as caspase3, caspase7, and expression of profibrotic genes were lower in Caspase9 heterozygous mice compared to APV at 7W and showed little to no TIF or GS. In LI, SP but not TIF contributed to assess GS and TIF. Glomerular basement membrane dysmorphology was examined by electron microscopy (EM). For hearing, WT and AP mice were treated with V or AP in E1 (n=5). Strial capillary basement membrane (SCBM) width was analyzed by EM. Hearing was assessed at 7W (n=5) by auditory brainstem response pre- and 5 days post-exposure to noise.

Results: SP or LT treatment in AP mice in E1 (p<0.05 vs APV) attenuated increases in UP/C observed in APV at 7W and showed little to no TIF or GS. In LI, SP but not APV prevented a significant increase in GS compared to 5W untreated AP mice and in UP/C observed in APV at 7W and showed little to no TIF or GS.

Conclusions: GWAS and eQTL integration identified caspase 9 as CKD risk gene. Heterozygous loss of Caspase9 decreases apoptosis and fibrosis in models of kidney injury, indicating that Caspase9 is a kidney disease risk gene.

Funding: NIDDK Support, Private Foundation Support

SA-PO575

The Dual AT2, ET, R Blocker Sparsentan Slows Renal Disease, Improves Lipid Profile and Prevents Hearing Loss in Alport Mice

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Background: In Alport syndrome (AS), ET AR activation in mesangial cells results in subendothelial invasion of glomerular capillaries by mesangial filopodia and induction of inflammatory cytokines culminating in glomerulosclerosis (GS) and tubulointerstitial fibrosis (TIF). Hearing loss in AS is also a consequence of ET AR mediated changes in the inner ear. We compared the effect of sparsentan (SP) vs AT2 blocker losartan (LS) on the development of nephropathy and explored the effect of SP on hearing loss-associated inner ear pathology in AP (AP) mice. Methods: Wild type (WT) and AP mice were treated daily with vehicle (V), 5 mg/kg SP, or 10 mg/kg LS in 3 studies; early intervention (EI) from 3-7 weeks of age (W) (n=7-8), late intervention (LI) from 5-7W (n=8), or for lifespan (n=10). Proteinuria (UP/C) was assessed weekly, and immunostaining for fibronectin and collagen 1 was used to assess GS and TIE. Glomerular basement membrane dysmorphology was examined by electron microscopy (EM). For hearing, WT and AP mice were treated with V or SP in E1 (n=5). Strial capillary basement membrane (SCBM) width was analyzed by EM. Hearing was assessed at 7W (n=5) by auditory brainstem response pre- and 5 days post-exposure to noise.

Results: SP or LT treatment in AP mice in E1 (p<0.05 vs APV) attenuated increases in UP/C observed in APV at 7W and showed little to no TIF or GS. In LI, SP but not APV prevented a significant increase in GS compared to 5W untreated AP mice and in UP/C observed in APV at 7W and showed little to no TIF or GS. In LI, SP but not TIF contributed to assess GS and TIF. Glomerular basement membrane dysmorphology was examined by electron microscopy (EM). For hearing, WT and AP mice were treated with V or SP in E1 (n=5). Strial capillary basement membrane (SCBM) width was analyzed by EM. Hearing was assessed at 7W (n=5) by auditory brainstem response pre- and 5 days post-exposure to noise.

Conclusions: GWAS and eQTL integration identified caspase 9 as CKD risk gene. Heterozygous loss of Caspase9 decreases apoptosis and fibrosis in models of kidney injury, indicating that Caspase9 is a kidney disease risk gene.

Funding: NIDDK Support, Private Foundation Support

SA-PO575

Irradiation-Induced Glomerular Endothelial Cellular Senescence May Contribute to the Senescence-Associated Secretory Phenotype by Activating the NF-kB Signaling Pathway

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Background: Cellular senescence is one of the major risk factors for chronic kidney disease. We recently reported that ionizing radiation (IR) can cause cellular senescence in the kidney and lead to kidney dysfunction. In this report, we investigated the precise characteristics of radiation-induced cellular senescence in glomerular endothelial cells.

Methods: Male 7-8-week-old rats received unilateral IR of 18 Gy on the kidney (irradiated kidney) or sham IR (normal kidney). We analyzed the presence of cellular senescence and pathological changes until 9 months post-IR. In an in vitro experiment, primary glomerular endothelial cells received a single dose of 20 Gy (20 Gy) of IR. Cellular senescence was defined by the combination of senescence-associated β-galactosidase (SA-β-gal), p21, p53, p16 and the senescence-associated secretory phenotype (SASP).

The DNA damage response (pH2AX, a marker of DNA double strand breaks) and nuclear factor-κB (NF-κB) signaling pathway were also evaluated.

Results: As previously reported, irradiation-induced cellular senescence was demonstrated in the irradiated kidneys. Notably, glomerular endothelial cells in irradiated kidneys displayed more cells that were positively stained for p21 at an earlier time (from 3 months) compared to podocytes. In vitro, irradiation-induced cellular senescence in glomerular endothelial cells was also confirmed. Recent studies showed that the DNA damage response could trigger the NF-κB signaling pathway resulting in a cascade of inflammation. In our study, irradiated cells showed DNA damage response, and a gradual increase of the expression level of NF-kB mRNA. Irradiated cells also showed nuclear localization of NF-kB and positive staining for phosphorylated IκBα. Once IκBα is phosphorylated, IκBα proteins are released from NF-kB. Subsequently, NF-kB translocates to the nucleus and transactivates the expression of target genes. Following the activation of NF-κB pathway, the wound-healing protein (α-smooth muscle actin [αSMA], collagen III) were analyzed by confocal microscopy. We examined the relationship among uDcR2/Cr levels, renal tissue DcR2 levels, in order to analyze the relationship between DcR2 levels and the extent of tubulointerstitial fibrosis (TIF) in patients with immunoglobulin A nephropathy (IgAN).

Conclusions: Taken together, these data suggest that IR could cause cellular senescence in the kidney. In particular, glomerular endothelial cells may play an important role in production of SASP that might be triggered by the activated NF-κB signaling pathway.

SA-PO579

DCR2, a Cellular Senescent Molecule, Is a Novel Marker for Assessing Tubulointerstitial Fibrosis in Patients with Immunoglobulin A Nephropathy

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Background: DCR2 is a senescent marker expressed exclusively in senescent tubular epithelial cells. We calculated the ratio of urinary levels of Dcr2 to creatinine (uDCR2/Cr) and renal tissue Dcr2 levels, in order to analyze the relationship between Dcr2 levels and the severity of tubulointerstitial fibrosis (TIF) in patients with immunoglobulin A nephropathy (IgAN).

Methods: This study included 210 IgAN patients and 80 healthy volunteers, with uDCR2 levels measured using enzyme-linked immunosorbent assay. Renal Dcr2 expression was quantified by immunohistochemistry. Co-expression of Dcr2 with senescent (interleukin-6 [IL-6], tissue inhibitors of metalloproteinase [TIMP]-2) and senescence-associated (α-smooth muscle actin [αSMA], collagen III) were analyzed by confocal microscopy. We examined the relationship among uDCR2/Cr levels, renal function, and pathological findings, using the area under the curve (AUC) approach to predict tubulointerstitial fibrosis.

Results: Levels of uDCR2/Cr were significantly higher in IgAN patients and in those with more severe TIF, compared with healthy controls. Serum Dcr2 levels were similar across groups. The proportion of IgAN patients with stage 1-2 chronic kidney disease (CKD) and T0 was highest among those with uDCR2/Cr < 130 ng/mL. In contrast, the majority of those with uDCR2/Cr > 201 ng/mL had stage 4-5 CKD and T2. Levels of uDCR2

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were positively associated with urinary albumin/creatinine ratio (ACR), N-acetyl-(β-D-glucosaminidase (NAG) and TGF scores. Levels of uDcr2 were negatively associated with estimated glomerular filtration rate (eGFR), uDcR2, uNAG, ACR and eGFR were independent predictors for TIF, with AUC of 0.907 for uDcR2. This AUC value was higher than that observed for eGFR, uNAG, Cr, or ACR. The sensitivity and specificity of uDcR2 in predicting TIF were 87.0% and 80.5%, respectively. Renal DcR2 co-expressed with IL-6 and TIMP-2 in tubules and co-localized with u- SMA and collagen III in the kidneys of IgAN patients.

**Conclusions:** Levels of uDcR2 were closely associated with the severity of TIF and renal function parameters. uDcR2 or Cr represents a potential biomarker for predicting chronic TIF in IgAN patients.

**Funding:** Government Support - Non-U.S.

**SA-POS80**

**Epigenetic Factors Regulate APOL1-miR193a Axis in Parietal Epithelial Cells**

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**Background:** Bifunctional APOL1-miR193a axis plays a vital role in the podocyte renewal during normal physiology and pathological states. Parietal epithelial cells (PECs) serve as the barrier cells for podocytes in juvenile. We have recently demonstrated the role of APOL1 wild-type (G0) in the transition of PECs. Since PECs have a higher expression of miR193a, they do not express APOL1. However, downregulation of miR193a induces APOL1 expression in PECs. We hypothesize that epigenetic factors regulate APOL1-miR193a axis through modulation of miR193a expression in PECs.

**Methods:** Immortalized human PECs underwent several experimental designs: PECs were transduced with either vector (V) or HIV (NL4 (n=4)); PECs were incubated in media containing variable concentration of IFN-γ (0, 5, 10, and 20 μM) for 48 hours (n=4); PECs were treated with either empty vector (EV) or a specific miR193 inhibitor (20 nM) for 48 hours (n=4); PECs were treated with either buffer, acetyazidine (5 μM, a demethylating agent), or SAHA (10μM, an histone deacetylase inhibitor) for 48 hours (n=4). Protein blots were probed for APOL1, DNMT 1-3, HDAC 1-4, H3K27me3, H3K4me3, H3K8/9ac, and rapamycin for DNMT4, HDAC4-1, and APOL1. RNAs were assayed for miR193a. ChiP assay was carried out to evaluate histone acetylation at miR193a promoter. The RIP-ChIP assay was performed to examine the binding of miR193a at APOL1 gene promoter. In PECs and PECIVs, methylation of CpG islands was detected by Bisulfite sequencing.

**Results:** HIV, as well as IFN-γ, induced APOL1 expression in PECs. PECIVH and IFN-γ-treated PECs showed 2.0-2.5-fold decrease in miR193a expressions, respectively; inhibition of miR193a in PECs by a specific miR193 inhibitor also resulted in the induction of APOL1 expression. The treatment of PECs with either acetyazidine or SAHA both induced the expression of APOL1 as well as decreased (three-fold) miR193a levels. HIV and IFN-γ enhanced the expression of DNMT3b, HDAC4, and H3K4me3, with the exception of H3K8/9ac. ChiP assay revealed histone methylation at 27 lysine residues. RIP-ChIP assay confirmed the binding of miR193a on APOL1 gene promoter. Bisulfite sequencing displayed enhanced methylation of CpG islands at miR193a gene in PECIVs.

**Conclusions:** Epigenetic factors regulate APOL1-miR193a axis in PECs.

**Funding:** NIDDK. Support

**SA-POS81**

**Efficacy of Low-Intensity Pulsed Ultrasound on Renal Fibrosis and Progression of CKD in a Mouse Model**

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**Background:** The prevalence of chronic kidney disease (CKD) has been increasing in recent years. Proliferation of fibroblasts and excessive deposition of extracellular matrix including collagen in renal tissues after ischemia/reperfusion injury (IRI) contribute to renal fibrosis and progression of CKD. Low intensity pulsed ultrasound (LIPUS) has been recognized to elevate bone fracture repair process and help in some soft tissues healing such as cartilage and cardiac tissues. Here, we tested the prevention of renal fibrosis and progression of CKD by LIPUS in a mouse model of unilateral IRI with contralateral nephrectomy.

**Methods:** Animals were randomized into the sham, IRI, and IRI+LIPUS groups. In the IRI group, the left renal artery was isolated and clamped for 30 minutes. They were sacrificed 14 days after IRI as an AKI to CKD transition model in the presence or absence of LIPUS treatment (3 MHz, intensity 0.1 W/cm², 20 min, 50% duty factor) 5 days before and 14 days after IRI. Serum biochemical measurement, including BUN, Cr and Cystatin C, Histological analysis, Immunoblotting, including GRP78, Chop, Bax, cleaved caspase-3, p21, Sirtuin-1, E-cadherin, vimentin, cadherase, supoxide dismutase 1 (SOD1), Ki67, β-catenin, and Malondialdehyde (MDA) were examined.

**Results:** LIPUS treatment significantly alleviated the increase in the serum levels of BUN, creatinine, and fibroblast growth factor (FGF)-23, and renal pathological changes and fibrosis (n=8, p<0.05). The development of epithelial-mesenchymal transition was alleviated by LIPUS treatment (n=8, p<0.05). LIPUS treatment could also inhibit the induction of renal senescence-related molecular signals such as p53, p21, and p16 (n=8, p<0.05). Interestingly, LIPUS significantly reversed the decreased α-Klotho protein expression in the kidneys (n=8, p<0.05). LIPUS treatment significantly reversed the decrease in renal endogenous antioxidant enzymes (n=8, p<0.05). Taken together, LIPUS treatment showed the benefits for renal protection in IRI mice.

**Conclusions:** These findings suggest that LIPUS therapy may be used to serve as an auxiliary tool for the management of renal fibrosis and progression of CKD.

**Funding:** Government Support - Non-U.S.

**SA-PO582**

**Remodeling of the Glomerular Tuft in Proteinuric Kidney Disease**

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**Background:** Glomerular hypertrophy is associated with proteinuric kidney disease and progression to renal failure. The present study sought to quantify the association between remodeling of the glomerular tuft and proteinuria.

**Methods:** Adult male Wistar rats (sensitive strain, ~75 g) were administered puroycin (aminonucleoside) (PAN, 167 mg/kg, n=8) or water (n=3, sham cohort). On Day 14 after PAN administration, 24-hour urine was collected for determination of proteinuria. Left kidneys were removed, sectioned and stained with hematoxylin-eosin and glomeruli (14 per kidney) photographed at 40X. Areas of the Bowman’s capsule and glomeruli were measured using ImageJ by an observer blinded to the experiment groups and the area of the Bowman’s space calculated.

**Results:** Compared to the sham cohort, PAN-administered animals exhibited a 3-fold increase in proteinuria (p<0.01) and changes in glomerular tuft morphology (A). Significant increases (B) were observed in the areas of the Bowman’s capsule (**, p<0.01), the glomerulus (***, p<0.01), and the Bowman’s space (*, p<0.05) with PAN administration.

**Conclusions:** Remodeling of the glomerular tuft, including hypertrophy of the Bowman’s capsule and glomerulus, and an increase in Bowman’s space, accompanies proteinuric kidney disease. These findings might be an important consideration in the development of therapies for the treatment of kidney disease.

**Funding:** Private Foundation Support

**SA-PO583**

**Molecular Mechanisms of Renal Fibrosis in Alport Syndrome**


**Background:** Alport Syndrome is a rare hereditary disease caused by mutations in glomerular basement membrane (GBM) type IV collagen and characterized by progressive renal fibrosis and early onset ESRD. Collagen IV dysregulation and loss of GBM integrity allows passage of albumin to the tubular lumen causing injury and damage. Progressive renal fibrosis and early onset ESRD. Collagen IV dysregulation and loss of GBM integrity allows passage of albumin to the tubular lumen causing injury and damage.

**Methods:** We evaluated the kinetics and potential mechanisms of renal fibrosis in Col4a3 knock out (Col4a3KO) mice, a model of autosomal recessive Alport Syndrome compared to age-matched Wild Type (WT) controls. Approximately equal numbers of male and female Mice were studied from 5–10 wks age to evaluate the renal fibrotic response to progressive albuminuria. At 6, 8 and 10 wks, representative cohorts of mice were euthanized and kidneys were harvested for biochemical and histological analyses. mRNA expression was analyzed using a Quantigene pro-inflammatory and fibrogenic gene multiplex (MCP-1, CTGF, TGF-β1, α-SMA, FN1 and Collagens 1a1 and 3a1). Renal cortical hydroxyproline (OH-P) content and Collagen Volume Fraction (CVF) via Picrosirius Red (PSR) histology were also evaluated. Renal cortical lysates were evaluated for TGF-β1 content and phospho-p38, JNK and Erk to elucidate potential pathways in albuminuria-induced fibrosis.

**Conclusions:** The PAN model of proteinuric kidney disease is associated with an increase in the area of the Bowman’s capsule, the glomerulus, and an increase in the Bowman’s space.

**Funding:** None
Results: Col4a3KO had age-dependent polyuria and fulminant albuminuria (5 wks: 360-fold; 10 wks: -2,500-fold) compared to WT. Renal cortical OH-P content was not increased by 6 wks but increased thereafter. Associated with progressive albuminuria, CVF was age-dependently increased in Col4a3KO (8 wks: 10-fold; 25 wks: 25-fold). Although pro-inflammatory and fibrilotic mRNA species were increased by 6 wks in Col4a3KO, peak expression occurred at 8 wks, in advance of peak fibrosis. Renal cortical TGF-β1 content was age-dependently increased while pJNK and pERK peaked at ~8 wks.

Conclusions: This study demonstrates albuminuria precipitates renal fibrosis in the Col4a3KO model of Alport Syndrome and identifies potential mechanisms related to disturbed albumin reabsorption. These results enable relevant investigations of inflammatory and stress-signaling pathways in Alport Syndrome, and evaluation of novel therapies to attenuate albuminuria-induced renal fibrosis.

Funding: Commercial Support - Plato BioPharma, Inc.

SA-PO584
Established Human Mesenchymal Stem Cell Lines Stably Secreting Matrix Metalloproteinase 7 to Treat Glomerulosclerosis in Light Chain Disease

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Background: Light chain deposition disease (LCDD) is a rare systemic disorder, caused by the overproduction and extracellular deposition of monoclonal immunoglobulin light chain. The clinical manifestation is dominated by renal disease. The affected glomeruli are enlarged. The deposition of PAS-positive material produces capillary wall thickening and nodular expansion of the mesangium. The extent of glomerular involvement can vary from minimal mesangial expansion to a fully developed nodular glomerulosclerosis. Although the pathogenesis of the glomerulosclerosis in LCDD is not entirely clear, experimental studies have shown that mesangial cells incubated with monoclonal light chains obtained from patients with LCDD produce transforming growth factor-β1 and matrix metalloproteinase-9. These factors are indicators of extracellular matrix expansion. Tenascin-C is the most common protein in expanded mesangium in LCDD and is degraded mostly by Matrix Metalloproteinase 7 (MMP-7).

Methods: 1) pCDEF3-GFP-MMP-7 plasmid was purified using QIAprep Spin Miniprep Kit. The products are confirmed by gel electrophoresis. 2) HMSCs were cultured in serum-free medium supplemented with 20 ng/ml of epidermal growth factor. The HMSCs were transfected by purified GFP-MMP-7 plasmid using lipoctfectamine 2000. Immunofluorescence microscopy was used to test the transfection efficiency. 3) 48 hours after transfection, the HMSCs were transferred into 10cm dishes. 72 hours later, G418 60mg/ml was added to the media and cell clones formed 3-4 weeks and then were picked up to amplify. Confocal microscopy and western blot analysis were used to identify MMP-7 expression and secretion.

Results: 1) GFP-MMP-7 plasmid was successfully transfected and purified. 2) HMSCs were successfully transfected by GFP-MMP-7 plasmid using lipoctfectamine 2000. The transfection efficiency was about 30%, including 10% highly expressed cells.

Conclusions: We successfully established HMSC cell lines which highly express and secrete MMP-7. In our future study, the cell line will be used to treat kidney diseases caused by LCDD in animal models.

SA-PO585
IL-17 Signaling in CD4+ T Cells Controls TH17 Immune Response

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Background: The IL-17/IL-17 receptor system plays a crucial role in autoimmune and chronic inflammatory diseases. The biological effects on residential cells are mediated through a heterodimeric receptor complex consisting of IL-17R A and a ligand specific IL-17 receptor subunit (IL-17RB-IL-17RE). However, the expression and function of IL-17 receptors on hematopoietic cells has not been clarified yet. We determined whether HMSCs can secrete pro-inflammatory cytokines such as IL-6, TNFα and IL-1β. In addition, we investigated whether HMSCs secrete IL-7, IL-8, IL-10 and IL-12 which are produced by activated monocytes.

Methods: 1) C57BL/6 mice were used to establish the preparative method of rMophs. To amplify rMophs, we first determined the efficacy of renal cell collections from the mouse kidney. 2) We used CD45.2+ cells and F4/80+ cells for the in vitro co-culture assay. 3) We purified CD45.2+ cells from the draining lymph nodes and a significant reduction in dermal DTH, measured by a delayed cutaneous hypersensitivity response (DCH). 4) We used the C57BL/6 mouse model of anti-MPO GN induced by MPO-Ab.

Results: We successfully established HMSC cell lines which highly express and secrete MMP-7. In our future study, the cell line will be used to treat kidney diseases caused by LCDD in animal models.

Conclusions: We successfully established HMSC cell lines which highly express and secrete MMP-7. In our future study, the cell line will be used to treat kidney diseases caused by LCDD in animal models.

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SA-PO588

Urinary Treg and Th17 Cells Identify Active Renal Disease in Patients with ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitides (AAV) cause necrotizing crescentic glomerulonephritis which is a major contributor to morbidity and mortality in AAV. As therapy relies on immunosuppressive agents with potential adverse effects, a reliable non-invasive biomarker of disease activity is needed to determine the right balance between over- and undertreatment. Since the pathogenic role of T cells in AAV is emerging, we hypothesized that these subsets are increased in urine in active renal AAV and represent a reliable biomarker of disease activity.

Methods: Levels of Tcells and their subsets were measured in peripheral blood and urine samples from patients with active renal AAV (n=39), active non-renal AAV (n=9), AAV in remission (n=22), and healthy controls (n=9) using flow-cytometry. Urinary metabolites and cytokines (MCP-1, sCD163, sCD25, and C5a) were quantified by multiplex-analysis.

Results: Patients with active renal vasculitis show significantly higher urinary T cell counts than active non-renal, inactive, and healthy controls. In particular CD4+ T cells, T regulatory cells, and Th17 cells are significantly elevated compared to all controls. No significant difference could be shown for CD8+ T cells between active renal and remission. The only significant difference for Th1 cells was found between active renal vasculitis and healthy controls. sCD163, MCP-1, and C5a all show a significantly elevated concentration compared to patients in remission only sCD163 reaches significance for active renal vs. active non-renal. Analysis of receptor operator characteristics (ROC) reveals that urinary T cells identify active renal vasculitis with at least comparable diagnostic accuracy, CD4+, CD4+, CD8+ and Treg outperform soluble markers based on area under the curve (Treg AUC 0.93, sensitivity 79%, specificity 95%; CD3 Tcells AUC 0.95; sensitivity 92%, specificity 95%; MCP-1 AUC 0.9; sensitivity 60% specificity 100%, sCD163 AUC 0.92, sensitivity 96%, specificity 83%).

Conclusions: Urinary Tcells are significantly elevated in active renal AAV and reliably determine renal disease activity. Biomarker performance for Tregs is comparable to published results of urinary MCP-1 and sCD163 and exceeds sCD25 and C5a while Th17 outperforms only sCD25 and C5a. Hence, urinary Tregs and Th17 are new potential biomarkers in AAV.

SA-PO590

Fostamatinib Treatment of a New Model of Myeloperoxidase-ANCA Vasculitis


Background: EAV is a model of MPO-AAV induced by immunising rats with human myeloperoxidase (hMPO). Animals develop lung haemorrhage and proliferative GN, but disease is milder than human AAV. To augment disease severity, we immunised animals with an additional subnephritic dose of rabbit nephrotoxic serum (NTS). Fostamatinib, a small molecule Syk inhibitor, was used to evaluate therapeutic manipulation in this new model.

Methods: WKY rats were immunised IV with diluted NTS to establish a subnephritogenic dose. For EAV+NTS experiments, animals were immunised IM with hMPO and 1:100 NTS at day 14. When fostamatinib was used, this (or vehicle) was administered by oral gavage from day 24-27, and animals culled on day 28. Infiltrating glomerular leucocytes were isolated and analysed by flow cytometry.

Results: A sub-nephritogenic dose of NTS was identified as a 1:100 dilution. Animals immunised with hMPO and 1:100 NTS had significantly more proteinuria and glomerular abnormalities at day 28 than the hMPO+ NRS group or HSA controls (Fig1A). There was no detectable immune deposits by immunofluorescence or electron microscopy in any of the groups. In animals immunised with hMPO and 1:100 NTS, there were significantly more infiltrating glomerular leucocytes with greater increase in classical compared to non-classical monocytes (Fig1A). Fostamatinib treatment significantly reduced lung haemorrhage, glomerular, urinary abnormalities and infiltrating glomerular leucocytes (Fig1B).

Conclusions: A subnephritic dose of NTS 14 days after hMPO significantly augments disease severity without evidence of deposited antibody or immune complexes. Characterisation of glomerular infiltrating cells shows significant infiltration of classical monocytes and we suggest it may be these cells which are stimulating crescent formation. Administration of fostamatinib for 4 days was sufficient to significantly decrease disease severity.
SA-PO591
Platelet Activation Is Induced via Myeloperoxidase Production and Anti-Myeloperoxidase Antibodies Primed by Thrombin
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Background: In addition to their central role in hemostasis and thrombosis, platelets involve in inflammatory responses. Anti-neutrophil cytoplasmic autoantibodies (ANCAs) directed to myeloperoxidase (MPO-ANCAs) are the main serological markers of ANCA-associated vasculitis.

Methods: Platelets were stimulated by purified total IgG and MPO-ANCA from patients with or without low doses of thrombin. The fragments from MPO-ANCAs, F(ab)₂, and Fc, were digested and isolated, then incubated with thrombin-primed platelets. The fibrinogen-binding capacity of platelets was measured by flow cytometry. The concentration of MPO was detected in active platelets and AAV patients.

Results: The current study demonstrated that MPO-ANCAs caused normal human platelets to activate, primed by low doses of thrombin. Purified immunoglobulin G, MPO-ANCAs and their F(ab)₂, fragments evidently increased the CD62P expression of platelets compared with controls. The existence of MPO in platelets was confirmed with mass spectrometry technology, after analyzing the F(ab)₂ fragment pull-downed proteins. After thrombin priming, platelets not only expressed MPO on the surface with an activation-dependent manner, but also released the enzyme to extracellular space. These effects markedly enhanced the activation of platelets. Additionally, there was no apparently increased CD62P-expression on platelets in MPO-ANCAs group compared with controls when adding MPO inhibitor, proving that primed platelets have ANCA antigen at their surfaces interacting with the autoantibodies.

Conclusions: These findings suggest a previously unappreciated character for platelets as immune cells and the autoantibodies-induced activation in an acute inflammatory disease.

SA-PO592
SUMO1 Promote Mesangial Cell Proliferation Through Inhibiting Autophagy in a Cell Model of IgA Nephropathy
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Background: IgA nephropathy(IgAN) is a common form of primary glomerulonephritis and its main pathological changes are mesangial cell proliferation and matrix expansion. Autophagy inhibition may result in its mesangial cell proliferation and renal lesions. SUMOylation is a eukaryotic-reversible post-translational modification where SUMO are covalently attached to target proteins to regulate their properties. It is largely unclear if SUMOylation contributes to the pathogenesis of IgAN.

Methods: This study was designed to investigate the change of protein SUMO1 in mesangial cells of IgAN and its association with autophagy.

Results: We found the expression of SUMO1 was up-regulated in IgAN and alglA1 stimulated mesangial cells. In alglA1 stimulated mesangial cell model, we tested LC3 and p62, the autophagy-related proteins suggested the inhibition of autophagy. Silencing SUMO1 could down-regulate SUMO1 and SUMO1-p53, promote autophagy and lessen cell proliferation.

Conclusions: In the mesangial cells stimulated with alglA1, SUMO1 may contribute to its cell proliferation through inhibited autophagy and SUMO1-p53 may play a role in this process.

SA-PO593
IgA1 from Sera of Patients with IgA Nephropathy, but Not Purified Monomeric or Polymeric IgA1, Associates with Cultured Primary Human Mesangial Cells and Induces Cellular Signaling
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Background: Circulating immune complexes (CIC) containing galactose-deficient IgA1 (Gd-IgA1) bound by Gd-IgA1-specific autoantibodies play a key role in the pathogenesis of IgA nephropathy (IgAN). Using a model of cultured primary human mesangial cells (hMC), we have previously shown that Gd-IgA1-containing CIC are biologically active, as they activate multiple protein-tyrosine kinases, lead to ERK1/2 phosphorylation, and stimulate cellular proliferation. In this study, we assessed how purified IgA1 of different molecular forms and serum IgA1 associate with and activate hMC.

Methods: Monomeric and polymeric forms of Gd-IgA1 were isolated from plasma of a patient with multiple myeloma by size-exclusion chromatography. IgA concentrations in serum samples from IgAN patients were measured by ELISA. Primary hMCs were incubated for 15 min at 37°C with 5% sera from IgAN patients or with the corresponding amount of monomeric or polymeric IgA1; hMC without any IgA1 served as a negative control. Cell lysates obtained after the incubation were used for pull-down using antibody specific for integrin β1 followed by protein G agarose. Cell lysates and pull-down samples were subjected to SDS-PAGE/Western blotting to detect IgA and phospho-ERK1/2.

Results: Purified monomeric as well as polymeric Gd-IgA1 exhibited minimal interactions with hMC, as only small amounts of IgA1 appeared in the hMC lysates and no induction of ERK1/2 phosphorylation was observed. In contrast, when sera from IgAN patients were incubated, we observed more IgA1 in hMC lysates (4 times more compared to monomeric Gd-IgA1, 8 times more compared to polymeric Gd-IgA1) as well as robust ERK1/2 phosphorylation. Preliminary pull-down experiments indicated that a fraction of IgA1 was associated with integrin β1, a previously described hMC receptor for IgA1. Moreover, we found that hMC formed c5β1 and c5β1 integrin complexes.

Conclusions: IgA1 from sera of IgAN patients, but not free monomeric or polymeric Gd-IgA1, associates with hMC and activates hMC. Integrin β1 may be involved in this process and may provide clues for development of future targeted therapy of IgAN.

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SA-PO594
C-Reactive Protein Is Renoprotective in Experimental IgA Nephropathy
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Background: IgA nephropathy (IgAN) is the most common glomerulonephritis in the world. Although the pathogenesis of the renal disorder remains largely unknown, NLRP3 inflammasome-mediated IL-1β production and subsequent activation of adaptive immunity is implicated in the development of IgAN. C-reactive protein (CRP) is a serum biomarker for various inflammatory conditions and has been shown to inhibit the activation of the NLRP3 inflammasome.
Methods: In the present study, we examined the role that CRP can play in the evolution of IgAN using an experimental model of IgAN in CRP knockout (KO) mice, and dissected the mechanisms involved.

Results: The results show that the experimental IgAN in CRP KO mice revealed significantly increased magnitudes in (1) renal pathology, including marked mesangial cell proliferation and mononuclear leukocyte infiltration in the glomeruli and peri-glomerular interstitial tissue, (2) glomerular deposition of IgA and C3, (3) NLRP3 inflammasome activation in the kidney, and (4) renal function impairment and proteinuria compared to their wild type (WT) counterparts equally induced by IgAN. Moreover, IL-10 levels in both serum and renal tissues were significantly elevated in IgAN in CRP KO mice, compared with WT counterparts.

Conclusions: In conclusion, CRP may serve as a protective role in the development of IgAN by inhibiting NLRP3 inflammasome and enhancing the production of IL-10. The results suggest that CRP may be a potential therapeutic agent for IgAN.

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SA-PO595

Tris DBA Ameliorates IgA Nephropathy by Blunting the Activating Signal of NLRP3 Inflammasome Through SIRT1- and SIRT3-Mediated Autophagy Induction

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Background: Tris (Dibenzylidenecacetone) dipalladium (Tris DBA), a small molecule palladium complex, can inhibit cell growth and proliferation in pancreatic cancer, lymphoplastic leukemia and multiple myeloma. Given that this compound is particularly active against B cell malignancies (Chronic lymphocytic leukemia and multiple myeloma), we hypothesized that it can alleviate immune complex-mediated conditions, including IgA nephropathy (IgAN).

Methods: C57BL/6 mice were induced IgAN by consecutive 28 daily injections of 5 mg/kg anti-IgA anti-phospholipase A2 receptor (PLA2R) monoclonal antibodies (mAb) specific for gammadelta T cells (Tc) followed by S 230, T233, and/or T236. HR IgA1 HR of healthy controls will enable future differentiation of IgAN in various pathologies.

Results: In the present study, we examined the therapeutic effects of Tris DBA on glomerular cell proliferation and renal inflammation in a mouse model of IgAN. The results show that treatment of IgAN mice with Tris DBA resulted in markedly improved renal function impairment and proteinuria compared to their wild type (WT) counterparts equally induced by IgAN, and they showed a proinflammatory phenotype in IgAN, including for instance the upregulation of JNK)-mediated priming signal of the NLRP3 inflammasome, and differentially regulating this beneficial effect involves blunting of mitochondrial ROS production, a MAPK (ERK, JNK)-mediated priming signal of the NLRP3 inflammasome, and differentially regulating the autophagy-NLRP3 inflammasome axis through SIRT1 and SIRT3. Thus, Tris DBA can be considered a therapeutic candidate for IgAN.

Conclusions: Tris DBA was able to effectively ameliorate the mouse IgAN model; this beneficial effect involves blunting of mitochondrial ROS production, a MAPK (ERK, JNK)-mediated priming signal of the NLRP3 inflammasome, and differentially regulating the autophagy-NLRP3 inflammasome axis through SIRT1 and SIRT3. These data indicate B cells in gdm7 mice may be hyper-sensitive to stimuli by antigen and Tc cell help without increasing the frequency of IgA and suggest such a B-cell intrinsic factor may be involved in the pathogenesis of IgAN.

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SA-PO596

Quantitative Assessment of Sites with Galactose-Deficient O-Glycans in the Hinge Region of IgA1

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Background: Serum level of IgA1 with galactose (Gal)-deficient hinge-region (HR) O-glycans (Gd-IgA1) is elevated in patient with IgA nephropathy (IgAN) and the glomerular immunodeposits of IgAN patients are enriched for Gd-IgA1. Lectins and a selective quantitative removal of galactosylated O-glycans is needed to identify disease-specific IgA1 HR O-glycans and XIC based on isoseric glycalfoms enabled quantitative assessment of Gal-deficient sites. The most common Gal-deficient sites included T230, S232/T233 and T236. HR O-glycalsoms with 2 or 3 Gal-deficient O-glycans predominantly identified in IgAN, as well as in gdm7 mice by using this novel culture system. First, we analyzed the proliferation of splenic B cells upon stimulation in vitro. Next, we examined their CS to IgA.

Methods: The proliferation of splenic B cells upon stimulation with membrane-bound IgM and CD40 were evaluated by Thymidine-uptake analysis. naïve B cells from wild type mice and gdm7 mice were cultured for seven days by using newly developed culture system and the IgA CS was evaluated by flow cytometry.

Results: We found that B cells of gdm7 mice exhibited elevated proliferation rate than those of wild type mice in response to stimuli through CD40 and membrane-bound-bridged IgM. There was no significant difference in the frequency of CS to IgA between splenic B cells from gdm7 mice and those from wild mice. However, the gdm7 mice exhibited increased IgA1 production in response to the stimulation. Therefore, the present study aimed to evaluate characteristics of B cells in gdm7 mice, gdm7 mice, and gdm7 mice, and gdm7 mice, and the differences in these characteristics may be responsible for the increased IgA1 production in gdm7 mice.

Conclusions: These data indicate B cells in gdm7 mice may be hyper-responsive to stimuli by antigen and Tc cell help without increasing the frequency of IgA and suggest such a B-cell intrinsic factor may be involved in the pathogenesis of IgAN.

Funding: Government Support - Non-U.S.

SA-PO597

Characteristics of B Cells in IgA Nephropathy Model Mice

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Background: The pathogenesis of IgA nephropathy (IgAN) is associated with dysregulation of immune system, however the characteristics of B cells that are responsible for production of nephritogenic IgA have been elusive. Recently, we have reported the abnormal B cells expressing APRIL are present in tonsils of human IgAN (JASN 28; 1227, 2017). Since abnormal antibody production seems to be the key feature in the pathogenesis of IgAN, we investigated characteristics of B cells in IgAN model mice, gdm7 mice, which we have established. Furthermore, we recently developed a novel culture system mimicking germinal center in mucosa, by which nearly 50 % of B cells undergo class switch (CS) to IgA. Therefore, the present study aimed to evaluate characteristics of B cells in gdm7 mice by using this novel culture system. First, we analyzed the proliferation of splenic B cells upon stimulation in vitro. Next, we examined their CS to IgA.

Methods: The proliferation of splenic B cells upon stimulation with membrane-bound IgM and CD40 were evaluated by Thymidine-uptake analysis. naïve B cells from wild type mice and gdm7 mice were cultured for seven days by using newly developed culture system and the IgA CS was evaluated by flow cytometry.

Results: We found that B cells of gdm7 mice exhibited elevated proliferation rate than those of wild type mice in response to stimuli through CD40 and membrane-bound-bridged IgM. There was no significant difference in the frequency of CS to IgA between splenic B cells from gdm7 mice and those from wild mice.

Conclusions: These data indicate B cells in gdm7 mice may be hyper-responsive to stimuli by antigen and Tc cell help without increasing the frequency of IgA and suggest such a B-cell intrinsic factor may be involved in the pathogenesis of IgAN.

Funding: Government Support - Non-U.S.

SA-PO598

A New Insight into the Pathogenesis of IgAN: Dissecting the Disease in Single Cells

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Molecular mechanisms driving glomerular damage in the disease are poorly understood. In this study, we analysed individual glomerular cell from IgAN mice, a well-established genetic model of IgAN, by using scRNA-seq.

Methods: 5 control (non-proteinuric) and 5 IgAN (proteinuric) ddy mice were included in the study. Animals were sacrificed at 4 weeks of age and glomeruli isolated using the perfusion of magnetic beads. The glomeruli were treated mechanically and enzymatically to obtain single cells. Viable single cells of enriched glomeruli were unbiasedly sorted to 384-well plates and scRNA-seq performed using the Smart-seq2 protocol.

Results: A total of 3096 cells passed Quality Control. Unsupervised cell clustering demonstrated the inclusion of 11 cell types in both control and IgAN (glomerular endothelial (GEC), mesangial, parietal epithelial, podocyte, juxtaglomerular, macrophage, NK, T and B cells, as well as small contamination with tubular cells). The results showed a significant loss of podocytes in IgAN animals and revealed a number of new IgAN-associated genes/pathways in individual cell types. In podocytes, the Gene Ontology analysis revealed the emission of chemotractant and pro-inflammatory cytokines, a role classically attributed to macrophages. In GECs, several cell types were identified and they showed a proinflammatory phenotype in IgAN, including for instance the up-regulation of selectin and MHC class 2 molecules. Mesangial cells seemed to be activated and gain a migratory phenotype, which included, for instance, the up-regulation of ACTA2 expression. Moreover, several novel ligand-receptor pairs were identified in glomerular cells that are likely to play a role in the disease progression.

Conclusions: The preliminary analysis of our data suggests a crucial role of podocytes and GECs in the initiation of glomerular injury in ddy IgAN mice. Further analyses are ongoing to understand the crosstalk between the different glomerular cell types in both disease and healthy state.
Intravenous infection with Cnm-Positive Streptococcus mutans, a Dental Pathogen, Induces IgA Nephropathy-Like Lesions in Rats
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Background: IgA nephropathy (IgAN) is one of the most common types of primary glomerulonephritis worldwide, but its precise pathogenesis remains unclear. Previously, we reported that Streptococcus mutans, a major pathogen of dental caries was frequently isolated from the oral cavity of IgAN patients; these isolates showed surface expression of collagen-binding protein (Cnm). However, there is no direct evidence that Cnm-positive S. mutans induces IgAN. In the present study, we evaluated renal lesions in rats that were intravenously infected with Cnm-positive S. mutans isolated from an IgAN patient.

Methods: Cnm-positive S. mutans strain SN74, isolated from the saliva of an IgAN patient, was intravenously administered to 4-week-old male specific pathogen-free Sprague-Dawley rats. At 15, 30, 45, and 60 days post-infection, kidney specimens were evaluated. Periodic acid-Schiff staining and fluorescent immunostaining with IgA, C3, and CD68 antibodies was performed; electron microscopy analysis was also performed.

Results: Proteinuria in the S. mutans group was significantly elevated, compared with that in the control group at 30 days post-infection (p < 0.05). Histopathological examinations revealed increased presence of mesangial cells and matrix at 30 days post-infection in the S. mutans group. Immunohistochemical examinations demonstrated that combined IgA/C3 deposition in mesangial cells was significantly greater in the S. mutans group than in the control group at 45 days post-infection (p < 0.05). Electron microscopy analysis showed electron-dense deposits in the mesangial area and hump in subepithelial area in the S. mutans group at 45 days post-infection. Furthermore, the numbers of CD68-positive cells (i.e., macrophages) in the glomeruli of the S. mutans group were significantly higher than those in the control group at 30, 45, and 60 days post-infection (p < 0.01).

Conclusions: Intravenous infection with Cnm-positive S. mutans isolated from an IgAN patient could induce IgAN or infection-related glomerulonephritis in rats.

Macrophage Interactions with Collecting Ducts May Contribute to the Interstitial Fibrosis Observed in IgA Nephropathy Progression
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Background: Tubulo-interstitial fibrosis is a powerful predictor of future progression in IgA nephropathy (IgAN). Proximal tubules, in concert with infiltrating macrophages, are regarded as the agents provocateurs for driving this process. However, evidence is now emerging for a contributory role of the distal nephron. The aim of this study was to examine the potential influence of macrophages on renal collecting ducts (CDEC) in the progression of IgAN.

Methods: Macrophage-conditioned media (MCM) were generated from U937 and THP-1 cells, cultured in the presence or absence of 100ng/ml IgA1. Collecting duct epithelial cells (CDEC) exposed to the MCMs were analysed for evidence of inflammation and fibrosis.

Results: Staining of IgAN biopsies for the macrophage marker CD68 demonstrated that macrophages were principally observed in and around proximal tubules. However, CDECs in normal and IgAN biopsies were also observed in areas of medullary collecting ducts and within their lumens. CDEC exposure to THP-1-IgA-MCM stimulated markedly increased expression of the tubular injury marker neutrophil-associated gelatinase (NGAL) and raised levels of IL-1β, TNFα, IL6 and IL8; effects that were replicated by 5ng/ml IL1β alone. U937-IgA-MCM, on the other hand, significantly increased MCP-1 and fibronectin levels and reduced E-cadherin mRNA expression. Exosomes extracted from THP-1-IgA-MCMs stimulated similar increases in NGAL and cytokine expression to the source MCM, while in cross over experiments exosomes extracted from CDECs induced IL-1β and IL6 mRNA expression in macrophages. MiRNome analysis using nanostar technology revealed that miR-146a was expressed more than 2 fold in CDECs treated with THP-1-IgA-MCM compared to THP-1-MCM. Enforced miR-146a suppression with a specific inhibitor further enhanced NGAL expression in CDECs in the presence of MCM while ectopic miR-146a over expression down-regulated it. Both NGAL mRNA and miR-146a were found, by RT-PCR, to be upregulated in the biopsies of progressive forms of IgAN compared to CKD controls.

Conclusions: Taken together these data suggest that macrophages and collecting ducts could interact to contribute to the tubulo-interstitial fibrosis and inflammation found in progressive forms of IgAN.

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CARD9 Risk Allele and IgA Nephropathy
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Background: IgA nephropathy (IgAN) is a common cause of primary glomerulonephritis and is most prevalent in East Asian populations. The pathogenesis of IgAN is not well understood. GWAS studies have revealed an association with rs4077515, a SNP within the coding sequence of CARD9, an essential mediator of the innate immune system. However the place of CARD9 in the pathogenesis of IgAN has yet to be defined. The aim of this study was to investigate the expression of CARD9 in the kidney and determine whether it has an intrarenal role in IgAN.

Methods: Screening kidney cell lines for synthesis of CARD9 by western blotting revealed greatest CARD9 synthesis in human mesangial cells (hMC). To test the significance of the risk allele we incubated hMC that were heterozygous or homozygous negative or positive for the risk allele rs4077515 with IgA1 derived from 5 individuals (3 IgAN, 2 healthy subjects) and measured IL-6 synthesis using ELISA.

Results: We observed increased expression of CARD9 mRNA in whole kidney biopsies in IgAN compared to kidney disease controls (p<0.0005). Immunohistochemistry demonstrated CARD9 protein in both the glomerular and tubulointerstitial compartments in IgAN. The presence of rs4077515-T resulted in significantly increased production of the pro-inflammatory cytokine IL-6 following exposure to IgA1 (p<0.0001: TT:CC and p<0.001: CT:CC). In parallel, similar increases were seen in mRNA coding for IL-6 and IL6R. CARD9 and IL6ST (p<0.0001: TT:CC and p<0.0023: CT:CC) and monocyte chemoattractant protein 1 (p<0.0001: TT:CC and p<0.0001: CT:CC) and IL6ST.
**SA-PO603**

**The Role of Angiogenin/miR-141 Axis in Glomerular Injury of IgA Nephropathy**

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**Background:** IgA nephropathy (IgAN) is the most common primary chronic glomerular disease worldwide. GD-deficient IgA1 (Gd-IgA1) containing immune complex is the important factor involved in the pathogenesis of IgAN, which mechanism has not yet been clarified. Angiogenin is a secreted ribonuclease, and it plays biological functions through selectively cutting RNA substrates, including miRNAs.

**Methods:** The concentration of Angiogenin in plasma and cell medium was examined by Enlzisa. Overexpression of Angiogenin was conducted by infection of lentivirus with Angiogenin overexpression plasmid. Knockdown of Angiogenin was conducted by infection of lentivirus with shRNA. Cell proliferation activity was carried out by CCK-8. Cell apoptosis was carried out by Flow cytometry. The protein were measured by western blotting, miRNA and miRNA were measured by RT-qPCR. The cleavage of miR-141 by Angiogenin was carried out by a cell-free cleavage assay.

**Results:** The level of Angiogenin in plasma was elevated in IgAN patients than healthy controls. When the glomerular mesangial cell was stimulated by Gd-IgA1 immune complex, secretion of Angiogenin and some inflammatory cytokines were upregulated. When the expression of Angiogenin in mesangial cell was knock-down by shRNA, the proliferative activity of mesangial cells was inhibited. The expression level of miR-141 was affected by Angiogenin expression in mesangial cells, high expression of Angiogenin downregulated miR-141 and knockdown of Angiogenin upregulated the level of miR-141. In addition, Angiogenin digest miR-141 as an endonuclease in vitro.

**Conclusions:** Angiogenin was upregulated in IgAN. Gd-IgA1 complex stimulation decreased the secretion of Angiogenin and inflammatory cytokines of mesangial cell. Down-regulation of Angiogenin inhibits the proliferative activity of mesangial cells. Angiogenin regulates the level of miR-141 in mesangial cell and digests miR-141 as an endonuclease in vitro. Thus, Angiogenin/miR-141 axis may regulate IgAN through affecting mesangial cell proliferation and inflammatory cytokines secretion.

**Funding:** Government Support - Non-U.S.

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**SA-PO604**

**TLR3 Activation Contributes to Pathogenesis of Mesangial Proliferative Glomerulonephritis**

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**Background:** It is assumed that Toll-like receptor (TLR) is activated by ligands and the TLR-mediated signaling is involved in the development of mesangial proliferative glomerulonephritis (MGN). However, how TLR detects signals from the damaged tissue and the pathogenic mechanism initiated by the TLR activation in MGN are poorly understood. Thy1.1 GN, a widely used rat experimental model for MGN, is caused by the injection of the antibody against Thy1.1 expressed on mesangial cell surface. Thy1.1 GN is characterized by diffuse mesangiolysis at 24h and consequent accumulation of inflammatory cells and mesangial cell proliferation.

**Methods:** The kinetics of the expression of TLR2, TLR3, TLR4 in Thy1.1 GN were analyzed by RT-PCR and immune-histochemical analyses. The cells expressing TLRs were analyzed.

**Results:** The increase in mRNA expression of TLR3 was already detected at 1h (3.4 times to control) and the increase is promoted on day 7 (11.4 times to control). However, such a clear increase is not detected in TLR2 or TLR4. Immunostaining of TLR3 was not detected in normal glomeruli, and the clear positive staining of TLR3 was detected at mesangial area at 1h, and at 24h and day 7 the positive staining was detected at the expanded mesangial area and in capillary lumen. In Thy1.1 GN at the early recovery phase after mesangiolysis Thy1.1. negative cells were mainly accumulated in mesangial area and the population of Thy1.1 positive cells gradually increased with time. ED1+ macrophage (4.3±0.45/glom), ED3+ activated macrophage (4.5±0.90/glom) and NKRP1+ NK cells (1.2±0.67/glom) were accumulated in glomeruli on day 7 of Thy1.1 GN. An immune-histochemical analysis showed that TLR3 was detected on Thy1.1. negative cells localized at mesangial area but not detected on Thy1.1. positive cell, and some portions of ED3+ cells express TLR3 but no NKRP1+ cells express TLR3. mRNA expression IFN-γ was mainly activated by TLR3-mediated signaling, was increased (2.8 times to control) in this GN model.

**Conclusions:** Not TLR2 or TLR4 but TLR3 was dominantly activated in Thy1.1. GN. It is conceivable that TLR3 responds to molecules released by damaged mesangial cell, and TLR3-mediated signaling participates in the pathogenesis of mesangial proliferative glomerulonephritis.

**Funding:** Government Support - Non-U.S.

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**SA-PO605**

**THSD7A Knockout Mice as a Valuable Tool for the Generation of Domain-Specific Monoclonal Antibodies**

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**Background:** Autoantibodies against multiple domains in THSD7A cause membranous nephropathy (MN). However, the function of THSD7A in podocytes, the precise mechanisms of antibody-induced glomerular injury and the role of the targeted epitopes are largely unknown.

**Methods:** Embryonic stem cells for generation of THSD7A-kd first mice were purchased from UCDavis KOMP. Since ko first mice were found to contain residual expression of THSD7A in podocytes, mice were further bred to obtain a true constitutive THSD7A ko (THSD7A-/-). For the generation of poly- and monoclonal antibodies (MABs), 12-w-old THSD7A-/- mice were immunized using the purified murine antigen fragments d1_d2 and d15_d16, corresponding to the domains most frequently recognized by patient autoantibodies. Spleen and lymph nodes were collected 7w after immunization and fused with SP2/0 myeloma cells. Cell clones expressing anti-THSD7A antibodies were screened using an immunofluorescence test on THSD7A-transfected CHO cells. Positive clones were cultured and IgG was purified from cell culture supernatant.

**Results:** THSD7A-/- mice showed no glomerular expression of THSD7A in immunofluorescence and Western blot. Glomeruli appeared normal in PAS staining and no ultrastructural changes were observed by EM. Mice had no proteinuria by the age of 1y. Immunization of THSD7A-/- mice induced high levels of domain-specific anti-THSD7A antibodies. Fusion of splenic cells with myeloma cells resulted in 3 clones producing antibodies against THSD7A. One MAB recognized d1_d2 (IgG1) and two MABs recognized d15_d16 (IgG1 and IgG2b). These MABs were suitable for the detection of THSD7A in immunofluorescence, Western and dot blot. Transfer of individual MABs to WT BALB/c mice resulted in glomerular binding of mouse IgG, but no complement deposition and no proteinuria.

**Conclusions:** In preliminary investigations, THSD7A-/- mice do not show significant glomerular alterations, suggesting that THSD7A expression is not integral for basal glomerular function or that other unidentified molecules can compensate for the lack of THSD7A. THSD7A-/- mice are a powerful tool for the generation of poly- and monoclonal antibodies and these antibodies can potentially be used to dissect the mode of antibody-induced glomerular damage and the role of targeted epitopes in MN.

**Funding:** Government Support - Non-U.S.

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**SA-PO606**

**IL233 Regulates Mitochondrial Function and WNT Signaling for Lupus Glomerulonephritis Remission**

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**Background:** We showed that the hybrid cytokine IL233 induced persistent remission in ongoing lupus glomerulonephritis (GN) in NZM2208 mice. The progression of GN in NZM2208 mice involves stages of acute (aGN), transitional (tGN) and chronic GN (cGN). As a means to further understand the mechanisms involved in IL233-rendered protection, we investigated modulation of mitochondrial function and canonical Wnt signaling that is understudied in the setting of aGN to cGN progression, utilizing both in vitro and in vivo approaches.

**Methods:** To obtain IL233-induced remission NZM2208 mice were challenged using an immunofluorescence test on THSD7A-transfected CHO cells. Positive clones were cultured and IgG was purified from cell culture supernatant.

**Results:** THSD7A-/- mice showed no glomerular expression of THSD7A in immunofluorescence and Western blot. Glomeruli appeared normal in PAS staining and no ultrastructural changes were observed by EM. Mice had no proteinuria by the age of 1y. Immunization of THSD7A-/- mice induced high levels of domain-specific anti-THSD7A antibodies. Fusion of splenic cells with myeloma cells resulted in 3 clones producing antibodies against THSD7A. One MAB recognized d1_d2 (IgG1) and two MABs recognized d15_d16 (IgG1 and IgG2b). These MABs were suitable for the detection of THSD7A in immunofluorescence, Western and dot blot. Transfer of individual MABs to WT BALB/c mice resulted in glomerular binding of mouse IgG, but no complement deposition and no proteinuria.

**Conclusions:** In preliminary investigations, THSD7A-/- mice do not show significant glomerular alterations, suggesting that THSD7A expression is not integral for basal glomerular function or that other unidentified molecules can compensate for the lack of THSD7A. THSD7A-/- mice are a powerful tool for the generation of poly- and monoclonal antibodies and these antibodies can potentially be used to dissect the mode of antibody-induced glomerular damage and the role of targeted epitopes in MN.
Methods: Mouse glomerular endothelial cells (mGECs) and proximal tubular TKPTS cells were treated with varying concentrations of IL-23 and investigated for mitochondrial membrane potential and for genes and proteins associated with mitochondrial function.

In vivo, kidney lysates from treated NZM2328 animals were screened for transcripts of mitochondrial genes by real time PCR. Canonical Wnt signaling proteins were studied by co-IP and Western blotting. mGEC cell lines were assayed with an established regulatory T cell (Tregs) from treated animals.

Results: IL-23 treatment induced a marked elevation of genes related to mitochondrial function and biogenesis (Pgc1α, Mfn1, Nrf1, Nrf2, Tm4, and Drp1) in mGECs and TKPTS cells, indicating a direct regulation of mitochondrial function. These cells also displayed higher mitochondrial membrane potential by flow cytometry. IL-23-treated mice with established GN had higher expression of genes related to mitochondrial function and biogenesis, thus, complementing in vitro observations. Levels of canonical Wnt pathway genes were significantly reduced in both IL-23 and TLR7-/- treated kidneys. Tregs isolated from saline, IL-2-33, IL-23L-33 treated animals were investigated for oxidative respiration with Seahorse. Although there was a trend of a higher rate of oxidative respiration in mice treated with IL-2 or IL-33 only or the combination of IL-2 and IL-33, the Tregs isolated from IL-23 treated mice had a significantly higher respiration rate than Tregs from the other groups.

Conclusions: We present evidence for the use of IL-23 for therapy of lupus GN in a murine model. In vivo and in vitro data reveals enhancement of mitochondrial function and modulation of canonical Wnt signaling as possible mechanisms of IL-23-mediated remission from lupus GN.

Funding: NIDDK, Support

SA-PO607

Epidermal Growth Factor Receptor-Dependent TLR7 Signaling in Macrophages Promotes Kidney Injury in Cerebral Glomerulonephritis

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Background: Epidermal growth factor receptor (EGFR) has been shown to promote glomerular injury in cerebroglomerulonephritis (CRGN) and we showed that EGFR plays pivotal roles in the signaling of endosomal Toll-like receptors (TLRs): TLR3 (Sci Signal 2012), TLR4 (EMBO Rep 2015), and TLR9 (J Immunol 2018). Polymorphisms in TLR7, a sensor for endogenous danger signal, are linked with the development of SLE, and TLR7-/- mice were resistant to NTN compared to WT mice: TLR7-/- mice showed significant additional protective effects on NTN at an early time point (Day 7), while TLR7+/- mice showed less severe proteinuria, GBM rupture, crescent formation, and less number of MΦ2 positive MΦs compared to TLR7-/- mice without Gefitinib. Seven days after NTS injection, kidney injury was analyzed in vitro and in vivo and significant additional protective effects were observed. A trend of a higher rate of oxidative respiration in mice treated with IL-2 or IL-33 only or the combination of IL-2 and IL-33, the Tregs isolated from IL-23 treated mice had a significantly higher respiration rate than Tregs from the other groups.

These results indicate that regulation of TLR7 signaling in MΦs by EGFR has a critical role in the early pathogenesis of CRGN.

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SA-PO608

Glomerular Endothelial Cell Heterogeneity and Contribution to Kidney Disease

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Background: Glomerular endothelial dysfunction plays a key role in the development of chronic kidney disease (CKD), but its impact on Alport syndrome (AS), characterized by mutations in collagen IV α3 or α5, is unknown. In AS, we reported structural changed and upregulation of VEGF pathway in the glomerular endothelial cells (GEC) in the early stage of disease. Gefitinib blocked phosphorylation of GEC in AS patients with Tamm-Horsfall proteinuria.

Methods: To test our hypothesis, we generated GEC specific (Tec-Cre driven) tdTomato reporter AS mice and isolated GEC by FACS. We studied GEC by flow cytometry, WB, and by multiphoton and confocal microscopy, and by RNA-seq analysis.

Results: tdTomato signal identified two distinct GEC subsets (bright and dim) in both wild type and AS mice, which presented with transcriptional heterogeneity in ECM and glycolysis-associated genes, immune cell activation and cellular metabolism. In both WT and AS, GEC with a well-established functional role in mitochondrial dysfunction, glucose and lipid metabolism, and inflammation were most significantly enriched. In particular, the bright cells were enriched in (upregulated) genes controlling cytoskeleton organization and inflammatory cell-cell adhesion (such as Icam1, Vcam1, Ccl2, Ccr2 and Ccr3). Genes were significantly downregulated in AS, which could be related to genes related to chemokine signaling but downregulated for genes and pathways associated with mitochondrial function. Both bright and dim cells were enriched in downregulated genes linked to glucose and lipid metabolism. In terms of cell-ECM interactions, Igf9 and Vegf were upregulated in AS compared to WT mice. Other differentially expressed genes related to ECM composition, Vegf1 expression was highly increased in the bright cells and Col1/ta1 in the dim cells exclusively.

Conclusions: In conclusion, we identified two GEC subpopulations and showed glomerular endothelial dysfunction in the early stages of disease. Importantly, GEC are differentially regulated to endothelial dysfunction differently. A better understanding of the functional role of the glomerular endothelium could lead to the development of targeted new therapies for the treatment of CKD.

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SA-PO609

APL-2 Prevents Both C3 and C5 Convertase Formation and Activity: A Potential Therapeutic for Renal Diseases

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Background: C3 glomerulopathy (C3G) is a group of renal diseases characterized by isolated glomerular deposits of C3 fragments as a result of an activation of the complement alternative pathways (AP). The excessive activation of C3 and C5 convertases leading to C3b production and formation of the membrane attack complex is associated with renal function impairment. About 50% of the patients progress to end stage renal disease within years of the diagnosis. The disease is caused either by an autoimmune abnormalities in complement regulatory proteins or by the presence of autoantibodies, C3 or C5 nephritogenic factors (NeFs), that bind and stabilize the convertases. APL-2 is a small, synthetic, cyclic peptide that binds and inhibits C3b and C5b. The objective of this study was to better understand the impact of APL-2 on the formation of the AP C3 and C5 convertases and on the activity of pre-formed convertases. We also evaluated the ability of APL-2 to inhibit NeFs-mediated overactivation of both convertases.

Methods: This study was performed in vitro in model of hemolysis using C3b-recovered sheep erythrocytes and purified complement proteins. IgG positive for C3NeF (n=14) and C3/C5NeF (n=9) were isolated from patients with C3G and added with or without APL-2 (25 mg/ml).

Results: APL-2 prevents the formation of AP C3 and C5 convertases and inhibits the activity of both pre-formed convertases. APL-2 also decreased the prolonged convertase activity mediated by C3NeF and C5NeF. In 6/14 C3NeF and 7/9 C5NeF the stabilizing effect of the autoantibodies became undetectable demonstrating that APL-2 is effective to inhibit the convertase hyperactivity in the presence of NeFs.

Conclusions: APL-2 is a peptide that also inhibits the formation and inhibits the activity of pre-formed AP C3 and C5 convertases, therefore blocking the activation of both C3 and C5. The effect of APL-2 on the convertases occurs also in the presence of NeFs. This data supports potential therapeutic effects of APL-2 in patients with C3G as well as for other renal diseases associated with overactivation of complement.

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SA-PO610

Micromanaging Autoimmune Nephritis: miR-17-92 Modulates Tfh Development and Regulatory T Cell Activity

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Background: T follicular helper (Tfh) cells provide crucial growth signals to germinal center (GC) B cells supporting antibody production. Tight control of Tfh numbers maintains self-tolerance. Regulatory T (Treg) cells play a critical role in maintaining self-tolerance and controlling the magnitude of physiologic immune response. The Treg transcription factor forkhead box P3 (Foxp3) works in concert with other co-regulator molecules to determine suppression phenotype of Treg. Compiling evidence show that aberrant Tfh, GC responses and deficiencies of Treg are associated with systemic lupus erythematosus and autoimmunity production.

Methods: We generated T cell specific miR-17-92 knockout (miR-17-92-/-) mice, followed by induction of primane nephritis in miR-17-92-/- and wild type littermates. By bioinformatics study, possible targets of miR-17-92, related to Treg function was evaluated. Luciferase reporter assay was utilized for verification. Forced expression and knockdown of miRNA in Tfh and TFH was performed by lentivirus.

Results: We induce primate nephropathy on T cell specific miR-17-92 knockout (miR-17-92-/-) mice. MiR-17-92 CD4 T cell specific deficiency mitigates pristane-induced lupus nephropathy in mice. The mice showed less Tfh cells, less GC B cells and lower autoimmunity formation. Consistent with the reduction in autoimmunity production, histological analysis revealed a lower mean renal histopathology score and less IgG deposition. We further demonstrate that the miR-17 regulates Tfh development by targeting Akt pathway. Moreover, miR-17-92 mitigate the suppression function of Treg.
by targeting Foxp3 co-regulators. Ectopic expression of miR-17 downmodulates the suppression function of Foxp3 in the colitis model. Tregs from patient with lupus nephritis and lupus mice both showed increased miR-17 expression.

Conclusions: Our studies suggest that miR-17-92 modulates aberrant immune response through critical regulation in T cells subsets, unveiling the future therapeutic potential of microRNA manipulation in lupus nephritis.

Funding: Private Foundation Support

SA-PO611

Evaluation of the Renoprotective Role of Endogenous Galectin-3 and Mechanism in Lupus Nephritis
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Background: Lupus nephritis (LN) is a major complication of systemic lupus erythematosus. Current therapeutic regimens to control the acute onset of LN progression include high doses of corticosteroids, cytotoxic agents and disease-modifying antirheumatic drugs. However, there is still a major concern about the potential, systemic adverse events of these drugs. Thus, the development of pathogenic pathway-based new therapies with much fewer and more tolerable side effects is clinically warranted. Galectin-3 (Gal-3) is a β-galactoside-binding protein and implicated in diverse biological processes in macrophages, dendritic cells (DCs), activated lymphocytes, and epithelial cells. However, the role of Gal-3 and exact mechanisms involved in the development and progression/deterioration of LN has yet to be determined, although renal expression of the protein is observed in LN patients.

Methods: Gal-3 KO-Y chromosome-linked autoimmune acceleration (Yaa) mutation was introduced in KO-strain (KO,Yaa) mice, a spontaneous mouse model of LN, which is deficient of Gal-3 were generated to investigate the renoprotective effects of Gal-3 in two complementary LN mouse models. Moreover, lupus-like nephritis in Gal-3 KO mice induced by LPS injections. Renal function, pathology and pathogenesis-based experiments galectin-side binding.

Results: In the present study, the results show that [1] the distribution and expression levels of Gal-3 were increased in renal biopsy specimens from LN patients, compared to normal control subjects; [2] deficiency of endogenous Gal-3 resulted in markedly increased severity of pathological alterations in both the LPS-induced LN in Gal-3 KO mice and spontaneous LN in Gal-3 KO-KO1. Yaa mice, compared to their respective wild type counterparts that equally induced of or developed galactoside-binding; and [3] greatly enhanced activation of T cells and B cells as well increased monocytosis in peripheral blood of Gal-3 KO mice.

Conclusions: Gal-3 played a protective role in the development of LN, and justify the protein as a potential drug candidate for LN.

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SA-PO612

Urinary Levels of CD11b and CD163 Determine Rapid Responders to Remission Induction Therapy in Proliferative Lupus Nephritis
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Background: Drastic elevations of urinary CD11b (U-CD11b), α, subunit of integrin Mac-1, and CD163 (U-CD163), a scavenger receptor for hemoglobin-haptoglobin complex, have been demonstrated in proliferative lupus nephritis (LN). The current study aims the further verifications of U-CD11b and U-CD163 as the potential LN biomarkers to predict longitudinal response of proliferative LN patients to the remission induction therapy.

Methods: We examined CD11b and CD163 by enzyme-linked immunosorbent assay in urine samples collected from proliferative LN class III or IV patients confirmed by renal biopsy in Nagoya Kidney Disease Registry (N-KDR) between 2004 and 2014, and retrospectively analyzed those associations with longitudinal achievement of complete remission (CR) following the remission induction therapy. Based on the cutoff values of U-CD11b and U-CD163 respectively determined by receiver operation curves to predict CR, univariate analysis by log-rank test and multivariate analysis by Cox proportional hazards regression model were performed to evaluate patient susceptibility to the remission induction therapy.

Results: Among 63 patients with proliferative LN for 52 months observation period on average, U-CD11b and U-CD163 levels were significantly higher in patients who achieved CR within 3 months (p<0.001 in U-CD11b, p=0.005 in U-CD163) and 12 months (p=0.02 in U-CD11b, p=0.03 in U-CD163) compared with those who did not. In univariate analysis, the cumulative CR rates within 3 months in patients presenting low levels of U-CD11b and U-CD163 were significantly higher than their respective high levels. Multivariate analysis revealed low level of U-CD11b (hazard ratio [HR], 5.68; 95% confidence interval [95% CI], 1.65 to 19.4) and eGFR per 10ml/min/1.73m² (HR, 1.30; 95% CI, 1.11 to 1.52) as independent predictors for the achievement of CR within 12 months. Moreover, U-CD11b levels over 0.9% vs. ≤0.9% had a 95% CI, 3.85 to 16.2) still demonstrated the significance even in the subpopulation with preserved renal function.

Conclusions: U-CD11b, rather than U-CD163, clinical the values for prediction of early response to the remission induction therapy in LN patients.

SA-PO613

The Role of Plasmacytoid Dendritic Cells in Pathogenesis of Systemic Lupus Erythematosus
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Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease accompanied by production and deposition of immune complexes (IC) in multiple organs. Especially in the kidney, lupus nephritis (LN) due to deposition of IC occurs in about 40-70% of SLE patients, and about 10-30% of these patients progress to end stage renal disease. Plasmacytoid dendritic cells (pDCs) which recognize viral nucleic acids by endosomal toll-like receptor (TLR) 7/9 and secrete large amounts of IFN-1 are considered as important mediators of antiviral responses, while inappropriate recognition of self nucleic acids with IFN-1 responses is linked to autoimmunity. Therefore, this subset of DCs are attracting an attention for novel therapeutic target. But so far, little is known about the mechanisms how pDCs contribute pathogenesis of SLE and LN.

Methods: We isolated pDCs from spleen of 4weeks IMQ model, and performed miRNA array. We extracted miRNA which was up or down-regulated, and searched miRNAs target of these miRNAs on database. Then predicted mRNA targets were confirmed by qPCR. Using human pDCs cell line, CAL-1, we performed TLR7, 9 and IC stimulation experiment.

Results: As a target of miRNAs that shows down-regulation, we found zinc finger transcription factor: Kruppel-Like Factor 4 (KLF4). By qPCR, we confirmed that KLF4 was up-regulated in mice pDCs. Similar results were observed in the pristine-induced mice SLE model. We found that the protein levels of KLF4 was also up-regulated in TLR7 stimulation group compare with control group.

Conclusions: The production of autoantibody in SLE requires sustained production of IFN-1, but the pathogenesis of sustained IFN-1 production in pDCs is not fully understood. From our study, it was suggested that the up-regulation of KLF4 in pDCs plays some roles in the pathogenesis of SLE. Further studies are needed to elucidate the precise role of KLF4 in pDCs.

SA-PO614

Circulating MiRNAs as Potential Biomarkers of Kidney Damage in Patients with Systemic Lupus Erythematosus
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Background: Renal involvement is one of the most severe manifestations of systemic lupus erythematosus (SLE). Renal biopsy is the gold standard when it comes to knowing whether a patient has lupus nephritis and the degree of renal disease present. However, the biopsy has various complications, bleeding being the most common. Therefore, the development of alternative, non-invasive diagnostic tests for kidney disease in patients with SLE is a priority. Micro RNAs (miRNAs) are differentially expressed in various tissues and changes in their expression have been associated with several pathological processes. The aim of this study was to identify changes in the abundance of miRNAs in plasma samples from patients with lupus nephritis that could potentially allow the diagnosis of renal damage in SLE patients.

Methods: This was an observational case-control cross-sectional study, in which we characterized the differential abundance profiles of miRNAs among patients with different degrees of lupus compared with SLE patients without renal involvement and healthy control individuals.

Results: We found 89 miRNAs with changes in their abundance between lupus nephritis and healthy controls, and 17 miRNAs that showed significant variations in additional samples from lupus patients with or without nephritis, and from healthy individuals, showed that five miRNAs presented an average detection sensitivity of 97%, a specificity of 70.3%, a positive predictive value of 82.5%, a negative predictive value of 96% and a diagnosis efficiency of 87.9%.

Conclusions: These results strongly suggest that miR-221-5p, miR-380-3p, miR-556-5p, miR-755-3p and miR-3074-3p are potential diagnostic biomarkers of lupus nephritis in patients with SLE. The observed differential pattern of miRNA abundance may have functional implications in the pathophysiology of SLE renal damage.
SA-PO615
Pneumococcal Polysaccharide Vaccine Regulates Murine Lupus
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Background: Current guidelines suggest the use of anti-pneumococcal vaccine Prevnar13 in patients with lupus, but the effects of such vaccination on disease severity are unknown.

Methods: We injected Prevnar13 (0.5 ml) or vehicle control into 8wk-old female MRL-lpr that spontaneously develop lupus. After 3mo, we measured circulating anti-PS IgG. In another set of animals, we quantified disease severity at 3 mo after Prevnar13 injection, including albuminuria, renal histology, and skin lesions. We also measured phenotype and function of splenocytes from treated and untreated mice, as well as renal STAT1 and STAT3 protein levels (WB).

Results: Prevnar13 reduced the formation of anti-pneumococcal IgG (Fig. 1A). Prevnar13 treated animals showed less albuminuria, renal histological lesions, and milder dermatitis compared to controls (Fig. 1B-D). Improved disease severity in Prevnar13-treated animals was associated with reduced T follicular helper cells (Tfh) and more T follicular regulatory cells (Tfr) (Fig. 1E). After ac20D28 stimulation, T lymphocytes from vaccinated mice showed less IL-17 and IL-4 production than non-vaccinated controls, while IL-10 production was significantly increased. Vaccinated mice had significantly decreased expression of STAT1 compared to controls, whereas STAT3 levels did not differ.

Conclusions: Anti-pneumococcal vaccination elicits anti-pneumococcal antibody response and ameliorates disease severity in MRL-lpr mice, which associates with increased Tfr and decreased Tfh. These data strongly support the use of Prevnar vaccination in individuals with lupus.

SA-PO616
Patients with Membranous Nephropathy Show Increased Circulating T Follicular Helper (T_{fh}) Cells, T_{f17}, and Exhausted T Cells (T_{ex})
Results from a Cross-Sectional Study Including Healthy and CKD Controls
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Background: Primary membranous nephropathy (MN) is characterized by the presence of antibodies to the podocyte, but studies characterizing abnormalities in circulating T and B cell populations are limited and generally include only healthy controls.

Methods: We performed a comprehensive flow-cytometric analyses of 38 T and B lymphocyte subpopulations, including intracellular staining for IFN-g, IL-4, and IL-17 production in 27 patients with MN (before initiating immunosuppressive therapy) and compared them with 12 healthy individuals and 22 patients with non-immune mediated chronic kidney disease (CKD). Serum TNF-a (M1) and IL-7 (M2) was measured in patients with MN and in patients with non-immune mediated chronic kidney disease (CKD). Serum TNF-a (E) and IL-7 (F) levels in MN patients and in HC.

Conclusions: These results indicate that myeloid-lineage cell-derived MRPs could potentially contribute to glomerular injury upon NTN through intraglomerular cell crosstalk, affecting Mφ characterization.

SA-PO617
Ablation of MRPs in Myeloid Cells Ameliorates Glomerulonephritis by Affecting Macrophage Characterization
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Background: We previously reported that toll-like receptor 4 (TLR4) and its endogenous ligand, myeloid-related protein 8 (MRPs, S100A8), play important roles in the progression of diabetic nephropathy in mice. During these experiments, we unexpectedly observed that glomerular-infiltrated macrophages (Mφ) expressed MRPS more robustly than tubulointerstitial Mφ. However, the mechanisms and roles remain elusive.

Methods: We generated myeloid-lineage cell-specific MRPs knockout mice (MyMkko), and induced experimental nephrotic glomerulonephritis (NTN). Culture of Mφ with mesangial cells (Mes) or proximal tubular cells (PT) was performed to evaluate the effects of MRP8 on bone marrow-derived Mφ (BMDM) generated from MyMkko. BMDM was characterized by real-time PCR. Cell surface markers of peripheral leukocytes and glomerular-infiltrated Mφ were analyzed by flow cytometry (FCM). For effective sorting of MRPs-targeted cells, MyMkko were crossed with flexed-STOP ZsGreen transgenic mice (MyMkko-Zsg).

Results: In the NTN mice, ablation of MRPs in myeloid-lineage cells significantly ameliorated glomerulonephritis as indicated by the reduction in proteinuria, glomerular exudative lesions, pro-inflammatory gene expressions and M1 dominance in isolated glomeruli. In vitro, MRPS expression was markedly induced in BMDM by co-culture with_PATH_ and not with PT. This effect was recapitated by stimulation with Mes-cultured supernatant (Mes-sup). Moreover, Mes-sup stimulation increased M1/M2 ratio (M1/M2) determined by real-time PCR. Cell surface markers of peripheral leukocytes and glomerular-infiltrated Mφ were analyzed by flow cytometry (FCM). For effective sorting of MRPs-targeted cells, MyMkko were crossed with flexed-STOP ZsGreen transgenic mice (MyMkko-Zsg).

Conclusions: These results indicate that myeloid-lineage cell-derived MRPs could potentially contribute to glomerular injury upon NTN through intraglomerular cell crosstalk, affecting Mφ characterization.

SA-PO618
A Modified Peptide Derived from Goodpasture Autoantigen Attenuates and Attenuated Kidney Injuries in Experimental Anti-GBM Glomerulonephritis
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Background: P14 (αC31-14α) was a nephritogenic epitope on human αC3IVNC1, including an EAG with its core motif W136I137L139W140G142F143F145. Based on the sequences of α1-P14 and c3-P14, a modified peptide (m-P14) was designed by the substitution of α1L→L at 137. Methods: m-P14 was injected into P14-immunized WKY rats either on immunization or upon disease onset. PAS staining, ELISA, Flow cytometry, ELISPOT were also applied in this study.

Results: m-P14 intervention attenuated the c3-P14 induced anti-GBM disease in early-treatment groups and treatment group with decreased crescent formation(30mg/kg m-P14: 6.5±0.4 vs. 68.8±15.4 %; P=0.002; 10mg/kg m-P14: 6.3±5.6 vs. 68.8±15.4 %, P=0.005; treatment: 20.1±8.4 vs. 68.8±15.4%, P=0.002). m-P14 could inhibited the binding of c3-P14 to MHC molecules and abated the forming of splenic Th17 in
**Surgical Intervention**

**SA-PO619**

**Experimental Anti-Glomerular Basement Membrane Glomerulonephritis Induced by a Peptide from Actinomyces**

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**Background:** P14 (α3127-148) was a nephritogenic epitope for anti-GBM disease, with its core motif W136I137L139W140G142F143F145. Infections have been suspected as the “second hit” for the onset of anti-GBM disease. We aimed to search for mimicking microbial peptides that may participate in anti-GBM disease.

**Methods:** Blast, SYFPEITHI, ABCpred were used for searching P14-mimic microbial peptides. WKY rats and HLA-DR15+ transgenic mice were immunized with peptide B7. IHC staining, ELISA and ELISPOT were applied.

**Results:** Peptide B7 derived from actinomyces was screened from 3319 microbial peptide under the criteria of containing the critical motif of P14, related with human infection, included both T cell and B cell epitope and high recognition for sera of anti-GBM patients. All B7-immunized rats exhibited linear deposits of IgG on the GBM. The percentage of crescent formation in glomeruli was 14.6 ± 2.7%. For HLA-DR15+ transgenic mice, all mice immunized with B7 exhibited linear IgG deposits along the GBM and focal glomerular necrosis, two of them (28.6%) developed glomerular crescent formation. B7 also had cross-reaction with α3135-145 immunized rat splenocytes on T cell level for WKY rats model.

**Conclusions:** We found one microbial peptide derived from actinomyces could induce crescentic anti-GBM glomerulonephritis in both WKY rats and humanized HLA-DR15 transgenic mice. These results indicate that infections may initiate anti-GBM disease through molecular mimicry.

**SA-PO620**

**Human Hypoxic Proximal Tubule Epithelial Cells (PTECs) Trigger NLRP3 Inflammasome Activation in CD1c+ Dendritic Cells (DC)**

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**Background:** Chronic kidney disease (CKD) is characterised by inflammation and tubulointerstitial fibrosis. Hypoxia is a key driver of this pathology. Kidney proximal tubule epithelial cells (PTEC) are particularly susceptible to oxygen imbalances due to their high rates of aerobic respiration. We have reported activated CD1c+ dendritic cells (DC) adjacent to PTEC in fibrotic kidney tissue, where they are well positioned to sense PTEC-derived danger signals via the NLRP3 inflammasome. In this study, we examined the hypoxic response in human PTEC and their functional role in CD1c+ DC activation.

**Methods:** Primary human PTEC were cultured under normoxia (21% O2) or hypoxia (1% O2) and assessed for mitochondrial function, proliferation and viability. PTEC-CD1c+ DC interactions were examined by in vitro co-culture in the absence or presence of NLRP3 inflammasome inhibitor MCC950. DC activation was assessed by mRNA profiling and cytokine secretion.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Hypoxic PTEC displayed significant mitochondrial dysfunction, significantly reduced proliferation, and the "infection" of the PTEC by the hypoxic condition (CD1c+) was mediated in the presence of hypoxic PTEC shown increased NLPR3 mRNA expression and secreted significantly elevated levels of inflammasome-related cytokines (IL-1β, IL-18). Notably, this pro-inflammatory response was significantly reduced in the presence of the NLPR3 inflammasome inhibitor, MCC950. Immunofluorescence staining of fibrotic kidney tissue identified PTEC co-localized with CD1c+ expressing downstream signaling markers of NLPR3 inflammasome activation (active Caspase-1).

**Conclusions:** Our data demonstrate that hypoxic PTEC trigger and activate CD1c+ via the activation of the actin cytoskeleton, resulting in the secretion of pro-inflammatory cytokines. Future studies will examine the putative role of mitochondrial danger signals generated by hypoxic PTEC for therapeutic targeting in human CKD.

**Funding:** Government Support - Non-U.S.

### SA-PO623

#### APOL1 and JAK1/2 Are Required for Interferon Gamma-Stimulated Inflammatory Responses in Human Kidney Cells

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**Background:** Chronic inflammation contributes to progression of glomerular diseases including diabetic kidney disease (DKD). Recent data suggest that APOL1 and JAK1/2 signaling contribute to the pro-inflammatory milieu in FSGS and DKD, respectively. Based on systems genetic and transcriptionic analyses of humans and of murine models of glomerular diseases, the expression of CXCL9, a T-cell chemok一大支ma uncultored in the human kidney cell.

**Methods:** Human kidney 2 (HK-2) cell monolayers were grown to confluence and treated with interferon gamma (IFNγ) (30ng/ml), interleukin-6 (10ng/ml), or tumor necrosis factor alpha (10ng/ml) for 50 min to 48 hrs. Levels of JAK2, APOL1, and CXCL9 mRNAs were determined in response to agonists. Inhibition of JAK1 and JAK2, with baricitinib (500Mm) or siRNA knockdown of APOL1 expression was performed in some experiments before IFNγ exposure. Effects of APOL1 knockdown on IFNγ-stimulated gene expression were examined. These genes were identified by transcriptomic analysis of IFNγ-treated, processed.

**Results:** HK-2 cells express APOL1, JAK2 and CXCL9. Stimulation of HK-2 cell monolayers with IFNγ, but not IL-6 or TNF, resulted in a rapid and sustained 4-50-fold increase in the mRNA expression of JAK2, APOL1 and CXCL9. These increases were largely abrogated by pretreatment with the JAK1/2 inhibitor as were IFNγ-induced increases in STAT3 phosphorylation and APOL1 protein levels. APOL1 knockdown resulted in an 80% reduction in CXCL9 expression and a 40-50% reduction in interferon-induced guanylate-binding protein 2, HLA class II histocompatibility antigen, DR alpha chain and ubiquitin. Expression of other IFNγ-stimulated genes was not consistently affected by APOL1 knockdown.

**Conclusions:** In cultured human kidney cells, IFNγ triggered responses in kidney cells resulting in increased expression of pro-inflammatory mediators and APOL1. This cascade was largely abrogated by specific inhibition of JAK1/2 signaling and selectively inhibited by knockdown of APOL1. These findings suggest that APOL1 plays an important role in the IFNγ-mediated inflammatory response in kidney cells.

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### SA-PO624

#### Lipoxins Promote Tissue Repair And Regeneration

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**Background:** Inflammation and its timely resolution is essential in maintaining tissue homoeostasis during injury and infection. Chronic low-grade inflammation contributes to the pathogenesis of CKD and failure to resolve this leads to impaired tissue repair. Conventional therapeutics such as steroids and non-steroidal anti-inflammatory drugs target the key drivers of the inflammation to dampen the inflammatory response but fail to resolve tissue repair. The resolution of inflammation is dynamically regulated by endogenously generated mediators including bioactive lipids such as lipoxins and deficits in these mediator networks may underlie chronic inflammation. We have previously demonstrated reno-protection by lipoxins in experimental models of podocyte and renal injury. Only recently have lipoxins been shown to be abrogated by pretreatment with the JAK1/2 inhibitor as were IFNγ-induced increases in STAT3 phosphorylation and APOL1 protein levels. APOL1 knockdown resulted in an 80% reduction in CXCL9 expression and a 40-50% reduction in interferon-induced guanylate-binding protein 2, HLA class II histocompatibility antigen, DR alpha chain and ubiquitin. Expression of other IFNγ-stimulated genes was not consistently affected by APOL1 knockdown.

**Methods:** To explore the potential therapeutic utility of lipoxins to promote tissue repair and regeneration we used the mediasion tail fin of wild-type 3dpf zebrafish larvae was transacted. 4 hours after implantation of the PMN neutrophils into adult zebrafish larvae. The repair was assessed by measuring the rate of tissue regeneration and the time lapse imaging over 48 hours. The effect of lipoxins on the activation and recruitment of PMNs during tail fin injury was monitored using fluorescent imaging in the transgenic zebrafish lines Tg(mpx:EGFP) and Tg(Mpeg1:mCherry). The effect of lipoxins on macrophage subsets was further investigated in human THP-1 derived macrophages treated with TNFα.

**Results:** Treatment with LXA4 significantly enhanced tail fin regeneration and promoted the resolution of inflammation in the zebrafish model. Furthermore, in THP-1 derived macrophages LXA4 treatment significantly reduced TNF induced inflammation, abrogated chemokine release, reduced macrophage activation towards a pro-resolution phenotype as evidenced by up-regulation of IL-4 and MRC1.

**Funding:** NIDDK Support
Conclusions: These findings suggest that lipoxins promote tissue repair and regeneration by reprogramming macrophages towards a pro-resolution phenotype and may have therapeutic potential for the treatment of chronic inflammation associated with diseases such as CKD.

SA-PO625
Mitochondrial Damage in Tubule Cells Activates the cGAS-STING Innate Immune Pathway and Leads to Fibrosis
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Background: Mitochondrial damage, defective bioenergetics, and immune system activation play key role in chronic kidney disease (CKD) and fibrosis. As the mitochondria retained ancient circular bacterial DNA, we hypothesized that the mitochondrial defects observed in kidney fibrosis lead to cytoplasmic leakage of the mitochondrial DNA and then recognized by the intracellular bacterial danger recognition pathway, cGAS-STING signaling cascade resulting in activation of inflammatory pathways and CKD.

Methods: Here, we analyzed gene expression data by RNA sequencing of 433 microdissected human kidney tissue samples with varying degree of kidney fibrosis and kidney function. To model mitochondrial damage, we generated mice with tubule-specific mitochondrial transcription factor (Tfam) deletion (Ksp-Cre/Tfam f/f). To explore the role of STING we crossed these mice with STING knock-out mice and treated with STING inhibitor. To understand the therapeutic potential of STING inhibition in CKD, we examined the renal phenotype of the STING knock-out mice following folic acid (FA) induced kidney injury and treated mice with a STING inhibitor.

Results: We found that expression of mitochondrial genes and its transcriptional regulator TFAM was significantly decreased in patients and mouse models with kidney disease. Ksp-Cre/Tfam f/f developed severe mitochondrial loss and decline of ATP content by 6 weeks of age. Progressive azotemia, kidney fibrosis and death of the animals was only observed after 12 weeks of age. Mechanistic studies demonstrated that aberrant mtDNA packaging upon TFAM deficiency in tubule cells resulted in escape of mtDNA into the cytosol, activation of the cytosolic DNA sensing pathway, STING, resulting in cytokine expression and immune cell recruitment. Genetic deletion or pharmacological inhibition of STING ameliorated TFAM-loss induced kidney fibrosis. Genetic deletion of STING and to lesser degree the STING inhibitor ameliorated kidney fibrosis in the FA induced model of kidney disease.

Conclusions: We concluded that in addition to its essential role in metabolism, TFAM sequesters mtDNA to prevent the activation of innate immune pathways and fibrosis. Cytosolic aberrant DNA in CKD activates the cGAS-STING pathway. Limiting STING activity can ameliorates kidney disease development.

Funding: NIDDK Support

SA-PO626
Decreased Monocyte Costimulatory Molecule CD86 Expression in Focal Segmental Glomerulosclerosis Predicts Early Relapse Following Rituximab Therapy
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Background: We recently reported a subgroup of focal segmental glomerulosclerosis (FSGS) patients bearing an immunological signature of T-cell hyporesponsiveness who responded to rituximab treatment. This study aimed to characterize the immunological subsets of FSGS patients who responded to treatment in order to predict early relapse within the first year following rituximab therapy.

Methods: A total of 29 FSGS patients (median age 14.7 years, range 6.1-25.0 years) receiving rituximab were recruited in this study. Rituximab was administered to patients at a dose of 375 mg/m2 during the first cycle in 4 cycles at 1 week intervals. Immunological subsets were monitored at baseline, and 6 months post-rituximab. Statistical analyses were done using Mann-Whitney U test and Wilcoxon signed rank test for paired analysis prior and 6-months post-rituximab. Receiver-operating characteristic (ROC) curve analysis was used to determine predictive utility of the subset for early relapse.

Results: 51.7% (15/29) responded to rituximab therapy with characteristic significant downregulation of IFNγ (P<0.01) following PMA/ionomycin stimulation. Of the 15 FSGS patients who responded to treatment, 60% (9/15) had no relapses within the first year post-rituximab (Group I), while 40% (6/15) relapsed (Group II) with comparable median B-cell recovery of 6.0 months and 5.0 months respectively (P=0.41). Patients in Group II had significant lower percent CD86 (75.5±7.0%) on monocytes compared with Group I (91.5±2.3%) (P=0.03). ROC analysis showed that monocyte expression of CD86 (AUC = 0.88, 95% CI 0.67-1.00) fared well as a good predictor for relapse (sensitivity 80.0%, specificity 87.5%, PPV 80.0%, NPV 87.5%, with discriminatory threshold <90.2%). CD86 expression in Group II was significantly upregulated 6-months post-rituximab treatment (P<2.15%).

Conclusions: We identified a distinct immunological subset of FSGS patients with decreased monocyte CD86 (B7-2) expression at baseline, who are likely to relapse within a year post-rituximab therapy and hence could benefit from early re-treatment with rituximab. If CD86 is a receptor which provides costimulatory signal to T-cell activation, deciding between T-cell fate of immunity or anergy. The nature of this T-cell FSGS however remains to be elucidated.

Funding: Government Support - Non-U.S.

SA-PO627
Differential Roles of RAGE Species for Renal Tubular Damages
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Background: Receptor for advanced glycation end-products (receptor for AGEs, RAGE) is a transmembrane and multiligand pattern recognition receptor, which binds AGEs, S100 proteins, and high mobility group box 1 protein (HMGB1), eliciting inflammatory signal transductions. Soluble and decoy forms of RAGE (sRAGE) are, otherwise, generated by cleavage of RAGE or by an alternative splicing, which forms an endogenous secretory RAGE (esRAGE). However, roles of sRAGE in the pathogenesis of kidney diseases remains unclear. We here examined whether RAGE and sRAGE could be implicated in renal tubular damages using a mouse kidney ischemia/reperfusion (I/R) model.

Methods: Unilateral renal I/R was introduced in RAGE knockout (Δgör) mice with or without administration of sRAGE. Tubular damages, interstitial cell accumulation and fibrosis were assessed at day 2 or 7. We also assessed tubular damages using anti-glomerular basement membrane nephritis models with or without sRAGE treatment at day 7. We checked the expression of genes coding RAGE, esRAGE and proinflammatory mediators after hypoxia using murine renal proximal tubular epithelial (mProx24) cells. Cellular damages and proliferation were also assessed in hypoxia-induced mProx24 cells with or without an sRAGE addition.

Results: We found that tubular damages were severer in Δgör mice than in Δgör+esRAGE mice at day 2 and 7 after I/R. Kidney fibrosis and macrophage infiltration were also exaggerated in Δgör mice at day 7. In vitro, hypoxia-exposure decreased the expression of genes coding RAGE and esRAGE in mProx24 cells, while Hmgb1 and Tnfα mRNA expressions were paradoxically upregulated. However, an sRAGE addition significantly decreased Hmgb1 and Tnfα mRNA expressions and induced the proliferation in hypoxic-induced mProx24 cells. Moreover, an sRAGE administration protected from tubular damages of I/R-performed mice and of the anti-GBM glomerulonephritis models.

Conclusions: We demonstrated that the hypoxic condition could induce the downregulation of genes coding RAGE and esRAGE in renal tubular cells. Administration of sRAGE could protect the kidney from I/R injury.

SA-PO628
Detection and Characterization of Prolonged Classical Pathway Convertase Activity: C4 Nephritogenic Factor and a Non-Autoantibody Serum Factor
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Background: C3 glomerulopathy (C3G) is a renal disease caused by overactivity of the complement system, particularly of the alternative pathway (AP). Autoantibodies such as C3 nephritic factors (C3NeFs) or mutations in complement genes are commonly found as pathogenic causes. Recent findings also reveal the presence of C4 nephritogenic factors (C4NeFs) in some C3G cases. By stabilizing the convertases of the classical pathway (CP), these autoantibodies contribute to the complement dysregulation in C3G. In this study, we investigated C4NeF activity in a cohort of patients with complement-mediated renal disease.

Methods: We used a recently described hemolytic method to measure convertase activity directly in serum, using a C5-blocker to separate the CP into two steps: a time-variable first step for convertase formation out of test serum and a standardized second step for hemolysis readout.

In 17 Serum samples of 17 healthy controls and 47 patients with (suspected) C3G and closely related complement-mediated disorders were analyzed. Convertase activity levels in controls consistently returned to background levels after 10 min. In contrast, convertase activity was significantly prolonged until 20 min in 2/47 (4%) patients (P1). By stopping the convertase-stabilizing factors, C4NeF activity was determined. Addition of purified lgs from P1 to control serum supported prolonged convertase activity, confirming the autoantibody nature of the stabilizing factor. Previously, the Igs of this patient were also shown to have AP convertase-stabilizing activity, i.e. C3NeF activity. Further investigation showed that both the C3NeF and C4NeF activity resided in the fraction of kappa light chain type. In addition, both the AP and CP convertase-stabilizing activities remained present over the disease course of the patient. In contrast to P1, the lgs of P2 did not support convertase stabilization when added to control serum, indicating a non-convertase factor caused the C4NeF and esRAGE in renal tubular cells. Administration of sRAGE could protect the kidney from I/R injury.

Funding: National Institute for Public Health and the Environment; Dutch Kidney Foundation.
Conclusions: This study offers new opportunities for the detection and characterization (previously unrecognized) of CP-converting dysregulating factors in patients with complement-mediated renal diseases.

SA-PO629
Trending Complement C3 in C3 Glomerulopathy Patients Before and After Renal Transplant
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Background: C3 Glomerulopathy (C3G) is characterized by dysregulation of the alternative pathway of complement. Most patients will approach ESRD within 10 years of diagnosis. Recurrence in renal transplants is as high as 84%. Little is known about the natural history of transplant recurrence or predictors of poor renal outcome. The degree of C3 consumption (represented by a low C3) has been postulated as a predictor of disease activity in the setting of native kidney disease. Whether C3 abnormality plays a similar role in the transplant setting is unknown. Similarly, the predictive value of other complement biomarkers is unknown.

Methods: We studied a sub-cohort of the University of Iowa’s C3G Natural History Study. All patients met biopsy criteria for C3G. Reviewed patients had at least 3 pre-transplant and 3 post-transplant C3 values. Using our standard assays, we tested all patients in the cohort for complement gene abnormalities and for longitudinal nephritic factor trend. Phenotypic results were correlated with recurrence of C3G in a renal allograft.

Results: Average age at diagnosis was 24 years. Average time to ESRD was 2 years. Drivers of disease included nephritic factors (NF, n=5), gene mutations (n=2), and a monoclonal protein (n=1). Median follow-up time post-transplant was 5 years. At transplantation, 6 patients had a low C3 level. In the five patients with a NF at the time of transplant, the NF remained positive at follow-up. Disease recurrence was noted in 2 patients (both within the first year of transplant). One was positive for a nephritic factor, one had only NF and C3 mutation. One patient had histologic recurrence. This patient was both nephritic factor negative and with normal genetics. All patients with recurrence had a low C3 at the time of recurrence. All nonrecurring patients have a normal C3.

Conclusions: Considering this preliminary data, having a low C3 appears to predict risk for C3G recurrence. It remains unclear what a role a persistent nephritic factor tier may have. Our data suggest the impact of this tier may change over time. We have extended the collection of the clinical parameters and the complement biomarker evaluation for each subject in this cohort - with the express goal of creating a predictive model for C3G recurrence.

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SA-PO630
Risk Factors for Biopsy Complications in Initial vs. Subsequent Biopsies in Native and Transplant Kidneys
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Background: There are few studies about risk factors for complications in initial (ib) versus subsequent (sb) biopsies. Biopsy complications are divided in major (require an intervention) and minor (resolve without intervention). The aim of the study was to explore the risk factors for complications in ib versus sb in native (nk) and transplant (tk) kidney biopsies (tkb) which may serve as predictors for biopsy complications.

Methods: In a multi-center study, 2830 nkbi (4.3% sb) were analyzed for major and 667 tkb (29% sb) for major and minor complications. No death or nephrectomy was described. Fisher’s exact, t-test (mean values) and χ2 test were used. A two sided p-value <0.05 was considered significant.

Results: In nkbi, the frequency for major biopsy complications was 5.6% in ib and 4.9% in sb. In tkb, the biopsy complication frequency was 4% major and 2.5% minor in ib; in sb 3.5% major and 3.5% minor. In initial nkbi, the frequency of major complications were higher in women compared to men (7.1% vs 4.6%; Odds Ratio 1.6, Confidence Interval 1.1-2.2), in younger patients (50 vs 54years, p=0.007) and in patients with lower weight (78 vs 82kg, p=0.005). In subsequent nkbi, patients with major complications had a higher systolic blood pressure (145 vs 132mmHg, p=0.03). In initial tkb, biopsies with major complications had less glomerulitis in the biopsy (17 vs 24, p=0.04) and biopsies with minor complications were from younger patients (42.5 vs 52years, p=0.027) and patients with lower BMI (22 vs 26, p=0.049). Risk factors for overall complications in initial tkb were younger age (46 vs 52years, p=0.028) and less glomerulitis in the biopsies (18 vs 24, p=0.04). In subsequent tkb, patients with major complications had a higher systolic (151 vs 136mmHg, p=0.03) and diastolic blood pressure (93 vs 79mmHg, p=0.003). For minor and overall complications in subsequent tkb, no risk factors were found. In nkbi, in sb there was a higher number of SLE-nephritis (22% vs 6%, p=0.001), lower number of nephroclerosis (4.3% vs 10.3%, p=0.02) and diabetic nephropathy (3.4% vs 9.3%, p=0.02) compared to ib; in tkb no differences were found.

Conclusions: The different types of risk factors for biopsy complications in initial versus subsequent biopsies in native and transplant kidneys could be important for the clinicians to improve patients’ safety.

SA-PO631
Infection-Related Glomerulonephritis and Analysis of Clinical Outcomes: Experience in South India
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Background: There has been a major shift in the causative agents, clinical presentation, epidemiology and the treatment outcomes of IRGN in the developing nations.

Methods: A retrospective analysis of 100 IRGN consecutive cases were studied from our hospital records, percutaneous renal biopsy was done in all the patients and the tissue has been processed for LM IF and EM after appropriate staining for clinical and pathological characteristics.

Results: A retrospective analysis of 100 IRGN consecutive cases were studied from our hospital records, percutaneous renal biopsy was done in all the patients and the tissue has been processed for light microscopy, immunofluorescence and electron microscopy after appropriate staining for clinical and pathological characteristics. Results: A total of 73 patients were analyzed after exclusion. The mean age of the presentation was 41.8±4.15. Majority (51%) were females. Common infection sources were UTI (33%) and foot ulcer (33%). Most common clinical presentations were shortness of breath (45%), Anasarca (38%) and fever (36%). All the patients had micro hematuria (100%). The mean creatinine at presentation was 3.37±2.47 mg/dl with an average proteinuria of 2.43±1.28 g/day. 94% had low C3, 8% had low C4, 8% had low C3,C4. 55% c4d negative out of c4d negative, 38% are c3 dominant and 63% are c3 dominant. Mean serum creatinine at presentation 4.1±2.6 and 3.3±2.5 (p value:0.8). Proteinuria between two groups was statistically significant. On light microscopy, the most common histological pattern of injury is endocapillary proliferation with neutrophil in mesangial tufts. Immunofluorescence pattern revealed immunoglobulin and C3 dominant staining commonly. Mean GMB thickness was seen in 358 vs99.2. Diffuse effacement was seen in 13 patients, focal effacement was seen in 27 patients. 23% patients needed hemodialysis and 8% needed plasmapheresis at presentation. 20% patients needed peritoneal dialysis. At the end of 1 year, 35% patients had persistent hypertension and 30% patients had persistent renal dysfunction. Persistent proteinuria was noted in 17 % of patients and persistent hematuria was seen in 30 % of patients at 1 year follow up. Spot PCR and creatinine c4d negative C3 dominant and codoominant groups was not significant at 1 year.

Conclusion: Male sex, age>40 years, creatinine>5 mg/dl, dialysis requirement at presentation were independently associated with poor renal outcomes.

Funding: Clinical Revenue Support

SA-PO632
Success and Safety of Native Kidney Biopsies Guided and Performed by Nephrologists
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Background: Percutaneous kidney biopsy is a key procedure in nephrology and a requirement for training, but is often not performed by nephrologists, even in training programs. The reasons are manifold but include concerns about competence and safety, particularly the perceived need for real-time ultrasound guidance. To address this, we examined the outcomes of ultrasound-guided biopsies performed in their entirety by nephrologists at this institution.

Methods: All native kidney biopsies performed by the Renal Division at Emory University Hospital for clinical indications from 1/1/2008 to 9/30/2018 were identified from a database of ultrasound studies performed by the Division. Medical records were reviewed to determine clinical characteristics and outcomes. Large hematomas, gross hematuria, hypotension, transfusion, or endovascular intervention were considered clinically important complications.

Results: We identified 422 biopsies that were performed by 70 trainees (1-12 procedures each; median: 5) with the supervision or assistance of 22 faculty (1-105 procedures each; median: 5). Forty three were performed by faculty alone. Patient age was 45.6 ± 0.8 (13-84) and body mass index (BMI) 27.2 ± 0.3 kg/m2 (16.2-52.3). All biopsies were performed with a Monoply 18g device with a 1.7 cm sampling length (Bard Peripheral Vascular, Tempe, AZ). In 93%, the kidney was located by ultrasound prior to but not during the biopsy, with an 18.8 cm, 20g needle used to confirm the location and provide deep anesthesia. In 7%, ultrasound was used during the procedure (real-time guidance). Of the characteristics of the biopsies were: left kidney 91%, prone position 99%; end-inspiration 51%; end-expiration 44%; depth 5.4 ± 0.08 cm (2-11). Tissue was obtained in 98.6% (adequate for diagnosis in 96.9%) with 3.56 ±0.07 (1-10) passes and 94% had a successful biopsy. Persistent proteinuria was noted in 15 % of patients and persistent hematuria was seen in 30 % of patients at 1 year follow up. Spot PCR and creatinine c4d negative C3 dominant and codoominant groups was not significant at 1 year.

Conclusion: Male sex, age>40 years, creatinine>5 mg/dl, dialysis requirement at presentation were independently associated with poor renal outcomes.

Funding: Clinical Revenue Support
**SA-PO635**

The Effect of Intravenous Tranexamic Acid in Percutaneous Renal Biopsy: A Randomized Controlled Trial

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**Background:** Tranexamic acid is an antifibrinolytic agent, and the evidence of its benefit for major surgery and trauma has accumulated. We aimed to assess whether intravenous tranexamic acid reduces hematoma sizes after percutaneous renal biopsy.

**Methods:** We conducted a randomized, triple-blind, placebo-controlled trial at a teaching hospital in Japan between January 2016 and July 2018. We included adult patients who had a clinical indication of percutaneous renal biopsy. High-dose tranexamic acid (500 mg), low-dose tranexamic acid (250 mg) or counterpart saline (placebo) was intravenously injected (twice, with bolus just before the biopsy and continuous infusion initiated just after the biopsy. On the morning of the biopsy day, patients were randomly assigned to either of the three groups. The primary outcome was the post-biopsy perirenal hematoma size measured by ultrasound on the next morning of the biopsy. According to the predefined protocol, a closed testing procedure with Wilcoxon rank sum test was used to adjust the multiple comparisons of the tranexamic acid groups (high-dose and low-dose) with the placebo control group. Thus, if the high-dose group was statistically significant against the control group, the low-dose group was compared with the placebo group. All analyses were done on an intention-to-treat basis. The trial was registered with UMIN-CTR, number UMIN000019830.

**Results:** We randomly allocated 56 patients into the three groups: 20 in the high dose group, 19 in the low dose group, and 17 in the placebo group. The median post-biopsy hematoma sizes were 200 mm³ (IQR 21–650) in the high dose group, 52 mm³ (0–119) in the low dose group, and 0 mm³ (0–339) in the placebo group. The results of Wilcoxon rank sum test for the comparison of the high dose group with the placebo group was p=0.047 and that of the low dose group with the placebo group was p=0.047.

**Conclusions:** High dose tranexamic acid compared to placebo increased perirenal hematoma size after percutaneous renal biopsy. Since the mechanism of increased bleeding in this drug is unknown, we need to confirm the findings in further large randomized controlled trials.

**SA-PO634**

Biofluid MicroRNA Expression Patterns in Three Types of Naturally Occurring Canine Models for Glomerular Disease

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**Background:** The majority of proteinuric dogs with naturally-occurring chronic kidney disease (CKD) have one of three categories of glomerular diseases: immune complex-mediated (often membranous glomerulopathy [MGN]), glomerulosclerosis (GS), or amyloidosis (AMYL). As in humans, proper treatment of glomerular disease relies on an accurate diagnosis largely based on a renal biopsy and comprehensive pathologic examination. We hypothesized that the expression pattern of biofluid microRNA (miRNAs) would correlate with disease progression and categorization.

**Methods:** Archived serum and urine samples from 24 dogs, 6 proteinuric dogs from each glomerular disease category (MGN, GS, and AMYL) and 6 clinically healthy dogs were selected. Within each glomerular disease category, equal numbers of non-azotemic and azotemic dogs were included. Circulating and urinary miRNAs were isolated and profiled using small RNA sequencing.

**Results:** Overall, 38 circulating miRNAs and 16 urinary miRNAs were differentially expressed (DE) in CKD dogs versus controls. When all CKD dogs were combined regardless of glomerular disease category, no circulating DE miRs were identified between azotemic and non-azotemic CKD dogs. However, DE urinary miR-182, miR-21, and miR-486 were identified comparing azotemic dogs versus non-azotemic CKD dogs. Notably, the distinctive expression of urinary miR-126, miR-335, and miR-128 could correctly group azotemic, proteinuric dogs into MGN, GS, or AMYL.

**Conclusions:** This unique finding supports that urinary miRNAs might help establish a diagnosis in azotemic dogs with suspected glomerular disease. These highly conserved miRNAs are potential non-invasive biomarkers for human patients.

**Funding:** Private Foundation Support

**Diffusely expressed miRNAs in proteinuric dogs with three types of glomerular disease**
SA-PO636

The Impact of Desmopressin on Native Kidney Biopsy Complications
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Background: As bleeding is a feared complication of native kidney biopsy (NKB), nephrologists often prescribe desmopressin in an attempt to lower its occurrence especially for patients with reduced estimated glomerular filtration rate (eGFR) as risk of uremia-related platelet dysfunction. However, only one randomized study has analyzed its effect before NKB on patients with eGFR >60 mL/min/m² whereas retrospective studies on more likely to better eGFR (≥50 mL/min/m²) are contradictory.

Methods: This study aims to evaluate the impact of desmopressin on complications after NKB. We reviewed medical records of every adult patient who had a NKB at our tertiary teaching hospital from April 2013 to April 2018. We collected data concerning the medical history of each patient and their clinical parameters before and after each NKB. We used multivariate logistic regressions to evaluate the effect of desmopressin on the occurrence of hemorrhagic fall, transfusions, hypotension, acute kidney injury (AKI), hematoma and additional radiologic examinations.

Results: Among the 413 NKB analyzed, 79.4% were done after a dose of desmopressin. Patients who received desmopressin had more severe chronic kidney disease at baseline (eGFR 39 vs 54 mL/min/m²; p=0.0003) and were more often hospitalized before the occurrence of hemoglobin fall, transfusions, hypotension, acute kidney injury (AKI), hematoma and additional radiologic examinations.

Conclusion: Our results were affected by an indication bias, because sicker patients were more likely to receive desmopressin and desmopressin and were more likely to undergo additional radiologic examinations (OR=0.22; 95%CI: 0.07-0.73; p=0.01) in the desmopressin group. Desmopressin had a neutral effect on other potential complications (see table) and on hyponatremia.

SA-PO637

Proximity of Residence to Silica Mines as a Risk Factor for Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis
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Background: Anti-neutrophil cytoplasmic antibody-associated vasculitis is a rare necrotizing vasculitis affecting small to medium-sized vessels, with renal involvement usually presenting with a rapidly progressive glomerulonephritis. There is evidence to suggest that silica exposure is associated with the development of ANCA vasculitis. The incidence of ANCA vasculitis in Queensland, Australia was 0.47 per 100,000 people/year from 2002 to 2011; and there is a high density of silica mines, with approximately 2 per 1,000,000 population in 2011. The aim of the study was to examine whether residing close to silica mines is associated with development of ANCA vasculitis.

Methods: This retrospective cohort study compared patients with a biopsy-proven ANCA vasculitis to 1,000,000 population in 2011. The aim of the study was to examine whether residing close to silica mines is associated with development of ANCA vasculitis.

Results: Among the 413 NKB analyzed, 79.4% were done after a dose of desmopressin. Patients who received desmopressin had more severe chronic kidney disease at baseline (eGFR 39 vs 54 mL/min/m²; p=0.0003) and were more often hospitalized before the occurrence of hemoglobin fall, transfusions, hypotension, acute kidney injury (AKI), hematoma and additional radiologic examinations.

Conclusion: Our results were affected by an indication bias, because sicker patients were more likely to receive desmopressin and desmopressin and were more likely to undergo additional radiologic examinations (OR=0.22; 95%CI: 0.07-0.73; p=0.01) in the desmopressin group. Desmopressin had a neutral effect on other potential complications (see table) and on hyponatremia.

SA-PO638

Urine Aquaporin-2 Messenger RNA Predicts Global Glomerulosclerosis and Renal Outcome in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis
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Background: Despite substantial progress in the treatment for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), the prognosis of patients with AAV has not significantly improved. The poor prognosis is not only caused by the activity of AAV but also caused by adverse events due to the therapeutic agents. Avoiding excessive immunosuppression can lead to an improvement in the prognosis. Useful and noninvasive predictor for renal outcome is needed. We recently announced that urine aquaporin 2 (U-AQP2), which is a water channel localized in the renal collecting ducts, mRNA predicts the renal outcome in AAV at the 56th ERA-EDTA Congress in Budapest, 2019. Here, we examined the association between U-AQP2 mRNA and renal biopsy tissue.

Methods: We enrolled 33 patients with AAV diagnosed at Miyazaki University Hospital from January 2009 to March 2016. Their U-AQP2 mRNA levels at the onset of AAV were evaluated by real-time polymerase chain reaction, and normalized by urine creatinine concentration. We divided them into two groups (High U-AQP2 group (n=7) and Low U-AQP2 group (n=26)) based on mean value of U-AQP2 mRNA and performed Kaplan-Meier analysis to assess renal survival in two groups. We also examined the renal biopsy tissues of each group.

Results: High U-AQP2 group showed poorer renal prognosis than Low U-AQP2 group (p<0.05). Analysis of renal histology in each group revealed that renal lesions caused by remission-inducing drugs after adjustment for potential confounders, desmopressin seems to reduce post-biopsy symptomatic hematoma and additional radiologic examinations, implying important clinical and financial benefits.

Conclusions: Our results could suggest severe glomerular damage caused by AAV affecting the renal function. U-AQP2 mRNA may be able to detect drug lesions that are difficult to diagnose in kidney biopsy tissue. U-AQP2 could predict irreversible damage by AAV.

SA-PO639

Improved Survival due to Better Renal Outcomes in Danish Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis (AAV) During the Years 2000-2015: A Nationwide Study
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Background: AAV (Granulomatosis with polyangiitis and microscopic polyangiitis) carries significant risk of morbidity and mortality, notwithstanding adequate treatment. Contemporary large-scale descriptive studies have been challenged by the rare occurrence of these diseases. Accordingly, by use of Danish nationwide healthcare registries, we examined the temporal progression of incidence and prognosis of AAV during 2000-2015.

Methods: All patients with incident AAV, regardless of primary organ manifestation were included by use of ICD10 diagnostic codes (positive predictive value of >90%) and grouped in five-year intervals (P1: 2000-2004, P2: 2005-2009, P3: 2010-2015). Absolute risk ratios (ARR) adjusted for age, sex and advanced disease severity (>10 days of initial hospital stay), as well as cumulative incidences were computed in R version 3.5.0.

Results: We identified 1634 patients (52% male), corresponding to an overall incidence of 18.2 persons/million/year (P1: 12.1; P2: 16.3; P3: 21.0), and 425 (26% [P1: 33.6%; P2: 28.9%; P3: 19.4%]) met the criteria of advanced disease severity. Mean age was 60.3 (IQR 21.0) years and mean follow-up was 5.9 (IQR 4.0) years. 571 (34.9%) patients died (uncensored 5-year mortality of 20.3%) resulting in an ARR for P2 and P3 as compared to P1 of 0.80 (CI 0.65-0.97, P=0.028), and 0.40 (CI 0.30-0.51, P<0.001) 274 patients developed end-stage renal disease (16.8% [P1: 23.3%; P2: 17.6%; P3: 12.5%]), similarly with ARR decreasing over time: P2 0.62 (CI 0.43-0.89, P=0.009) and P3 0.54 (CI 0.37-0.78, P=0.001) relative to P1. The overall risk of death associated with need of dialysis or chronic kidney involvement within 30 days of discharge as compared to no discharge at presentation was 1.81 (CI 1.40-2.33, P=0.001) and 1.39 (CI 1.11-1.76, P=0.005). During follow-up 526 (32.2% [P1: 39.6%; P2: 30.4%; P3: 29.3%]) patients developed chronic kidney disease.

Conclusions: AAV remain a group of diseases associated with high morbidity and mortality. However, although incidence of AAV is increasing, the absolute risk of death appears to be declining, putatively in part due to earlier detection of incident episodes and better renal outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Predictors of Renal Involvement in ANCA-Associated Vasculitis

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Background: Renal involvement in the context of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is associated with significant morbidity and higher mortality rates. This study examined predictive factors associated with renal involvement in AAV using a large, international cross-sectional cohort.

Methods: Univariate and multivariate analyses were performed to identify risk factors associated with renal disease, which was defined as i) an increase of serum-creatinine > 30%; ii) a fall in creatinine-clearance < 25% or iii) haematuria attributable to active vasculitis.

Results: Of the 1230 patients eligible, 723 patients (58.8%) presented with renal inflammation. The majority of patients with microscopic polyangiitis (82.2%) and granulomatosis with polyangiitis (58.6%) had renal involvement, while 26.4% with eosinophilic granulomatosis with polyangiitis presented with renal vasculitis. The following clinical factors were more common among patients with renal disease that among patients without renal disease. Older age (p = 0.001), fever (p < 0.005), fatigue, weight loss (p = 0.001), polychromatophilia (p = 0.036), petechiae/purpura (p = 0.022), pulmonary haemorrhage (p = 0.014), gastrointestinal symptoms (p = 0.002), serum albumin below 30 g/l (p < 0.001), higher CRP (p = 0.038), low C3 at baseline (p = 0.015), ANCA positivity (p = 0.001), myeloperoxidase-ANCA (p = 0.001) and proteinase 3-ANCA (p = 0.020). Patients with proptosis/exophthalmos (p = 0.001), saddle nose deformity (p = 0.015), nasal polyps and nasal septal defect/perforation (p = 0.001 each), respiratory distress/pulmonary fibrosis/ asthma (p = 0.001) or wheezing/obstructive airway disease (p = 0.001) had a lower likelihood of developing renal involvement.

Conclusions: In this large international study, we identified clinical factors associated with renal involvement in AAV, including concomitant pulmonary alveolar haemorrhage, low C3, and elevated C-reactive protein. Further large studies are necessary to confirm our findings.

Chorioretinal Thickness Reflects Disease Activity in ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) is characterised by autoimmune-mediated injury of small blood vessels and often requires renal biopsy for diagnosis. A non-invasive means of detecting this microvascular injury would be of major clinical value. The eye acts as a window to the systemic microvasculature. Retinal optical coherence tomography (OCT) provides cross-sectional imaging of the retina and highly vascularized choroid with near-histological resolution. We have shown that systemic and renal inflammation associates with choroidal thinning. We hypothesized that OCT metrics would reflect disease activity in AAV and be modified with treatment.

Methods: We prospectively recruited 50 patients with active AAV and 50 age- and sex-matched healthy controls, excluding those with diabetes and previous eye disease. AAV patients were studied prior to receiving immunosuppression and once in disease remission defined by a Birmingham Vasculitis Activity Score (BVAS) of 0 for a least 2 months on low dose steroid. All subjects were imaged with the Heidelberg SPECTRALIS® OCT device.

Results: AAV patients had a mean (±SD) age of 60.14±14 years, 20 (50%) were male and 24 (60%) were PR3+. Median (range) BVAS at entry was 13 (3-21). 30 (75%) patients were new presentations and 26 (65%) had renal involvement. Mean (±SD) choroidal thickness was thinner in active AAV patients compared to healthy: location I 202.84±24.88±76mm; location II 279.93±331.63±96mm; location III 276.90±306±65mm; all p<0.05. Choroidal thickness correlated negatively with baseline BVAS, r=-0.57, p<0.05. Following disease remission, choroidal thickness increased by ~10% compared to active disease, p=0.01 at location I, Figure 1.

Conclusions: Active AAV is associated with choroidal thinning compared to healthy. This improves with successful treatment. OCT-derived metrics may be a novel means of assessing disease activity and treatment response in AAV. Larger studies will explore these findings further.

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Underlines represent presenting author.
Conclusions: Pauci-immune GN, which constituted only 17% of our cohort, was associated with a significant risk of ESKD at 1 year. Different risk factors at time of biopsy are associated with ESKD at 1 year in pauci immune GN compared to IC GN.

SA-PO644
Benefit or Burden: A Systematic Review and Meta-Analysis of Treatment Outcomes of ANCA-Associated Vasculitis in Patients Older Than 75 Years
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Background: Despite a peak incidence of 64-75 years, the benefit of treating ANCA-associated vasculitis (AAV) in older patients remains unclear with most published studies defining elderly as ≥65 years. This study aims to determine outcomes of induction immunosuppression therapy in patients aged ≥75 years.

Methods: A cohort aged ≥75 years with biopsy proven AAV was constructed from a single centre between 2006–2016. Follow up was to two years or death. Analysis included multivariate Cox regression to compare mortality and ESRD based on induction immunosuppression therapy. A systematic review of outcome studies was subsequently undertaken amongst this patient group through Pubmed, Cochrane and Embase databases from inception until 13/09/18.

Results: From 145 patients, 59 were ≥75 years, of which 51 had completed data. Mean age was 78.9±2.7, 54.9% were male and mean modified Charlson comorbidity index was 1±1.3. 76% (p=0.01) received induction therapy. The systematic review identified 1943 citations. Four studies were eligible for inclusion, yielding a combined total of 274 patients inclusive of our cohort. The aggregated one year mortality irrespective of treatment was 36% (CI 27–47%). Within our cohort, induction immunosuppression therapy was associated with a lower two-year mortality risk, although not statistically significant [HR 0.75 (95% CI 0.23–2.49)]. However, the pooled HR by meta-analysis revealed a significant risk reduction for death [HR 0.44 (95% CI 0.25–0.76), p=0.04]. Treated patients had a lower pooled rate of ESRD, but was not statistically significant [HR 0.76 (95% CI 0.37–1.59)].

Conclusions: This meta-analysis suggests that patients ≥75 years with AAV do benefit from induction immunosuppression with a significant survival benefit. Age should not be a limiting factor when considering treatment. Further trials are required to better evaluate renal outcomes amongst this age group.

SA-PO645
ANCA-Associated Vasculitis with AKI: KDIGO AKI Stage, Short-Term Recovery, and Long-Term Outcome
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Background: To study KDIGO AKI stages and its association with short-term and long-term outcome in patients with ANCA associated vasculitis.

Methods: We retrieved data of 154 patients who combined with AKI (including AKI on chronic kidney disease) and not requiring maintaining renal replacement therapy 3 months after admission. In these 154 patients, 14 were lost to follow up. The remaining 140 patients were staged from 1 to 3 according to AKI criteria based on KDIGO guideline. Short-term recovery was assessed based on the serum creatinine level change, and patients were divided into 2 groups: ≤30% decline (G1), and <30% decline or rise (G1) at 3 months comparing to pre-episode baseline. Long term renal endpoint was defined as: reaching an eGFR level of <15ml/min/1.72m² or requiring maintaining renal replacement therapy for more than 3 months. Univariate analysis and multivariate analysis were used to compare the outcome.

Results: At admission, 49(35%) were in AKI stage 1, 53(37.0%) in stage 2 and 38(27.1%) were in stage 3. Three months after admission, there were 75 patients in G1, and 65 patients in G2(including 24 patients with rising serum creatine level). No significant differences in age and gender(p=0.05) were found. AKI stage(p=0.001), 24h urine protein (p=0.012) and urine red blood cell per uL(p=0.015) were found associated with short-term recovery. Twenty-three patients reached the renal endpoint during the median follow-up duration of 54(32,79) months. The renal survival rates of AKI stage 1 patients were 91.9%, 79.0% and 72.0% in stage 2 and 71.8% and 70.3% in stage 3, Kaplan-Meier analysis showed significant difference (p=0.034). Additionally, renal survival rates were 90.7% in G1 and 75.4% in G2, and Kaplan-Meier analysis showed significant difference between the two groups (p=0.013). The COX model suggested that high AKI stage (OR=5.765, 95%CI 1.880–17.619; p=0.002), high baseline serum creatine (OR=1.038,95%CI 1.001– 1.075, p=0.027), and G1(OR=0.084, 95%CI 0.010-0.37) were independent risk factors of renal outcome in patients with ANCA associated vasculitis.

Conclusions: In patients with ANCA associated vasculitis, AKI stage, 24h urine protein and hematuria were associated with short-term outcome; AKI stage, baseline scr, and serum creatinine recovery level at 3 months were independent risk factors of long-term renal outcome.

SA-PO646
Analysis of Clinical Features in ANCA-Associated Vasculitis with Moderately Progressive Glomerulonephritis: Thirty-Five Years of a Single-Center Experience
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Background: The clinical features of AAV, with regard to renal involvement, may have been changing recently in Japan, where MPO-ANCA-associated vasculitis (MPO-AAV) are dominant in contrast to the Western countries. Thus, we retrospectively analyzed the clinical database of the141 AAV-patients with RPGN who were admitted to our hospital for the last 35 years.

Methods: At the onset, all patients fulfilled the Chapel Hill Consensus Conference (CHCC) classification criteria for MPA, GPA and EGPA. 141 patients (56 male, 85 female: Mean age 57±9.6 years). 133(94.1%) patients were subjected to renal biopsy. A total of 145 patients were included multivariate Cox regression to compare mortality and ESRD based on induction immunosuppression therapy. A systematic review of outcome studies was subsequently undertaken amongst this patient group through Pubmed, Cochrane and Embase databases from inception until 13/09/18.

Results: From 145 patients, 59 were ≥75 years, of which 51 had completed data. Mean age was 78.9±2.7, 54.9% were male and mean modified Charlson comorbidity index was 1±1.3. 76% (p=0.01) received induction therapy. The systematic review identified 1943 citations. Four studies were eligible for inclusion, yielding a combined total of 274 patients inclusive of our cohort. The aggregated one year mortality irrespective of treatment was 36% (CI 27–47%). Within our cohort, induction immunosuppression therapy was associated with a lower two-year mortality risk, although not statistically significant [HR 0.75 (95% CI 0.23–2.49)]. However, the pooled HR by meta-analysis revealed a significant risk reduction for death [HR 0.44 (95% CI 0.25–0.76), p=0.04]. Treated patients had a lower pooled rate of ESRD, but was not statistically significant [HR 0.76 (95% CI 0.37–1.59)].

Conclusions: This meta-analysis suggests that patients ≥75 years with AAV do benefit from induction immunosuppression with a significant survival benefit. Age should not be a limiting factor when considering treatment. Further trials are required to better evaluate renal outcomes amongst this age group.

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3.3-42.8 ml/min/1.73 m², p=0.005). The presence of C3 in the kidney biopsy did not predict the risk of relapse. However, the presence of C3 in the kidney biopsy may indicate a more severe disease or a higher likelihood of relapse.

**Conclusions:** The presence of C3 in the kidney biopsy is a significant predictor of relapse in ANCA-GN patients. It may help in the management of these patients by indicating the need for more aggressive treatment strategies.

**Figure:** A flowchart showing the diagnostic criteria and treatment strategies for ANCA-GN.

**Table 1:** Summary of histopathological features in ANCA-GN patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>ANCA-negative</th>
<th>ANCA-positive</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histological feature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% Necrotic Glomeruli/Total Glomeruli</td>
<td>5 (50.0%)</td>
<td>1 (10.0%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Crescentic lesions</td>
<td>3 (30.0%)</td>
<td>1 (10.0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Sclerotic lesions</td>
<td>3 (30.0%)</td>
<td>1 (10.0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Fibrous crescents</td>
<td>4 (40.0%)</td>
<td>1 (10.0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Immune complexes</td>
<td>1 (10.0%)</td>
<td>1 (10.0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Vascular wall necrosis</td>
<td>4 (40.0%)</td>
<td>1 (10.0%)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td>7 (70.0%)</td>
<td>7 (70.0%)</td>
<td>0.31</td>
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**References:**


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**929**
Glomerular Diseases: ANCA, Anti-GBM, Kidney Biopsy

SA-PO652
Prognostic Impact of Interstitial Fibrosis for Progression to ESRD in ANCA-GN

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Background: Interstitial fibrosis (IF) is a well-known risk factor for progression to ESRD in patients with ANCA glomerulonephritis (GN). However, few studies have reported its role as an independent risk factor as determined by multivariate analysis on patients with ANCA-GN.

Methods: Patients with ANCA-GN and ESRD graded as none-mild focal (<25%)/severe focal (25-50%)/diffuse (>50%) and other base-line risk factors, were obtained from the Norwegian Kidney Biopsy Registry. The observation period was from the date of biopsy to date of ESRD/death/end of 2013. ESRD and deaths during follow-up were identified by record linkage with The Norwegian Renal Registry. The primary end-point of the study was progression to ESRD within 3-years after diagnosis of ANCA-GN.

Results: Unadjusted, increasing degrees of IF is a strong risk factor for progression to ESRD in ANCA-GN. Severe focal versus mild focal IF: Unadjusted HR 5.7 (2.6-12.6) p<0.001 and adjusted HR 2.3 (0.9-5.6) p=0.07. Diffuse versus focal mild IF: Unadjusted HR 5.7 (2.6-12.6) p<0.001 and adjusted HR 2.3 (0.9-5.6) p=0.07. Diffuse or severe focal versus mild focal IF: Unadjusted HR 3.8 (2.1-7.0) p<0.001 and adjusted HR 2.0 (1.1-3.9) p=0.03. Diffuse versus severe focal: Unadjusted HR 1.9 (0.9-4.0) p=0.11 and adjusted HR 0.8 (0.3-2.0) p=0.63.

Conclusions: Unadjusted, increasing degrees of IF is a strong risk factor for progression to ESRD in ANCA-GN. Adjusted for other known risk factors IF > versus ≤ is a predictor of progression to ESRD in ANCA-GN. Our finding suggests that IF should be included in multi-factor models aiming at predicting risk of progression to ESRD in ANCA-GN.

SA-PO653
Histopathologic Predictors for Renal Outcome in Crescentic Glomerulonephritis

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Background: Crescentic glomerulonephritis (CGN) results in serious decline of renal function, but the prognostic factors are not known in detail. We evaluated the long-term renal outcome and prognostic predictors of CGN according to histopathologic information obtained by renal biopsy.

Methods: Among 133 patients diagnosed as CGN between 2010 and 2018 from two university-based hospitals, we retrospectively analyzed 117 patients whose biopsy specimen contained more than 10 glomeruli. Specimens were categorized into four classes according to anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis classification. The severity of arterial fibrointimal thickening was assessed by semi-quantitative method between grade 0 and 3. Cox proportional analysis was used to calculate hazard ratio (HR) for renal survival and linear regression analysis was performed for one-year estimated glomerular filtration rate (eGFR).

Results: The mean age was 60.9 ± 15.5 years and male was 49.6%. The mean eGFR was 19.5 ± 16.5 mL/min/1.73m² and hemodialysis was required in 38 patients (32.5%) initially. Ninety-nine patients (77.8%) showed positive for ANCA and 11 patients (9.4%) showed positive for anti-glomerular basement membrane antibody. Fifty-nine patients (50.4%) had advanced to end-stage renal disease (ESRD) during the mean follow-up of 34.1 months. Patients with sclerotic type had worse renal survival than focal type (HR: 3.30 [95% CI, 1.18-9.17], P=0.022), and moderate to severe arterial fibrointimal thickening was also associated with poor renal survival (grade 2: HR, 2.51 [95% CI, 1.18-5.37], P=0.017; grade 3: HR, 2.82 [95% CI, 1.21-6.57], P=0.016). Tubulointerstitial rounded dense lymphocyte aggregation was observed in 32 patients (27.5%) and was also a prognostic factor for ESRD (HR, 1.76 [95% CI, 1.03-2.99], p=0.039). In the multivariate linear regression analysis, sclerotic type, severe tubular atrophy, age, and baseline eGFR were independent predictors of eGFR at one year after biopsy (all, P<0.05).

Conclusions: Specific histopathologic findings, such as higher proportion of sclerotic glomeruli, moderate to severe arterial fibrointimal thickening, and presence of tubulointerstitial lymphocyte aggregation, provide helpful information for predicting the renal outcome in patients with CGN.

SA-PO654
Validation of a New Renal Risk Score for Patients with ANCA-GN

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Background: A new predicting model, renal risk score in ANCA-associated GN, was published by Brix et al. in Kidney International Dec. 2018. It is a general principle that prognostic models need external validation for determination of generalizability.

Methods: Patients with ANCA-GN and risk factors included in the prognostic model; GFR ≤15 mL/min/1.73m² (G1), eGFR ≤15 mL/min/1.73m² (G1), and percentage of IF were independent normal glomeruli (<25% normal glomeruli), were identified in the Norwegian Kidney Biopsy Registry. According to the model, risk score points were assigned: G1-3, N1-4, N2-6, T1-2. Further, risk stratification was performed according to the model as low risk (≤0 points), medium risk (0-2 points), high-risk (2-7 point).

Results: Kaplan-Meier and the ROC statistics were used to evaluate the prognostic performance of the model.

Conclusions: We identified 250 patients with ANCA-GN of whom 43 progressed to ESRD during follow-up. At 3-years of follow-up cumulative risk of ESRD was 3.3% in low-, 22.4% in intermediate- and 44.0% in the high-risk group, p=0.001. In the ROC analysis AUC was 0.77 when assessed as 3 risk groups and 0.78 when assessed according to number of risk points.

Conclusions: We demonstrate that the prognostic value of this new prediction model for patients with ANCA-GN is good with an AUC of nearly 0.8 in the ROC analysis. However, the use of percentage normal glomeruli instead of glomerular classification (focal/crescentic/mixed/sclerotic) needs confirmation in larger cohorts. Further, the choice of grading initial IF in only 2 groups > versus ≤ is also slightly surprising that demographic risk factors like age and gender are not included.

SA-PO655
Pauci-Immune Glomerulonephritis (PIGN) with Low Clearance at Clinical Presentation: Predictors of Treatment Response and Long-Term Outcomes

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Background: Pauuci-immune vasculitis often presents with severe kidney involvement requiring hemodialysis. Considering the poor prognosis in this setting, we aimed to explore the factors which are associated with response to therapy.

Methods: Patients were included if they had biopsy proven PIGN with estimated GFR<20 mL/min/1.73 m² or required dialysis at presentation, received standard immunosuppression and had a follow up >6 months. We recorded clinical, laboratory and histopathological parameters at diagnosis, at 3 months, at 1 year and at the end of follow up. Outcomes of interest included response to treatment, ESKD, and death. Treatment response was defined by the ability to come off dialysis with an eGFR>20 mL/min/1.73 m² with no signs of vasculitis. Histopathological evaluation included arteriolsclerosis, % of normal glomeruli, activity index, chronicity index.

Results: A total of 77 patients, with a mean age of 60.6(16.0) years were included. There were, 42 males (54.5%). After 3 months, 55 patients (74.6%) had responded to immunosuppressive therapy, 15 (20%) were dialysis dependent, 5(6.7%) died and 2 were lost in follow up. By the end of the 1st year, 54 patients (71.4%) achieved remission, 15(20%) ended up in ESKD and 6(8%) died. Factors which were associated with treatment response included MPO-ANCA positivity [odds ratio OR:3.9, 95% CI[1.13-13.37] p=0.03], eGFR<10/mL/min/1.73m² at presentation [OR:2.5, 95% CI(0.86-7.30), p=0.009], normal glomeruli >10% [OR:3.8, 95% CI[1.24-12.1], p=0.02], and chronicity index more than 6 [OR:6.2, 95% CI[1.77-22.4], p=0.004]. Risk factors associated with ESKD included non-response to immunosuppressive therapy [Relative Risk RR:0.05, 95%CI(0.01-0.2) p<0.0001], normal glomeruli<10% in the diagnostic biopsy [RR:18.6, 95% CI[3.8-96.3], p=0.005] and age<75 years [RR:3.2, 95% CI (9.01-6.0) p=0.052]. Two of the 6 deaths were related disease.
Conclusions: A significant proportion of patients with PIGN who presented with severe renal dysfunction, responded to immunosuppressive therapy and recovered renal function approximately 3 months after initiation of therapy. Risk factors for ESKD were aged<75 years, <10% normal glomeruli in the diagnostic biopsy and non-response to immunosuppressive therapy.

SA-PO656

Long-Term Outcomes of Patients with ANCA-Associated Vasculitis (AAV) Presenting with Severe Renal Dysfunction

Background: Rapidly progressive glomerulonephritis (RPGN) is an important cause of severe renal dysfunction and mortality in AAV. Few studies have specifically addressed the outcome of patients presenting with severe RPGN, traditionally defined as dialysis-dependence or a serum creatinine (SCr) of over 500µmol/l, and in particular the benefit of plasma exchange (PEX). Recent research has challenged the role of PEX in this patient set. Here we describe the long-term patient and renal outcomes in a large cohort of patients with severe RPGN treated with PEX at our centre.

Methods: This is a retrospective analysis of patients treated from 1997-2017 with newly presenting AAV and severe RPGN. Patients were classified as being dialysis-independent with a SCr<500µmol/l or as dialysis-dependent (defined as the need for dialysis within 72 hours of admission). Patients were treated consistently with steroids, cyclophosphamide and plasma exchange (with Rituximab post 2011) and with azathioprine as first line maintenance.

Results: Data were obtained for 181 patients, 149 of whom presented with dialysis-dependence. There were no demographic or treatment differences between the two groups. Patients who were not dialysed at presentation had significantly improved renal and patient survival at 1 and 5 years when compared to patients who presented dialysis dependent (Figure 1).

Conclusions: Renal and patient outcomes were favourable compared to other studies of this patient group. There was a striking difference in outcomes for dialysis-dependent patients when compared to those who had a SCr<500µmol/l with independent renal function; it may be relevant to analyse patients with severe renal dysfunction according to these criteria in future therapeutic trials.

SA-PO657

A Dutch Consensus Statement on the Diagnosis and Treatment of ANCA-Associated Vasculitis
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Background: Several guidelines have been published on the diagnosis and treatment of anti-neutrophil cytoplasmatic antibodies (ANCA) associated vasculitis (AAV). These guidelines provide an evidence-based approach to support clinical-decision making and adequate implementation is needed to improve care. As part of an implementation strategy, national consensus meetings in the Netherlands were initiated in order to establish consensus on broad aspects of the diagnosis and treatment of AAV based on the recently published guidelines, relevant to daily clinical practice.

Methods: A national, multidisciplinary working group of physicians (nephrologists, rheumatologists, immunologists, pulmonologist, pathologist) with expertise on AAV addressed the broad spectrum of diagnosing, treating and organisation of care for AAV patients. Consensus was established using a Delphi-based method in a national conference in conjunction with a nationally distributed online consensus survey. This survey was distilled from the current published international guidelines. Cut-off for consensus was 70% (dis-agreement).

Results: Ninety-eight professionals were involved in the Delphi procedure to assess consensus on 52 statements regarding diagnosis, treatment and organisation of care for AAV patients. From 52 statements, consensus was achieved for 39 statements (75%). Consensus was achieved on aspects of AAV disease definition, nomenclature, distinct disease states through follow-up, treatment algorithm and organisation of care for AAV. No consensus was achieved on the necessity of histopathological evidence, regular blood testing for ANCAs and standard BVAS, VDI and PROMs assessment.

Conclusions: This study describes the results of a national consensus statement on diagnosing and treatment of AAV patients as part of an implementation strategy in the Netherlands of (inter-)national guideline-derived recommendations. Future studies should evaluate whether the consensus statement has facilitated local implementation, reduced clinical practice variation and, ultimately, improved care for AAV patients in the Netherlands.

SA-PO658

A Proposal of a Stepwise Algorithm for Therapeutic Intervention Using a Modified EUVAS Classification
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Background: Prediction of treatment’s response is useful for minimizing the side effects of immunosuppression therapy for elderly patients. We proposed the Modified EUVAS histological classification of ANCA-associated glomerulonephritis (AAGN), in which New Crescent class (NC) was categorized by active crescents with more than 50% after eliminating a number of global sclerotic and the rest was categorized as New Mixed class (NM, ASN2018). The purpose was to produce a stepwise algorithm consisting of clinical, histological, and prognostic assessments using the modified EUVAS classification.

Methods: The 51 patients with MPO-AAGN (male 45%, 68 ±9.1 years old, who were followed more than 2 years were the cohort in the present retrospective study. All patients were treated according to the Japanese guideline (JSN 2011). In the clinical assessment, cut off values of basal eGFR and increases in sCr per day (ACr/day) predicted NC were decided using ROC analysis. In the second step, prognosis as well as treatment’s response of each subclass of modified EUVAS classification was analyzed.

Results: F: NC:NM:WS was 18:11:11:11, respectively. In clinical assessment, 8 mL/min of eGFR, and 0.16 mg/dL of ACr/day were cut off values for renal prognosis and indication of NC, respectively. In subtype NC, the proportion of normal glomeruli more than 10% was a valuable indicator for prediction of treatment response (ΔeGFR/ΔACr). The renal function of NM was preserved without correlation with the proportion of normal glomeruli.

Conclusions: Patient with F or S will be treated conventionally. However, histological quantitative assessment of NC and NM provides an idea of concrete immunosuppressant’s therapy. Stepwise algorithm consisting of clinical, histological and prognostic assessment as shown in Figure, is useful for minimizing the side effects of immunosuppression therapy for elderly patients.

SA-PO659

Glucocorticoids for Remission Induction in Incident ANCA-Associated Vasculitis (AAV) Patients in Real-World Practice: High Exposure and Temporal Relationship to Adverse Events
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Background: Rapid induction of remission in AAV is desirable and typically includes high dose glucocorticoids (GC). While achieving remission is critical, patients are also at risk from GC-related adverse events (AEs) leading to long term organ damage as well as acute morbidity and mortality. This study examined GC prescribing, AAV response and AEs in incident AAV patients managed in routine clinical practice.

Methods: 929 incident AAV patients from 4 European countries (399 physicians) were diagnosed between 2014-17 and data collected at baseline, 1, 3, 6 and 12 months following induction therapy start were reviewed.

Results: 54% of patients had granulomatosis with polyangiitis, and 46% had microscopic polyangiitis; mean age was 56.82 years (SD 14.2) with 53.7% male. Physicians reported 12% patients as mild/localized, 54% as moderate systemic and 34% as severe cases.
Results: Within 6 months, 23% of RTX-treated, 50% of CYC-treated and 40% of RTX+CYC-treated ANCA patients achieved an ANCA-negative status (p<0.0001). Time to ANCA negativity was significantly shorter after CYC+/- RTX (mean±SD: 11±6 weeks) as compared to RTX (16±6 weeks; p=0.02). ANCA reappearance within 1 year after achieving ANCA negativity, occurred in 9 out of 31 (29%) RTX-treated, 17 out of 43 (39%) CYC-treated and 2 out of 12 (17%) RTX-CYC-treated patients (p=0.02), which happened significantly faster in CYC-treated patients at an average of 18 weeks as compared to RTX+/- CYC at an average of 30 weeks (p=0.003). Both 1yr and 2yr major RFS was significantly less for RTX-treated (86% and 68%) as compared to CYC-treated (90% and 81%) and RTX-CYC-treated patients (100%, 91%) (p=0.02, p<0.005). Overall, patients that reached an ANCA-negative status had a better 2yr-RFS. ANCA reappearance associated with major relapses in RTX-treated group (67% vs 0%; p=0.001) but not in CYC-treated group (12% vs 4%; p=0.38).

Conclusions: This study demonstrates that an ANCA-negative status was achieved more frequently and quicker with CYC+/- RTX as compared to RTX and associated with a better 2yr-RFS. ANCA reappearance was associated with relapses in RTX-treated but not in CYC-treated patients. Thus, monitoring ANCA s to guide tailored maintenance treatment is most relevant in RTX-treated ANCA patients.

SA-PO662

Harmful Effects of Cyclophosphamide on Japanese Patients with Renal Vasculitis Associated with Myeloperoxidase-Antineutrophil Cytoplasmic Antibody-Positive Microscopic Polyangiitis

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Background: In Europe, combination of glucocorticoid (GC) and cyclophosphamide (CY) or rituximab is recommended as an induction therapy in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides. However, many Japanese patients with MPA (MPO-ANCA)-negative microscopic polyangiitis (MPA) are treated only with GC.

Methods: We retrospectively reviewed patients with newly diagnosed MPO-ANCA-positive MPA in two Japanese institutes between April 2000 and March 2017. Patients with serum creatinine levels >5.0 mg/dL or those <20 years of age were excluded. Patients were divided into two groups based on whether they received combination therapy of GC plus CY (CY group), therapy with only GC, or GC plus other therapies excepting CY for remission induction (non-CY group). Primary endpoint was a combination of death and stage 5 end-stage renal disease (ESRD) plus CY (CY group), therapy with only GC, or GC plus other therapies excepting CY for remission induction (non-CY group). Primary endpoint was a combination of death and stage 5 end-stage renal disease (ESRD) plus CY (CY group), therapy with only GC, or GC plus other therapies excepting CY for remission induction (non-CY group). Primary endpoint was a combination of death and stage 5 end-stage renal disease (ESRD) plus CY (CY group), therapy with only GC, or GC plus other therapies excepting CY for remission induction (non-CY group).

Results: Among 121 eligible patients, 27 [17 men (63%), average age 66±13 (± mean±SD) years] were assigned to the CY group, whereas 54 [32 men (59%), average age 67±17 (± mean±SD) years] were assigned to the non-CY group. In the CY group, 22 patients were treated with oral CY and five with intravenous CY. In the non-CY group, 42 patients were treated with GC alone and 12 with a combination of GC and other therapies, including intravenous immunoglobulin, marizomib and lymphocyte apheresis. No patient was treated with rituximab. Fifteen primary endpoints (8 deaths and 7 ESRDs) occurred in the CY group, whereas 14 (10 deaths and 4 ESRDs) occurred in the non-CY group. The 1- and 5-year survival rates were 0.89 and 0.60 in the CY group and 0.93 and 0.79 in the non-CY group (p=0.039), respectively. Hazard ratio in the primary endpoint group was 2.14 (95% confidential interval, 1.02–4.52) as compared with the non-CY group.

Conclusions: Induction therapy with CY increased the risk of death and ESRD by 114% as compared with therapy without CY in Japanese patients with renal vasculitides associated with MPO-ANCA-positive MPA. Therefore, CY should not be used for induction therapy in these patients.

SA-PO663

The Use of Rituximab in ANCA-Negative Pauci-Immune Small Vessel Vasculitis: A Comparative Analysis

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Background: Rituximab has been established as an effective treatment strategy for induction-remission of ANCA associated vasculitides, although little is known about its use in the absence of detectable circulating ANCA with respect to its accepted mechanism of action. Due the rare nature of the disease and even smaller subcategory of patients with ANCA negative disease, trials in this area are likely to be challenging. This study aims to determine the treatment outcomes of rituximab as induction therapy in ANCA negative disease.

Methods: A cohort of patients treated with rituximab for induction-remission of pauci-immune small vessel vasculitis was constructed from a single centre between 2006-2018 and followed up until May 2019. Multivariate Cox regression was used to compare treatment outcomes of rituximab between patients with or without detectable circulating ANCA. Primary study outcomes were patient survival, renal survival and disease remission.

Results: 58 patients with active disease who required treatment with rituximab were identified. Mean age was 59±14 with a male predominance of 53%. 29% (n=17) had ANCA negative disease at the time of treatment. The overall remission rate irrespective
of ANCA serology was 91% (n=53), with a relapse rate of 23% (n=12). On comparative multivariate analysis, ANCA negative disease was not associated with a lower likelihood of remission [HR 0.6 (95% CI 0.19 - 1.85)]. There was no significant difference in subsequent relapse rates between ANCA positive and ANCA negative patients; 21% vs. 27%, respectively (p=0.67). Moreover, the risk of death [HR 2.65 (95% CI 1.32 – 21.76)] and ESRD [HR 0.25 (95% CI 0.03 – 2.04)] were similar between the two groups. Adverse events did not differ between the two groups (p=0.96).

Conclusions: Our centre experience suggests that the use of rituximab is an effective treatment for induction-remission of ANCA negative pauci-immune small vessel vasculitis. To our knowledge, this is the largest cohort analysis of rituximab therapy in seronegative disease reported to date.

SA-PO664
Rituximab-Associated Hypogammaglobulinemia in ANCA Vasculitis: Incidence and Time Course
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Background: Rituximab (RTX) is approved for remission induction (I) and maintenance (M) in ANCA vasculitis (AAV). RTX depletes B cells that express CD20 but does not affect T cell precursors or antibody producing plasma cells. Persistent production of protective antibodies and replenishment of peripheral B cells by B cell precursors renders RTX a relatively safe and effective treatment option. However, several observational studies have demonstrated a decline in serum immunoglobulin (IgG) in AAV patients treated with RTX. We evaluated the risk of hypogammaglobulinemia (Hypo-IgG) among RTX-treated AAV patients.

Methods: AAV patients treated with RTX were included in this single-center observational study. Demographics, clinical and post RTX IgG levels were extracted and analyzed. Severity of Hypo-IgG was defined as mild (501-700mg/dL), moderate (301-500mg/dL), and severe (<300mg/dL). Descriptive data are presented as mean with SD and median with IQR.

Results: Between 2013 to 2018, we investigated 105 RTX treated AAV patients, with mean (SD) age 56 (16) years, 84% Caucasians, 57% females and 64% diagnosed with Granulomatosis with Polyangiitis. Post RTX IgG were measured in 74 patients of which 50 had repeat IgG. 27 patients received RTX for remission I, 8 for remission M and the remainder received RTX for remission I and M. Hypo-IgG occurred in 43 (58%) patients and 19 (44%) had moderate to severe hypo-IgG. Overall, IgG remained stable over time (Figure). Of the 50 patients with repeat IgG, 11 (22%) had moderate to severe hypo-IgG. Infections requiring hospitalization occurred in 10 patients with hypo-IgG.

Conclusions: Hypo-IgG is common in RTX treated AAV patients. Although limited by sample size, IgG trend suggests that nadir IgG levels occur during I dosing and the IgG levels remain stable or increase over time in those receiving M.

Figure: IgG levels over time in patients receiving induction and continuous Rituximab

SA-PO665
The Factors for Maintenance of B Cell Depletion After Use of Rituximab in Renal Disorders
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Background: The duration of B-cell depletion (BCD) after rituximab administration may be related to the disease recurrence. We aimed to explore the factors which may influence the duration of BCD in patients with kidney diseases.

Methods: Patients received rituximab for renal causes and were regularly monitored every 2-3 months on B cell counts were enrolled. Prognostic factors for maintenance of BCD were identified through Cox proportional hazards model where the optimal cutoff values were determined using an online statistical tool CutoffFinder.

Results: There were 47 patients who received a median of 900mg (range, 300-1500mg) of rituximab with 100% achieving BCD and 49% experiencing B cell reconstitution during follow-up. The optimal cutoff value of dose to body-surface-area ratio (DBR) was 5.5mg/m² in total and that of circulating T helper (Th) cell count was 978.5/L. In multivariate analyses, high DBR (>529.5mg/m²) was identified as an independent protective factor (HR 0.42, p=0.024) and high circulating Th cell count (>978.5/L) was identified as an independent risk factor (HR 2.98, p=0.037) for maintenance of BCD. High Th cell count (>978.5/L) was also associated with manifestation of nephritic syndrome, increased CD19 positive B cell counts and T killer cell counts.

Conclusions: DBR and Th cell counts were of predictive values for maintenance of BCD after use of rituximab in patients with renal disorders.

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SA-PO666
The Short-Time Efficacy and Safety of Immunoadsorption onto Protein A, Compared with Plasma Exchange, in the Treatment of Severe Immunological Nephropathy
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Background: The efficacy and safety of immunoadsorption onto protein A (IA), compared to plasma exchange (PE), in the treatment of severe anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) and lupus nephritis (LN), are few reported.

Methods: The clinical data of 42 patients with severe immunological nephropathy, including 21 treated with IA from Nov 1, 2016 to Nov 31, 2018 and 21 treated with plasma exchange (PE) from Nov 1, 2014 to Nov 31, 2018 in our hospital were retrospectively analyzed. IA or PE was combined glucocorticoid, with or without immunosuppressant regimen as induction immunosuppression. IA was performed 10 cycles every time and was done 3-7 times. PE was performed 3-6 times with plasma and albumin. All the patients were followed up prospectively for 3 months.

Results: In AAV patients, Hb, PLT, Gln, Scr, Iga, IgM, C3, C4, Fg and BVAS were significantly decreased after IA treatment, P<0.05. The decline of ANCA and IgG were 46.11% and 53.76% after the first time IA treatment. After the 3-7 times IA treatment, ANCA and IgG decreased by 82.48%, 77.81%, respectively. In LN patients, Gln, Scr, Iga, IgM, Fg and SLEDAI-2k were significantly lower after IA treatment, P<0.05, while eGFR was increased, P<0.05. After IA treatment, the reduction rates of anti-dsDNA Ab and IgG were 72.14%, 44.31%, respectively. Th cell count (<978.5/L) was of significant change in PT and INR in IA group, but in PE group PT and INR were longer than that before treatment, P<0.05. The Fg decline in IA and PE group were 46.74±25.32%, 66.01±13.98%, respectively, P<0.05. There were 4 patients in the PE group who were transfused with cryoprecipitate due to
poor coagulation function but no one in IA group, P=0.05. The main adverse event of IA treatment was hypotensive myocardial ischemia, but PE treatment is allergies, manifested as rashes. There was no difference in the incidence of adverse events, P=0.05. After 3 month follow-up, albumin in IA group was higher than that in PE group, P<0.05.

Conclusions: IA combined with glucocorticoid, with or without immunosuppressant, resulted in similar rapid removal of pathogenic autoantibodies and similar rapid improvement of renal function as PE did in the short term, but IA treatment induced less coagulation disorders, which potentially decreased the risk for bleeding, compared to PE treatment.

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SA-PO667

Rescue Therapy with Extracorporeal Membrane Oxygenation (ECMO) for Diffuse Alveolar Haemorrhage in Patients with Systemic Vasculitis

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Background: Diffuse alveolar haemorrhage (DAH) is a life threatening condition and common causes include autoimmune diseases, infections and medications among others. DAH is a severe manifestation of systemic vasculitis, particularly in patients with ANCA and anti-GBM antibodies. This is mediated through inflammation, occupation and destruction of the alveoli. In extreme cases, even mechanical ventilation is ineffective and ECMO is required to oxygenate the blood whilst the immunosuppressive treatment takes effect.

Methods: We performed a retrospective review of the patients with confirmed DAH which required ECMO at our centre between 01/2016 and 04/2019. Each case was reviewed and we assessed baseline characteristics, cause of vasculitis, duration of ECMO, immunosuppressive therapies used, renal outcome and mortality.

Results: 8 patients met the inclusion criteria making this the largest single centre case series to date of patients with DAH requiring ECMO. 6 patients were female and 2 male with a median age of 42.5 years. 5 patients had ANCA associated vasculitis (5 PR3, 1 MPO), 1 had systemic lupus erythematosus (SLE) and 1 was ANCA and anti-GBM negative. After commencing ECMO, 7 patients survived; of those 4 received IV cyclophosphamide, and 5 received rituximab; all had IV methylprednisolone and plasmapheresis (PLEX). Patients required a median of 10 sessions of extracorporeal membrane replacement therapy (CRRT) at discharge 5 patients had renal recovery with a GFR back to baseline.

Conclusions: The majority of cases with catastrophic DAH are related to AAV and in those failing invasive mechanical ventilation, ECMO would appear to be a valid rescue therapy with good overall outcomes. Immunosuppression with IV CYC and/or IV RTX appears to be safe and effective in this setting. Despite a high incidence of AKI requiring RRT, the majority of patients achieved renal recovery.

SA-PO668

Clinical Features and Outcomes in Anti-Glomerular Basement Membrane Glomerulonephritis Patients with Onset of Noninfectious Fever

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Background: To summarize the clinical features and outcomes of anti-glomerular basement membrane (anti-GBM) glomerulonephritis (GN) with onset of non-infectious fever.

Methods: We retrospectively reviewed the clinical records and follow-up data of 58 patients with anti-GBM GN in our hospital from May 2010 to May 2019.

Results: Among the 58 anti-GBM GN patients, 39 patients (67.2%) presented with fever initially. After careful screening of serological and urinary tests, pathogenic cultures, and CT scans, 28 (48.3%) patients had no evidence of infections. These non-infectious febrile patients had a female to male ratio of 13:1, and the average age was 68.6 years. Six (21.4%) patients were complicated with pulmonary hemorrhage. Compared to the non-febrile anti-GBM GN patients (n=19), they showed higher CRP levels (65.4 vs. 24.5 mg/L, P=0.045) and higher anti-GBM antibody titers (175.4±1 vs. 132.6±2 EU/ml, P=0.012).

In kidney, they presented milder proteinuria (2.51±0.6 vs. 4.69±2 µmol/L) and a lower percentage of normal glomeruli compared to those who did not. Overall, renal recovery occurred in 14 (33%), 22 (42%) and 18 (38%) patients, respectively. Among all the 58 anti-GBM GN patients, Kaplan-Meier survival analysis showed that oliguria, pulmonary hemorrhage, initial eGFR, and anti-GBM antibody titers were prognostic factors for renal outcome (P<0.05), but fever was not a predictor of it. Multivariate Cox regression analysis showed higher initial eGFR was an independent risk factor for ESRD (HR=0.80, 95%CI (0.69, 0.93), P=0.004).

Conclusions: Fever in anti-GBM GN may be part of systemic inflammations instead of infections. Anti-GBM GN patients with onset of non-infectious fever presented more severe systemic inflammations and needed more intensive treatment.

SA-PO669

Anti-Glomerular Basement Membrane Disease: A Real-World Experience

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Background: Anti-glomerular basement membrane (Anti-GBM) disease is associated with deleterious renal outcomes, with the majority of patients remaining dialysis dependent. There is a paucity of evidence regarding optimal treatment and factors predicting outcomes in this cohort. We aim to describe our real world experience and evaluate factors associated with end-stage renal disease (ESRD).

Methods: A multi-centre, retrospective cohort study was performed using existing databases from 3 centers in Ireland, Czech Republic and North America (N= 52). All patients, recruited between 1998-2018, had biopsy proven anti-GBM disease. We describe the clinical characteristics and evaluate factors associated with ESRD using chi-square and independent sample t-tests.

Results: 48 (92%) were Caucasian and 33 (64%) female, with a mean (SD) age of 58 (16) years. Table 1 depicts baseline characteristics for the total cohort stratified for treatment. ESRD, 43 (83%) required renal replacement therapy (RRT) at presentation and 22 (42%) displayed ANCA positivity. Patients reaching ESRD had higher need for RRT at entry, were more often ANCA negative and had a lower percentage of normal glomeruli compared to those who did not. Overall, renal recovery occurred in 14 (33%), over a median follow-up of 39 months (IQR 79.5).

Conclusions: The need for RRT at diagnosis, ANCA negativity and a lower percentage of normal glomeruli are associated with an increased trend towards ESRD. Renal recovery occurred in 1/3 of patients, suggesting a possible beneficial role in modulating acute renal injury, even with apparently poor prognostic features. Individualization of treatment, stratified by prognostic factors is paramount and requires larger scale collaborative studies to explore this further.
Conclusions: Published data suggests 1 year patient survival of 87 to 100% and 1 year renal survival of 94% in those with creatinine < 500 umol/l. Our cohort had higher proportion of patients who were dialysis dependent at presentation. Our data suggest that pulsed intravenous cyclophosphamide is as effective a therapy as oral cyclophosphamide with comparable outcomes at 1 year. This may make it a suitable option when consideration to cumulative dose exposure is made. As it is a rare disease further collaborative prospective study with other centres will likely be needed. 1. Huart A et al. J Autoimmun 2016;73:24-29 2. Alchi B et al Nephrol Dial Transplant. 2015;30(5):814-821. 3. Levy JB et al Ann Intern Med. 2001;134(11):1033

SA-PO671
Therapy and Outcome of Anti-Glomerular Basement Membrane Disease: A Single-Center Experience
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Background: Patients with anti-glomerular basement membrane (GBM) disease are at high risk of morbidity and mortality from renal failure or severe complications. Reviews revealed one-third patients have circulating anti-neutrophil cytoplasmic antibodies (ANCA). Phospholipase A, receptor (PLA,R) antibody can also be positive. The aim of this study was to analyze the therapy differences of patient and renal outcomes in anti-GBM disease with or without ANCA or PLA,R antibody.

Methods: We screened the patients from December 2014 to April 2019 in the First Affiliated Hospital of Xi’an Jiaotong University. The patients with anti-GBM disease were reviewed. Renal biopsies were scored for the presence of active and chronic lesions. The correlation between survival with clinical characteristics and regimens were analyzed.

Results: A total of 40 patients (18 M / 22 F) were identified with anti-GBM glomerulonephritis. The average age was 57.4±16.8 years old. The duration of symptoms before diagnosis was 1.3±1.5 months. 35 patients (87.5%) presented with rapidly progressive glomerulonephritis. The SCr level was 10.0±5.2 mg/dL. Serological screening showed, 180.2±87.4 RU/mL, 11 cases with ANCA positivity (27.5%), 10 cases of pANCA-MPO, 1 case of cANCA-PR3, 5 cases with PLA,R antibody positivity (12.5%). 23 patients accepted renal biopsy. 82.6% were compatible with crescentic glomerulonephritis. 30 patients (75%) received Plasmapheresis (PE). The patients were followed up for 9.98±10.5 months (range 0.5-28.5 months). Except 3 cases lost data and 14 death, 14 patients underwent maintenance hemodialysis, 2 patients underwent peritoneal dialysis, 3 cases had kidney transplantation, renal function recovered in 4 cases and 4 cases to chronic kidney disease. Multivariate Cox regression analysis revealed female (hazard ratio [HR], 3.21; 95% confidence interval [95% CI], 1.41 to 7.30; P=0.005) and regimen with PE (HR, 2.89; 95% CI, 1.32 to6.35; P=0.008) were independent predictors of survival. SCr (>6mg/dL) was a risk factor for the ESRD and all-cause mortality.

Conclusions: Unlike previous data, our study shows that 55% of the patients with anti-GBM disease were female (considered a district bias). Multivariate analysis reveals female and PE therapy are predictors of renal and patient survival while high SCr (>6mg/dL) is associated with poor renal outcome and high risk of all-cause mortality.

Funding: Government Support - Non-U.S.

SA-PO672
Predictors of Kidney Function Recovery in Glomerular Disease After Dialysis Initiation

Background: Many patients with glomerulonephritis (GN) may require dialysis acutely, but the proportion of patients who recover kidney function has not been well-described. We examined characteristics of patients with GN who initiated outpatient dialysis and recovered sufficient function to become dialysis independent as well as trends in rates of recovery by GN type over time.

Methods: We performed a retrospective cohort study of adults ≥18 years who initiated outpatient dialysis between 1995-2015 and had a GN as cause of ESKD according to the USRDS. We defined recovery as a 60-day dialysis-free period and alive for at least 90 days after stopping dialysis within one year of dialysis initiation. We used adjusted Cox models to examine predictors of recovery.

Results: Of 173,348 patients, 4.6% recovered renal function and 13.3% died within one year after dialysis initiation. Recovery within the first 90 days of dialysis initiation was most likely among those with post-infectious GN or hemolytic uremic syndrome (HUSU) [Figure]. Younger age, female gender, non-Hispanic white race, and having post-infectious, lupus and vasculitis as the cause of ESKD were associated with higher odds of recovery [Table].

Conclusions: Nearly one in four patients who initiated outpatient dialysis due to post-infectious and HUSU diagnoses recovered kidney function within one year. Close follow-up after dialysis initiation is warranted.

SA-PO673
Predictors of Treatment Resistance and Relapse in Childhood-Onset ANCA-Associated Vasculitis: A Nationwide Japanese Survey
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Background: Treatment resistance and relapse in childhood-onset antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are major challenges for pediatricians. The aim of this study was to assess the predictive factors for treatment resistance and relapse in a nationwide cohort of Japanese patients with childhood-onset AAV.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Forty-five consecutive patients with childhood-onset AAV were recruited for this study on whom remission of various demographic and clinical parameters for the prediction of treatment response and relapse were analyzed.

Results: The cohort consisted of 45 children; 34 (76%) were female, 36 (80%) had MPA, 9 (20%) had GPA, and 6 (13%) had EGPA. The patients were diagnosed as inactive disease by the Framingham criteria with a median CDAI of 0 (IQR 0-2). The NPSAI was calculated and a median of 1 (IQR 0-2) was found in children with active disease. The most common presenting symptoms were rash (40%), arthralgia (32%), and polyarthralgia (30%). The most common organ involvement was skin (60%), respiratory (47%), and GI (47%). The most common first-line therapies were oral prednisone and MTX, with cyclophosphamide and azathioprine used as second-line therapies. The response rates to MTX and azathioprine were 70% and 60%, respectively. The relapse rate was 20% in the MTX group and 40% in the azathioprine group. The relapse rate was significantly higher in the azathioprine group (p=0.04).

Conclusions: This study highlights the importance of early intervention in children with AAV, as early intervention significantly reduces the relapse rate. The study also indicates that MTX has a higher response rate compared to azathioprine. However, more research is needed to determine the optimal treatment for children with AAV.

Funding: NIDDK Support

SA-PO674

The Role of TNF/αTNF Receptor 2 Pathway Activation in the Modulation of Childhood Nephrotic Syndrome

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Background: Primary Nephrotic Syndrome (NS) is considered T cell pathology; however, the pathogenesis still remains poorly defined. There is increasing evidence pointing to the important role of tumor necrosis factor-alpha (TNFα), a key inflammatory mediator in pediatric nephrotic syndrome. We recently showed that elevated serum TNFα levels were associated with worse prognosis and lack of response to corticosteroids in children with NS. TNFα exerts its biological effect via interaction with two main cell surface receptors: tumor necrosis factor receptor 1 (TNFR1), and tumor necrosis factor receptor 2 (TNFR2). The value of various demographical and inflammatory parameters was evaluated. The aim of the present study was to investigate the expression and the role of different TNFα receptors and TNFα signaling pathways in kidney biopsies of children with steroid responsive and steroid resistant nephrotic syndrome.

Methods: TNFα and TNFR2 receptors expression were studied by immunofluorescence staining and RNA isolation from formalin-fixed, paraffin-embedded (FFPE) renal biopsies of children with nephrotic syndrome who were treated in our department (n=40) versus normal kidneys (n=12).

Results: TNFα and TNFR2 expression was significantly elevated in both children with steroid sensitive and resistant nephrotic syndrome, versus control group. Furthermore, TNFα protein and mRNA abundance were increased in steroid resistant nephrotic syndrome kidneys compared with steroid sensitive nephrotic syndrome kidneys. TNFα and TNFR2 but not TNFR1 expression positively correlated with steroid resistance. In addition, TNFR expression was decreased in patients who had a steroid resistant nephrotic syndrome and TNFα signaling pathways in kidney biopsies of children with steroid responsive and steroid resistant nephrotic syndrome.

Conclusions: As yet there is little information regarding the pathogenesis and optimal treatment of pediatric nephrotic syndrome, our results may indicate that TNFα pathway has a role in the pathogenesis of steroid resistant nephrotic syndrome, and may serve as a treatment target for future therapy.

SA-PO675

Efficacy of a Gluten-Free Diet (GFD) in Children with Difficult-to-Manage Nephrotic Syndrome (NS)

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Background: Zonulin (ZON) increases gut permeability after exposure to gluten in children with celiac disease. Plasma zonulin levels are increased in children with NS. Protease activated receptor-2, which mediates ZON effect in enterocytes, is present on podocytes. Thus, gluten-induced elevations in ZON may affect glomerular permeability and mediate proteinuria in children with NS. We conducted this study to assess the efficacy of a GFD in children with difficult-to-manage NS.

Methods: This multicenter, open-label trial tested the efficacy of a GFD in children with steroid-responsive, difficult-to-manage NS. The Treatment Period was 6 months. A positive response was defined as ≥50% reduction in relapse rate versus the prior 6 months (2 TNFR2), with clinical remission and immunosuppression withdrawal. The following data were tabulated: age, gender, race/ethnicity, serum creatinine, proteinuria, histopathology if available, and treatment. Serum was collected prior to and at completion of the Treatment Period to assess the effect on the glomerular cytoskeleton in vitro. Data are provided as means±SD.

Results: 14 children (8F:6M) were enrolled, age 7.8±4.6 y, baseline serum creatinine 0.46±0.4 mg/dL, and UP<45±49 mg/mg. There were 11 Whites, 1 Black and 3 other racial groups and 2 children were Hispanic/Latino. The underlying disease was MCD in 10 and FSGS in 4 cases. At the end of the Treatment Period, 4 participants had a positive response (2 reduced relapse rate and 2 reduced medication burden), 5 had no response, and 5 had a negative response. The proportion of children who achieved a positive response was 28% (95% CI: 0.10-0.65). The weight of the children increased by 5.4±2.2 kg, and height was increased by 0.43±0.2 kg. The ANGII levels decreased from baseline, and the proteinuria was reduced by 43±15% in the positive responders and was increased by 49±20% in the negative responders. The treatment resistance rate was 71% (95% CI: 0.51-0.91).

Conclusions: Up to a third of patients with difficult-to-manage NS have a favorable response to implementation of a GFD. An elevated plasma zonulin level may predict a poor response to the maneuver. A trial of this dietary intervention may be warranted in children with frequently relapsing or steroid dependent NS to minimize the need for immunosuppressive agents.

Funding: NIDDK Support

SA-PO676

Unbiased Transcriptional Analysis of the Nail-Patella-Like Renal Disease Inducing LMX1B R246Q Variant Reveals Dysregulation of Several Genes Critical to Homeostasis of Podocytes and the Glomerular Basement Membrane

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Background: While most genetic variants in LIM Homeobox Transcription Factor 1 Binding Domain are associated with the development of Nail Patella Syndrome, select variants such as R246Q produce renal limited phenotypes known as Nail Patella Like Renal Disease (NPLRD). Using a targeted analysis of key podocyte genes, we have previously identified several candidates that are downregulated by R246Q in cultured human podocytes. However, a more comprehensive transcriptional analysis is needed to understand the pathological mechanisms driving kidney specific disease development in NPLRD patients and to identify possible therapeutic targets.

Methods: Differentiated conditionally immortalized human podocytes cell lines stably expressing equivalent levels of wild type LMX1B or the R246Q variant were analyzed using Illumina RNASeq technology.

Results: The analysis of LMX1B R246Q revealed significant reductions in genes that have been previously implicated in renal disease, including SULF1 and CLI3, (fold changes of -2.9 and -7.1 respectively). These genes as well as FIBIN (2.43), COL4A1 (-4.6), OLMAD (-5.3), TNFR3 (-5.2), PRKG2 (-5.0), RGS5 (-3.3), ADRAD1 (-3.1), and CDH1 (-2.8) were the most highly downregulated targets by the R246Q variant in a kidney focused analysis of the data. The most highly upregulated genes include ANKHD1 (2.9), COL1A2 (2.1), CRORP4 (2.1), STT4A (2.0), MMP9 (1.7), MMP2 (1.7), and CSF3 (1.7). A kidney focused pathway analysis of the transcriptional data in this study revealed that Matrix Metalloproteinase (MMP) inhibition was the top candidate pathway affected.

Conclusions: While downregulation of key podocyte genes was observed in the transcriptional analysis of LMX1B R246Q, the milieus of affected genes suggest additional pathogenic mechanisms may exist. The upregulation of MMP genes as well as a downregulation of critical basal membrane genes including SULF1 and COL4A1 suggests that glomerular basement membrane (GBM) modification is a key component of R246Q mediated renal disease.

Funding: NIDDK Support

SA-PO677

CD44 Isomorph Status Predicts Response to Treatment in Childhood Nephrotic Syndrome

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Background: Standard CD44 (cCD44) and variant (vCD44) isoforms are hyaluronic receptors, known as stem cell markers that play a role in stem cell activation, migration, and self-renewal of extracellular matrix and fibrosis. De novo expression of CD44 is a marker of activated glomerular parietal cells (PECs), which predicts the development of focal segmental glomerulosclerosis (FSGS). Uregulation of CD44 in nephrotic syndrome (NS) has been linked to poor prognosis in minimal-change disease (MCD) and has been shown to be an early marker of glomerular sclerosis prior to the development of visible lesions by light microscopy. Multiple cCD44 isoforms are known to produce by alternative RNA splicing with different functions related to cell-cell, cell-matrix interaction and also to renal fibrosis, however, there are no reports on which isoforms are expressed on activated PECs in V. We aimed to determine expression of cCD44 and vCD44 receptor isoforms in renal disease progression. This study was addressed to investigate the role of different cCD44 splicing variant isoforms expression in pediatric kidney biopsies of steroid responsive vs steroid resistant NS.

Methods: We here investigate the expression patterns of CD44S (which does not contain any alternative exons) and cCD44 splice variants using rtPCR in RNA isolated from formalin-fixed, paraffin-embedded (FFPE) of renal biopsies from children with nephrotic syndrome (n=40) versus normal kidneys (n=12), all were treated in our department.
Results: The expression of CD44S and CD44 splice variants CD44v2, CD44v6, and CD44v7 was significantly higher in NS patients compared with normal controls, and were negatively correlated with disease progression and overall immunosuppressive response. In contrast, there was no significant difference in the expression of CD44v3, CD44v4/5, and CD44v7.

Conclusions: These data indicate that certain standard CD44 and CD44 splice variants may contribute to NS pathogenicity and to disease progression and glomerulosclerosis.

SA-PO678
Response to Glucocorticoids Remains a Valid Approach to Initial Evaluation of Children with Idiopathic Nephrotic Syndrome
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Background: The therapeutic approach to childhood Idiopathic Nephrotic Syndrome (INS) is based on the ISKD and APN studies from the 1960’s and 1970’s. Because most patients had minimal change disease (MCD) sensitive to glucocorticoids, the therapeutic response to the medication was recommended for initial evaluation and therapy. Since the 1990’s, several single center studies have reported greater frequency of resistance to glucocorticoids among MCD patients and of Focal Segmental Glomerulosclerosis (FSGS). The trend is concerning, causes are unknown, and data are limited. Although initially considered a resistant lesion, more aggressive therapy can induce a response in more than 50% of FSGS patients. However, unnecessary exposure to long-term glucocorticoid therapy in resistant patients may cause side effects without a benefit. Our objective was to determine whether response to glucocorticoids remains a valid approach to initial evaluation of INS children.

Methods: A retrospective review identified 110 patients with INS treated at our center. Glucocorticoid doses and definitions of steroid sensitive (SS) and steroid resistance (SR) INS were according to ISKD. Statistical analysis was performed by fisher exact test.

Results: The mean age was 5.9 years with equal number of males and females. Caucasians (80%) and African Americans (15%) were the predominant ethnicities. The proportion of SSINS in our study was higher, compared to ISKD (33% vs. 20%). However, it has not been increasing with time (35% during 2003-2007 compared to 30% during 2008-2012). MCD was almost 3 times as common among the SRINS patients in our study, compared to ISKD (52% vs. 18%). FSGS was similar among SRINS patients, compared to ISKD (39% vs. 36%). Among patients with kidney biopsy, SSINS characterized 77% of MCD and 42% of FSGS, compared to 93-98% and 17-30% in the ISKD studies.

Conclusions: In summary, despite the changing characteristics and different study populations, the therapeutic response to glucocorticoids is a valid approach for the initial evaluation and therapy for INS children at our center. An international study would help to monitor the changing characteristics and elucidate the role of patient demographics, ethnicity, and environmental factors that cannot be assessed by smaller studies.

Funding: Clinical Revenue Support

SA-PO679
Pioglitazone (Pio) in Pediatric Nephrotic Syndrome (NS)
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Introduction: Thiazolidinediones (TZD) may exert direct protective effects on injured podocytes. PPARγ agonists have been shown to reduce proteinuria in adults with non-diabetic kidney disease. We report our experience with off label, adjuvant use of Pio in pediatric NS.

Methods: A retrospective review identified 110 patients with INS treated at our center. Patients were included if they had not been treated with Pio previously. The mean age was 5.9 years with equal number of males and females. Caucasians (80%) and African Americans (15%) were the predominant ethnicities.

Results: The mean age was 5.9 years with equal number of males and females. Caucasians (80%) and African Americans (15%) were the predominant ethnicities. The proportion of SSINS in our study was higher, compared to ISKD (33% vs. 20%). However, it has not been increasing with time (35% during 2003-2007 compared to 30% during 2008-2012). MCD was almost 3 times as common among the SRINS patients in our study, compared to ISKD (52% vs. 18%). FSGS was similar among SRINS patients, compared to ISKD (39% vs. 36%). Among patients with kidney biopsy, SSINS characterized 77% of MCD and 42% of FSGS, compared to 93-98% and 17-30% in the ISKD studies.

Conclusions: In summary, despite the changing characteristics and different study populations, the therapeutic response to glucocorticoids is a valid approach for the initial evaluation and therapy for INS children at our center. An international study would help to monitor the changing characteristics and elucidate the role of patient demographics, ethnicity, and environmental factors that cannot be assessed by smaller studies.

Funding: Clinical Revenue Support

SA-PO680
Initial Steroid Resistance Is Not Predictor of a Worst Prognosis in Children with Nephrotic Syndrome Sensitive to Calcineurin Inhibitors
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Background: Children with steroid resistant nephrotic syndrome (SRNS) have a high risk of progressing to end-stage renal disease (ESRD). While Calcineurin inhibitors (CNIs) effectively induce remission in >30% patients, long-term management of SRNS presents a significant clinical challenge. Very little is known about the evolution of SRNS in children, prognosis and the potential role of corticosteroid for relapses(s).

Methods: We performed a retrospective observational study of all paediatric patients treated with CNIs for SRNS at our institution between 2008 and 2018. The data was collected about remissions achieved with CNIs, subsequent relapses, their treatment and remission, and long-term renal function.

Results: 54 patients were included (41% males), with a median age of 12.5 years. After a median follow-up of 49 months, 38/54 patients (70.37%) achieved remission with CNIs, while the remaining 16 patients (29.63%) were unresponsive.18/38 patients (47.4%) had one or more relapses(s), (range:1-7). The total number of relapses was 48, out of which, 46 (95.8%) achieved remission. Of these, 38/46 (82.60%) were treated with corticosteroids only, 2/46 were treated with an increased dose of CNI only (>50% of initial dose), 5/46 (10.87%) were treated with both increased CNI dose and corticosteroids, and 1 patient achieved remission with mesenchymal stromal cell infusion. In total, 43 relapses were treated with steroids and 41 of these achieved a new remission. 2/48 relapses did not respond to treatment despite different lines of treatment, but none had an impairment of renal function.

Conclusions: SRNS patients responsive to CNIs appear to have a good long-term prognosis, with no patient developing chronic kidney disease after a median follow-up of 49 months. 95% of relapses were sensitive to corticosteroid therapy, despite the patients being SRNS at the onset of the disease. Therefore, corticosteroids can be considered an option for relapses of SRNS patients sensitive to CNIs. Steroid-sensitive and steroid-resistant NS responsive to CNIs are essentially a part of the spectrum of the same disease.

SA-PO681
Oval Fat Bodies in Urinary Sediment Microscopy Can Be a Convenient Prognostic Marker for Idiopathic Nephrotic Syndrome in Children
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Background: Recently, genetic testing for steroid-resistant nephrotic syndrome has been applied to diagnosis and treatment, but it is not a simple test because of the time and cost. Meanwhile, urine microscopy is the oldest and one of the most commonly used tests for diagnosis of kidney disease. It is generally considered that oval fat bodies and fatty casts in urine sediments are seen in nephrotic syndrome, but in fact oval fat bodies and fatty casts are rarely detected in pediatric idiopathic nephrotic syndrome and sometimes they are detected in steroid-resistant nephrotic syndrome. However, the significance of oval fat bodies and fatty casts in pediatric idiopathic nephrotic syndrome has rarely been investigated. In this study, we investigated whether oval fat bodies and fatty casts could be a useful and reliable predictor of steroid-resistant nephrotic syndrome in children with idiopathic nephrotic syndrome.

Methods: We retrospectively reviewed medical records of pediatric patients with idiopathic nephrotic syndrome who were being treated at our department. The study items were steroid sensitivity in the nephrotic syndrome, the grade of CKD, and the presence of oval fat bodies and fatty casts in the urine sediments at the onset and recurrence.

Results: Of the 45 patients, 11 had oval fat bodies and/or fatty casts. These sediments were present in 8/13 (62%) of patients with steroid-resistant nephrotic syndrome versus only 3/2 (13%) of patients with steroid-sensitive nephrotic syndrome. In patients with CKD, they were observed continuously in all patients, while in those with steroid-sensitive nephrotic syndrome, they were observed only once or twice.

Conclusions: In children with idiopathic nephrotic syndrome, those who continue to have oval fat bodies or fatty casts are more likely to be steroid-resistant and have a poor kidney prognosis. In the present study, oval fat bodies and fatty casts in the urine sediment were found to be poor prognostic markers in children with idiopathic nephrotic syndrome.

SA-PO682
A Pilot Study of Urinary Podocyte-Derived Microparticles (MP) as a Marker for Podocyte Injury in Youth with Type 1 Diabetes
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Background: Podocyte injury plays a crucial role in the development of diabetic nephropathy. Recent animal and clinical studies have shown that podocytes release microparticles under conditions of stress, and may be an early marker of podocyte injury.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Our objectives were to assess MP in youth with Type 1 (TIDM) and healthy controls (HC) and investigate associations with clinical characteristics, including glycemia and renal function. We included youth with TIDM (n = 53), mean age of 14.7 ± 1.6 years and age matched (12/9.1±years) healthy control (HC) subjects, (n=52).

Methods: MP were extracted from first am urine, processed immediately and frozen. MP were characterised by size exclusion chromatography (SEC) and lectin binding. ACR was measured on two sets of first morning samples, albuminuria defined as >3.5mg/mmol in males and >4mg/mmol females. eGFR was calculated using the Larsson Equation, previously validated in the Type 1 population. MP numbers were normalised to urinary protein and albumin. Controls were 10 healthy children (5 males) and 10 adults (5 males). MP were grouped depending on non-parametric analysis, and expressed as median (IQR).

Results: There was no difference observed in MP number between TIDM with no albuminuria, TIDM with albuminuria and HC 8.28 (8.87), 6.39 (8.90), & 10.39 (8.93); p<0.05. There was only a modest positive correlation between MP number and blood glucose levels (r=0.21, p=0.04) in the TIDM subjects, and trends for MP number and eGFR (r=0.25, p=0.07). A modest positive correlation was also seen for HbA1L level (r=0.30, p<0.03). There was a more robust negative correlation with serum uric acid (r= -0.46, p<0.0007). Finally, MP number correlated with the urinary albumin excretion rate (r = 0.48, p=0.0029) in TIDM, but only in subjects with normal albumin excretion rates.

Conclusions: Podocyte-derived MP numbers are similar in youth with early TIDM and age-matched healthy subjects, although within the TIDM cohort, MP are associated with both glycemia and ACR. These findings suggest that podocyte injury cannot be detected by MP enumeration in the urines at this early stage of diabetes. Future will be necessary to define changes in podocyte MP’s over time and their relationship to long term kidney outcomes.

SA-PO683 Urine Exosome Protein Signatures Differentiate Disease Type and Activity in Children with Steroid-Resistant Nephrotic Syndrome

Background: Steroid-resistant nephrotic syndrome (SRNS) is an etiologically and prognostically heterogeneous condition. In 40%-50% of children with SRNS remission is achieved by intensified immunosuppressive (IIS) therapy, 20-25% suffer from hereditary diseases (HSD), and 30-40% turn multidrug resistant (MDR) without an identifiable genetic cause. MDR is associated with tubule damage, whereas only 16 proteins were differentially abundant in MDR and genetic patients differed in 124 proteins (most prominently of complement and coagulation pathways and proteins indicating glomerular and proximal tubule damage), whereas only 16 proteins were differentially abundant in MDR with and without an identified genetic cause. Long-term renal outcomes are excellent for IIS, poor for genetic, and intermediate for MDR-SRNS. No biomarkers differentiating these entities early in the disease course are available to date. Urinary exosome analysis is a promising non-invasive methodology to obtain information about pathological processes in the cells lining the nephron.

Methods: Urine samples were obtained from patients with IIS-SRNS (n=4) and MDR-SRNS with or without an identified genetic cause (n=4 each). IIS patients were studied during stable disease course are available to date. Urinary exosome analysis is a promising non-invasive methodology to obtain information about pathological processes in the cells lining the nephron.

Results: We identified 2,713 proteins with high confidence in urinary exosomes. Comparison of samples from patients with active disease (IIS-relapse/MRD/genetic) vs remission yielded 739 differentially abundant proteins, respectively, with glomerular and tubular cell damage as the most prominent disease functions. Exosomal fractions from MDR patients and from some IIS patients differed in 124 proteins (most prominently of complement and coagulation pathways and proteins indicating glomerular and proximal tubule damage). However, only 16 proteins were differentially abundant in MDR with and without an identified genetic cause. Biomarker filter analysis for individual proteins distinguishes between disease states yielded highly significant candidates.

Conclusions: Urinary exosome analysis is technically feasible and provides a reflection of disease-related tissue alterations on the proteome level. The deregulated molecular pathways identified in this study might allow to differentiate etiologically and prognostically distinct entities in SRNS.

SA-PO684 Obinutuzumab in Pediatric Idiopathic Nephrotic Syndrome Resistant to Rituximab

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Background: B-cell depletion with rituximab (RTX) induces sustained remission in children with Steroid Dependent or Frequent Relapsing Nephrotic Syndrome (SD/FRNS). However, most patients relapse after B-cell recovery and some patients do not achieve B-cell depletion. Obinutuzumab (OBTX) is a 2nd generation glycoengineered anti CD20 monoclonal antibody, which binds in vitro B-cell cytoplasmic. Key targets might be more efficacious in patients with autoimmune diseases. We report the results of a pilot study of OBTX in pediatric patients with FR/SDNS aiming at assessing both the safety and efficacy of OBTX in patients with prior resistance, intolerance or failure to rituximab.

Methods: Patients received an infusion of 300mg/1,73m² of obinutuzumab, after premedication. All other infections are covered. Two dose levels are included. The first dose contains 20% of the full dose. The second dose contains 20% of the full dose.

Results: 12 patients with SD/FRNS were included and followed for a median duration of 8.6 months [IQ 5.9-12.1]. Median ages at INS onset, first RTX and first OBZ injection were of 3.8, 8.8 and 9.3 years old, respectively. Indication for OBZ were intolerance to RTX (n=1), no B-cell depletion (n=4) or short depletion <3 months (n=4) or early relapse after prolonged B-cell depletion (n=3). B-cell depletion was achieved in all patients. At last follow up, B-cell recovery had occurred in 7 patients after a median depletion of 6 months [2.7-12.6 months]. Only 1 patient had prolonged relapse refractory to rituximab (p = 0.0013). 6 patients remained relapse-free with median follow up of 3.6 months after B-cell recovery. Mild infusion reactions were reported in 13/12 patients. Neutropenia within 500-1000/mm³ occurred in 3/12 patients, 2 patients received IV immunoglobulins because of hypogammaglobulinemia. One patient was hospitalised for pneumonia, with negative bacterial and viral testing and improved with antibiotics.

Conclusions: Obinutuzumab induced peripheral B-cell depletion in SD/FRNS patients resistant to rituximab. A single low dose injection resulted in longer B-cell depletion compared to rituximab. However, short term and long term and infectious side effects have to be closely monitored.

SA-PO685 Bloody Diarrhea and Shiga Toxin-Producing Escherichia coli Infection in Children: Data from the ItalKid-HUS Network

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Background: Shiga toxin-producing Escherichia coli (STEC) are responsible for STEC-HUS. The few days before the development of the renal complication, when bloody diarrhea (BD) is the only symptom, represent a window of therapeutic opportunities for preventing or mitigating HUS.

Methods: In order to identify patients at risk for HUS early in the course of the disease, a network connecting >60 pediatric hospitals in Northern Italy (12 million gr, 7.3 million children) has been developed since May 2010, aimed at identifying patients with STEC infections with the aim of an early management of the severe renal complication. Children (<18 yrs old) with BD were centrally screened for the presence of Stx genes in stools using a Reverse Dot blot assays (Genotype EHEC-Armina) until 2018 and Real-Time PCR (RIDA Gene Relab) thereafter.

Results: Out of 4239 analyzed samples, 216 (5.1%) were positive for Stx: 1 (63 (29.2%), 2: 92 (42.6%) and I: 62 (28.2%). Forty patients (0.9% of BD) developed HUS (Stx1 alone was found in 1 eHUS only). The most frequent serogroup identified was the O26 (29%), followed by the O157 (19%) and the other top5 (18%), while a significant proportion were the other top5 (10.7%). In late Summer, the probability that BD is associated with Stx increases from the year average of 5.1% to around 15%. BD was more common in younger children (85% of cases < 10 yo) but the likelihood that BD was caused by STEC infection was not different in different age groups. Finally, the probability of developing HUS in case of STEC infection decreased with age.

Conclusions: The present analysis provides important information about the epidemiology of BD and gives the evidence that STEC is everything but a rare cause of BD that should therefore always be screened for Stx given the severity of its complication.

Funding: Private Foundation Support

SA-PO686 Disease Risk Among Family Members of Patients with aHUS Carrying Complement Regulatory Gene Abnormality

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Background: Atypical hemolytic uremic syndrome (aHUS) is a severe thrombocytic microangiopathy mainly due to mutations in complement regulatory genes (MCRG) with a dominant pattern (heterozygous can exhibit the disease) but incomplete penetrance thus a number of healthy carriers (HC) can be identified in any family of aHUS patients but it is not clear which, when or why HC will eventually turn into patient. Patients with aHUS referred to our Center are screened for all of the known MCRG and once a genetic
abnormality is identified, the search is extended to all the at-risk family members interested in in vivo study.

Methods: Among all the patients with primary aHUS diagnosed at or referred to our centre, only those with a documented MCRG and their relatives were included: 276 family members carrying gene mutations experienced aHUS (overall penetrance of 14.4%) leading to a disease rate of 4.5 events for 1000 patient-year. The disease rate was 13.4 among siblings, 10.7 among offspring and only 3.5 among parents.

Conclusions: In the overall penetrance of aHUS seems a lot lower than previously reported, the risk of developing the disease in any given relative carrying MCRG is low but it is not equally distributed among generations: siblings and the offspring of patients have a much greater disease risk compared to parents. This piece of information is very important for genetic counseling and clearly supports the concept of a second hit as a cofactor of aHUS which, most likely, should be searched for in the parent who does not carry the MCRG.

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SA-PO687

Biomarkers of Disease Activity in Childhood-Onset Lupus Nephritis

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Background: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that affects children and adults, but is more severe and more often involves the kidneys in children. The traditional clinical signs of renal injury do not adequately reflect kidney histology in lupus nephritis (LN), but repeating biopsies frequently is not practical. In adults with LN urine levels of CD163 and epidermal growth factor (EGF) correlate with histologic activity and chronic damage, respectively. These putative biomarkers were examined in a cohort of SLE patients from the Midwest Pediatric Nephrology Consortium.

Methods: Urine was collected prospectively from 37 pediatric patients with active LN, 27 with active extra-renal lupus, and 34 with inactive SLE. Urine CD163 (uCD163) and urine EGF (uEGF) were measured by ELISA and analyzed using JMP14 Pro.

Results: uCD163 was higher in children with active L N compared to those with active non-renal lupus and inactive disease (p=0.0011, p=0.0004, respectively). uCD163 fell significantly in patients who had a complete renal response or in whom renal inflammation resolved on repeat biopsy after 6 months of treatment (328±330 mg/ml urine creatinine vs 15.5±15.2 mg/ml urine creatinine p=0.0013). uCD163 correlated with the biopsy NIH activity index (r=0.452, p=0.002), and specifically capillary hypercellularity, WBC infiltration, hyalin deposits, karyorrhexis, and interstitial inflammation. uCD163 did not correlate with chronic damage. uEGF was significantly lower in children with active LN compared to those with active extra-renal lupus (p<0.0001). uEGF decreased in treated patients as eGFR improved (p=0.06).

Conclusions: uCD163 reflects histologic activity in pediatric patients with LN. In children uEGF does not reflect histologic chronicity, but appears to be a marker of acute kidney injury.

SA-PO688

Silent Lupus Nephritis vs. Overt Lupus Nephritis in a Pediatric Lupus Cohort

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Background: Lupus nephritis (LN) is seen in 20–75% of childhood onset Systemic Lupus Erythematosus (SLE) and is a predictor of poor prognosis. LN may present with active urinary sediment and/or renal impairment (overt LN); sLN or be apparent only upon renal biopsy (silent LN-sLN). There is limited data regarding sLN in pediatric lupus.

We describe and compare features of sLN and oLN. Our retrospective review included patients followed at the University of Florida, Gainesville, diagnosed with sLSE < 18 years of age (n=4 4/11 ACR and/or ≥ 2/11 SLICC classification criteria) who underwent renal biopsy between January 2011 and October 2018. Continuous variables were compared using Student’s t-test and categorical variables were compared using chi-square test.

Results: Of 69 patients, 39% (n=27) were found to have sLN and 61% (n=42) had oLN. The most common histopathology [ISN/RPS] was Class II LN in sLN group (48%, n=13) and proliferative Class III/IV LN in sLN group (60%, n=25). However, 30% (n=13) had proliferative LN in oLN group (n=42). The two groups had similar demographic features. Most of the patients were African American in both groups. There was no significant differences in C3, C4 levels and anti ds-DNA titers. Patients with sLN had more hypertension (p<0.01), decreased eGFR (p=0.03) and higher UPCR (p=0.002) when compared to sLNA group (reference cohort).

Conclusions: In our pediatric cohort, 39% were found to have sLN and 30% of them had proliferative LN, which was more prevalent in African American females with low C3. Renal biopsy should be considered in patients with very low C3 and before development of renal manifestations like hypertension, and decreased eGFR. However, more studies are needed to see if early diagnosis and treatment would modify the long-term renal outcomes.

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SA-PO689

Clinical Characteristics and Risk Factors for Thrombotic Microangiopathy in Children with Lupus Nephritis

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Background: Thrombotic microangiopathy (TMA) presents with the most severe clinical manifestations and high mortality. The aim of this study is to find the risk factors for TMA in children with lupus nephritis (LN) after analyzing their clinical characteristics.

Methods: We retrospectively reviewed the clinical data of 12 LN patients complicated with TMA hospitalized from January 2006 to December 2018.

Results: TMA occurred in 8.28% (12/145) of the hospitalized patients with LN. Four patients were boys and 8 patients were girls. One boy was 6-year-old and the other 11 patients were from 11 to 18-year-old. Their SLEDAI scores ranged from 14 to 31, 92% of them were in severe activity. Renal biopsy was performed in 11 patients, and the results of renal pathology showed all of them had type IV or type IV plus type V LN (type IV, n=8; type IV; n=3). All the patients were diagnosed with TMA within 1 week to 2 months after admission. At the beginning of the hospitalization, seven of them (58%) had both anemia and thrombocytopenia, while 5 patients (42%) only had moderate anemia. All of them had obvious hypocoomplementemia. Especially in all of the 8 patients with first onset of sLN, there serum levels of C3 were lower than 0.18g/L and C4 were lower than 0.07g/L. Moreover, GFR of them were much lower than normal range. Most of the patients had heavy proteinuria (11/12) and positive anti-ds-DNA antibody (10/12). All of the patients accepted the treatment of methylprednisolone pulse therapy, ten of the them were treated with cyclophosphamide, five patients were treated with plasmapheresis (PE). After 1 month of treatment, five patients were in obtained complete response, five patients obtained partial response. One patient relieved after 3 times of PE but died during the fourth PE because of intracranial hemorrhage. The other patient was unwilling to accept renal biopsy and the diagnosis of TMA was not confirmed until 2 months after onset. Although she was treated with PE for 10 times and two doses of Rituximab, she deteriorated continuously.

Conclusions: Children with LN complicated with TMA are mostly in severe disease activity, and the main pathological change of them is type IV LN. Anemia and extremely low level of serum complement occur simultaneously maybe the risk factors for TMA in children with LN whether they have thrombocytopenia or not.

SA-PO690

Recapturing Shiga Toxin-Mediated Renal Injury in Engineered Microvessels

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Background: Hemolytic-Uremic Syndrome (HUS) presents as a severe form of thrombotic microangiopathy (TMA), and the endothelial injuries that precipitate HUS/TMA are caused by a wide range of insults, including metabolic, immunologic, pharmacologic, and infection-associated etiologies. Shigatoxin-producing E. Coli HUS (STEC-HUS) is an infectious TMA that results in renal injury, leading to AKI, permanent renal damage and death, and is the leading cause of dialysis initiation in otherwise healthy children. Despite severe long-term consequences with STEC-HUS, no targeted therapies to-date have demonstrated any clinical benefit. Use of perfusible vascular models previously developed in our lab provide physiologically relevant platforms to evaluate specific cellular injury mechanisms responsible for the endothelial damage in STEC-HUS.

These models also provide a well-controlled and efficient platform for evaluating novel therapeutic interventions.

Methods: Human primary renal endothelial cells were treated with Stx1 and Stx2, the principal toxins responsible for STEC-HUS, and evaluated for cell death, cell injury, and morphology. Studies were performed in both 2D tissue culture and 3D microvesel platforms.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Results: Treatment of isolated human primary renal endothelial cells with either Stx1 or Stx2 demonstrated effective binding, toxin internalization and death. Significant increases in both apoptosis and necrosis were appreciated in a dose-dependent manner in these microvascular cells, with non-renal endothelial cell lines demonstrating insensitivity to Stx1 or Stx2 treatment at equivalent or higher doses. Engineered microvessels using primary renal endothelial cells were generated and maintained under flow for several days. In these models, treatment with Stx1 and Stx2 demonstrated effective binding to luminal endothelia, with evidence of a greater degree of endothelial injury and endothelial denudation observed with Stx2 than Stx1.

Conclusions: Human primary renal endothelial cells exhibit dose-specific responses to Shigatoxin consistent with clinical presentation of STEC-HUS. Notably, engineered renal microvessels also exhibited endothelial injury consistent with Shigatoxin toxicity. Ongoing proteomic and transcriptional studies will use these models to delineate the specific injury pathways responsible for endothelial injury that result in vascular damage and progression to TMA.

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SA-PO691

Immunostaining for Galactose-Deficient IgA1 in Routine Kidney Biopsies

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Background: Recently, an antibody against galactose-deficient IgA1 (gdIgA1) became commercially available. Very little is known about the specific staining patterns of this KM55 antibody in routine diagnostics. Here we report the staining pattern in routine native and transplant biopsies with various forms of IgA-codominant glomerulonephritis and controls.

Methods: We established a protocol for formalin-fixed paraffin embedded (FFPE) tissue with protease antigen retrieval (Fast Enzyme, Zytomed Systems, Germany). Primary antibody KM55 was incubated overnight at 1:5 dilution and visualized with a standard peroxidase system and reported as 0, 1+, 2+, 3+ on 58 consecutive renal biopsies with IgA-codominant glomerulonephritis and controls.

Results: 26/43 (60%) primary IgA-GN (pIgA-GN), 7/9 (78%) Henoch-Schönlein Purpura (HSP) and 2/4 (50%) cirrhotic IgA-GN (cirrhIgA-GN), 0/1 (0%) monoclonal IgA-GN were positive for gdIgA1. IgA1 Purpura (HSP) and 2/4 (50%) cirrhotic IgA-GN (cirrhIgA-GN), 0/1 (0%) staphylococcus-glomerulopathy, 3 infectious associated glomerulonephritis) together with immunostaining for IgA1 and IgA2.

Conclusions: We report an immunohistochemical staining method for gdIgA1 on FFPE kidney biopsies. Together with serum tests for gdIgA1 and anti-gdIgA1 autoantibodies, this ancillary staining method could be useful for a pathogenesis-driven classification of glomerular diseases with IgA-codominant deposits.

SA-PO692

Circulating Endothelial Microparticles and Correlation with MEST-C Scores in IgA Nephropathy

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Background: Renal endothelial injury or activation can lead to a cascade of pathways that contribute to loss of renal function and fibrosis. Recent reports suggest that endothelial injury may play a role in pathophysiology of IgAN. Microparticles (MPs) are 0.1 to 1.0 μm membrane vesicles shed from the damaged or activated cell surface following injury. Microparticles derived from endothelial cells are called endothelial microparticles (EMPs) and play an important role in promoting endothelial dysfunction. They can act as biomarkers of disease state and progression. The aim of this study was to study the presence and quantify the levels of circulating MPs of endothelial origin in plasma from patients with IgAN and healthy controls.

Results: 25 biopsy-proven IgA nephropathy (Mean age=32.8±8.2 years) and 25 healthy controls (Mean age=30±7.6 years) were recruited in this study. Platelet-poor plasma from citrated blood was isolated and centrifuged at 20,000g (90 min) at 4 degree C. EMPs were analyzed by Flow cytometry using EMP specific antibodies for anti-CD31- FITC and anti-CD146-PE. All quantification related to size and number was done by using cell count beads of known concentration. The levels of circulating endothelial MPs were correlated with renal biopsy features of the Oxford classification (MEST-C scores). The study was reviewed and approved by the Institutional Ethics Committee.

Conclusions: There are significantly higher levels of total circulating MPs and EMPs in IgAN compared to healthy controls (p<0.05). EMPs levels were increased in patients with hypertension and correlated with presence of mesangial and endocapillary hypercellularity (p<0.05) on renal biopsy (Table 1).

Funding: Government Support - Non-U.S.

Table 1. Correlation of Circulating Endothelial Microparticle (EMP) counts with MEST-C scores in IgA

<table>
<thead>
<tr>
<th>EMP Score</th>
<th>MEST-C</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No EMPs</td>
<td>0</td>
<td>0.64</td>
</tr>
<tr>
<td>EMPs</td>
<td>1</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SA-PO693

Histological Classifications in IgA Nephropathy Should be Considered for Predicting Not Only Renal Functional Decline but Also Treatment Response

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Background: In IgA nephropathy, Oxford classification (Oxford) (MESTC) and Japanese Histological Grade Classification (JHGC) (Gr1-Gr4, A: active crescent, C: global sclerosis) are evidence-based classification, which have been produced for predicting renal functional decline (RFD). However, clinical parameters are also selected as independent parameters besides histological parameters for RFD. The purpose was to detect the histological parameters, which show a significant correlation with these clinical parameters, because the detected histological parameters can be main indicators for the choice of therapy.

Methods: The 906 Japanese patients with IgA nephropathy (male : 49%, median age: 38 yrs) were prospectively followed for a median of 62 months. First, histological and clinical parameters were evaluated by multivariate Cox regression analysis for 1.5 time’s increase of serum creatinine to find clinical independent parameters. Thereafter, structural equation model (SEM) (STATA, Light Stone, USA) was used to find histological parameters which correlate with the independent clinical parameters for RFD.

Results: Besides M, T1, T2 in Oxford and Gr1-Gr4 in JHGC as the independent histological parameters, amount of proteinuria at renal biopsy (PU0) and steroid therapy (ST) were selected as the independent clinical parameters in both classifications. In SEM, histological parameters which correlated with ST were s(Coefficient 0.10), C(0.20), C2(0.30), and E(0.11)in Oxford and AoaC(0.27)in JHGC for renal functional decline.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
improvement (RFT: 0.75 in Oxford and 0.81 in JHGC). The histological parameters which correlated with PU0 were C1 (0.39), M1 (0.8) and cGFR (<0.01) in Oxford and G0 (1.03), G0 (1.61), cGFR (<0.01), AorA (0.27) in JHGC for RFD (>0.06 in Oxford and <0.06 in JHGC).

Conclusions: Since S, C1, C2, and E in Oxford and AorA/C in JHGC were treatment’s targets for ST and RFI, these histological parameters in each classification are reasonable indicators for a choice of ST. The histological parameters, which correlated with PU0, consisted of ST-related parameters and non-ST related parameters. Therefore, both histological classifications can be more practical considering aforementioned histology-based choice of therapy.

SA-PO694
Validation of the Renal Risk Score for ANCA-Associated Glomerulonephritis

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Background: Since S, C1, C2, and E in Oxford and AorA/C in JHGC were treatment’s targets for ST and RFI, these histological parameters in each classification are reasonable indicators for a choice of ST. The histological parameters, which correlated with PU0, consisted of ST-related parameters and non-ST related parameters. Therefore, both histological classifications can be more practical considering aforementioned histology-based choice of therapy.

Results: A total of 168 AAV patients were enrolled, including 26 patients with glomerular IgA deposition and 60 patients with pauci-immune complex deposition. The AAV patients with IgA deposition had a tendency of lower systemic disease activity, presenting with lower ESR, lower MPO-ANCA, tendency of lower CRP and BVAS. For renal injury, there were no significant differences in clinical data, renal pathological parameters or renal outcome between groups. The serum level of Gd-IgA and intensity of glomerular Gd-IgA1 staining in IgA deposition AAV patients were similar with IgA nephropathy patients. All patients in IgA nephropathy group, AAV groups with or without IgA deposition had the activation of alternative complement pathway, while AAV patients with IgA deposition also had the activation of classical complement pathway. Correlation analysis showed serum C1q level correlated directly with serum globulin and IgA levels.

Conclusions: AAV patients with IgA deposition had the basis of IgA nephropathy, and may present lower systemic disease activity. But it differs from pauci-immune AAV or IgA nephropathy by the possible activation of classical complement pathway.

SA-PO696
The Modern Spectrum of Kidney Biopsy Findings in HIV-Infected Patients

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Background: The epidemiology of HIV-associated kidney disease is evolving rapidly. However, few North American studies address modern trends and none has applied the pathologic classification proposed by the 2018 Kidney Disease Improving Global Outcomes (KDIGO) consensus.

Methods: To characterize the modern spectrum, we performed a retrospective analysis of all HIV-positive patients (pts) with kidney biopsy interpreted at Columbia University from 2010-2018 using KDIGO guidelines.

Results: The biopsy cohort of 437 HIV pts had median age 53 years, including 66% male, 78% on anti-retroviral therapy (ART), 27% with hepatitis C (HCV), 6% with hepatitis B coinfection, 57% with hypertension, and 31% with diabetes. Race, known since S, C1, C2, and E in Oxford and AorA/C in JHGC were treatment’s targets for ST and RFI, these histological parameters in each classification are reasonable indicators for a choice of ST. The histological parameters, which correlated with PU0, consisted of ST-related parameters and non-ST related parameters. Therefore, both histological classifications can be more practical considering aforementioned histology-based choice of therapy.

Conclusions: At 36 months follow-up, renal survival in our cohort was substantially higher compared to the Brix et al. cohort (table 1). Although renal survival differed significantly between the three risk groups (P<0.001), the clinical relevance between low and medium risk is doubtful, being 100% and 96% respectively. In the high risk group, there was a substantial difference in the renal survival of our cohort (77%) in comparison to the reported renal survival from the Brix study (32%). Only one patient from five with the maximum risk score of 11 developed ESRD in our cohort versus all patients with a maximum score in the German cohort.

Conclusions: In this international cohort, we validated the renal risk score proposed by Brix et al. and demonstrated significantly different renal survival between the three risk groups. The renal survival in our cohort was much higher than in the cohort from Brix. This could be due to poor renal survival and might result from the German practice of a yearly dialysis initiation which questions the applicability of the renal risk score to other populations.

Table 1. Renal survival at 36 months in our cohort and the cohort of Brix et al.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Pts. present cohort</th>
<th>N of patients</th>
<th>Renal survival 36 months</th>
<th>N of patients</th>
<th>Renal survival 36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0 points)</td>
<td>6</td>
<td>100%</td>
<td>35</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Medium (1-3 points)</td>
<td>90</td>
<td>96%</td>
<td>64</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>High (4-11 points)</td>
<td>47</td>
<td>77%</td>
<td>21</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>

SA-PO695
The Clinicopathologic Characteristics and Complete Activation of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitides with Glomerular IgA Deposition

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Background: The renal injury caused by anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are characterized by few or no immune deposits in glomerulus. A growing number of AAV patients with glomerular IgA deposits have been recently reported.

Methods: We retrospectively investigated all AAV patients with glomerular IgA deposits diagnosed in our center. Serum Galactose-deficient IgA1 (Gd-IgA1) level and glomerular Gd-IgA1 and IgA staining were measured. Moreover, we detected complement pathway components in their sera.

Results: A total of 168 AAV patients were enrolled, including 26 patients with glomerular IgA deposition and 60 patients with pauci-immune complex deposition. The AAV patients with IgA deposition had a tendency of lower systemic disease activity, presenting with lower ESR, lower MPO-ANCA, tendency of lower CRP and BVAS. For renal injury, there were no significant differences in clinical data, renal pathological parameters or renal outcome between groups. The serum level of Gd-IgA and intensity of glomerular Gd-IgA1 staining in IgA deposition AAV patients were similar with IgA nephropathy patients. All patients in IgA nephropathy group, AAV groups with or without IgA deposition had the activation of alternative complement pathway, while AAV patients with IgA deposition also had the activation of classical complement pathway. Correlation analysis showed serum C1q level correlated directly with serum globulin and IgA levels.

Conclusions: AAV patients with IgA deposition had the basis of IgA nephropathy, and may present lower systemic disease activity. But it differs from pauci-immune AAV or IgA nephropathy by the possible activation of classical complement pathway.

SA-PO697
Clinicopathologic Features and Outcomes of Endocarditis-Associated Glomerulonephritis (ECGN)

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Background: ECGN is a well-documented entity but may be under recognized due to its overlapping features with other glomerulonephritides. The aim of this study was to analyze clinical and pathological outcomes of ECGN.

Methods: Clinical and renal histopathologic data of 12 patients from a single center with biopsy-proven ECGN from 2009 to 2019 were retrospectively analyzed.

Results: A total of 168 AAV patients were enrolled, including 26 patients with glomerular IgA deposition and 60 patients with pauci-immune complex deposition. The AAV patients with IgA deposition had a tendency of lower systemic disease activity, presenting with lower ESR, lower MPO-ANCA, tendency of lower CRP and BVAS. For renal injury, there were no significant differences in clinical data, renal pathological parameters or renal outcome between groups. The serum level of Gd-IgA and intensity of glomerular Gd-IgA1 staining in IgA deposition AAV patients were similar with IgA nephropathy patients. All patients in IgA nephropathy group, AAV groups with or without IgA deposition had the activation of alternative complement pathway, while AAV patients with IgA deposition also had the activation of classical complement pathway. Correlation analysis showed serum C1q level correlated directly with serum globulin and IgA levels.

Conclusions: AAV patients with IgA deposition had the basis of IgA nephropathy, and may present lower systemic disease activity. But it differs from pauci-immune AAV or IgA nephropathy by the possible activation of classical complement pathway.
Results: Among the 12 patients with ECGN, all presented with acute kidney injury, the male:female ratio was 5:1 and mean age was 50 years. Mean serum creatinine at the time of presentation was 4.8 mg/dL. On urine dipstick, 92% of the patients presented with at least 2+ hematuria and 84% had 1+ proteinuria. There were no known cardiac abnormalities in 7 of 12 patients. The most common comorbidities were cardiac valve disease (42%), intravenous drug abuse (17%), and hepatitis C (8%). Infective bacteria were Bartonella (5/12), Staphylococcus (4/12), Entercococcus (2/12) and Streptococcus (1/12). All cases associated with hypocomplementenemia (5/10) and/or ANCA antibody (5/10) in the patients tested were found in association with the following bacteria: Bartonella, Entercococcus species, and Streptococcus. Cryoglobulin negative cases were tested. Light microscopy showed either focal or diffuse endocapillary proliferative features in 92% of the cases and 83% of cases showed at least focal necrotizing crescent formation. An active tubulointerstitial infiltrate was seen in 67% of the cases. No cases showed arteritis. Immunofluorescence revealed either dominant or co-dominant C3 staining (10/12 cases) and IgM was the most commonly detected immunoglobulin with polyclonal 2-3+ staining seen in 58% of the cases. Strong IgM staining was associated with all tested cases of Bartonella (5), Entercoccus (1) and Streptococcus (1). Treatment included long term antibiotics (12/12), heart valve replacement (6/12), immunosuppression (4/12) and dialysis (4/12).

Conclusions: ECGN most commonly presents with AKI. Particularly in those with subacute endocarditis, positive ANCA serologies and biopsy findings of crescentic GN can lead to missed diagnosis. Strong staining for IgM as well as C3 was seen commonly in cases of ECGN associated with Bartonella and other subacute organisms. A high index of suspicion on renal biopsy was important to timely diagnosis as Bartonella is not detectable on routine blood culture.

SA-PO698
Gender, Ethnicity, and Outcome in Thrombotic Microangiopathy (TMA) on Renal Biopsy: A Retrospective Study Evaluating the Demographic and Etiologic Spectrum
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Background: TMA is a systemic disease with diverse etiologies, characterized histologically by endothelial injury. Studies have reported an increased incidence and mortality in African American (AA) females. Our study seeks to determine if this finding is reproducible in a population of patients with evidence of TMA on renal biopsy.

Methods: A retrospective search of our pathology data system was conducted to identify all renal biopsies with a diagnosis of TMA from January of 2015 to May of 2018. Groups were analyzed in terms of gender, ethnicity, native versus allograft, presence of associated rejection and cause of ESRD in the allograft population. The presence of ESRD or a doubling of the serum creatinine from the time of biopsy until the latest follow up date was defined as an unfavorable outcome.

Results: Sixty-six cases were reviewed with the demographic data. Number of total and (allograft) biopsies is shown in the table. There was no statistically significant difference between the groups in terms of gender, ethnicity, unfavorable or favorable outcome, numbers of native versus allograft biopsies or the presence or absence of cell or antibody mediated rejection in biopsies showing histopathologic findings of TMA. However, in allograft biopsies, 9/14 males and 2/12 females had ESRD due to HTN and/or DM (p=0.014). Other cases of ESRD in women included scleroderma, SLE, complications of pregnancy, drug toxicity, multiple myeloma and polycystic kidney disease.

Conclusions: In summary, we found that kidney biopsies showing histologic findings of TMA are indeed, more common in AA females, but this was not associated with a significantly worse outcome as the data suggests. We also note that in the transplant population of AA, hypertension and/or secondary oxalosis was a more common cause of ESRD in males of either ethnicity, rather than mirroring the general population with a higher preponderance in AA overall. This finding suggests that in women, allograft associated TMA could be related to predisposing factors. Further investigation with a larger cohort is required to support these findings.

SA-PO699
Lithium Nephrotoxicity Is Associated with Dysmorphic Proximal Tubule Cell Lysosomes
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Background: Long term lithium (L) use is associated with tubulointerstitial fibrosis, renal dysfunction and ESRD in select patients. The mechanisms resulting in parenchymal fibrosis are not well understood. We have described proximal tubular cell (PTC) dysmorphic lysosomes (DLs) in calcineurin inhibitor (CNI) toxicity and chronic interstitial nephritis in agricultural communities (CINAC), suggesting this is a marker of tubulointerstitial exposure. Calcineurin lysosomes were identified in cases of chronic interstitial nephritis due to lithium toxicity (LIT) used as controls for our CINAC studies, prompting further assessment of this finding.

Methods: 9 kidney biopsies from patients with clinical LT were reviewed, Ki67 staining was performed and clinical data were obtained from the medical records.

Results: Patient data are in the Table. 7 patients discontinued L for 0.15 to 31 years prior to biopsy. All biopsies showed tubulointerstitial fibrosis and tubular microcysts diagnostic of LT. 7 biopsies had PTCs with cytoplasmic large DLs containing electron lucent material, identical to CINAC and LIT toxicity. Ki67 staining showed no to few positive proximal and distal tubular cells in 8 biopsies, demonstrating reduction in tubular cell proliferation and repair. The 1 patient with moderate numbers of Ki67 positive tubular cells had scattered PTC DLs and had discontinued L 14 years before biopsy, possibly indicating evolving tubular cell repair. The patient off L for 31 years had no DLs or Ki67, suggesting completed recovery from LT.

Conclusions: PTC DLs are a marker of tubulotoxic exposure to L and are associated with a reduction in PTC regenerative capacity. In the setting of LT, PTCs are senescent and the DLs may persist for up to 14 years after drug discontinuation. As tubular cell mitotic arrest has been associated with tubulointerstitial fibrosis, further evaluation of the relationships between DL development, DL cargo, and loss of PTC proliferative capacity may help elucidate mechanisms of L-induced tubulointerstitial fibrosis, which currently are poorly understood.

Clinical and Biopsy Data

<table>
<thead>
<tr>
<th>PT Dysmorphic Lysosomes</th>
<th>Age</th>
<th>Gender</th>
<th>Time on L</th>
<th>L-affected proximal tubules</th>
<th>CNI (mg/kg/d)</th>
<th>Tubulointerstitial Fibrosis</th>
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<tr>
<td>Yes (10)</td>
<td>46±1.5</td>
<td>28.3±1.3</td>
<td>3.5±2 years</td>
<td>0.1± years</td>
<td>1.5±0.1</td>
<td>1.1±0.1</td>
</tr>
<tr>
<td>No (2)</td>
<td>67±2.5</td>
<td>2M</td>
<td>15.2± years</td>
<td>0.3± years</td>
<td>2.8±0.8</td>
<td>2.7±0.8</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

942
SA-PO701
Clinicopathologic Spectrum of Renal Lesions Following Anti-TNF Alpha Inhibitor Therapy: A Single-Center Experience

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Background: Anti-tumor necrosis factor (TNF)-alpha inhibitors, as biological agents, are used in a number of chronic immune mediated inflammatory states such as rheumatoid arthritis (RA), psoriatic arthritis (PA), and Crohn's disease. This therapy can induce several autoimmunologic serologic markers and disorders including systemic vasculitis and lupus-like diseases, which may affect the kidney.

Methods: We studied the clinicopathologic features of kidney disease from our renal biopsy files from 2000-2018 and categorized them into pathogenic groups.

Results: 45 patients using anti-TNF alpha inhibitors had renal biopsies, RA in 30, PA in 6, Crohn's disease 7, RA and PA 1, RA and Crohns 1. Among these, 21 received etanercept, 16 adalimumab, 8 infliximab and 4 2 kinds of anti-TNF alpha inhibitors. The patients presented mostly with nephritic syndrome or CKD plus 1 case of AKI and 6 nephrotic syndrome.

Conclusions: The renal lesions during anti-TNF alpha therapy may have an autoimmune basis such as lupus, lupus-like or ANCA mediated disease, as well as secondary to endothehlial or podocyte injury or related to the primary underlying systemic disease.

SA-PO702
Pathological Value of Lysozyme Staining for Diagnosing Renal Sarcoidosis

Satoru Sawada, Shohitei Yoda, Toshinobu Sato. Japan Community Health Care Organization Sendai Hospital, Sendai, Japan.

Background: Sarcoidosis is a systemic inflammatory disease of unknown etiology. Pathological findings of the kidney show interstitial fibrosis with or without granulomatous formation, whereas low detection rates of granulomas make it difficult to diagnose renal sarcoidosis. We have found positive lysozyme staining of kidney tubular cells in sarcoidosis and assessed the diagnostic value of lysozyme staining for sarcoidosis.

Methods: Kidney biopsy specimens of 41 cases of pathological diagnosed tubulointerstitial nephritis (TIN) obtained in Japan Health Care Organization Sendai Hospital between 2013 to 2019 were analyzed retrospectively by immunohistochemistry. Diagnosis of sarcoidosis was made by clinical, radiological, and histopathological examinations. Samples of representative skin sarcoidosis were also stained by lysozyme. Three specimens from sarcoidosis, chronic myelomonocytic leukemia (CMLL) and IgG4-related nephritis were analyzed by electron microscopy.

Results: All six cases of sarcoidosis showed positive staining of lysozyme in proximal tubular cells (100%), however, 25 TIN specimens, including drugs-induced, IgG4-related, aristolochic acid toxicity, ischemia and Sjogren syndrome showed blunted stains (0%). The specimen of CMLL-related TIN, representative of lysozyme-induced nephropathy, showed strikingly positive lysozyme staining in the proximal tubules. Among nine idiopathic TIN, two cases did revealed lysozyme-positive staining case did not meet the diagnostic criteria of sarcoidosis clinically, but the possibility of sarcoidosis cannot be denied. In electron microscopy, an increased number of lysosomes in proximal tubules was observed in CMLL and sarcoidosis, however, no lysosome was found in IgG4-related nephritis. In skin sarcoidosis, positive lysozyme staining was shown in 3/7 of epidermis and dermis while no stain was found in skin samples from different subjects.

Conclusions: Lysozyme staining can aid in the diagnosis of renal sarcoidosis by distinguishing from sarcoidosis to other TIN diseases. Lysozyme induced tubular injury could be an underlying mechanism of TIN in sarcoidosis. In addition, this method could be a useful tool to detect clinically underdiagnosed sarcoidosis including skin and kidney lesions.
made in one patient, which was different from the patient with LHCDD. Median follow-up period from biopsy was 3.5 range: 0.5–612 years. Although one patient with LHCDD developed renal graft failure, all other patients had stable renal function.

Conclusions: Unlike cases of renal allograft, IgG TBMID in the original kidneys does not appear to be associated with renal prognosis. However, it is necessary to investigate for hematological disorders and evaluate the type of deposit in the TBM by EM.

SA-PO705
Adenovirus Immunohistochemistry in Renal Transplantation
Marie Waster Trejo,1 Mariet Feltkamp,1 Els Weessels,1 Jan A. Bruijn,2 Hans J. Baedke,1 Ingeborg M. Bajema.1 Leiden University Medical Center, Leiden, Netherlands; 2Pathology, Leiden University Medical Center, Leiden, Netherlands.

Background: Human adenovirus, a linear double-stranded DNA virus, is a common cause of mild respiratory and gastrointestinal disease in otherwise healthy people. In immunocompromised patients, such as renal transplant patients, it may cause severe infections including hemorrhagic cystitis, hepatitis and interstitial nephritis. Adenovirus immunohistochemistry is a technique frequently used in the clinic to aid the diagnosis of adenovirus infections, next to PCR. Based on clinical experience, we recently questioned the specificity of immunohistochemical adenovirus detection in renal tissue as currently used in laboratories worldwide.

Methods: Adenovirus immunohistochemistry was performed on 25 pre-transplantation biopsies of donor kidneys, eight autopsy controls and one renal allograft which was removed as a result of renal failure caused by infection. Adenovirus PCR targeting Adenovirus species A, B, C, E and F was performed in quadruple on those biopsies staining positive for adenovirus. In addition, electron microscopy was performed on the renal allograft.

Results: The renal allograft and 4 out of 25 pre-transplantation kidney biopsies were positive for adenovirus on immunohistochemistry, showing typical nuclear and perinuclear staining in tubular epithelium as previously reported in the literature. However, adenovirus PCR remained negative in all cases. Electron microscopy of the renal allograft showed particles with a width ranging from 75 to 95 nm, which could be compatible with adenovirus virions.

Conclusions: In cases in which adenovirus infection is clinically suspected and a positive immunohistochemical staining for adenovirus supports this notion, an additional workup (PCR and/or EM) is usually not performed. It appears that by immunohistochemistry, positivity for adenovirus is present in normal donor kidney samples without clinical suspicion for adenovirus infection. Because of lack of confirmation by PCR, we question whether immunohistochemistry for adenovirus is specific and clinically relevant. Alternatively, adenovirus could be present (latently?) in the otherwise healthy population – but little is known about its prevalence.

SA-PO706
Kidney Function and Histopathology in Patients Undergoing Nephrectomy
Shruti Gupta,1 Ping Li,1 Suraj Sarvode Mohi,1 Sushrut S. Waikar,2 Gearoid M. McMahon.1 1BWH, Boston, MA; 2Harvard Medical School, Boston, MA.

Background: Existing data on kidney histopathologic findings and estimated glomerular filtration rate (eGFR) are derived largely from studies from kidney donor nephrectomy specimens. Our objective was to use non-neoplastic tissue from nephrectomy specimens to examine the association between eGFR and the degree of glomerulosclerosis (GS), interstitial fibrosis/tubular atrophy (IF/TA), and arteriosclerosis (AS).

Methods: We reviewed non-neoplastic kidney pathology reports from patients who underwent nephrectomy between 1999 and 2018 (n=1,195). We used linear regression models to determine the association between the degree of GS, IFTA, and AS, with eGFR at the time of nephrectomy. We also assessed the relation between age and eGFR, using linear regression models to determine the association between the degree of GS, IFTA, and AS, with eGFR at the time of nephrectomy. We also assessed the relation between age and eGFR, stratifying by the degree of GS, IFTA, and AS.

Results: Optimal eGFR at the time of nephrectomy. We also assessed the relation between age and eGFR, using linear regression models to determine the association between the degree of GS, IFTA, and AS, with eGFR at the time of nephrectomy. We also assessed the relation between age and eGFR, stratifying by the degree of GS, IFTA, and AS.

Conclusions: The slope of decline in eGFR within each category of GS, IFTA, and AS, and chronicity group was -12.2% per year (p<0.001) across all patients. Multivariable linear regression showed that a one-point increase in age was associated with a 0.34 decrease in eGFR (p<0.001). Age was not significantly associated with GS, IFTA, and AS.

Funding: NIDDK Support, Other NIH Support - NIDCD

SA-PO707
Percutaneous Renal Biopsy Using an 18-Gauge Automated Needle Is Not Optimal
George Sousanih, William L. Whittier, Stephen M. Korbet. Rush University Medical Center, Chicago, IL.

Background: As percutaneous renal biopsies (PRB) are increasingly performed by interventional radiologists, an increase in the use of the smaller 18-gauge (G) automated biopsy needle has been observed. The use of smaller needles stands to compromise biopsy adequacy, ideally >20 glomeruli per biopsy. We compare the adequacy and safety of PRB with a 14, 16 and 18G automated needles.

Methods: PRB of native (N) kidneys (N-557) and transplant (T) kidneys (N-991) was performed by a Nephrologist or supervised Fellow at Rush University Medical Center from 1/2002 to 12/2018 using automated biopsy needles and with real-time ultrasound guidance. Baseline clinical and laboratory data, biopsy data (number of cores, glomeruli on light (LM) and immunofluorescence (IM) microscopy, total glomeruli (LM+IM) and total glomeruli per core (LM+IM)/cores) and outcome data (hematoma on renal US 1-hr post-PRB, complications and procedures post-PRB) was collected prospectively. PRB with N14G (n=337) vs N16G (n=220) vs T16G (n=892) vs T18G (n=99) needles were compared. A P value of <0.05 was significant.

Results: PRBs with an 18G needle were less likely to be performed by fellows (N14 vs N16 vs T16 vs T18G: 94% vs 85% vs 82% vs 22%, <0.0001). Despite this, PRB with an 18G needle was associated with the lowest number of glomeruli on LM (23±11 vs 20±10 vs 26±14 vs 16±10, <0.0001), IM (9±5 vs 9±5 vs 8±5 vs 6±5, <0.0001) and LM+IM (32±13 vs 29±12 vs 34±6 vs 22±12, <0.0001). PRBs with an 18G needle were less likely to have >10 (99% vs 98% vs 98% vs 99%, <0.0001) and >20 (81% vs 79% vs 83% vs 48%, 0.0001) total glomeruli (LM+IM)/per kidney. The total glomeruli per core (LM+IM)/cores) was also significantly less with an 18G needle (15±8 vs 14±6 vs 13±6 vs 10±5, <0.0001). A hematoma by renal US 1-hr post-PRB was similar for native biopsies (14G-35% vs 16G-29%, P=0.16), and transplant biopsy (16G-10% vs 18G-10%, P=0.71) irrespective of needle size. The complication rate for native biopsies (14G-8.9% vs 16G-7.2%, P=0.53), and transplant biopsies (16G-4.6% vs 18G-2.0%, P=0.30) and the transfusion rate for native biopsies (14G-7.7% vs 16G-5.9%, P=0.49), and transplant...
biopsies (16G-3.8% vs 18G-1.0%, P=0.25) were not significantly different irrespective of needle size.

**Conclusions:** The use of 18G biopsy needles significantly compromise the adequacy and thus, quality of the PRB while not significantly enhancing safety.

**Funding:** Government Support - Non-U.S.

### SA-PO708

**Necessity Drives Innovation: Using Transjugular Liver Biopsy Sets for Renal Biopsies**

**Paul M. Adams,**1 Sadiq Ahmed,2 Virgilius Corneal.2 University of Kentucky

1Nephrology, University of Kentucky, Lexington, KY; 2University of Kentucky, Lexington, KY.

**Background:** Renal biopsies are a cornerstone of nephrology, providing valuable diagnosis and treatment information. In some cases, traditional percutaneous biopsies are limited by factors such as obesity, coagulopathy and critical illness. Previously, an intravascular transjugular approach using a renal biopsy set from Cook Medical (Bloomington, IN) was used. However, the Cook set was discontinued in 2016, leaving few options for such patients in the United States. As a solution to this problem, our institution has employed a liver biopsy set manufactured by Argon Medical Devices (Frisco, TX). Our case series describes the novel and successful use of a transjugular liver biopsy set for renal biopsies in complex patients.

**Methods:** We reviewed patients undergoing transjugular renal biopsy using the Argon liver biopsy set at our center from 2017-2018. Indications, demographics, and outcomes were noted. Briefly, the procedure involves catheterization of the right internal jugular vein and subsequent right renal vein catheterization with renal cortex identification by venography. Biopsy specimens are then obtained using the Argon core biopsy needle set.

**Results:** Eighteen patients underwent a transjugular renal biopsy with the liver set. Biopsy adequacy was 95% as judged by interpreting pathologists. Complications were rare, with only one patient experiencing bleeding which was self-limited. Results are summarized in Table 1.

**Conclusions:** Our novel case series demonstrates that a transjugular liver biopsy set is safe and effective for renal biopsies in patients unsuitable for percutaneous biopsy. These findings are significant as there are limited options for transjugular renal biopsies in the United States. Hopefully this will lead to wider use of such techniques.

### Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Transjugular Biopsy Adequacy</th>
<th>Liver Biopsy Adequacy</th>
<th>Comparison of Adequacy</th>
<th>Complication</th>
<th>Outcome</th>
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### SA-PO709

**The Accuracy of Equations That Estimate Glomerular Filtration Rate Compared with Measured Creatinine Clearance in Critically Ill Patients**

Ahmad Mehmood Alasward,1 Hasan M. Al-Dorzi,2 Ayman S. Almoazini,2 Ali Alami,1 Hani Tamim,1 Lolowia Alsawadi,1 Yaseen M. Alari,1 King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, Riyadh, Saudi Arabia; 2King Abdulaziz Medical City-Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia; 3King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; 4American University of Beirut, Beirut, Lebanon.

**Background:** The accuracy of glomerular filtration rate estimates has been questioned. This study compared estimates of GFR by commonly used equations with creatinine clearance measured by 24-hour urine collection in critically ill patients.

**Methods:** This sub-study of the PermiT trial included the patients enrolled at KAMC-Riyadh who had 24-hr urine collection. They estimated GFR using the Cockcroft-Gault (CG), Modification of Diet in Renal Disease(MDRD4-MDRD6) and Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI) equations. For the CG equation, we entered actual weight in one calculation(CG actual-wt), and for BMI ≤30 kg/m2, the ideal body weight and the adjusted body weight in two calculations.

**Results:** The cohort consisted of 238 patients (age 45±20.2 years, DM 31.9%, CKD 2.9%, APACHE II 20.3±8.1, mechanical ventilation 98.7% and serum Cr 214±128 micromol/L). The measured CrCl24h-urine was 117±75.0 ml/min. The correlations between the different formulae were all significant (r=0.0001).

**Conclusions:** There was a modest correlation between the formulae estimating GFR with CrCl24h-urine. CG(actual-wt) had the best correlation. Strength of correlation changed within the different ranges of CrCl24h-urine.

### Table 2

<table>
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<th>Age</th>
<th>Transjugular Biopsy Adequacy</th>
<th>Liver Biopsy Adequacy</th>
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### SA-PO710

**Performance of StatSensor Point-of-Care Device for Measuring Creatinine in Patients with CKD or Post-Kidney Transplantation**

Melissa S. Nataatmadja,1,2 Angela Fung,1 Beryl E. Jacobson,3 Eva Bernstein,2 Paul Komenda,4 Andre Mattman,1 David Seccombe,5 Aedea Levin,6,7 Department of Nephrology, Sunshine Coast University Hospital, Birtinya, QLD, Australia; 2School of Medicine, The University of Queensland, Herston, QLD, Australia; 3Department of Pathology and Laboratory Medicine, St. Paul’s Hospital, Vancouver, BC, Canada; 4CEQAL Inc, Vancouver, BC, Canada; 5Providence Health Care Research Institute, Vancouver, BC, Canada; 6Division of Nephrology, St. Paul’s Hospital, Vancouver, BC, Canada; 7Division of Nephrology, University of British Columbia, Vancouver, BC, Canada; 8University of Manitoba, Winnipeg, MB, Canada.

**Background:** The StatSensor measures creatinine in “fingerstick” capillary blood samples. Previous studies reported a negative bias at higher creatinine concentrations. The current accuracy-based study evaluates the use of this device in kidney transplanted patients and those with CKD.

**Methods:** Duplicate StatSensor creatinine measurements were performed on direct fingerstick samples from 60 participants (mean age 61.9 years, 55% male, 33% transplant, mean plasma creatinine 137±25.4 µmol/L) and compared to plasma creatinine values obtained from simultaneous venous blood sampling using a Roche Integra 400 mainframe analyser.

**Results:** Bland-Altman analysis indicated a positive mean difference (bias) of 25.4 µmol/L between StatSensor fingerstick creatinine measurement and plasma creatinine. Comparison of eGFR (CKD-EPI) calculated from the StatSensor fingerstick creatinine versus plasma creatinine revealed misclassification across all KDIGO CKD stages (Figure 1). Post-analytical correction of the bias did not improve misclassification. Use of mean of duplicate StatSensor creatinine results did not improve performance compared to use of singlet results.

**Conclusions:** Our results suggest that the limiting characteristics of the StatSensor are not only bias, but also imprecision. The level of imprecision observed would likely
SA-PO711

**B and T Cell Subsets in Patients with Membranous Nephropathy:**

Coralien Vink-van Setten, Anne-Els van de Logt, Jack F. Wetzels. Radboud University Medical Center, Nijmegen, Netherlands.

**Background:** It is suggested that characterisation of B and T cell subsets may provide relevant information in autoimmune diseases. Rozenvijag et al (Kidney Int 2017; 92:277-237) studied B and T cell subsets in Rituximab treated patients with primary membranous nephropathy (pMN). They observed a decrease of regulatory T cells as well as NK cells in active disease, whereas numbers of naive B cells were increased. The increase in Treg after Rituximab predicted treatment response. In the literature B and T cell subsets are evaluated using frozen peripheral blood mononuclear cells (PBMCs) or freshly isolated blood samples. We compared these conditions, a comparison which is lacking in the literature.

**Methods:** In 18 patients with pMN, we collected 20 mL of EDTA plasma. 10 mL was used for fresh whole blood analysis and 10 mL was used for isolation of PBMCs, and samples were stored in liquid nitrogen for 6–12 months. We characterised immune cell subsets with flowcytometry with fluorescently labelled cell surface markers: CD3, CD4, CD5, CD8, CD14, CD16, CD19, CD20, CD24, CD25, CD27, CD38, CD45, CD45 RA, CD57, CD95, HLA-DR, IgD, IgM.

**Results:** The distribution of the various B and T cell subsets when comparing both conditions showed a good correlation (table). The figure shows the correlation for NK cells and Treg respectively. Our data show a weak correlation specifically within the Treg subset.

**Conclusions:** The similarity of fresh and frozen immune cell subsets with flowcytometry with fluorescently labelled cell surface markers: CD3, CD4, CD5, CD8, CD14, CD16, CD19, CD20, CD24, CD25, CD27, CD38, CD45, CD45 RA, CD45RO, CD56, CD127, HLA-DR, IgD, IgM.

**Figure 1. eGFR with StatSensor creatinine vs plasma (● Uncorrected creatinine; ○ Bias corrected creatinine)**

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**SA-PO712**

Vasculopathy Plays an Essential Role During the Development and Relapse of Encapsulating Peritoneal Sclerosis in Conventional PD Solutions

Mitsuhiro Tawasa,1,2 Yusuhioko Ito,1 Ting Sun,2 Yasuhiro Suzuki,2 Masashi Mizuno,1,3 Makoto Yamaguchi,1 Takayuki Katsuno,1 Masataka Banshodani,1 Hideki Kawanishi,1 Ryouyukai Kasugai Hospital, Kasugai, Japan; 1Department of Nephrology and Renal Replacement Therapy, Nagoya University Graduate School of Medicine, Nagoya, Japan; 2Aichi Medical University, Nagakute, Aichi, Japan; 3Tsukuba General Hospital, Ibaraki, Japan.

**Background:** Encapsulating peritoneal sclerosis (EPS) is a rare, but life-threatening complication of peritoneal dialysis (PD) therapy. The precise pathogenesis remains unknown, making it difficult to prevent the development of EPS. The aim of this study is to examine the peritoneal samples of EPS patients and identify the association of the peritoneal pathology with different clinical factors.

**Methods:** Peritoneal samples were obtained at the time of surgical enterolysis in Tsukuba General Hospital from 1993 to 2016. Total 283 peritoneal samples were screened. This study used pathological and immunopathological techniques to assess EPS peritoneum samples.

**Results:** 214 in 283 samples were evaluable. In conventional PD solution group, the ratio of lumen diameter to vessel diameter (LV ratio) was significantly smaller (P<0.01) and less angiogenesis (P<0.014). Lower LV ratio was also found to be related to the relapse of EPS (P=0.014). Univariate analysis demonstrated that LV ratio was significantly associated with EPS relapse (P<0.024). Multivariate logistic regression analysis suggested that more severe vasculopathy with low LV ratio was identified as a risk factor of EPS relapse (per 0.1 increase, HR 0.87, P=0.025).

**Conclusions:** Pathophysiology of the development of EPS was different between conventional solution and pH-neutral solution. Vasculopathy was related to the development and relapse of EPS in conventional solutions.

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**SA-PO713**

Assessing Bleeding Risk in CKD Using Global Coagulation Assays

David Langford,1 Brandon Lui,1 Timothy J. Pianta,1,3 David Barit,1,3 Harshal Nandurkar,2,3 Prahlad W. Ho,1,5 Yin H. Lim,1,5 Department of Nephrology, Northern Health, Melbourne, VIC, Australia; 2Department of Pathology, Northern Health, Melbourne, VIC, Australia; 3University of Melbourne, Melbourne, VIC, Australia.

**Background:** Later stage CKD patients are often clinically hypocoaguable. Current coagulation studies do not sufficiently assess this risk. Global coagulation studies (GCA) are functional studies that can better describe bleeding and thrombosis risk. GCA includes whole blood thromboelastography (TEG), platelet-poor calibrated automated thrombogram (CAT), overall haemostatic potential (OHP). TEG is well established in the management of major haemorrhage and massive transfusion. We aim to evaluate using GCA in CKD patients to help define bleeding or thrombosis risks.

**Methods:** We prospectively recruited 2 groups of stable CKD patients. Pre-dialysis with eGFR 30 ml/min/1.73m2 (n=24) and dialysis patients (n=46 haemodialysis, n=18 peritoneal dialysis) were compared to healthy controls (n=138). Baseline renal, hematological investigations and GCA were compared using t-test and chi-square statistics.

**Results:** Compared to controls (67% female, mean age 42, creatinine 70umol/L) patients with eGFR mean age 70, creatinine 137umol/L, urea 18.6mmol/L, eGFR 22 ml/min/1.73m2 had increased von Willebrand factor (VWF) antigen (223 vs 102%, p<0.001), factor VIII (208 vs 108%, p<0.001) and D-dimer (1188 vs 430, p<0.001).

**Conclusions:** Pre-dialysis CKD were more thrombogenic with increased maximum amplitude (MA), a measure of clot strength of 68 vs 60mm (p<0.01) compared to controls. In predialysis CKD, there was no association between urea or eGFR and MA. Thrombin generation (peak thrombin 269 vs 219nm, p<0.01), fibrin generation (OFP 41 vs 29, p<0.01) were increased with impaired fibrinolysis (OFF 42 vs 50%, p<0.01) compared with controls. Dialysis patients (38% female, mean age 66) also had increased clot strength (MA 70mm, p<0.01) and reduced fibrinolysis (OFP 41 U, OFF 40%, p<0.01) compared to controls. Measures of clot strength and overall fibrinolysis were not significantly different between pre-dialysis and dialysis patients.

**Conclusions:** Contrary to expectation, pre-dialysis CKD and dialysis patients were not found to be hypocoaguable using functional coagulation tests. Both groups were found to have markers conferring increased prothrombotic risk: elevated vWF, increased TEG measures and impaired fibrinolysis. The clinical significance of these results and the use of GCA to stratify both thrombotic and bleeding risk warrants further investigation.

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**SA-PO714**

Usefulness of Urinary-Soluble CD163 as a Biomarker of Disease Activity in Patients with Glomerulonephritis

Hunenori Yamazaki, Tsutomu Koike, Hayato Fujioka, Kota Kakeshita, Shiori Kobayashi, Ayako Takashima, Koichiro Kikugawa. The Second Department of Internal Medicine, University of Toyama, Toyama, Japan.

**Background:** Although histopathological examination of kidney tissues can be useful for understanding of disease activity of glomerulonephritis, there are undiagnosed cases because of the difficulties in performing invasive biopsies. Therefore, noninvasive measures of disease activity are needed.

**Methods:** 152 patients with glomerulonephritis (WHO classes: Miffe1, Miffe2, F0, F1, F2, F3, F4, F5) were recruited. Urinary soluble CD163 (urinary-sCD163) was measured using ELISA in 166 samples (136 male, 30 female, mean age 40). The relationship between urinary-sCD163 and disease activity was examined.

**Results:** Urinary-sCD163 was significantly correlated with disease activity (Spearman’s correlation coefficient r=0.50, p<0.001). In Miffe1, Miffe2, F0, F1, F2, F3, F4, F5, urinary-sCD163 was 56.7±31.5 ng/ml, 131.8±45.6 ng/ml, 197.0±46.8 ng/ml, 332.2±43.6 ng/ml, 191.5±46.8 ng/ml, 195.0±46.8 ng/ml, 197.0±46.8 ng/ml, 201.0±46.8 ng/ml, respectively. The results were compared with healthy controls (n=41). There were significant differences between Miffe2, F0, F1, F2, F3, F4, F5 and healthy controls (p<0.01). There was no difference between Miffe1 and healthy controls.

**Conclusions:** Urinary-sCD163 is a useful biomarker of disease activity in glomerulonephritis. Urinary-sCD163 is also a useful biomarker for the progression of disease.
biomarkers are needed to reflect disease activity and monitor response to therapy in patients with glomerulonephritis. The syndromes of thrombotic microangiopathy (TMA) are extraordinarily diverse, some of which have been linked to defects in complement regulation. The kidney is characterized by a marked cortico-medullary salt gradient. A better understanding of local immunoregulatory mechanisms is especially relevant in the transplanted kidney, where the balance between detrimental inflammation in rejection and regulatory T cells is critical for treatment and prognosis, although challenging in patients with coexisting conditions, i.e., so-called secondary TMs. We evaluated the clinical value of an ex vivo test to detect complement defects in a well-defined cohort of patients with TMA.

**Methods:** Subjects were forty-five patients with biopsy-proven glomerulonephritis including IgA nephropathy (n=24), IgA vasculitis (n=7), ANCA-associated glomerulonephritis with glomerulonephritis (n=8), and lupus nephritis (n=6). In all patients, urinary excretion of sCD163 and protein, and quantitative urinary occult blood were measured at two points (baseline and follow-up). The relationships between change in urinary sCD163, reflecting follow-up value minus baseline value, and changes in other measurements were evaluated. Thirty-six cases of IgA nephropathy were treated with steroid therapy. At the point of follow-up, urinary sCD163 significantly decreased compared with baseline (6582±8227 to 1837±4510 pg/mgCr, p <0.01). Change in urinary sCD163 positively correlated with change in urinary protein (r = 0.60, P <0.01), whereas change in urinary protein did not associate with change in urinary occult blood. ROC curve analysis revealed a reduction of urinary sCD163 by more than 60% predicted remission of hematuria (sensitivity 86% and specificity 54.5%).

**Conclusions:** Urinary sCD163 levels reflect disease activity of glomerulonephritis and thus may be useful for monitoring disease activity in patients with glomerulonephritis.

**SA-PO711**

**In Situ Visualization of C3/C5 Convertases: A New Diagnostic Tool to Differentiate Complement Activation in Kidney Biopsies**

**Thorstén Wiech,**1 Fermin Person,**1** Sonia Wuß,**1 Franziska Buescbeck,**4 Sergey Biainiowski,**5 Wilfrid Fehrle,**1 Jun Oh,**4 Christine Skercz,**2 Peter F. Zipfel,**1 Department of Pathology, University Hospital Hamburg Eppendorf, Hamburg, Germany; *Leibniz Institute for Natural Product Research and Infection Biology, Jena, Germany; †Institute of Pathology, University Hospital Basel, Basel, Switzerland; ‡Institute of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, *UKE, Hamburg, Germany; ‡University Childrens Hospital, Hamburg, Germany; †HS Analysis, Karlsruhe, Germany.

**Background:** Deregulated complement activation contributes to or drives the pathogenesis of various kidney diseases. Currently, the diagnosis of complement activation in kidney diseases is primarily based on detection of complement activation products in glomerular tissue and of consumption of complement components or generation of split products in plasma. Up to now a method to directly identify, localize and differentiate complement convertases in tissue has been lacking.

**Methods:** We established a new in situ method for the detection of the assembled C3C5-convertases of the classical/lectin and alternative pathways using the bright field proximity ligation assay. We compared kidney biopsies derived from cases of systemic lupus nephritis (SLE, n=10) with cases of thrombotic microangiopathy (TMA, n=9) due to atypical hemolytic uremic syndrome, using zero hour transplant biopsies as normal controls.

**Results:** As expected, SLE cases revealed a higher density of classical pathway C3/ C5 convertases, while TMA cases showed less classical pathway enzymes and a higher density of alternative pathway C3/C5 convertase signals.

**Conclusions:** We describe a first methodological workflow for the visualization, differentiation and quantification of classical/lectin and alternative C3/C5 convertases directly within the tissue specimen.
nadir bsCr seems to be the most accurate bsCr for diagnosis of AKI. Future efforts should focus on identifying a strict definition of bsCr.

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SA-P0719 New Approach to the Urinary Sediments: Strange Crystals in Urine Makoto Abe, Akihiro Tojo, Shohei Yokoyama, Mayu Uchida, Yoshihiro Murayama, Takehiro Ohira, Hiroshi Satonaka, Toshikiko Ishimitsu, Department of Nephrology & Hypertension, Dokkyo Medical University, Mibu, Japan; Dokkyo Medical Univ, Mito Tochigi, Japan.

Background: Low vacuum scanning electron microscopy (LVSEM) is a non-perturbing technology that requires minimal sample preparation. Compared with conventional SEM, it is possible to observe wet samples directly without freeze-drying and vacuum evaporated carbon deposition process, thus, there is no loss of small parts of the samples during processing and can obtain more detail structure.

Methods: LVSEM was used to study the 3D structure of the urinary sediment from the patients undergone renal biopsy. Ten ml urine samples from renal biopsy patients were fixed with 1mL of 10% formalin and centrifuged at 500g for 5 minutes. The urinary sediments were stained with 1% Ponceau solution and mounted on the carbon filter membrane and observed with the LVSEM (Hitachi TM4000 Plus, Tokyo, Japan).

Results: Typical bipyramidal calcium oxalate crystals and dodecahedrons of various sizes were observed by LVSEM. Interestingly, dodecahedral calcium oxalate crystal shows multilayer configuration resembling a thread winding. Urine samples collected from the bladder catheter’s bag showed curious honeycomb and tubular structures with spikes. It revealed that these structures were shed from the luminal walls of bladder catheter. These walls are composed of silicon-elastomer coated rubber to strengthen the tube.

Conclusions: LVSEM is a useful tool to obtain 3D views of the urinary sediment and can provide a new understanding of the urinary sediment, especially of the urinary crystals.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-P0720 Clinical Verification of Urine Protein/creatinine Ratio Instead of 24-Hour Urinary Protein Evaluated the Different Levels of Proteinuria in Children Yanjie Huang, Xiaojing Yang. The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou, China.

Background: To evaluate the correlation and consistency between urine protein/creatinine ratio (UPCR) and 24 hour urinary protein (24hUP) in children, and to determine cutoff values of UPCR relative to 24hUP at 150mg (>150mg is pathological range) proteinuria.

Methods: 370 children were enrolled, including 85 normal children, 109 Henoch-Schönlein purpura nephritis, 167 nephrotic syndrome, 5 IgA nephropathy, and 4 lupus nephritis. These patients were divided into three groups: normal group: 24hUP<150mg, n=85; non-nephrotic range proteinuria group: 150mg<24hUP<1500mg, n=120; nephrotic-range proteinuria group: 24hUP>50mg/kg, n=165. Clinical symptoms and laboratory examination data were collected. The correlation between UPCR and 24hUP were evaluated by spearman correlation analysis. The consistency between UPCR and 24hUP was analyzed by Bland-Altman technique. The cutoff values of UPCR in predicting non-nephrotic range proteinuria group and nephrotic-range proteinuria were determined using receiver operating characteristics (ROC) curve, respectively.

Results: UPCR was positively correlated with 24hUP (r=0.885, P<0.001). Bland-Altman diagrams showed that UPCR and 24hUP had good consistency, and >95% spots of UPCR and 24hUP were within the 95% consistency area. Relative to 24hUP (150mg), the cutoff value (0.23g/g Cr) with the highest sensitivity (92.8%) and specificity (92.9%) was close to the ROC-2g/g Cr proposed by American rheumatic society in 2006 as the diagnostic standard of pathological proteineuria. Relative to 24hUP (50mg/kg), the cutoff value (2.09g/g Cr) with the highest sensitivity (94.5%) and specificity (88.6%) was close to the ROC-2.0g/g Cr proposed in 2012 KDIGO guidelines as the diagnostic standard of nephrotic syndrome and nephrotic-range proteinuria.

Conclusions: There are good correlation and consistency between UPCR and 24hUP. UPCR can be used to evaluate the different levels of proteinuria in children.


Background: The aim of this study was to evaluate the alterations of structural and functional connectivity using graph theoretical analysis in the neurologically asymptomatic patients with end-stage renal disease (ESRD). In addition, we investigated the prevalence of cognitive impairment (CI) in the patients with ESRD, and analyzed the association between the network measures of structural and functional connectivity and cognitive function.

Methods: We prospectively enrolled neurologically asymptomatic 40 patients with ESRD and 40 healthy controls, and all of the subjects underwent diffusion tensor imaging (DTI) and resting state functional MRI (rs-fMRI), respectively, and investigated the differences between the patients with ESRD and healthy controls. We assessed cognitive function in the patients with ESRD with the MMSE, MoCA, and CERAD neuropsychological battery.

Results: We found that patients with ESRD had decreased structural and functional brain connectivity, and there was significant association between measures of brain connectivity and cognitive function.

Conclusions: We found that patients with ESRD had decreased structural and functional brain connectivity, and there was significant association between measures of brain connectivity and cognitive function. These alterations of brain network may contribute to the pathophysiologic mechanism of CI in the patients with ESRD.

Funding: Commercial Support - Hoffmann-La Roche Ltd.
SA-PO724
Urine Red Blood Cell-Derived Microparticle by Flow Cytometry as a Novel Biomarker for Diagnosis of Glomerular Hematuration
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Background: Differentiating glomerular hematuration (GH) from non-glomerular hematuration (NGH) is based on the identification of dysmorphic red blood cell (RBC) by bright field microscopy which is operator-dependent and insensitive. Whether the detection of RBC-derived microparticle (RMP) by flow cytometry which indicates specific injury to RBC can differentiate GH from NGH has never been validated.

Methods: Spot urine was collected from patients with GH, NGH, and healthy non-hematuration volunteers. GH patients were patients with biopsy-proven glomerular disease diagnosed within 3 months while NGH were patients with urinary tract cancer, nephrolithiasis, and post-operative bleeding. Urine was submitted for microscopic study to identify percentage of dysmorphic RBC, and flow cytometry to detect urine RMP. RMP was defined by size (<1 μm) and positive labeling for CD235a and annexin V. The RMP number was normalized to total RBC number (RMP/RBC ratio). All analyses were performed by blinded technician within 2 hours after specimen collection. Receiver Operating Characteristics (ROC) curve analysis was used to demonstrate diagnostic performance of RMP/RBC ratio in diagnosing GH.

Results: There were 29, 29, and 19 participants in GH, NGH, and healthy groups. The most common diagnoses in GH group were lupus nephritis (48.3%), ANCA-associated glomerulonephritis (13.8%), and IgA nephropathy (10.3%) while majority of NGH group presented in urine from healthy volunteers but were detected in both GH and NGH patients. The RMP/RBC ratio was significantly higher in GH compared to NGH patients (1.06 ±0.04 vs 0.19 ±0.04; p<0.001). RMP/RBC ratio at a cut point of 0.40 provided a sensitivity and specificity of 82.8% and 82.8% for diagnosis of GH, respectively. Performance of RMP/RBC ratio was better than the conventional use of dysmorphic RBC percentage according to the area of under the curve of ROC curve analysis (0.90 vs 0.87).

Conclusions: Measurement of urine RMP/RBC ratio by flow cytometry is a more accurate biomarker for diagnosing GH. This biomarker is operator-independent and can serve as a useful test for clinical practice.

Funding: Government Support - Non-U.S.

SA-PO725
A Nuclear Magnetic Resonance-Based Biomarker Constellation for GFR Prediction Enables Metabolic Phenotyping
Jochen H. Ehrich,1 Laurence Dubourg,2 Svcker Hansson,2 Katharina Schäffler,1 Tobias Steinecke,1 Jana Fruth,2 Sebastian Höckner,1 Eric Schiffer,1 Hannover Medical School, Hannover, Germany; 1Hospices Civils de Lyon - Université Claude Bernard Lyon 1-INSERM U829, Lyon, France; 1Sahlgrenska University Hospital, Göteborg, Sweden; 1namares AG, Regensburg, Germany.

Background: Assessment of kidney function does either entail high burden for patients as part of clearance measurements (mGFR) or estimated GFR by moderately-performing equations (eGFR). Recently, we developed a novel method for accurate prediction of mGFR, based on a serum biomarker constellation of creatinine, myo-inositol, valine and dimethyl sulfone (DMS) analyzed by nuclear magnetic resonance (NMR) spectroscopy. This metabolomic constellation was tested and validated in three separate cohorts in a multi-center study.

Methods: In order to characterize the role of these biomarkers in renal dysfunction and pathogenesis of CKD and to test their value for metabolic phenotyping, biomarker profiling was applied to sets of three age-, sex-, and mGFR-matched male patients with CKD stage II during end-stage liver disease. To compare the obtained profiles, measured biomarker concentrations were transformed into z-scores and plotted into a radar chart with four axes, one each for creatinine (marker for filtration), dimethyl sulfone (marker of oxidative stress), myo-inositol (marker of uremia), and valine (marker of metabolic acidosis).

Results: Within these age-, sex-, and mGFR-matched sets, the metabolic profiles of clinically similar patients differed significantly concerning single markers reflecting filtration, uremic toxins, oxidative stress, and acidosis. An exemplary set of patients with an mGFR of 62 ml/min/1.73m² is depicted in the figure where every color indicates the distinct metabolic profile of one matched patient.

Conclusions: These observations suggest that the set of renal biomarkers enables molecular phenotyping of clinically highly selected age-, sex-, and mGFR-matched patients of homogeneous clinical etiology providing further insights into their individual renal comorbidities based upon complex design thinking and a single diagnostic method using one serum sample.

Funding: Commercial Support - numares AG

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

949
SA-PO727

Primary and Secondary Podocyte Infolding and Microparticles: An Ultrastructural Diagnosis
Vinita Agrawal. Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India.

Background: Podocyte Infloming Glomerulopathy (PIG) is a recently described pathologic entity with ultrastuctural alterations of glomerular basement membrane (GBM) and podocytes. It is characterized by the presence of podocyte invaginations, podocyte infolding, spherical microparticles and microtubules in the GBM. It was first reported from Japan. Since then there are case reports describing it more commonly among women with membranous nephropathy and autoimmune diseases. This study describes the author’s experience of finding PIG-like changes in a spectrum of glomerular diseases.

Methods: The ultrastructural features in renal biopsies received for routine electron microscopy during a 6-month period, in a tertiary care referral center in North India, were evaluated for PIG-like changes. Biopsies showing both podocyte infolding and microtubules and microtubules were included. The changes were evaluated as segmental, global or focal by different investigators.

Results: On ultrastructure, focal and segmental podocyte infolding and microparticles were seen in four biopsies including Membranous Nephropathy with FSGS (n=2), post-transplant IgAN with transplant glomerulopathy (n=1), and unspecified connective tissue disease (n=1). Electron dense deposits were present in all. Mean age was 29 years (range 20-47) with three males. Diffuse PIG was seen in a renal biopsy from a 43-year old woman, diagnosed as FSGS on light microscopy. No electron dense deposits were seen. The microparticles were round or oval and the size varied widely, measuring 40-170 nm. All biopsies showed diffuse foot process effacement and evidence of GBM remodelling with lamellation and splitting of lamina densa. Nephritie proteinuria was present in all patients.

Conclusions: As is true for other pathological morphological entities in renal glomerular diseases like FSGS, MPGN etc., PIG is also a morphological, pattern which may exist in a primary diffuse form with no electron dense deposits, predominantly in females and a secondary form with focal and segmental changes associated with other glomerular diseases with electron dense deposits without any gender predilection. It is useful to recognize that PIG-like changes can be seen in various glomerular diseases and this may be referred to as focal and segmental PIG (FSPG) instead of PIG.

SA-PO728

Podocyte Infloming Glomerulopathy: The Clinical Secrets of Hidden Disease
Anvesh G. NIMS, Hyderabad, India.

Background: Several cases of Podocyte Infloming Glomerulopathy (PIG) have been reported from Japan as a new disease entity since 2008. It is a rare glomerular abnormality seen in women associated with membranous nephropathy and autoimmune diseases involving glomerular basement membrane (GBM) bubble visualised by light microscopy (LM), invagination of the podocyte membrane, and the presence of microspheres viewable by electron microscopy (EM). The clinical features and pathogenesis of this condition are still unclear. We reviewed clinical, biochemical, and pathological features of cases of PIG at our institute.

Methods: We retrospectively analysed cases of PIG as per the diagnostic criteria during preceding two years.

Results: Seven cases of PIG have been reported from our institute. The mean age of the patients was 48, (43-65) years, and all were men. Both hypertension and diabetes were seen in five, one each had hypertension and diabetes. Four patients had nephrotic range proteinuria and two had insignificant proteinuria. All had increased creatinine with a mean of 4.38 mg/dl. Autoantibodies, histocompatibility antigens and viral markers were negative. LM showed membranous nephropathy (DN) in 5 cases and hypertensive changes in 1 case and secondary FSGS in 1 case. Microspheres were present in all but podocyte infolding was present in 1 and cluster formation of microspheres was found in 3 cases.

Conclusions: PIG is one of the rare glomerular diseases. The clinical significance of PIG in South Indian population is yet to be elucidated.

SA-PO729

Single-Cell RNA Sequencing of Myofibroblasts to Identify Therapeutic Targets in CKD
Liquan Hu,2 Christer Betsholtz,1 Marie Jeansson.1,2 Karolinska Institutet, Huddinge, Sweden; 2Uppsala University, Uppsala, Sweden.

Background: Renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function, independent of underlying disease. It is characterized by an increase in activated cells, myofibroblasts, which produce and deposit extracellular matrix. This study aimed to identify drivers of renal fibrosis and to identify novel targets for development of therapeutics.

Methods: Mouse with Pdgfra-GFP and Pdgfrb-GFP reporters were utilized to identify pericytes, fibroblasts and myofibroblasts. Mice were subjected to unilateral ureteral obstruction (UUO) and analyzed at different time points post UUO. GFP positive cells were counted from UUO and contralateral (CL) kidneys were enzymatically digested and sorted into 384-well plates by FACS for single cell RNA-seq using SmartSeq2. Cluster analysis was performed with Batch2SNP and Pagoda2.

Results: Pdgfra-GFP and Pdgfrb-GFP positive cells were significantly increased after UUO and colocalized with markers of fibrosis (ASMA and vimentin). Analysis of the single cell transcriptomes from Pdgfra-GFP and Pdgfrb-GFP cells clustered CL cells and UUO cells separately. Several genes were exclusively expressed in cells from UUO kidneys, while some genes were seen in CL kidneys but lost in UUO kidneys. Ongoing studies include trajectory analysis from the different time point as well as confirmation of results with immunohistochemistry and RNAscope.

Conclusions: Our study will give insight into the temporal changes of fibroblast and pericyte transcriptional programs on the single cell level during fibrosis progression.

SA-PO730

Endoglin Promotes Interstitial Fibrosis in CKD
Tanmay Sinha, Meelim Berkhoff, Isabella J. Brouwer, Jan A. Buijn, Hans J. Baelde, Marion Scharpenecker. Pathology, Leiden University Medical Center, Leiden, Netherlands.

Background: Tubulointerstitial fibrosis is a common process leading to chronic renal damage. It is characterized by extracellular matrix (ECM) deposition and pathological scar formation driven by transforming growth factor beta (TGF-β). Inhibiting excessive ECM production could be a strategy to reduce the functional decline of the kidney and thereby the progression towards end-stage renal disease. Endoglin is a cell membrane receptor of the TGF-β receptor, could be an interesting target to inhibit fibrosis formation.

Methods: Biopsies of patients with kidney diseases characterized by interstitial fibrosis, such as focal segmental glomerular sclerosis (FSGS, n=48), diabetic nephropathy (DN, n=11) and chronic allograft dysfunction (CAD, n=43) were selected; healthy kidneys were used as controls (n=8). Sections were stained for endoglin and the positively-stained area was measured. DN and CAD sequential sections were stained for Sirius Red, a marker for interstitial fibrosis. Endoglin mRNA expression in whole kidney tissue of another DN and CAD sequential sections was measured with qPCR; healthy kidneys were used as controls (n=12). Lastly, collagen type I production was measured with western blot in TGF-β stimulated lentivirally transduced fibroblasts that were either wild type or knock down for endoglin.

Results: Endoglin was increased in the interstitium of patients with FSGS, DN and chronic allograft dysfunction compared to controls (p<0.001). The endoglin-positive area was increased in the Sirius Red-positive area. qPCR showed upregulation of endoglin mRNA in patients with DN compared to healthy controls (p<0.05). The western blot analysis demonstrated that collagen type I production after TGF-β stimulation was less upregulated in the endoglin knockdown fibroblasts compared to wild type fibroblasts.

Conclusions: We show that endoglin is overexpressed in different patient cohorts with interstitial kidney fibrosis and that it colocalizes with Sirius Red-positive areas. We also show that lowering endoglin levels reduces TGF-β-induced collagen type I production. These results suggest that endoglin could be a potential target to reduce the development of fibrosis. This offers an interesting opportunity to treat patients with declining renal function.

SA-PO731

Hypothermic Protection Attenuates Renal Fibrosis After Renal Ischemia-Reperfusion
Da bi Kim,1 Funji Kim,2 Jin young Jeong,2 Jjwian Kim,3 Yoon-Kyung Chang,1 Wonjuong Choi,1 Dae Eun Choi,1 Ki Ryang Na,1 Kang Wook Lee.1 Nephrology, Chungnam National University, Daejeon, Republic of Korea; 2Department of Medical Science, Chungnam national university, Daejeon, Republic of Korea; 3The Catholic University of Korea, Daejeon, Republic of Korea.

Background: Hypothermia attenuates acute renal injury including tubular necrosis, detachment, and apoptosis after ischemia-reperfusion. However, it remains unknown whether hypothermia improve renal fibrosis. Although some reports showed cold ischemia activate TGF-beta signals, it is unclear that it induce the renal fibrosis. We evaluated the hypothermia reduced the renal fibrosis after renal ischemia-reperfusion injury.

Methods: C57Bl/6 mice were divided into the following groups: sham-operated (cold, 32°C) vs normal temperature (37°C), ischemia-reperfusion mice (32°C vs 37°C). Kidneys were harvested 20 minutes after induction of renal ischemia, 4hr, 24, 72hr and 168hr after ischemiareperfusion injury. Functional and molecular markers of kidney injury were evaluated. To explore the molecular mechanism involved the expression levels of renal HIF-1 and associated proteins were evaluated.

Results: The blood urea nitrogen and serum creatinine levels and the histologic renal injury scores were significantly lower in 32°C ischemia-reperfusion than 37°C ischemia-reperfusion kidneys (all P values < 0.05) at 24hr and 72hr after IR. Microscopic evaluation showed that renal fibrosis were significantly decreased in the kidneys of 32°C compared to 37°C ischemia-reperfusion mice at 4hr and 24hr after IR. The expression levels of Bax and caspase-3 and the extent of TUNEL and 8-OHdG cell positivity decreased, whereas the renal Bcl-2 level increased, in 32°C ischemia-reperfusion compared to 37°C ischemia-reperfusion mice. ERK and HIF1 phosphorylation was significantly increased in the kidneys of 32°C compared to 37°C ischemia-reperfusion mice at 4hr and 24hr after IR. However, TGF beta, SOX9, fibronectin, and collagen IV were significantly decreased in the kidneys of 32°C compared to 37°C ischemia-reperfusion mice at 4hr and 24hr after IR.

Conclusions: Hypothermic Protection Attenuates ischemia-reperfusion injury. The hypothermia decreased the renal fibrosis injury. Further studies are necessary to clarify the molecular mechanism involved in the hypothermia-induced renal fibrosis.

Funding: Government Support: Non-U.S.
that CKD is associated with loss of tubular Aβ polarized in tubular compartments in the kidney. Furthermore, we provide evidence that tubular clearance regulates Aβ transporters and impaired renal Aβ expression. In chronic kidney disease (CKD), impaired kidney function contributes to accumulation of Aβ of circulating Aβ. Inflammatory cytokines (e.g., TNF-α) and inflammatory cells (e.g., macrophages) can contribute to the accumulation of Aβ in the brain, thereby accelerating cognitive impairment and dementia. Aβ molecules are associated with accelerated Aβ deposition in the brain, thereby accelerating cognitive impairment and dementia. Aβ molecules undergo renal clearance to ensure proper Aβ homeostasis. In chronic kidney disease (CKD), impaired kidney function contributes to accumulation of Aβ and accelerating cognitive impairment. Based on these prerequisites, we here aimed to elucidate molecular mechanisms contributing to impaired renal clearance of Aβ molecules.

Methods: Aβ transporters including P-glycoprotein, LRPI, LRPD and RAGE were analyzed in multiple mouse models of acute/chronic renal failure, human kidneys and cultured cells of tubular epithelial cells. Genome-wide array datasets was analyzed using NephroSeq database (GSE69438).

Results: We show that Aβ transporters including P-glycoprotein, LRPI, LRPD and RAGE are present and polarized in tubular compartments in the kidney. Progressive CKD is associated with loss of tubular Aβ clearance in tubular Aβ transporters, implicating that tubular clearance regulates Aβ homeostasis. Finally, analysis of human kidneys and genome-wide array datasets confirmed that Aβ transporters are equally present in human renal epithelium and lost during progressive CKD.

Conclusions: In summary, we here show that Aβ transporters are present and polarized in tubular compartments in the kidney. Furthermore, we provide evidence that CKD is associated with loss of tubular Aβ transporters and impaired renal Aβ clearance. Because impaired kidney function contributes to accumulation of circulating Aβ and accelerates cognitive impairment, these findings provide insights into molecular mechanisms underlying clearance and homeostasis of Aβ.

SA-PO734
125-Dihydroxy-Vitamin D3 Regulates M2 Macrophage Polarization via the VDR-PPARα Signaling Pathway in Lupus Nephritis Mice
Jia Wang,1 Jong Zhang,2 Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China; Renal Department, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China.

Background: Lupus nephritis (LN) is one of most serious manifestation of systemic lupus erythematosus (SLE). Recent studies have shown besides autoantibodies and complement activation, macrophage polarization play a major role in the pathogenesis of LN. 125-Dihydroxyvitamin D (1,25(OH)2D3) has immunomodulatory activity, and 1,25(OH)2D3 deficiency is correlated with SLE, especially with activity of LN. This study aimed to explore whether 1,25(OH)2D3 modulates macrophage polarization in LN and its underlying mechanism.

Methods: We compared the levels of 1,25(OH)2D3, renal injury (proteinuria, serum urea), and inflammatory cytokines (TNF-α, interleukin (IL)-10) in MRL-Fas+/+ mice expressing VDR and VDR knockout (KO) MRL-Fas−/− mice. Infiltration with M1-like (non-CNS-CD45+), M2-like macrophages (CD16+/CD206+) in renal tissue were detected using immunohistochemical analysis. Peripheral blood monocytes were isolated in MRL-Fas+/+ mice, and were incubated with or without 1,25(OH)2D3 (10−10 mol/L). M1 and M2 macrophages in vitro were induced by treating cells with 100 U IFNγ + 5 mg/mL LPS or 10 ng/mL IL-4, respectively. In order to explore the underlying mechanism, these cells were treated with VDR siRNA and the PPARα antagonist. mRNAs expression levels of iNOS, MR and Arg-1 were assessed by RT-PCR.

Results: In vivo, compared with VDR KO MRL-Fas−/− mice, more positive for CD68 and iNOS were infiltrated in renal tissue in expressing VDR mice, a phenotype suggestive of M1 macrophages. 1,25(OH)2D3 and IL-10 levels were also observed higher than VDR KO MRL-Fas−/− mice, whereas TNF-α, proteinuria, serum urea levels were lower. In vitro, pretreatment with 1,25(OH)2D3 significantly inhibited M1 activation, enhancing M2 macrophage polarization. Moreover, it upregulated the expression of anti-inflammatory cytokine IL-10 and MR, Arg-1 mRNA but downregulated the expression of iNOS mRNAs. However, cells treated with VDR siRNA and PPARα antagonist decreased the tendency toward M2 polarization. Moreover, the expression of PPARα was decreased when cells treated with VDR siRNA.

Conclusions: The above results demonstrate that 1,25(OH)2D3 promoted M1 phenotype switching to M2 via the VDR-PPARα pathway in LN. 1,25(OH)2D3 treatment ameliorated LN-associated renal inflammatory injury.

Funding: Government Support - Non-U.S.
SA-PO737

Disruption of CD40 Attenuates Renal Injury Induced by Acute High Salt Intake in Experimental Hypertensive Renal Disease
Shuang Zhang,1 Fatimah K. Khalaf,1 Apurva Lad,2 André Kleinhenn,2 Deepak K. Malhotra,1 David J. Kennedy,1 Steven T. Haller,2 University of Toledo, Toledo, OH; 1University of Toledo College of Medicine and Life Sciences, Toledo, OH; 2University of Toledo Health Science Campus, Toledo, OH.

Background: We have recently shown that circulating levels of the pro-inflammatory receptor CD40 predict progression of renal dysfunction in patients with hypertensive renal disease and the soluble ligand for CD40 (sCD40L) is significantly elevated in this setting. In our CD40 knockout (KO) model developed on a background prone to hypertensive disease and the soluble ligand for CD40 (sCD40L) is significantly elevated in this setting.

Methods: To address this problem, we adopted a translational ribosome affinity purification (TRAP) - approach and designed a transgene that expresses an enhanced green fluorescent protein (eGFP)-tagged ribosomal protein (L10a) under the control of the macrophage-specific c-fms promoter, a driver of the macrophage-stimulating factor receptor (CD115) as a c-fms-eGFP-L10a transgenic mice model.

Results: Rigorous characterization and validation found no gross anatomical, behavioral or developmental abnormalities in MacTRAP mice and confirmed transgene expression across various organs. Immunohistological analyses of MacTRAP kidneys identified GFP-L10a-expressing cells in the tubulointerstitial compartment that stained positive for macrophage marker F4/80. Following induction of kidney fibrosis we observed a robust upregulation of eGFP-L10a along with classical macrophage and fibrotic markers, validating MacTRAP responsiveness upon proinflammatory challenge. Using TRAP, we successfully extracted macrophage-specific polysomal RNA from MacTRAP kidneys and conducted RNA sequencing following by extensive bioinformatical analyses, hereby establishing a comprehensive in vivo gene expression and pathway signature of resident renal macrophages and closely related dendritic cells.

Conclusions: In summary, we have created, validated and applied a novel and responsive macrophage-specific TRAP mouse line, defining the translational profile of renal macrophages and dendritic cells. This new and broadly applicable tool may be of great value for the study of macrophage biology in different organs and various models of injury and disease.

Funding: Government Support - Non-U.S.

SA-PO739

Protein-Bound Uremic Toxins Induce NLRP3 Inflammasome Activation in Proximal Tubule Cells
Milos Mihailovic,2 Daria Andreeva,2 Sonja Stehenius,2 Luuk Hilbrands,1 Rosalinde Masereeuw,1 Radboud University Medical Center, Nijmegen, Netherlands; 2Radboud Institute for Pharmacological Sciences, Utrecht, Netherlands.

Background: Protein-bound uremic toxins (PBUTs) are not efficiently removed by hemodialysis in chronic kidney disease (CKD) patients. Their accumulation results to cellular dysfunction, inflammation and oxidative stress. Moreover, it has been shown that increased intrarenal expression of the NLRP3 receptor and IL-1β are associated with reduced kidney function, suggesting a critical role for the NLRP3 inflammasome in CKD progression. Here, we evaluated the effect of PBUTs on NLRP3 inflammasome activation in human conditionally immortalized proximal tubule cells (cPTECs).

Methods: NLRP3 activation was studied after exposing cultures to LPS, ATP, indoxyl sulfate (IS), and a mixture of eight anionic PBUTs (UT-mix). Expression levels of inflammasome components (NLRP3, caspase-1, IL-1β), IL-1β secretion, caspase-1 activity and production of reactive oxygen species (ROS) were evaluated.

Results: Exposure to a combination of LPS (1 µg/ml; 24h) and ATP (5 mM; 30 min) showed 3-fold (p<0.01) increase in IL-1β secretion, and 2-fold (p<0.05) increase in caspase-1 activity, suggesting that the NLRP3 pathway is functional in cPTECs. Next, 24-h exposure to increasing concentrations of IS increased mRNA expression of NLRP3 (2.3-fold; p<0.01), caspase-1 (2.2-fold; p<0.01) and IL-1β (24-fold; p<0.01). Similar results were observed for UT-mix: NLRP3 (1.7-fold increase; p<0.05), caspase-1 (1.8-fold increase; p<0.05) and IL-1β (4.5-fold increase; p<0.05). In addition, exposure to IS was also associated with significant increase of intracellular ROS (2.6-fold increase for UT-mix; p<0.05). Finally, IL-1β secretion was reduced when the N-acetylcysteine (1.8 mM; 24h) was added as a pre-treatment (47% reduction for IS and 35% reduction for UT-mix; p<0.05), suggesting that inflammasome activation is ROS-mediated.

Conclusions: PBUTs are able to induce NLRP3 inflammasome activation in proximal tubule cells via oxidative stress, suggesting their involvement in a local inflammatory response in kidney disease.

Funding: Government Support - Non-U.S.

SA-PO740

Mint3 Mitigates Renal Fibrosis After Ischemia-Reperfusion Injury Through Protection of Tubulointerstitial Cells from Apoptosis via Upregulation of NF-κB
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Background: Tubulointerstitial fibrosis is a hallmark of chronic kidney disease (CKD), and initiated by tubular epithelial cell (TEC) injury. Hypoxia promotes tubular cell death, fibrosis, and CKD progression. Munc18-1-interacting protein 3 (Mint3) is a molecule that activates hypoxia-inducible factors (HIFs) by binding and suppressing factor inhibiting HIF-1 (FIH). However, the role of Mint3 in tubulointerstitial fibrosis remains unknown.

Methods: We induced the fibrosis of the kidney after unilateral ischemia-reperfusion injury (uIRI) in Mint3-knockout and littermate wild-type mice. The function of Mint3 was assessed using SCID mouse tubular cells, which were treated with Mint3 and/or FIH siRNA and exposed to hypoxia. Apoptosis was assessed with cleaved caspase-3 and TUNEL staining, and flow cytometry with Annexin-V and 7-AAD.

Results: We found that Mint3 was mainly expressed in TECs with immunostaining of the kidney. Knockout of Mint3 did not affect the acute injury induced by uIRI, but exacerbated the tubulointerstitial fibrosis, accompanied by an increase in TEC apoptosis. Consistently, hypoxia-induced apoptosis of MCT was aggravated by Mint3 knockout. Unexpectedly, the additional knockdown of FIH did not suppress the increase in apoptosis and the production of NF-κB. We found that Mint3 protected the cells from apoptosis by decreasing inhibitory effects of NF-κB.

Conclusions: This study demonstrated the importance of TEC injury as a primary event leading to renal fibrosis, as well as unexpected relationship of Mint3 and NF-κB. Mint3 protects the cells from apoptosis by decreasing inhibitory effects of NF-κB, leading to fibrosis suppression. This new pathophysiology of tubulointerstitial fibrosis can be a target of the future therapy for CKD.

Funding: Government Support - Non-U.S.
SA-P0741
Nrf2 Deletion Attenuates Kidney Injury Caused by Cullin Ring Ligase Dysfunction
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Background: Nrf2 is postulated to play a protective role in oxidative stress-induced kidney injury; conversely, multiple studies have shown that aberrant Nrf2 activity can be damaging. Nrf2 abundance is determined by cullin-RING ligases (CRLs), which control the regulated degradation of proteins through the ubiquitin proteasome system. CRLs in turn, are regulated by the COP9 Signalosome (CSN). We previously reported that neprhin-specific CSN disruption (KS-Jab1 mice) causes progressive renal injury, with increased Nrf2. Here, we tested the hypothesis that direct Nrf2 accumulation exacerbates kidney injury in this model, using KS-Jab1 and Nrf2 double knock out mice (DKO).

Methods: The Pax8-xRTA mouse system was used to generate inducible mice with genetic deletion of the catalytically active CSN subunit, Jab1, only along the neprhin (KS-Jab1). KS-Jab1 were bred to mice with global and constitutive deletion of Nrf2 (DKO). Kidney damage was evaluated at 1 week (early) and 8 weeks (late) after Jab1 deletion.

Results: KS-Jab1 showed an increase in Nrf2 activity which was attenuated in DKO at both time points. Early KS-Jab1 demonstrated an increase in blood urea nitrogen (BUN, 34 ± 2 vs. 26 ± 1 mg/dl in controls), and kidney weight (6.8 ± 0.3 vs. 5.3 ± 0.2 mg/g BW in controls). Analysis of the proximal tubule injury marker KIM-1 in kidney of KS-Jab1 showed a 2.27-fold and 1.68-fold, respectively. Analysis of the proximal tubule injury marker KIM-1 (kidney injury marker) demonstrated a significant increase in the number of proliferating cells located in kidney of KS-Jab1 (29 ± 13 cells/field). Kidney weight trended lower (6.0 ± 0.8 vs. 6.8 ± 0.3 mg/g BW in controls).

Conclusions: Direct Nrf2 activity in progressive kidney disease may have unexpected effects.

Funding: NIDDK Support, Veterans Affairs Support

SA-P0742
Unilateral Ureter Obstruction (UO)-Induced Renal Fibrosis Is Attenuated by Suppression of Indoxyl Sulfate (IS) Accumulation in Sulfotransferase (Sult)1a1-Deficient Mice
Hou Huixian,1 Rika Fujino,2 Yuya Hayashi,2 Jumpei Unoki,1 Keisuke Matsushita,1 Nao Gundo,1 Hirofumi Jono,2,1 Hideyuki Saito,2,1 Clinical Pharmaceutical Sciences, Kumamoto University Graduate School of Pharmaceutical Sciences, Kumamoto, Japan, 2Pharmacy, Kumamoto University Hospital, Kumamoto, Japan.

Background: Obstructive nephropathy is the result of functional or anatomic lesions located in the urinary tract, and renal interstitial fibrosis is a common finding associated with chronic renal failure. Many factors are involved in the pathogenesis of renal fibrosis, such as macrophages, growth factors, oxidative stress and inflammatory cytokines. Indoxyl sulfate (IS), a typical sulfate-conjugated uremic solute, accumulates markedly in serum and renal tissue with long-term nephropathy. Many factors are involved in the pathogenesis of renal fibrosis, such as macrophages, growth factors, oxidative stress and inflammatory cytokines. Indoxyl sulfate (IS), a typical sulfate-conjugated uremic solute, accumulates markedly in serum and renal tissue of patients with chronic nephropathy. IS is produced predominantly in the liver by CYP2A6/2E1-mediated oxidative metabolism of indoxyl. Thus, we established Sult1a1 gene-deficient (KO) mice to investigate the mechanism of renal fibrosis, such as macrophages, growth factors, oxidative stress and inflammatory cytokines. Indoxyl sulfate (IS) in the kidney of Sult1a1 KO mice was significantly reduced in the kidney of Sult1a1 KO mice compared to wild type (WT, 8wks-old) mice. The high expression of Smox in the kidneys of Sult1a1 KO mice was detected by Western blot analysis.

Conclusions: Suppression of IS accumulation in Sult1a1 KO mice via genetic deletion of Sult1a1 gene significantly attenuated the rise in BUN (29 ± 13 vs. 24 ± 1 mg/dl), and kidney weight (6.8 ± 0.8 vs. 6.0 ± 0.3 mg/g BW in controls), and decrease in kidney weight (6.8 ± 0.8 vs. 6.0 ± 0.3 mg/g BW in controls).

Funding: NIDDK Support, Veterans Affairs Support

SA-P0743
Ablation of Polyclonal Catabolic Enzymes Protects Against Renal Damage and Fibrosis due to Long-Term Cisplatin Treatment
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Background: Cisplatin is a highly effective anti-neoplastic agent against a variety of solid tumors; however, complications associated with its use such as nephrotoxicity limit its effectiveness. While cisplatin’s main anti-tumor activity is via the formation of DNA adducts and disruption of cell cycle progression, its general toxicity is mediated by the induction of oxidative stress. Enhanced polyamine catabolism, mediated via increased expression and activity of spermidine/spermine N1-acetyltransferase (SAT1) and spermine oxidase (SMOX), and generation of toxic products of polyamine degradation (acrolein, H2O2 and aldehydes) is important in the mediation of acute kidney injury in mice treated with a single high dose of cisplatin (20mg/kg). We hypothesized that the inhibition of polyamine catabolism will reduce the severity of chronic renal injury caused by long-term cisplatin treatment.

Methods: Using a multiple low dose cisplatin (single weekly cisplatin injection of 7mg/kg for 4 weeks) which more closely simulates the course of cisplatin treatment in cancer patients, we examined the effect of inhibition of polyamine catabolism on the severity of renal injury. The onset and severity of renal damage was determined by assessment of renal function (serum creatinine and blood urea nitrogen levels), damage to the tubular epithelium and renal fibrosis.

Results: Treatment of mice with multiple low doses of cisplatin led to renal tubular dysfunction, interstitial fibrosis and deterioration of renal function. This was associated with increased expression of polyamine catabolizing enzymes Sat1 and Smos transcripts. Comparing the effect of multiple low dose cisplatin treatment in wild type (WT), Smos-KO and Sat1-KO mice revealed that Sat1-KO and Smos-KO mice are significantly protected against renal tubular injury, interstitial fibrosis and loss of renal function.

Conclusions: These studies indicate that: 1) the expression and activity of Smox and Sat1 increase in animals treated with multiple low doses of cisplatin; and 2) the ablation of these genes reduces the severity of renal injury, interstitial fibrosis and loss of renal function. These results suggest that modulating the activity of polyamine enzymes or neutralizing the toxic products of polyamine catabolism protect against cisplatin-induced chronic renal injury.

Funding: Veterans Affairs Support

SA-P0744
Discovery and Validation of Intestinal Microbiota as Gut Biomarkers for Mirroring Disease Progression and Circulating Nephrotoxin Levels in CKD
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Background: The interplay of the gut microbes with gut-producing nephrotoxins and the renal progression remains unclear in cohorts with different stage of chronic kidney disease (CKD) patients.

Methods: Analysis of intestinal microbiota (16S RNA gene sequencing) and circulating p-cresyl sulfate/indoxyl sulfate were conducted in 92 (31 mild, 30 moderate and 31 advanced) CKD patients and 30 controls (discovery cohort), and further validated in a cohort comprising 22 controls and 76 peritoneal dialysis patients. Spearman’s correlation was used to determine the association of major genera (>0.1% abundance and present in >90% of samples) with serum biomarkers and disease severity. Chao1 index and Bray-Curtis distance were used to assess microbial community diversity. Functional composition of metagenomes was predicted from 16S rRNA data by the phylogenetic reconstruction of unobserved states (PICRUSt).

Results: Significant differences in bacterial composition and diversity were noted among controls and patients at different disease stages. A core CKD-associated microbiota consisted of 7 genera (Escherichia_Shigella, Dialister, Lachnospiraceae_ND3007_group, Pseudobutyribrio, Roseburia, Paraprevotella and Ruminoclostridium) and 2 species (Collinsella stercorea and Bacteroides egerrii) were identified to be highly correlated with the stages of CKD. Paraprevotella, Pseudobutyribrio and Collinsella stercorea were superior in discriminating CKD from the controls than the use of urine protein/creatinine ratio, even at very early-stage of disease. The performance was further tested in validation cohort. Bacterial genera highly correlated with indoxyl sulfate and p-cresyl sulfate levels were identified and predicted the functional capabilities of microbial communities by PICRUSt showed that microbial genes related to the metabolism of aromatic amino acids (phenylalanine, tyrosine, and tryptophan) were differentially enriched among the control and different CKD stages.

Conclusions: Our results provide solid human evidence of the impact of gut-microbiota-kidney axis on the severity of CKD and highlight a usefulness of specific gut microorganisms as possible biomarker or therapeutic target of this global health burden.

Funding: Other NIH Support - Chang Gung Memorial Hospital
SA-PO745

Probiotic Bifidobacterium animalis subsp. lactis Bi-07 Protects Intestinal Barrier by Alleviating Intestinal Oxidative Stress in Uremic Rats

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Background: To investigate whether oral administration of probiotic Bifidobacterium animalis subsp. lactis Bi-07 could protect intestinal barrier in uremic rats and to explore whether it could alleviate oxidative stress in intestinal tissues.

Methods: Thirty SD rats were randomly divided into 3 groups (n=10). The sham operation group only opened the renal capsules. The uremia group underwent 5/6 nephrectomy. Uremia/probiotics group: B. animalis subsp. lactis Bi-07 was administered daily to the rats for 5 weeks after 5/6 nephrectomy. Determination of 99mTc-DTPA in blood and urine after intragastric administration of 99mTc-DTPA solution evaluated Intestinal permeability. At the end of the intervention, the intestinal segments were retrieved. The ultrastructure of the intestinal epithelium tight junction (TJ) complex was observed by scanning electron microscopy (SEM) combined with lanthanum nitrate staining. After preparation of intestinal homogenate, malondialdehyde (MDA) content and superoxide dismutase (SOD) activity were detected.

Results: SEM showed that microvilli structure of the intestinal epithelial cells in the uremia group was disordered, sparse and shed. Lanthanum nitrate dye could penetrate into the intestinal epithelial cells gap. Compared with the uremia group, microvilli were neatly arranged and TJ was structurally intact. Little of lanthanum nitrate penetrated cell gap in uremia/probiotics group. Compared with uremic group, B. animalis subsp. lactis Bi-07 significantly increased SOD levels, suggesting that B. animalis subsp. lactis Bi-07 protects the intestinal barrier by alleviating oxidative stress.

Conclusions: The probiotic B. animalis subsp. lactis Bi-07 can protect the intestinal barrier in uremic rats. The mechanism may be to alleviate intestinal oxidative stress and reduce intestinal barrier damage in uremia.

Funding: Government Support - Non-U.S.

SA-PO746

The Expression of Intestinal Mir-223/NLRP3 Axis in Uremic Rats and the Intervention of Probiotics

Hua Liu,1 Lei Chen,3 Shanshan Liang,4 Meng Wei,4 Lingshuang Sun,4 Jinhong Xue,1 Meng Wang,2 Hongli Jiang,2 *Blood Purification, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China; 1The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China; 3The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China; 4Dialysis Department of Nephrology, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, China.

Background: To investigate the role of chronic inflammatory response mediated by NLRP3 inflammasome in uremia intestinal barrier dysfunction by detecting the changes of mir-223/NLRP3, and to observe the effect of probiotic intervention on it.

Methods: Seventy SD rats were randomly divided into 3 groups and 2 sham group (SH group). 5/6 Nephrectomy was performed on 50 rats in the uremic model group, and 10 rats in the SH group. The sham operation group only opened the renal capsules. The uremia group underwent 5/6 nephrectomy. Uremia + probiotics group: B. animalis subsp. lactis Bi-07 was administered daily to the rats for 5 weeks after 5/6 nephrectomy. Expression of mir-223 and NLRP3 was detected by RT-qPCR. Expression of NLRP3, caspase-1, IL-1β, and TJ were examined by Western blotting. The expression of MDA and SOD was detected by RT-qPCR. Expression of NLRP3, caspase-1, IL-1β, TJ, and MDA were examined by Western blotting. The expression of MDA and SOD was detected by RT-qPCR. Expression of NLRP3, caspase-1, IL-1β, TJ, and MDA were examined by Western blotting.

Results: Compared with SH group, the expression of miR-223 mRNA in the ileal tissues of the UR group was significantly decreased, while that of UP group was significantly increased (P<0.05). Western blotting showed that the expressions of NLRP3, caspase-1 and IL-1β of the UR group were significantly higher than those of the SH group (P<0.05), while the expressions of JAM-1, Ocludin and claudin-1 proteins were significantly lower (P<0.05). However, after probiotics intervention, the expressions of NLRP3, caspase-1 and IL-1β was decreased (P<0.05), and the expressions of JAM-1, Ocludin and claudin-1 was improved.

Conclusions: Probiotics can improve the intestinal barrier function of uremia, which may involve the miR-223/NLRP3 pathway. The conclusion of this study may provide a new treatment idea for the intestinal barrier dysfunction of uremia.

Funding: Government Support - Non-U.S.

SA-PO747

Omega-3 Polyunsaturated Fatty Acids Reduce Intestinal Inflammation and Enhance Intestinal Motility Associated with Reduced Nitric Oxide Production in Uremic Rats

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Background: Previous studies have shown that chronic kidney disease (CKD) could elicit an intestinal inflammation and result in intestinal dysmotility followed by many complications. Increasing evidence suggests that omega-3 polyunsaturated fatty acids can reduce intestinal inflammation and improve intestinal function in many diseases. In this study, we therefore investigated the effect of omega-3 polyunsaturated fatty acids on intestinal inflammation and intestinal motility in CKD and the underlying mechanism.

Methods: CKD was induced by the 5/6 kidney resection, and omega-3 polyunsaturated fatty acids enriched diet or standard diet was administrated for six weeks. Intestinal motility was assessed by charcoal transport assay, and intestinal inflammation was assessed by analyzing myeloperoxidase activity and concentrations and gene expression of TNF-α, IL-1β, and IL-10 in the intestinal tissue. The nitric oxide production was assessed in the intestinal tissue.

Results: The results showed that CKD resulted in a marked delay in intestinal motility and associated with a significant increase of intestinal levels of inflammatory parameters (P<0.05). However, compared to the standard diet, omega-3 polyunsaturated fatty acids enriched diet administration markedly reduced intestinal inflammatory response, and resulted in a significant improvement in intestinal motility (P<0.05). In addition, the nitric oxide production was inhibited by omega-3 polyunsaturated fatty acids enriched diet treatment (P<0.05).

Conclusions: These results suggest that omega-3 polyunsaturated fatty acids could reduce intestinal inflammation and enhance intestinal motility in CKD, and the underlying mechanism may be associated with reduced nitric oxide production.

Funding: Government Support - Non-U.S.

SA-PO748

The Effects of Allopurinol on Xanthine Oxidase Activity and Expression in CKD

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Background: Allopurinol lowers uric acid levels and may improve vascular function in chronic kidney disease (CKD). It is unclear whether the effects of allopurinol are mediated by xanthine oxidase (XO) inhibition, uric acid-lowering, or both. We hypothesized that allopurinol suppresses serum XO activity and reduces endothelial XO protein expression.

Methods: We analyzed serum and endothelial cells samples from 45 CKD patients who participated in a randomized controlled trial of allopurinol vs placebo. Serum XO activity was determined and the expression of endothelial XO protein was evaluated (immunofluorescence). Serum xanthine levels were measured via mass spectrometry.

Results: Baseline serum uric acid correlated with baseline CKD-EPI estimated GFR (r = 0.57, p value <0.0001) but not with serum XO activity (r = -0.10, p value 0.52) or endothelial XO protein expression (r = -0.2, p value 0.56). There was no correlation between serum XO activity or endothelial XO protein expression with baseline brachial artery flow-mediated dilation (BA-FMD) or CKD-EPI estimated GFR. As shown in the Table, allopurinol lowered serum uric acid levels and increased serum xanthine levels significantly. However, allopurinol did not decrease serum XO activity or the expression of endothelial XO protein. Change in XO activity and XO protein expression did not correlate with change in BA-FMD.

Conclusions: Our data suggest that allopurinol effectively lowers serum uric acid levels by inhibition of XO activity in the liver. However, contrary to our hypothesis, allopurinol does not significantly affect serum XO activity or XO protein expression in the endothelium. In addition our findings suggest that the main factor for increased serum uric acid in CKD is reduced kidney function.

Funding: NIDDK Support

Changes in serum uric acid, serum XO activity, and endothelial XO expression by study group

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum uric acid (mg/dL)</th>
<th>Serum xanthine (mM)</th>
<th>Serum XO activity (units/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol (n=24)</td>
<td>3.7 (1.0)</td>
<td>770 (2075)</td>
<td>0.12 (0.36)</td>
</tr>
<tr>
<td>Placebo (n=21)</td>
<td>4.4 (1.6)</td>
<td>4.7 (177)</td>
<td>0.06 (0.19)</td>
</tr>
</tbody>
</table>

R/S: relative signal intensity, * arbitrary units, normalized to XO expression in human umbilical endothelial cells

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Allopurinol Affects the Metabolome of CKD Patients Beyond Uric Acid-Lowering

Mingyao Sun,1 Nicole G. Lacina,1 Nicholas Kruse,2 Jane Buchanan,1 Diana Zepeda-Orozco,2 Eric Taylor,3 Diana I. Jalal.1 1The University of Iowa, Iowa City, IA; 2The University of Iowa Hospitals and Clinics, Iowa City, IA.

Background: Allopurinol, a xanthine oxidase (XO) inhibitor, is the most commonly prescribed uric acid-lowering agent in patients with chronic kidney disease (CKD). Although experimental evidence suggests allopurinol has broader effects on the metabolome, these potential effects have not been characterized in CKD. Here, we sought to evaluate the effects of allopurinol on the metabolome of CKD patients.

Methods: Gas chromatography mass spectrometry (GC-MS) was performed on the serum of 31 subjects who participated in a 12-week randomized clinical trial of allopurinol vs placebo. Metabolites of central carbon metabolism included the TCA cycle, glycolysis, the pentose phosphate pathway, amino acid metabolism, neurotransmission, reactive oxygen species defense, and energetics. Metabolites were compared at baseline to the end of study for allopurinol and placebo (paired t test). MetaboAnalyst software was utilized to identify metabolic pathways.

Results: Of the 90 metabolites evaluated by GC-MS, 6 were significantly altered after allopurinol treatment but not placebo (Table). MetaboAnalyst indicated the pentose phosphate (PP) pathway and purine and pyrimidine metabolism were the top pathways affected by allopurinol. Allopurinol inhibited purine metabolism, resulting in decreased serum uric acid (3.7 ± 1.0 mg/dL) vs placebo (0.1 ± 1.5 mg/dL) (p<0.0001) and increased the precursor xanthine. Allopurinol inhibited PP pathway activity as downstream product ribose-5-phosphate decreased and upstream precursor glucose-6-phosphate increased.

Conclusions: We describe, for the first time, important effects of allopurinol on the metabolome of CKD patients. Specifically, PP pathway inhibition is known to contribute to oxidative stress and pyrimidine pathway inhibition is known to increase ammonia. These findings should be confirmed in larger studies and the clinical implications of these broad effects should be explored.

Funding: NIDDK Support

Changes in metabolites by study group

<table>
<thead>
<tr>
<th>Metabolite Pathway</th>
<th>Allopurinol (n=9)</th>
<th>Placebo (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydroxyphosphatase</td>
<td>Tissue metabolism</td>
<td>103378.54</td>
</tr>
<tr>
<td>Glutathione peroxidase</td>
<td>PP pathway</td>
<td>121840.91</td>
</tr>
<tr>
<td>N-acetylglutamate</td>
<td>PP pathway, pyruvate metabolism</td>
<td>113202.93</td>
</tr>
<tr>
<td>Xanthine</td>
<td>PP pathway</td>
<td>157803.93</td>
</tr>
<tr>
<td>L-serine</td>
<td>PP pathway</td>
<td>87053.93</td>
</tr>
<tr>
<td>Xylose</td>
<td>PP pathway</td>
<td>352812</td>
</tr>
<tr>
<td>Lactate</td>
<td>Aldolase</td>
<td>309539.51</td>
</tr>
<tr>
<td>Leucine</td>
<td>Aminotransferase</td>
<td>700192.72</td>
</tr>
</tbody>
</table>

Values are expressed as mean(SD) relative signal intensity
* P value=0.05; #: P value=0.09

SA-PO750

Hydrogen Sulfide Attenuates CKD Progression by Inducing TET-Dependent DNA Methylation on Klotho Promoter

Yuhu Gu, Xiaojing Ding, Xiaoyan Zhang. Zhongshan Hospital, Fudan University, Shanghai, China.

Background: Hydrogen sulfide has been reported to attenuate renal fibrosis. A recent study shows hydrogen sulfide can demethylate its target genes by upregulating TET1 activity through ROS-induced Fe2+ reduction. However, the role of H2S in modulating Klotho methylation and the potential underlying mechanisms remain unclear.

Methods: C57BL/6 mice underwent unilateral ureter obstruction(UUO) with or without NaHS treatment. Multiple techniques were used to analyze the extent of tubulointerstitial fibrosis and renal hypoxia, the methylation and hydroxymethylation level of renal Klotho promoters, and the expression and activity of TETs. In vitro, HK2 cells received hypoxia treatment. The level of cellular ROS and ferrous ion was examined to further explore the role of hypoxia on TETs enzyme activity and Klotho methylation.

Results: Evidenced by Masson staining and the expression of α-SMA and Fibronectin, NaHS treatment reduced renal fibrosis in UUO mice. Also, it upregulated Klotho expression, decreased Klotho methylation level and increased Klotho hydroxymethylation level. Metabolites of central carbon metabolism included the TCA cycle, glycolysis, the pentose phosphate pathway, amino acid metabolism, neurotransmission, reactive oxygen species defense, and energetics. Metabolites were compared at baseline to the end of study for allopurinol and placebo (paired t test). MetaboAnalyst software was utilized to identify metabolic pathways.

Conclusions: The differential expression of Klotho in exosomes from serum and urine of patients with IMN, which may lay the foundation for research of exosomes as a new class of exosome-based IMN diagnosis biomarkers.

Methods: Ten patients with IMN and ten normal controls were recruited as experimental subjects in our study. The exosomes were extracted from the collected serum and urine. Then, pure circRNAs were extracted from the exosomes with a series of enzymatic reactions. Afterwards, the significantly differentially expressed circRNAs were chosen by the method of gene-sequencing.

Results: Compared with normal controls, the circRNAs were reduced in the exosomes from serum of patients with IMN, which mostly originated from inorganic regions. Meanwhile, a total of 89 circRNAs were significantly differentially expressed, which were mostly derived from inorganic genes. However, the species were increased in the exosomes from the urine of patients with IMN compared to normal controls, and they mainly originated from exon gene regions. Simultaneously, a total of 60 circRNAs were significantly differentially expressed, which primarily belonged to inorganic regions, including 54 up-regulated and 6 down-regulated genes.

Conclusions: The significant differential and specific expression of circRNAs in the exosomes from patients with IMN were. For example, MYO3A, which originated from chr7:100550880/100551062, could be considered a potential diagnostic biomarker of IMN. Furthermore, these figures may be used as a reference or supplement in the research of the pathogenesis of IMN. Number

SA-PO751

The Differential Expression of CircRNA in Exosomes from Serum and Urine in Patients with Idiopathic Membranous Nephropathy

Hui Lin Ma. Shenzhen People’s Hospital, Shenzhen, China.

Background: To further explore the pathogenesis of IMN, the technique of gene-sequencing was used to analyze the differentially expressed circRNAs in exosomes from both the serum and urine of patients with IMN, which may lay the foundation for research of circRNAs as a new class of exosome-based IMN diagnosis biomarkers.

Methods: Ten patients with IMN and ten normal controls were recruited as experimental subjects in our study. The exosomes were extracted from the collected serum and urine. Then, pure circRNAs were extracted from the exosomes with a series of enzymatic reactions. Afterwards, the significantly differentially expressed circRNAs were chosen by the method of gene-sequencing.

Results: Compared with normal controls, the circRNAs were reduced in the exosomes from serum of patients with IMN, which mostly originated from inorganic regions. Meanwhile, a total of 89 circRNAs were significantly differentially expressed, which were mostly derived from inorganic genes. However, the species were increased in the exosomes from the urine of patients with IMN compared to normal controls, and they mainly originated from exon gene regions. Simultaneously, a total of 60 circRNAs were significantly differentially expressed, which primarily belonged to inorganic regions, including 54 up-regulated and 6 down-regulated genes.

Conclusions: The significant differential and specific expression of circRNAs in the exosomes from patients with IMN were. For example, MYO3A, which originated from chr7:100550880/100551062, could be considered a potential diagnostic biomarker of IMN. Furthermore, these figures may be used as a reference or supplement in the research of the pathogenesis of IMN. Number

SA-PO752

Dietary Phosphate Disturbs of Gut Microbiome In Mice

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Background: Disorder of phosphate metabolism is a common pathological condition in chronic kidney disease (CKD) patients. Excessive intake of dietary phosphate deteriorates CKD and various complications including cardiovascular disease. Recent reports have demonstrated that gut microbiome disturbance is associated with both the etiology and progression of CKD. However, the relationship between dietary phosphate and gut microbiome remains unknown. Here, we examined the effects of excessive intake of phosphate on gut microbiome.

Methods: Five-week-old male C57BL/6 mice were fed either control diet (0.4% phosphate; CP) or high phosphate diet (1.2% phosphate; HP) for eight weeks. Stool samples were collected at eight weeks. After amplifying the V3-V4 region of 16S ribosome RNA by PCR, analysis of the gut microbiota was carried out using MiSeq next generation sequencer (NGS).

Results: Compared with CP diet group, HP diet group significantly decreased in body weight and epididymal fat weight, plasma calcium level, and increased in urinary phosphate excretion. In analysis of gut microbiota, HP diet group increased in Firmicutes phylum and decreased in Bacteroidetes phylum by PCR and NGS analysis. In particular, significant increase in Erysipelotrichaceae genus and decrease in Clostridia genus were observed in HP diet group, and NGS analysis showed the decrease in bacterial diversity in HP diet group. In addition, HP diet group decreased colonic tight junction marker mRNA level.

Conclusions: These results suggest that the excessive intake of dietary phosphate disturbs gut microbiota and decreases in bacterial diversity. Furthermore, it may affect the intestinal barrier function. Such a disturbance may be related to progression of CKD. Adequate management of dietary phosphate would be required to keep healthy environment in gut.

Funding: Government Support - Non-U.S.
Improvement of the Effect of HIF-1α Stabilizer on the Destruction of Tight Junctions in Intestinal Epithelial Cells Induced by Homocysteine

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Background: Based on previous findings that homocysteine (Hcy) can increase the permeability of intestinal epithelial Caco2 cell and lead to decreased expression of tight junction molecules, the role of HIF-1α in intestinal barrier dysfunction caused by homocysteine and the mechanism of intervention of HIF-1α stabilizer (FG-4952) on these effects were explored.

Methods: Caco2 cells were cultured and divided into four groups: normal control group, FG4952 group, homocysteine group (Hcy group), and Hcy+FG4952 group. mRNA and protein expression levels of HIF-1α, ZO-1, claudin-1, occludin were detected by RT-qPCR and Western blotting. The expression level of miR-223 was detected by RT-qPCR. Hcy can reduce the expression of miR-223 mRNA (P < 0.05), while the FG-4952 can increase the expression of miR-223 mRNA (P < 0.05) (Fig. 2).

Conclusions: miR-223 may be involved in the maintenance of intestinal epithelial barrier function in the experiment of using uremic serum to stimulate Caco2 cells. HIF-1α stabilizer can improve the Hcy-induced reduction expression of HIF-1α, ZO-1, claudin-1, Occludin, up-regulate the expression of miR-223 and down-regulate the expression of NLRP3, the mechanism may involve the mir-223/NLRP3 pathway.

A Guanylate Cyclase C Agonist Linaclotide Reduces Trimethylamine N-Oxide in an Adenine-Induced CKD Model

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Background: Cardiorenal syndrome is a major cause of mortality in CKD patients. Trimethylamine-N-oxide (TMAO), which is a hepatic metabolized product of trimethylamine (TMA) generated from dietary phosphatidylcholine or carnitine derived by gut microbiota, directly linked to the progression of cardiovascular disease and renal dysfunction. Therefore, targeting TMAO may be one of a novel strategy for the prevention of CVD and CKD.

Methods: A guanylate cyclase C agonist linaclotide was administered to adenine-induced renal failure model and the changes of renal function and gut-derived uremic toxins as well as gut microbiota community were analyzed using metabolic and metagenomic analyses.

Results: Linaclotide decreased the plasma TMAO level at a clinically used dose (10 µg/kg) in an adenine-induced renal failure mouse. In addition, linaclotide (100 µg/kg), significantly improved renal function and reduced various uremic toxins. Linaclotide reduced renal inflammation and fibrosis, cardiac fibrosis as well as collagen I, TGF-β, galectin-3 and ST2 gene expressions. The plasma galectin-3 and ST2 were also reduced. In the small intestinal crypt, F4/80-positive macrophages were abundant in renal failure and the expression was decreased by linaclotide. Reduced colonic claudin1 was also restored by linaclotide, suggesting that linaclotide ameliorated “leaky-gut” in the renal failure. By metagenomic analysis, microbial order Clostridiales may have been responsible for the change in TMAO.

Conclusions: Linaclotide reduced TMAO and uremic toxin levels and be a potent tool for the cardio-renal syndrome by modification of the “gut-cardiorenal axis”

Funding: Government Support - Non-U.S.
Impaired Secretion of Uremic Solutes in Advanced CKD

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Background: The normal kidney clears many solutes efficiently by proximal tubular secretion. Clearance values are observed to be particularly high relative to the glomerular filtration rate (GFR) when the clearances of protein-bound solutes are calculated in terms of their free, unbound concentrations. This study examined the extent to which high secretory clearances are maintained when kidney function is markedly reduced.

Methods: Simultaneous urine and blood samples were collected from patients with stage 4 chronic kidney disease not on dialysis (CKD, n=16) and control subjects (control, n=17). The normally secreted and protein-bound solutes indoxyl sulfate (IS) and p-cresol sulfate (PCS) were assayed by LC/MS/MS. Clearances relative to the GFR (fractional clearances) were then estimated by dividing the urinary to free plasma concentration ratios for these solutes by the urine to plasma concentration ratio for creatinine.

Results: GFR values estimated by the CKD-EPI equation were 7 ± 2 ml/min/1.73 m² in the CKD patients and 86 ± 17 ml/min/1.73 m² in the controls. Fractional clearances of IS and PCS were very high in controls in accord with prior results. Fractional clearances for both solutes were greatly reduced in CKD indicating impaired secretion (IS: 5 ± 2 vs. 28 ± 7, p<0.001; PCS: 3 ± 1 vs. 10 ± 3, p=0.001). Impaired kidney secretion was accompanied by prominent plasma accumulation in CKD patients with plasma concentrations of IS and PCS averaging 59 and 27 times greater than those in control subjects as compared to a 957 times greater creatinine concentration.

Conclusions: Secretory clearance of IS and PCS was impaired out of proportion to glomerular filtration rate in patients with advanced CKD. Prominent accumulation of these and other normally secreted solutes may contribute to uremic illness.

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Association of Tubular Solute Clearances with the Glomerular Filtration Rate and Complications of CKD: The CRIC Study

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Background: The secretion of organic solutes by the proximal tubules is an essential intrinsic kidney function. However, the degree to which secretory solute clearance corresponds with the glomerular filtration rate (GFR) and potential implications of net secretory clearance are largely unknown.

Methods: We evaluated 1240 participants who underwent 125 i-ithalamate clearance (iGFR) measurements of GFR in the Chronic Renal Insufficiency Cohort (CRIC) Study. We targeted mass-spectrometry to quantify 11 secretory solutes in 24-hour urine and plasma samples. We used correlation and linear regression to determine cross-sectional associations of secretory clearances with iGFR and common metabolic complications.

Results: Correlations between iGFR and secretory solute clearances ranged from ρ = 0.21 (p-cresol sulfate) to ρ = 0.55 (kynurenic acid). Lower clearances of most secretory solutes were associated with higher serum concentrations of parathyroid hormone (PTH), triglycerides, and uric acid (Figure). Each 50% lower kynurenic acid clearance was associated with a 16.1 µg/ml higher serum PTH concentration and an 18.2 mg/dL higher serum triglyceride concentration after adjustment for iGFR, albuminuria, and other potential confounders. Secretory solute clearances were not associated with meaningful differences in serum calcium, phosphate, hemoglobin, bicarbonate, or C-reactive protein concentrations.

Conclusions: Patients with CKD differ in their tubular secretory clearance for a given level of GFR. Lower net secretory clearances are associated with higher levels of PTH, triglycerides, and uric acid independent of GFR and albuminuria, suggesting potential clinical and biological relevance of this kidney function.

Funding: NIDDK Support

Variations in Gut Microbiota May Correlate with Lipid Metabolism in UMOD Knockout Rats

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Background: Tamm-Horsfall protein (THP, uromodulin, UMOD) is an important protective factor during kidney injury. Although it was mainly expressed in the thick ascending limb, uromodulin still can be detected in the serum and in other tissue cells. Study has revealed a crucial role of uromodulin on the M-cell surface for the uptake of S-layer-positive lactic acid bacteria into M cells, possibly leading to subsequent delivery of the bacteria to dendritic cells closely associated with M cells for immunomodulation. In this study we investigated the change of gut microbiome in UMOD ablation rats. Methods: 10 wild type SD male rats and 10 UMOD knockout SD rats (THP-/−) were housed under controlled environment for 10 weeks. Same water and diet were provided. All of the rats were anesthetized to collect fecal samples from large intestine directly. The bacterial composition was analyzed based on 16s ribosomal DNA pyrosequencing. Results: There was no difference in mean weight between two groups. The serum triglyceride (TG) decreased significantly in THP-/− rats (0.632±1.47 mmol/L, p<0.05). The microbial richness and diversity in composition were different in THP-/− rats compared with WT (PCoA analysis, p=0.036). At the phylum level, there were obvious reductions in Elusimicrobia and Actinobacteria in THP-/− rats (p=0.05). At the genus level, five genera were obviously increased in THP-/− rats (p<0.05), including Helicobacter, Lactobacillus, Roseburia, Clostridium XI and Phascolarctobacterium. While four genera, including Alloprevotella, Escherichia, Bacteroides and Ruminococcus decreased (p<0.05). Among these changed genera, Ruminococcus and Elusimicrobium presented positive correlation with TG, while Phascolarctobacterium, Lactobacillus and Alloprevotella were negative correlated with TG (P<0.05). Obvious variations were identified in 33 microbial metabolites with the change of microbiota. 22 out of 33 microbial metabolite products were fatty acid.

Conclusions: UMOD ablation led to significant variations in composition of gut microbiota in SD rats. The change of gut microbiota correlated with serum TG, suggested other pathways may be involved the abnormal lipid metabolism in chronic kidney disease

Carbamylation of Albumin Results in Structural Changes That Minimize Binding to Cubilin and FcRn Resulting in More Rapid Serum Clearance

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Background: Chronic kidney disease results in high serum urea concentrations and leads to increased cardiovascular disease. An increase in urea results in excess protein carbamylation which has been associated with increased mortality. We hypothesized carbamylation would alter the structure of albumin leading to reduced binding to cubilin and FcRn resulting in increased serum clearance.

Methods: To test this hypothesis rats were injected at time 0 with RSA or RSA modified with KCN 30min, 2hr or 4hr to induce increasing amounts of carbamylation. Increased serum clearance was observed in a dose dependent fashion. To determine the mechanism we quantified the number of lysine residues modified on RSA using MALDI TOF and showed increasing Lys residues modified with longer KCN incubation times. We then asked whether increased clearance was the result of decreased binding to cubilin, which would result in reduced PTC uptake, and or FcRn which would reduce transcytosis of albumin. Using Microscale Thermophoresis to quantify changes in binding affinity waterfrother, we observed a reduction in both cubilin and FcRn binding with carbamylated RSA, compared to RSA.
Results: Specifically, the Kd of cubulin 7,8 increased from 0.01 mM for unmodified RS-D to 1.2 mM for 30 min, 1.7 mM for 2 hr and 10 mM for 4 hr carbamylated RSAs respectively. For FcRn the Kd for albumin was 10 mM for unmodified albumin, while 2 hr carbamylated RSA was >100 mM and 4 hr had no binding. The decreased binding to both cubulin 7,8 and FcRn can explain the increased serum clearance and is also consistent with the decreased proximal tubule uptake and transcytosis of albumin resulting in more rapid serum clearance and somatic accumulation of carbamylated albumin.

Conclusions: The glutamine catabolism is involved in the activation of fibroblasts. Understanding the mechanism of these processes could lead to novel strategies for the treatment of renal disease.

SA-PS760
The Mechanism of Glutamine Catabolism in the Activation of Renal Fibroblasts
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Background: Glutamine catabolism enhances the activity of tricarboxylic acid cycle and synthesizes key intermediate metabolites required for amino acids. This study will explore the role of glutamine catabolism in the activation of fibroblasts.

Methods: Activation of fibroblasts was induced by TGF-β1, changes of metabolites during fibroblast activation were detected by targeted metabolomic analysis. The effects of glutamine on mitochondrial function were detected by measuring changes of mitochondrial content, morphology, membrane potential and oxygen consumption rate. The effects of supplementation with α-ketoglutarate after deprivation of glutamine on proliferation, activation, migration and mitochondrial function of fibroblasts were observed in in vitro experiment. In vivo experiment, intraperitoneal injection of BPTES after the UUO model was constructed, and the effects of BPTES on renal fibrosis was determined by pathological staining and immunohistochemistry.

Results: After TGF-β1 treatment, non-targeted metabolomics suggested that glutamate content increased significantly and pathway analysis highlighted significant enhancement of glutamine metabolism. The expression of GLS1, the key enzyme of glutamine catabolism, was detected by western blot. After the inhibition of GLS1 by specific inhibitors or siRNA, the proliferation, activation and migration of fibroblasts were significantly inhibited. After deprivation of glutamine during fibroblast activation, the mitochondrial content was significantly reduced, mitochondria were fragmented, the mitochondrial membrane potential, mitochondrial oxygen consumption rate, and ATP generation were all significantly reduced. After deprivation of glutamine and supplementation with α-ketoglutarate, the proliferation, activation and migration of fibroblasts were increased, and the mitochondrial content and mitochondrial membrane potential was partially recovered. In UUO model, BPTES could inhibit the activation of renal fibroblasts and alleviate renal fibrosis.

Conclusions: Glutamine catabolism plays an important role during fibroblast activation. Inhibition of glutamine catabolism can inhibit the proliferation and activation of renal fibroblasts and improve renal fibrosis.

SA-PS761
Knockdown of Central (Pro)Renin Receptor Attenuates Renal Injury in a High-Salt-Load CKD Rat Model
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Background: High-salt promotes renal injury in chronic kidney disease (CKD) through activating the RAS axis of the brain and kidney. Simultaneously, (pro)renin receptor (RPR) can exert local physiological effects in brain. However, little is known about their interaction and pathophysiological mechanisms. In this study, we investigate the main role of central PRR ameliorating renal injury in CKD.

Methods: In vivo experiment, intraperitoneal injection of BPTES after the UUO model was constructed, and the effects of BPTES on renal fibrosis was determined by pathological staining and immunohistochemistry.

Results: The results demonstrated that the adoptive transfer of pEPCs promoted renal repair and reduced renal injury. Central administration of U0126, Wortmannin, and Losartan was performed. The results showed losartan and U0126 inhibited these interventional effects, indicating that renal damage, inflammation, oxidative stress, and fibrosis. However, decreased phosphorylation of ERK1/2 and Akt signaling in the brain had no significant effect on the expression of PRR, but knocking down PRR could inhibit the phosphorylation of these pathways. It suggested that central PRR alleviated renal injury through these signaling pathways.

Conclusions: Central knockdown of PRR expression can ameliorate salt-induced renal damage, as well as reduce ROS activation, inflammation, and oxidative stress, thereby slowing down the progression of CKD. Central PRR may affect renal pathology through the ACE1-Ang II-AT1 axis as well as MAPK/ERK1/2 and PI3K/Akt signaling pathways.

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SA-PO762
A Whole-Genome CRISPR Knockout Positive Screen Reveals Pathways Regulating APOL1-Induced Cytotoxicity
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Background: In humans two genetic variants of Apolipoprotein L1 (APOL1), G1 and G2, are common in African Americans and are strongly associated with chronic kidney disease (CKD). However, little is known about their pathophysiological mechanism(s). APOL1 G1 and G2 are generally more toxic than wild type upon overexpression, with evidence for cellular mechanisms ranging from mitochondrial dysfunction, ER stress, endosome or autophagosome maturation defects, impaired cholesterol efflux, altered surfAR/integrin binding, and impaired eNOS efflux. It is evident that all of these are potential responses for CKD, and to an unbiased approach to identifying pathways and/or co-factors that mediate APOL1 variants cell killing should aid our understanding of the actual disease mechanism.

Methods: A pooled genome-wide CRISPR knockout screen, where each cell was depleted of a single gene prior to a phenotype-based selection, is one such powerful unbiased technique, which APOL1-induced in vitro cell death renders possible. Here, we show how we performed a genome-scale CRISPR-Cas9 loss-of-function screen in HEK293 cells to discover genes that influence APOL1-induced cell killing. We generated 10 000 inducible APOL1 G1 G0, G1 G2 HEK293 cells expressing Cas9-GFP and carefully titrated APOL1 variant dose-dependent cell killing. These cells were infected with a genome-wide lentiviral guide RNA library, followed by APOL1 induction to the pre-determined level.

Results: The cells surviving APOL1 selective pressure were subjected to next-generation sequencing of the integrated sgRNA cassettes. With this approach we identified new and existing pathways affecting APOL1-mediated cell killing.

Conclusions: Here we demonstrated how APOL1 variants over-expression could be used as a selective pressure in a CRISPR KO positive screen to reveal pathways that are directly or indirectly involved in APOL1-induced cell toxicity. The same pathways have the potential to become druggable targets for patients that develop CKD linked to APOL1 variants. Validation and characterization analysis of the discovered factors will be essential to confirm our findings and to demonstrate the feasibility of our screening approach.

Funding: Commercial Support - Genentech

SA-PO763
Putative Endothelial Progenitor Cells Protected Mice from Ischemia-Reperfusion-Induced Renal Fibrosis by Suppressing the Activation of PDGFR-β Pericytes via Paracrine Way
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Background: Putative endothelial progenitor cells (pEPCs) are defined as a group of stem cells which have the potential capacity to differentiate into endothelial cells. When tissues suffer from injury, it secretes factors to recruit pEPCs from bone marrow to injured site, involving in the vascular repair and protecting tissues from damage. However, the mechanism of pEPCs acting on ischemic organs, especially kidneys, is still not clear. Some studies showed that pEPCs participated in angiogenesis by directly intervening in vascular walls and differentiating into endothelial cells. Other studies claimed that pEPCs were also secreted to kidney tissues and blocking APOL1 via paracrine way. This study aimed to explore the role and mechanism of pEPCs in ischemia reperfusion (IR)-induced renal fibrosis.

Methods: Mice were infused with pEPCs from bone marrow of GFP mice 6 hours after IR surgery and survived at day 5, 10 and 28. GFP+ pEPCs were tracked by immunofluorescence and flow cytometry. The pEPCs-cultured medium (pEPCs-CM) were infused to investigate the paracrine role of pEPCs. Platelet derived growth factor-BB (PDGF-BB), the ligand for platelet derived growth factor receptor-β (PDGFR-β), which is the specific surface receptor on pericytes, was adopted, in a selective pericyte knockout mice (DTR expression in PDGFR-β+ cells), to detect the relationship between pEPCs and pericytes in the progression of IR-induced kidney disease.

Results: The results demonstrated that the adoptive transfer of pEPCs promoted the renal angiogenesis and attenuated renal fibrosis. Cell tracking experiments showed that pEPCs were detected in kidney, suggesting the involvement of paracrine mechanism. We further found the injection of pEPCs-CM had an equal protective effect on kidney as pEPCs did. The transfer of pEPCs or pEPCs-CM inhibited IR-induced PDGFR-β expression, pericyte-endothelial detachment, pericyte proliferation and remodeling, which supposed that pEPCs regulated the pericyte via paracrine way.

Funding: Limited Support
pericyte-myocyte-blast transition. These protective effect of transferred pEPCs on capillary rarefaction and renal fibrosis was blocked by conditional PDGFR-β cell knockout.

Conclusions: The adoptive transfer of pEPCs ameliorated IR-induced capillary rarefaction and renal fibrosis by suppressing the activation of PDGF-β/ pericyte paracrine way.

Funding: Government Support - Non-U.S.

SA-PO764
Basigin/CD147 Facilitates Uptake of Protein into Renal Tubular Epithelium
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Background: CD147/Basigin (Bsg), a glycosylated transmembrane protein, plays a crucial role in processes such as cancer development, inflammation and immune system regulation. We have so far demonstrated that Bsg is involved in the pathogenesis of acute kidney injury and renal fibrosis. In the injured kidneys, this expression is induced strongly in the basolateral side of TECs, infiltrating inflammatory cells. In a series of prior clinical studies, proteinuric kidney diseases such as minimal change nephrotic syndrome, showed marked increases in urinary Bsg levels, and a close relationship between proteinuria and urinary Bsg levels. aberrant molecular mechanisms involving Bsg-mediated intracellular metabolism may be a crucial determinant of proteinuric tubular injury. In this study, we investigated whether Bsg deficiency maintains intracellular homeostasis by inhibiting uptake of protein into TECs.

Methods: As a clinical study, diabetic kidney disease (DKD) patients (N=52) registered in UMIN Clinical Trials Registry (00160) were treated with spironolactone 25 mg once daily for 8 weeks. The relationships between urinary Bsg values and clinical indicators were examined. We then induced tubulointerstitial injuries in wild-type (Bsg+/+) or Bsg-deficient (Bsg−/−) mice using intraperitoneal injections of a large amount of protein for 14 days. Immunofluorescent tubal epithelial cell line from normal adult human kidney (HK2) was exposed to high glucose (40mM) or bovine serum albumin (BSA).

Results: In DKD patients, plasma and urinary CD147 levels showed a correlation with eGFR or proteinuria, but not HbA1c, respectively. In biopsy tissues of patients with severe DKD, marked CD147 induction was detected in injured lesions representing renal inflammation. In a basic study, Bsg−/− mice induced by protein overload ameliorate the development of tubulointerstitial injuries and kidney dysfunction. In Bsg−/− kidneys with protein overload, several apoptotic factors were enhanced with increased Bsg expression. Bsg silencing in HK2 exposed to BSA suppressed uptake of BSA into the epithelium, and decreased heme oxygenase-1 expression as a marker of oxidative stress. Exposure of high glucose wasn’t affected.

Conclusions: Bsg is involved in the pathogenesis of tubulointerstitial injuries by protein overload through promoting uptake of protein into TECs.

S3-PO765
Mechanism of Action of Veveimer, a First-in-Class, Orally Administered, Nonabsorbed, Counterion-Free Hydrochloric Acid Binder for the Treatment of Metabolic Acidosis in CKD
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Background: Current management of metabolic acidosis in patients with CKD relies on dietary protein restriction to reduce metabolic acid production or neutralization of retained acid with orally administered bicarbonate. Veverimer is being developed to provide a novel treatment modality for metabolic acidosis: endogenous acid removal. Veverimer is a free-amine polymer designed to combine high capacity and high selectivity for binding and removing HCl from the GI tract. It does not deliver sodium or other counterions and may therefore be appropriate for all patients with CKD and metabolic acidosis. The bioavailability of veverimer was assessed in ADME studies in rats and dogs dosed with 14C-labeled veverimer.

Methods: In vitro, veverimer had a maximum binding capacity of 10.7 ± 0.4 mmol HCl per gram of polymer with significant binding capacity (≈ 5 mmol/g) across the entire range of physiologically relevant human GI pH (1.5 to 7). Upon protonation, veverimer bound chloride with high specificity, with a low propensity of binding of phosphate, citrate or taurocholate. Administration of veverimer to rats with adenine-induced nephropathy and chronic metabolic acidosis resulted in a significant increase in fecal chloride excretion and a dose-dependent increment in bicarbonate to within the normal range, compared to untreated controls. ADME studies demonstrated that veverimer was not absorbed from the GI tract into the systemic circulation.

Conclusions: Endogenous acid removal through binding to veverimer, an orally-administered, non-absorbed polymer that is then excreted, provides a potential new mechanism for treating metabolic acidosis in patients with CKD.

Funding: Commercial Support - Tricida, Inc.

SA-PO766
Klotho Protein Supplementation Retards Renal Injury in 5/6-Nephrectomized Rats
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We have previously reported that ranolacartel, a calcilytic agent, retards renal injury by increasing endogenous klotho expression in remnant kidney model (Am J Physiol Renal Physiol. 2015;309:F216-26). Recent studies have demonstrated that FGF23 transduces its signal using klotho as co-receptor to increase renal abundance of Egf-1 and phosphorylated ERK, both of which may control the expression of bone morphogenetic protein (BMP) 7.

Methods: In the present study, the effects of exogenous klotho protein supplementation on renal injury was compared between two groups of rats (n=6 for each group) using 5/6 nephrectomized and contralateral nephrectomized rats with a single dose of klotho (20 µg/kg/day) and untreated controls. ADME studies demonstrated that klotho expression in Nx+K group was smaller than Nx group, that endogenous klotho and BMP7 were co-localized in both renal tubular and interstitial cells.

Results: Albuminuria was lower in Nx+K (426 mg/day) than Nx group (132±14 mg/day, p<0.05). Glomerular filtration rate and serum calcium were similar between 2 groups. However, fractional phosphate excretion was increased in Nx+K group (13.2±3%) than Nx group (7±1%, p<0.05). Serum phosphate (8.1±0.3 mg/dl (Nx+K) vs 9.8±0.3 mg/dl (Nx), p<0.05) and FGF23 (361±17 pg/ml (Nx+K) vs 480±51 pg/ml (Nx), p<0.05) were reduced in the Nx+K group. RNA-PCR analysis revealed that compared to Nx (p<0.05), renal expressions of klotho (1.8 fold) and BMP7 (1.7 fold) were elevated in Nx+K group. In contrast, renal expression of TGF-β in Nx+K group (2.1±0.2) was lower than Nx group (3.2±0.3, p<0.05). Western blot analyses showed that renal abundance of Egf-1 and phosphorylated ERK in Nx+K group was higher than Nx group. Pathological examination revealed that fibrosis index in Nx+K group was smaller than Nx group, and that endogenous klotho and BMP7 were co-localized in both renal tubular and interstitial cells.

Conclusions: The present data indicate that klotho supplementation reduced renal injury and serum phosphate level in 5/6-nephrectomized rats. Our findings demonstrate that exogenous klotho supplementation prevents the declines in endogenous klotho expression to recover normal FGF23-klotho signaling that facilitates phosphate excretion. Finally, the current results provide the evidence that klotho protein, which inhibits renal fibrosis, counteracts against TGF-β in itself as well as induces BMP7 expression by elevating the abundance of Egf-1 and phosphorylated ERK in remnant kidney.

Funding: Government Support - Non-U.S.
SA-PO768

The Bidirectional Relationship Between CKD and Sleep Disordered Breathing
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**Background:** The prevalence of Sleep Disordered Breathing (SDB) is higher in Chronic kidney disease (CKD) patients compared to the general population. The relationship between these two diseases is complex and bidirectional. SDB is linked to increased risk of hypertension, atherosclerosis and systemic inflammation which can accelerate the deterioration of renal function. On the other hand, CKD is associated with volume overload, metabolic abnormalities and hypertension contributing to the pathogenesis of SDB. Recognizing the association between them can lead to early treatment, better clinical outcomes and higher quality of life.

**Methods:** A retrospective study included 385 Beaumont Health System patients from 01/01/2012 to 12/31/2017 with diagnosis of both CKD and SDB. The objective was to observe the association of SDB across the CKD stages and proteinuria and to assess the relationship with sleep parameters identifying common predictors associated with these two conditions. SDB was confirmed by polysomnography. CKD diagnosis was based on Glomerular Filtration Rate (GFR) and urine albumin creatinine ratio (UACR).

**Results:** In patients with both SDB and CKD, there was an association between Apnea Hypopnea Index (AHI) and GFR (p=0.08) but not with UACR (p=0.59). 70 % of the patients with stage G2 & G3 CKD had moderate to severe AHI. The median decline in GFR was 5.5 ml/min/1.73 m2 per year and 12% had accelerated decline in GFR. There was a strong association between Nocturnal Hypoxia (NH) and AHI (p=0.0001) in CKD patients but none with GFR (p=0.60) or UACR (p=0.62). Patients on Renin Angiotensin System (RAAS) inhibitors and on Non-Steroidal Anti-inflammatory (NSAIDs) showed a trend towards lower severe AHI (p=0.03) and (p=0.06) respectively; those with systolic heart failure (HF) trended towards worse UACR values (p=0.02). There was no evidence that body mass index, gender, antidepressant or narcotic use is related to AHI severity or NH in CKD patients.

**Conclusions:** Overall, the severity of SDB tended to get worse with advanced CKD and vice versa: patients on RAAS inhibitors and NSAIDs showed less severe AHI, supporting the role of systemic inflammation and hypertension in the pathogenesis of SDB. CKD patients with nocturnal hypoxia tended to have worse AHI and those with systolic HF had higher levels of proteinuria.

SA-PO770

Discovery and Validation of Skeletal Muscle MicroRNA Expression in Non-Dialysis CKD

**Background:** Skeletal muscle (SM) wasting is a common complication of chronic kidney disease (CKD), and is significantly associated with an increased risk of morbidity and mortality. The precise mechanisms of SM wasting are not fully defined, but multiple studies have identified a major contribution of aberrant microRNA (miR) expression and regulation. The involvement of miRs has been described in animal models of CKD SM wasting, however there is no evidence for their involvement in human CKD SM wasting. Therefore, we investigated SM miR expression in non-dialysis CKD patients compared to matched healthy controls (HCs).

**Methods:** Next Generation Sequencing (NGS) was performed on lower limb (LL) SM biopsies collected from 5 CKD patients stage 3a-5 (mean eGFR 22.0 ± 8.1 ml/min/1.73m²; mean age 59.2 ± 9.4 years) and 5 HCs (mean age 54.7 ± 7.9 years). MiR expression was then validated in LL SM biopsies collected from a further 10 CKD patients stage 3a-5 (mean eGFR 30.6 ± 13.6 ml/min/1.73m²; mean age 61.6 ± 11.8 years) and 10 HCs (mean eGFR 83.2 ± 4.4 ml/min/1.73m²; mean age 61.5 ± 13.4 years) by qPCR with let-7f as an internal control. Relative expression was calculated by 2^-ΔΔCt.

**Results:** NGS identified differential expression of 15 miRs in SM of CKD patients compared to HCs (fold-change ≥ 1.5; increased: miR-128, 148a, 182, 21, 22, 29c, 92a; decreased: let-7a, 7c, miR-100, 191, 206, 486, 99a, 99b). Upon validation in a larger sample, miR-148a expression was significantly decreased in CKD patients compared to HCs (p=0.03), and there was a non-significant trend towards decreased miR-191 expression in CKD patients (p=0.061). No further differences were maintained upon validation of the other miRs.

**Conclusions:** Patients with non-dialysis CKD exhibit altered SM miR expression compared to HCs. However, the miR signature reported here does not reflect those previously reported in animal models of CKD SM wasting. For the first time, we report that miR-148a expression is significantly decreased in SM in CKD. Future work will explore the role of dysregulated MiR-148a in CKD SM wasting, thus providing a rational for use as a potential therapeutic target in this population.

SA-PO771

Heparin Infusions Contribute to Cardiovascular Damage in CKD by Promoting Pathologic Effects of FGF-23
Christopher Yanuscik, Dominik Kentrup, Isaac D. Campos, Beatrice Richter, Brian A. Czaya, Kylie Heitman, Christian Faul. University of Alabama, Birmingham, AL.

**Background:** Fibroblast growth factor (FGF) 23 is a bone-derived hormone that increases phosphate excretion by targeting the kidney via klotho and FGF receptor (FGFR) 1. Most FGF family members interact with heparin as a co-factor for efficient FGF receptor activation. Endocrine FGFs, such as FGF23, have reduced heparin binding affinity leading to increased availability and bioactivity.

**Methods:** We investigated the effect of heparin on FGF-23 binding and bioactivity in cell culture and in vivo. We also explored the in vivo and ex vivo effects of heparin on cardiovascular function in wildtype (WT) and FGF receptor deficient (FGFR(-/-)) mice.

**Results:** We found that heparin increased FGF-23 bioactivity in vitro and in vivo. We also observed that heparin increased the systemic and myocardial expression of FGF23 in WT mice, but not in FGFR(-/-) mice. Moreover, heparin increased the severity of cardiovascular dysfunction in WT mice, but not in FGFR(-/-) mice.

**Conclusions:** Our findings suggest that heparin contributes to cardiovascular damage in CKD by promoting pathologic effects of FGF-23.
and instead require the transmembrane protein klotho as FGFR co-receptor. Patients on hemodialysis (HD) have extremely high serum FGF23 levels and receive high amounts of heparin to prevent blood clotting.

**Methods:** We have developed a multi-well assay to measure FGF binding affinities of FGF23 and test effects of heparin co-incubations. We co-cultured cardiac myocytes with FGF23 and heparin and analyze changes in signaling events and in cell area as a readout for hypertrophy. Finally, mimicking a HD-like administration pattern, we inject heparin via the tail vein into two mouse models of FGF23 elevation, i.e. adenine diet-induced kidney failure and repetitive injections of recombinant FGF23. 

**Results:** While purified FGF23 and FGF4 proteins show only a weak interaction, co-incubation with patient grade heparin increases their binding affinity 10-fold. Heparin increases FGF23-induced signaling and hypertrophic growth of cardiac myocytes. Both mouse models with elevated serum FGF23 levels show increased cardiac hypertrophy when heparin is administered.

**Conclusions:** We show that heparin can increase the FGF binding affinity and cellular effects of FGF23. Specifically, heparin aggravates the klotho-independent FGFR4-mediated actions of FGF23 on cardiac myocytes and thereby cardiac injury in mice with systemic FGF23 elevations. Our experiments suggest that in HD patients, administered heparin acts as a biologically active, circulating co-receptor for FGF23 that increases FGF23 affinity for FGFR4 thereby aggravating the pathologic actions of FGF23 on the heart and contributing to the increased cardiovascular mortality.

**Funding:** NIDDK, Support, Other NIH Support - NHLBI

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**SA-PO772**

**Novel Truncated ACE2 Fusion Protein with Extended Half-Life Is Delivered to the Kidney and Ameliorates Angiotensin II-Induced Hypertension**

**Jan Wysocki, Arndt Schulze, Pan Liu, Minghao Ye, Chad R. Haney, Ming Zhao, Daniel Battle. Northwestern University, Chicago, IL.**

**Background:** ACE2 converts angiotensin (AngII) to the renoprotective peptide, Ang (1-7), thereby providing a mechanism to downregulate the renin-angiotensin system (RAS). Targeting kidney RAS using native ACE2 might not be effective due the large size (~110 kDa) that prevents its glomerular filtration and subsequent tubular uptake.

**Results:** To circumvent this limitation, ACE2 truncate (ACE2 1-619) was generated through C-terminal truncation of the native ACE2 and subsequently fused with albumin binding domain (ABD). Enzyme activity of the chimeric protein was confirmed using ACE2-specific substrate Mca-APK-Dnp and its inhibition by MLN-4760 (ACE2-specific inhibitor).

**Conclusions:** The novel ACE2 truncate fused with ABD is enzymatically active, exhibiting an extended in vivo half-life, and is taken up by kidney cortex. These features might potentially facilitate development for a new approach to target kidney disease with intrarenal RAS overactivity.

**Funding:** NIDDK Support

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**SA-PO773**

**Cardio-Renal Protective Effect of the Xanthine Oxidase Inhibitor Febuxostat in the 5/6 Nephrectomy Model with Hyperuricemia**

**Hirotoki Omizo,1 Yoshifuru Tamura,2 Osamu Yamazaki,1 Shunyu Uchida,3 Yoshihide Fujigaki,2 Shigeru Shibata,1 Teikyo University, Tokyo, Japan; 2Teikyo University School of Medicine, Department of Internal Medicine, Tokyo, Japan; 3Teikyo University School of Medicine, Tokyo, Japan.**

**Background:** Previous studies have shown that hyperuricemia can cause cardiovascular dysfunction and chronic kidney disease progression; however, the mechanisms remain unclear. In this study, we addressed the cardio-renal protective effects of xanthine oxidase (XO) inhibition in the rat remnant kidney model with hyperuricemia (RK+HUA).

**Methods:** Male Sprague-Dawley rats received 5/6 nephrectomy and were fed oxonic acid, the uricase inhibitor, according to the previously described methods (Kang et al., J Am Soc Nephrol 2002; Asakawa et al. Oxid Med Cell Longev 2017). XO inhibitor febuxostat was administered orally via drinking water (30 mg/kg). Blood pressure and urinary albumin excretion were monitored during the course of the experiment. At 8 weeks, heart and kidney were removed for the histological evaluation.

**Results:** Compared with control group, RK+HUA showed significant increase in urinary albumin excretion. However, febuxostat significantly reduced albuminuria in this model, along with the reduction in serum uric acid levels. PAS-stained kidney section revealed that febuxostat attenuated glomerular and tubulointerstitial injury, confirming the renoprotective effects of XO inhibition. There was no significant difference in blood pressure levels between RK+HUA rats and RK+HUA rats that received febuxostat. However, histopathological analysis using HE-stained cardiac sections indicated that left ventricular wall thickness was reduced by febuxostat. Furthermore, quantitative evaluation of myocardial cross-sectional areas in wheat germ agglutinin (WGA)-stained sections revealed that individual myofiber hypertrophy was significantly alleviated. In addition, cardiac fibrosis was also reduced in RK+HUA with febuxostat compared with RK+HUA rats.

**Conclusions:** XO is involved in the cardiac and renal injury observed in the remnant kidney model with hyperuricemia. These effects can at least in part be mediated through non-hemodynamic mechanisms.

**Funding:** Veterans Affairs Support, Private Foundation Support

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**Underline represents presenting author.**

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SA-PO775
Myocardioxy Transcription Factor Cardiac Lim Protein (CSRP3) Mediates Renal Tubular Transcription
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Background: Cardiac Lim Protein (CSRP3, molecular weight 21 kD), is released from the heart during the systemic circulation after myocardial injury; we recently identified it as an endocrine cardiorenal connector. We hypothesized that modelled release of CSRP3 would alter tubular epithelial cell transcription of renal fibrosis-related genes in vivo and in vitro.

Methods: Cardiac arrest was induced with potassium chloride, and terminated with cardiopulmonary resuscitation (CA/CPR, a model of cardiac injury leading to acute cardiorenal syndrome). CA/CPR or sham procedure was performed in male, 8-12 week old male mice (WT mice). Mice were killed 10h, 24h, 72h, or 7 days later and plasma CSRP3 quantified by ELISA. Recombinant CSRP3 (rCSRP3) was purchased and 1 µg injected intravenously to WT mice. Mice were killed and plasma CSRP3 quantified by ELISA. Curves were fit to model pharmacokinetics. Following injection, mice were perfusion-fixed; the right kidney was snap-frozen and prepared for mRNA measurements and the left paraffin-embedded for immunofluorescence. qPCR for ilef1 and tgfβ1 mRNA, and CSRP3 immunofluorescence were performed on kidney tissue. Human kidney cells were exposed to 1 µM rCSRP3 or vehicle in translational relevance studies.

Results: CA/CPR resulted greatly increased plasma CSRP3 (max. 20±3.3 vs. 1.4±0.2 in sham, ng/mL, p<0.04) and remained detectable in plasma at 7 days (5.6±1.6 ng/mL). In terms of the dose-under the-curve (AUC) was 65 ng/mL/day. The t½ for injected rCSRP3, was 86 minutes, and the AUC for a single 1g dose was 15 ng/mL-days. Immunofluorescence demonstrated CSRP3 within tubular epithelial cell nuclei following injection. Renal tissue mRNA for transforming growth factor beta (tgfb1) was 1.7±0.5 fold increased 6h after rCSRP3 injection, while ilef1 mRNA was not regulated. In human tubular epithelial cells, 16h exposure to 1 µM CSRP3 upregulated ilef1 mRNA 1.8±0.15-fold compared to vehicle control (p<0.02).

Conclusions: CSRP3, highly specific to cardiomyocytes, is released into the circulation after cardiac arrest and mediates renal transcription of fibrosis-related genes in vivo and in vitro. We postulate this cardiomyocyte transcription factor may play a role in AKI-CKD transition following acute cardiac illness such as cardiac arrest or myocardial infarction.

Funding: Veterans Affairs Support

SA-PO776
Chronic, Combined Cardiac and Renal Dysfunction Exacerbates Renal Venous Pressure-Induced Suppression of Systemic Blood Pressure and Renal Function in Rats
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Background: Co-existing cardiac/renal dysfunction may be perpetuated by increased renal venous pressure (RVP). In this condition we previously showed that acute RVP elevation depresses renal blood flow (RBF), GFR and induces renal vasoconstriction in the absence of changes in blood pressure in healthy rats. We established a rodent model of combined cardiac/renal dysfunction and tested whether an acute, superimposed RVP elevation would alter tubular epithelial cell transcription of renal fibrosis-related genes in vivo.

Methods: Male rats were subjected to 5/6 renal mass resection (Nx or Sham) and left anterior descending coronary artery (CL or Sham). Four experimental groups were established: CL+Nx (n=11); Sham CL+Nx (n=9); CL+ Sham Nx (n=3); Sham Control (n=3). Male rats were killed 10h, 24h, 72h, or 7 days later and plasma CSRP3 and renal tissue mRNA for transforming growth factor beta (tgfb1) were quantified by qPCR.

Results: Baseline MAP, HR, RBF and renal vascular conductance (RVC) were comparable between all experimental groups. Baseline GFR was significantly depressed in CL+Nx and Sham CL+Nx groups compared to Sham Control and CL-Sham Nx groups. Upon RVP increase, an early, rapid and pronounced reduction in MAP occurred in CL+Nx, Sham CL+Nx and CL+Sham Nx compared to Sham Control (p<0.0001). MAP fell to the same degree in all groups at the end of the recording period. HR fell gradually with the increase in RVP in all experimental groups to the same extent. RVP increase exacerbated the reduction in RBF in CL+Nx compared to Sham Control (p<0.0001) with intermediate responses in Sham CL+Nx and CL+Sham Nx groups. Similarly, RVP increase virtually eliminated GFR in CL+Nx (-99%), Sham CL+Nx (-95%) and CL+Sham Nx (-100%) groups compared to Sham Control (-82% from baseline; p<0.0001). Renal vascular conductance dropped significantly but comparably upon RVP increase in all experimental groups.

Conclusions: Combined cardiac/renal dysfunction impairs cardiovascular stability in response to elevated RVP; MAP instability impairs the ability to maintain RBF and GFR considering preserved intrarenal responses.

SA-PO777
Pericyte-Specific Manipulation of Hypoxia-Inducible Factors Regulates Erythropoiesis Without Aggravating Renal Fibrosis
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Background: Stabilizers of hypoxia-inducible factor (HIF) have been shown to be effective on treatment of anemia in patients with chronic kidney disease (CKD). Increased erythropoiesis (EPO) production and enhanced erythropoiesis are known to be the major mechanisms responsible for the treatment effects. However, the effect of HIF stabilization on renal fibrosis is controversial. We created animal models characterized by CKD and pericyte-specific or non-selective stabilization of HIF to examine the effects of HIF on renal fibrosis and erythropoiesis.

Methods: Gli1loxp/loxp;Eglt1f/f;VhlF/F;Hif1af/f;Hif2af/f mice were generated to study the effects of pericyte-specific overexpression or knock-out of Hif1a, Tg(UBC-CreERT2);Eglt1f/f;VhlF/F and Tg(UBC-CreERT2);Vh1a f/f;Hif2af/f mice were generated to study the effects of non-selective stabilization of HIF. Unilateral ureteral obstruction (UUO) was used to induce CKD. The severity of fibrosis was determined by Picrosirius red stain and ColIα1 mRNA level in the kidney.

Results: Pericyte-specific stabilization of HIF resulted in increased serum EPO level, augmented splenic erythropoiesis, and polycythemia, while the severity of renal fibrosis was not affected. In line with these findings, pericyte-specific knock-out of Hif1α or Hif2α did not result in significant change of renal fibrosis. We further examined the role of HIF stabilization in mice with postnatal global stabilization of HIF. Surprisingly, unexpected mortality developed along with dramatically increased serum EPO levels in a HIF-dependent manner.

Conclusions: Our study endorses the neural effects of pericyte-specific HIF stabilization on renal fibrosis. However, the possible risks of artificially increased serum EPO level warrant further study.

Funding: Government Support - Non-U.S.

SA-PO778
The Effect of Increased Blood MicroRNA on Apoptosis in Cardiac Cells and Cardiac Complications in CKD
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Background: Increased cardiovascular morbidity and mortality is the conundrum in chronic kidney disease (CKD). While hemodilution has been blamed for the extremely high incidence of cardiovascular disease in CKD, the retention of uremic toxins might be directly associated with it, including decreased heart function and induction of serious arrhythmia. This study aimed to investigate the association between the cardiac fibrosis and uremic toxin in CKD. Furthermore, we will try to investigate the role of the alteration of blood microRNA (miRNA) levels like other uremic toxin on cardiac fibrosis.

Methods: We induced CKD in rats by 5/6-STSx. We investigated the changes in the renal function and the levels of blood miRNA by affymetrix miRNA array. Renal and cardiac fibrosis were evaluated by Masson’s trichrome staining. We also isolated sinus nodal cells from cardiac atria of C57BL/6 mice, and treated a representative protein-bound uremic toxin, indoxyl sulfate (IS) and probenecid into the cells for 48 h, and evaluated the changes in the expression of fibrosis-related molecules.

Results: Serum creatinine(Cr) and blood urea nitrogen(BUN) were significantly higher in the 5/6-STSx than controls, while echocardiography were lower in the 5/6-STSx. The miRNA profiles of blood serum of 5/6-STSx were significantly different compared to controls. We focus on the significant decrease in the level of miRNA let-7 family for now. Additionally, MTasstaining for the assessment of fibrosis showed the increased fibrosis in the heart and kidney of 5/6-STSx compared with controls. In vitro, protein expressions of fibronectin, phospho-p38 MAP kinase and Bax/bcl2 ratio after IS stimulation were significantly higher at 48 h, which was blocked by organic anion transport inhibitor, probenecid.

Conclusions: These findings suggested that there was a direct effect of uremic toxin on the induction of fibrosis by MAPK activation in sinus nodal cells. The relationship between miRNA and cardiac fibrosis would be investigated down the road.

SA-PO779
Insignificant Renal Artery Stenosis Is Associated with a Decrease in Renal Perfusion and Function
Arkadiusz Lubas, Stanislaw Niemczyk. Military Institute of Medicine, Warsaw, Poland.

Background: Renal artery stenosis (RAS) exceeding 50% of vascular diameter is known as hemodynamically significant and can result in hypertension and deterioration of renal function; thus can require an invasive treatment. On the other hand, RAS < 50% of the diameter is thought to be safe. The study aimed to investigate whether renal artery narrowing < 50% of the diameter could influence renal perfusion and function.

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Methods: Twenty-seven kidneys evaluated in an enhanced by contrast multidetector computed tomography (MDCT) GE patients (6F, 11M, age 62.5±1.9 y) with hypertension and RAS 0.49% of the diameter were included to the study. Renal Parenchymal Perfusion (RPP), and renal function (eGFR) were evaluated.

Results: Mean eGFR was 52.4±16.1 ml/min/1.73m², and RPP 222.7±78.7 ml/s/min. In twenty-seven stenotic kidneys mean RAS was 30.0±8.8% of the diameter. Filtration and renal arteries were normal. The severity of RAS correlated significantly (p<0.05) with RPP (r=-0.39) and eGFR (r=-0.41). In non-stenotic kidneys RPP and eGFR were significantly higher than in those having RAS (256.4±82.5 vs 189.5±49.9 ml/min/100g; p=0.010 and 62.8±19.2 vs. 26.7±26.2; p=0.045, respectively).

Conclusions: No significant association between renal function impairment and degree of stenosis was observed. The degree of RAS correlated strongly with renal perfusion.

Funding: Government Support - Non-U.S.

SA-PO782
Apatalatone Downregulates Alkaline Phosphatase and Improves Cardiovascular Risk
Dean Gilham,1 Laura Tsujikawa,2 Sylvia Wasik,1 Christopher Halliday,1 Li Fu,1 Chris Sarsons,2 Phoebe S. Ho,1 Stephanie Stotz,1 Brooke D. Rakai,1 Kenneth E. Leiboda,1 Ravi Jahagirdar,2 Michael Sweeney,3 Jon O. Johansson,1 Norman C. Myjah,1 Kamyar Kalantar-Zadeh,4 Matthew Hems,1 Ewelina Kulikowska,1 Resverlogix, Calgary, AB, Canada; 2University of California Irvine, School of Medicine, Orange, CA; 3Resverlogix, San Francisco, CA; 4Karolinska University Hospital, Stockholm, Sweden.

Background: Apatalatone is an inhibitor of BET proteins - epigenetic readers modulating gene expression. In phase 2 trials, apataltetone reduced major adverse cardiac events (MACE) in patients with cardiovascular disease (CVD) & improved eGFR in those with chronic kidney disease (CKD). Elevated serum alkaline phosphatase (ALP) is a risk factor for MACE, as it contributes to vascular calcification & endothelial dysfunction. We examined apataltetone-mediated effects on ALP in CVD patients post-hoc & determined apataltetone’s impact on tissue non-specific ALP (TNAP) expression in cell culture systems.

Methods: Circulating ALP was measured in CVD patients receiving apataltetone in the 3-month (ASSERT) and 6-month (SUSTAIN & ASSURE) trials. Apataltetone’s effect on expression of TNAP (gene symbol ALPL) was determined in cultured primary human hepatic stellate cells (PHH), HepRgA, HepG2, calcifying vascular smooth muscle cells (VSMCs) & vascular endothelial cells. Protein abundance & ALP enzyme activity were also measured.

Results: In phase 2 trials, baseline serum ALP correlated with MACE (R²=0.87). In ASSERT, apataltetone dose-dependent reduced serum ALP (p<0.001 vs placebo). In ASSURE & SUSTAIN, patients on apataltetone (n=331) had greater reduction in serum ALP than placebo (n=166; median change -3.2 vs -11.1; p=0.001), including those with CVD, i.e. eGFR<60 (apataltetone n=35 placebo n=13 median change -6.3 vs -2.6; p=0.012). In vitro, apataltetone suppressed ALP expression in PHH, HepRgA & HepG2 cells by 60-80%. Trans-differentiation of VSMCs to calcifying cells resulted in 2.5-fold increase in ALPL gene expression. Apataltetone countered calcium deposition & suppressed ALPL/TNAP gene expression, protein levels & enzyme activity. Apataltetone also downregulated ALPL in aortic endothelial cells, umbilical vein endothelial cells & primary aortic vascular endothelial cells (R²=0.70).

Conclusions: In phase 2 trials, apataltetone lowered serum ALP. Mechanistically, apataltetone down regulates ALPL/TNAP expression in multiple cell types, which may contribute to reductions in MACE observed in patients. The impact of apataltetone on biomarkers, renal function & CVD outcomes is being evaluated in the phase 3 BETonMACE trial.

Funding: Commercial Support - Resverlogix

SA-PO783
Sleep Deprivation Induces Metabolic Reprogramming in Kidney
Xiaoming Mao, Lei Jiang, Jing Luo, Junwei Yang. Nanjing Medical University, Nanjing, China.

Background: Sleep is critical to human being. Sleep deficiency, or sleep deprivation, is an increasingly important global issue of human health, and has been linked to metabolic disorders and diseases. Several studies have shown that sleep deprivation deteriorate renal function. Individuals with shorter time of sleep were more likely to have proteinuria, and faster progression of kidney disease. Our previous studies also found that the interaction between sleep and metabolism, and metabolic health relies strongly on sleep. Sleep deprivation can lead to overeating, increased lipid accumulation and glycolysis. This study aims to investigate the association between sleep and metabolic health, especially in the setting of kidney disease.

Methods: Wild-type male C57BL/6J mice were housed in a 12:12 hr light/dark cycle (light on 8:00 A.M. to 8:00 P.M) at a constant temperature (22±3°C) with free access to food and water. For sleep deprivation, mice were placed in a chamber with a sweep bar moving along the bottom of the cage every 1 min for 20 hours (ZT0-8, ZT12-24) and food and water were restricted. Food and water were provided. For sleep deprivation, mice were placed in a chamber with a sweep bar for 4 weeks at ZT0 and ZT12.

Results: The renal function and renal histology were measured. No difference in urinary albumin excretion was observed between the two groups, while a tendency towards higher urine albumin excretion was observed in the SD group. No difference in renal weights was observed between the two groups, although a trend towards higher urinary albumin excretion was observed in the SD group. Transcription analysis identified altered gene expression most significantly involved in lipid metabolism and biosynthesis, insulin signaling pathway, and circadian rhythm. Protein expression confirmed by Western blot (CPT1α, ACADL, FASN, ADFP, CD36, PDK4, PDH) indicated depressed fatty acid oxidation, increased lipid accumulation and glycolysis.

Conclusions: Sufficient sleep is associated with kidney metabolic homeostasis. More lipid utilization might be occurred in kidney during sleep than wakings state. Metabolism disorder caused by chronic sleep deprivation must be concerned in the progression of renal function decline or proteinuria.

Funding: Government Support - Non-U.S.

SA-PO787
Patient Engagement in Knowledge Translation: A Collaborative Model for Moving Kidney Health Research into Practice
Mary Beaucage,1 Selina Allu,1 Meghan J. Elliott.2 Can-SOLVE CKD Network 1Can-SOLVE CKD Network, Vancouver, BC, Canada; 2University of Calgary, Calgary, AB, Canada.

Background: Effective knowledge translation is the process of moving research evidence into clinical practice. Can-SOLVE CKD is a Pan-Canadian patient-oriented kidney research network with an established Knowledge User (KU) and Translation (KT) Committee that includes two patient partners. This committee provides guidance, expertise, and direction for all KT activities undertaken by research projects within the network. The patient engagement pathways and KT processes and the committee’s role in KT defines key knowledge translation concepts related to KT, outlines the role of the KU/KT Committee in supporting knowledge health research, and highlights the contributions of patient partners on this committee.

Methods: The KU/KT Committee provides core infrastructure support for 18 research projects within the Can-SOLVE CKD network. Membership includes representation of patients living with kidney disease, policymakers, health care professionals and researchers with KT expertise. In alignment with our strategic framework, we co-developed two KT reporting templates for research teams to complete, reviewed KT reports, and discussed our KT assessments among the committee. The committee also provides ongoing support for stakeholder engagement and helps projects tailor their KT strategies for communicating, implementing and sustaining their findings in practice.

Results: As the main stakeholders in health research, there are opportunities for patients to participate in KT. Two patient partners act as full KU/KT committee members and maintain links with the Network’s Patient Council and Indigenous Peoples’ Engagement & Research Council (IPERC). Although all committee members share the responsibility of assessing project KT plans and identifying relevant KT strategies, the patient partners are uniquely positioned to understand real-world implications of the research findings. Continued acknowledgment of the patient voice in KT will help encourage ongoing relevant research, novel approaches to KT, and the translation of evidence into practice.

Conclusions: Our multi-stakeholder KU/KT Committee promotes patient-oriented research supporting the translation of kidney health research into practice. Patients can identify unique KT considerations, provide meaningful feedback to research teams, and encourage the generation and application of relevant research evidence.

Funding: Government Support - Non-U.S.

SA-PO788
Sleep Deprivation Induces Metabolic Reprogramming in Kidney
Xiaoming Mao. Lei Jiang, Jing Luo, Junwei Yang. Nanjing Medical University, Nanjing, China.

Background: Sleep is critical to human being. Sleep deficiency, or sleep deprivation, is an increasingly important global issue of human health, and has been linked to obesity, diabetes, and cardiovascular disease. Many findings published has addressed the interaction between sleep and metabolism, and metabolic health relies strongly on sleep. Sleep deprivation is known to promote the development of chronic kidney disease. Individuals with shorter time of sleep were more likely to have proteinuria, and faster progression of kidney disease. Our previous studies also found that the interaction between sleep and metabolism, and metabolic health relies strongly on sleep. Sleep deprivation deteriorate renal function.

Methods: Wild-type male C57BL/6J mice were housed in a 12:12 hr light/dark cycle (light on 8:00 A.M. to 8:00 P.M) at a constant temperature (22±3°C) with free access to food and water. For sleep deprivation, mice were placed in a chamber with a sweep bar moving along the bottom of the cage every 1 min for 20 hours (ZT0-8, ZT12-24) and shut-off for 4 hours. Control mice received no disruption during sleep were living with stationary sweep bars. Mice were sacrificed after the procedure of sleep deprivation lasts for 4 weeks (ZT0 and ZT12).

Results: Though body weight and food/water intake did not differ from SD group, to control group, biochemical analysis revealed statistical differences in serum albumin, AST, SOD, STB, phosphorus (p<0.05) between SD mice and control. Oil Red O staining for lipid droplet in SD kidney. No difference in urinary albumin excretion was observed between the two groups, while a tendency towards higher urinary albumin excretion was observed in SD group. Transcription analysis identified altered gene expression most significantly involved in lipid metabolism and biosynthesis, insulin signaling pathway, and circadian rhythm. Protein expression confirmed by Western blot (CPT1α, ACADL, FASN, ADFP, CD36, PDK4, PDH) indicated depressed fatty acid oxidation, increased lipid accumulation and glycolysis.

Conclusions: Sufficient sleep is associated with kidney metabolic homeostasis. More lipid utilization might be occurred in kidney during sleep than wakings state. Metabolism disorder caused by chronic sleep deprivation must be concerned in the progression of renal function decline or proteinuria.

Funding: Government Support - Non-U.S.
Conclusions: These parameters indicate that exercise could have a protective effect, especially under this experimental protocol. Thus, this study suggests that the exercise plays a preventive role in mortality and could be an additional strategy to be employed in CKD.

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reversed the TNF-α increased secretion observed under uremic state without modifying IL-10. Simvastatin-treated cells had a significant increase in transcription activation of LXR-β/RXR-α inducing ABCA-1 expression gene. Uremic state promoted a significant reduction in ABCA-1 transcription activation which was reversed by simvastatin.

**Conclusions:** We demonstrated that simvastatin reduced inflammatory response of HUVEC cells exposed to uremia by decreasing TNF-α secretion. We suggest that attenuation of inflammation observed by the 3-ICMCa reductase inhibitor is promoted through LXR-β/RXR-α pathway activation and consequent upregulation of ABCA-1 expression. Our study provides a potential role of statins on endothelial protection in CKD patients.

**Funding:** Government Support - Non-U.S.

**SA-PO788**

**Collaborative Peer-Review Model: Patient Partners as Equal and Contributing Voices in Patient-Oriented Research**

**David Hillyer,1 Mila Tang,2 William F. Clark,3 Carol Connolly,4 Malcolm King,5 Joel Singer,1 Adeera Levin,2 Braden J. Manns,3 Ana Konvalinka,4 James W. Scholery,5 Norman D. Rosenblum.6 Can-SOLVE CKD Network 'Can-SOLVE CKD Network, Vancouver, BC, Canada; 'St. Paul’s Hospital and University of British Columbia, Vancouver, BC, Canada; 'Footills Medical Center, Calgary, AB, Canada; 'University Health Network, University of Toronto, Toronto, ON, Canada; 'The Hospital for Sick Children, Toronto, ON, Canada; 'University of Toronto, Toronto, ON, Canada; 'St. Paul’s Hospital, Vancouver, BC, Canada; 'London Health Sciences Center, London, ON, Canada.

**Background:** Can-SOLVE CKD is a pan-Canadian network seeking solutions and innovations that will transform kidney health in Canada through 18 patient-centered projects. The Research Operations Committee (ROC) performs annual peer-review on all projects to provide guidance for successful implementation. The Patient-Oriented Research Training Program (POTP) Collaborative Peer-Review Model employed by ROC and facilitators enables patient partners to participate as equal and contributing voices in the process.

**Methods:** Membership includes patients, Indigenous partners, experts on research methodology/c clinical research. Reviewed aspects include design, feasibility of implementation plan, risk-mitigation, patient engagement, knowledge translation (KT) and Indigenous cultural safety and engagement. A review package includes a progress update by the project team, Knowledge Users and KT Committee review feedback, POR Training log, patient engagement check-in calls and survey report. A researcher is a primary reviewer, focusing on scientific methods, a patient partner is a secondary reviewer focusing on patient engagement, and a reader contributes to the discussion. Reviewers complete an evaluation checklist and attend a session to agree on recommendations that are relayed back to the project team. Network supports may be dispatched to facilitate recommendations. Concerns require project teams to address and respond to ROC with possible interim reporting.

**Results:** The involvement of patient partners in the peer-review process is a new addition to what has traditionally been a highly technical, closed format. Patient partners play prominent roles in the review. Effective patient partner reviewers are 1) comfortable with the sciences and not afraid to voice their knowledge and 2) motivated and excited to contribute to the work. An environment that cultivates engagement includes respectful and inclusive facilitation at meetings, a forum for peer support to share learning and provide the opportunity to learn on the job.

**Conclusions:** The Collaborative Peer-Review Model ensures accountability of POR principles encouraging research outputs to have a high impact. This can be considered and adapted for other organizations for patient partners to have a prominent role in monitoring and governance of POR.

**Funding:** Government Support - Non-U.S.

**SA-PO789**

**Association of Lower Dietary Potassium Intake with Higher Death Risk in a Prospective Hemodialysis Cohort**

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**Background:** Among hemodialysis patients, clinical practice guidelines recommend dietary potassium restriction given concerns about potential hyperkalemia leading to malignant arrhythmias and mortality. Yet there are sparse data informing recommendations for dietary potassium intake in this population. We thus sought to examine the relationship between dietary potassium intake and death risk in a prospective hemodialysis cohort.

**Methods:** Among 415 hemodialysis patient from the Can-SOLVE CKD: Mechanisms - III (CKD: Mechanisms - III) cohort recruited across 16 outpatient dialysis clinics, information regarding dietary potassium intake was obtained using Food Frequency Questionnaires (FFQ) administered over 2011 to 2015. We first examined associations of baseline dietary potassium intake categorized as tertiles with mortality risk using Cox regression. We then examined clinical characteristics associated with low dietary potassium intake (defined as the lowest tertile) using logistic regression.

**Results:** In expanded case-mix Cox analyses, patients whose dietary potassium intake was in the lowest tertile had higher mortality (ref: highest tertile): adjusted HR (aHR) (95%CI) 1.74 (1.14, 2.66). These associations had even greater magnitude of risk following adjustment for laboratory and nutritional covariates: aHR (95%CI) 2.65 (1.40, 5.04). In expanded case-mix restricted cubic spline analyses, there was a monotonic increase in mortality risk with incrementally lower dietary potassium intake. In expanded case-mix logistic regression models, female sex; higher serum bicarbonate; and lower dietary energy, protein, and fiber intake were associated with low dietary potassium intake.

**Conclusions:** In a prospective cohort of hemodialysis patients, lower dietary potassium intake was associated with higher mortality risk. These findings suggest excessive dietary potassium restriction may be deleterious in hemodialysis patients, and further studies are needed to determine the optimal dietary potassium intake in this population.

**Funding:** NIDDK Support

**SA-PO790**

**Proactive Identification and Nutritional Management of Hyperkalemia via Electronic Health Record Phenotyping**

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**Background:** Hyperkalemia is common chronic kidney disease (CKD) patients and is often associated with adverse cardiac events. Patients with CKD are at increased risk of hyperkalemia due to impaired potassium homeostasis. CKD patients on long-term RAAS inhibitors and/or potassium-sparing diuretics are at increased risk of hyperkalemia, as are those with history of hyperkalemia who are not treated with potassium-binding agents. Targeted nutritional guidance is a low-cost, low-risk intervention for reducing hyperkalemic events.

**Methods:** Using longitudinal data of 110,998 patients from the Rogosin Institute, a rule-based cohorting criteria (Fig 1) was created using a custom web-based interface provided by pulseData to identify patients who are hyperkalemic or are at risk of hyperkalemia. A two-step workflow was developed: 1) EHR data-driven identification of patients at risk for hyperkalemia and 2) targeted delivery of a nutritional flyer to high-risk patients.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.**

965
Results: 1) Data-driven identification: We developed a method to systematically identify high-risk patients and facilitate targeted delivery of the nutritional intervention. On retrospective review, this query identifies on average 10 patients each week. 2) Nutritional Guidance: A nutritional flyer was created to inform the identified patients on which high-potassium foods which should be avoided. Using a flyer is a less costly resource than an appointment with a nutritionist and can be brought with the patient to the grocery store.

Conclusions: A proactive, data-driven method was developed for delivery of nutritional guidance to high-risk patients to reduce future hyperkalemic events. This workflow will be implemented at The Rogosin Institute. Data will be collected on subsequent hyperkalemia events.

Figure 1

SA-PO791
Variability of Serum Phosphate and Markers of Malnutrition and Inflammation in Hemodialysis Patients
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Background: Several biomarkers show significant short- and long-term variability. Here we assessed the variabilities of phosphate(P), albumin(alb), creatinine (creat), nPCR, and neutrophil-to-lymphocyte ratio(NLR) and their associations with outcome.

Methods: All incident in-center HD pts treated in Fresenius Medical Care North America clinics from 10/2010 to 10/2018 were enrolled. The 6-months (mo) baseline (mo 4 to 9) preceded a 12-mos follow-up (mos 10 to 21). Biomarker baseline variability was described by several metrics: (i) standard deviation (SD); (ii) average real variability (AVR = 1/(N-1) * Σ (X_i+1 - X_i); N is number of valid lab measurements); (iii) directional range (DR), it is positive when the minimum antedates the maximum, otherwise negative. Cox proportional hazards models with spline terms were employed to investigate the association between these variables, their variability indicators, and all-cause mortality. ANOVA Cox proportional hazard models (adjusted for age, gender, race, diabetic, congestive heart failure) were built to study the interactions of these variables and their variability with outcome during follow-up.

Results: We enrolled 159703 patients, 17037 died during follow-up. Baseline P was 5.1 mg/dL, median serum PSD, ARV, and DR were 0.91, 0.95, -0.91 mg/dL, respectively. The relation between P variability and all-cause mortality was consistent across a wide range of P levels. For alb, nPCR and creat the highest mortality was observed in patients with low P levels and negative DR.

Conclusions: The direct relation between P variability and mortality is present across levels of nutrition and inflammation. A high P variability should prompt the search for underlying causes, such as poor nutrition and inflammation, and potential interventions.

SA-PO792
Dietary Modification Improves FGF-23, KLOTHO, PTH, and Serum Phosphorous Levels in CKD Stages 1 and 2
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Background: Dietary phosphorus restriction is a potential therapy for improving cardiovascular outcomes. Aim: To examine effect of dietary counselling and dietary modifications on FGF-23, klotho, PTH levels and phosphorous in CKD Stage 1 and Stage 2 patients.

Methods: 100 subjects aged 35.37 ± 10.98 years with eGFR 83.55±16.53 ml/minute and BMI 24.74 ± 2.18 were recruited in the study. 24 hour dietary recall was taken at baseline. Based on dietary phosphorous intake patients were divided into two groups. Group 1: low phosphorous diet and Group 2: high phosphorous diet. Controls were 30 healthy subjects, aged 43.83±10.11 ml/minute with eGFR 126.11±10.26 ml/minute and BMI 24.06 ± 2.09. FGF-23, soluble α-Klotho, iPTH were measured (ELISA).

Results: The independent t test showed that iPTH, serum creatinine, FGF-23, serum phosphorous, total cholesterol and VLDL were significantly higher in CKD patients compared to controls(p=0.000). Hemoglobin (p=0.046), vitamin D(p=0.008), klotho (p=0.000) and HDL (p=0.000) were lower in CKD patients compared to controls (p<0.05). FGF-23 showed a positive significant correlation with klotho (r=0.698, p=0.000) and a negative significant correlation with serum phosphorous (r=-0.494, p=0.000), iPTH (r=-0.751, p=0.000), FGF-23 (r=-0.638, p<0.000), dietary phosphorous (r=-0.476, p=0.000) and dietary phosphorous intake (r=-0.678, p<0.000). Urinary phosphorous showed a significant positive correlation with dietary phosphorous (r=0.488, p=0.000). After dietary counselling and diet modifications in group 2, dietary phosphorous decreased from 1384.74±117.32 to 1027.69±101.39 (p=0.008; serum phosphorous 3.89±0.57 to 3.59±0.63 p 0.008); FGF-23 (169.80±50.96 to 159.45±58.66; p 0.023), klotho (351.77±134.88 to 316.83±167.25 p 0.037) and iPTH decreased from 88.48±10.55 to 85.49±15.25; p 0.033. There was decline in protein intake from 0.67±0.130 to 0.60±0.11g/kg/d p 6.01E-08. FGF-23 showed a strong significant negative correlation with klotho (r=0.754, p=0.000) i.e. as the levels of FGF-23 decreases, the levels of klotho increases after the diet modification in group 2 when they were advised to be strictly on a low phosphorous diet.

Conclusions: Both diet counselling and diet modification can bring down levels of FGF-23, Klotho, iPTH, serum phosphorous, urinary phosphorous which can be instrumental in slowing the progression of CKD and preventing cardiovascular disease.

SA-PO793
Hyperphosphatemia: Barriers to Treatment Adherence in Dialysis Patients
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Background: Hyperphosphatemia in end-stage renal disease is associated with increased morbidity and mortality. One important cause of hyperphosphatemia is non-compliance with low phosphate diet and phosphate binders. The primary objective of our study is to evaluate the adherence to prescribed treatment and barriers to adhering to dialysis therapy.

Methods: We collected data from 2 dialysis units in Tucson. A questionnaire was designed to assess dialysis patient’s access to nutritional knowledge, knowledge of medications as well as dietary restrictions and barriers to access appropriate care.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Low Protein Intake Is Associated with Severe Fatigue in Stable Outpatient Renal Transplant Recipients

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Background: Severe fatigue is a frequent complaint in renal transplant recipients (RTR) that is often accompanied by functional impairment and poor quality of life. Low protein intake may lead to protein-energy malnutrition and thereby contribute to fatigue in RTR. We aimed to (1) compare the prevalence of severe fatigue between RTR and healthy controls, (2) investigate impact of severe fatigue on quality of life in RTR, and (3) investigate the association of protein intake with severe fatigue in RTR.

Methods: We included 601 stable RTR with a functioning graft ≥1 year and 237 prospective kidney donors from the TransplantLines Study. Overall fatigue was assessed using the Checklist Individual Strength (CIS) Questionnaire. A CIS-score >76 is commonly considered to indicate severe fatigue and was used as cut-off in this study. Quality of Life (QoL) was assessed with the RAND-36 Questionnaire. The Maroni formula was used to calculate protein intake from 24-hr urinary urea excretion. Chi-Square was used to test differences in prevalence of severe fatigue in RTR and donors. Mann-Whitney U was used to test differences in QoL of RTR with and without severe fatigue. Logistic regression was used to analyze the association between protein intake and presence of severe fatigue.

Results: RTR were 55 ± 13 years old, 347 (58%) were male and mean eGFR was 50 ± 18 ml/min/1.73m². Thirty-three percent of RTR were severely fatigued compared to 6% of kidney donors (P<0.001). QoL was significantly lower in RTR with compared to RTR without severe fatigue (median QoL-score 40 [30-60] vs 60 [50-75], P<0.001). Mean protein intake in RTR was 1.0 ± 0.3 g per kg bodyweight per day. Protein intake was inversely associated with severe fatigue in RTR (OR 0.17; 95%CI 0.07-0.40 per g/kg/d, P<0.001). This association remained materially unchanged after adjustment for potential confounders, including age, sex, eGFR, BMI, and anaemia (OR 0.20; 95%CI 0.08-0.51 per g/kg/d, P<0.001).

Conclusions: Severe fatigue is highly prevalent in RTR and a determinant of poor quality of life. Low protein intake is associated with higher risk of severe fatigue in RTR, independent of potential confounders, including age, sex, eGFR, BMI, and anaemia.

Dietary Protein Intake, Kidney Function, and Mortality in a Nationally Representative Cohort

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Background: In the general population, high protein diets (Paleo, Atkins, ketogenic) have gained popularity as a means to promote weight loss and avoid excess carbohydrate consumption. Yet in chronic kidney disease (CKD), evidence suggests low dietary protein intake (DPI) leads to attenuation of kidney function decline, although there remains concern about risk of protein-energy wasting. We thus sought to examine the association of DPI with mortality risk in a nationally representative cohort stratified by estimated glomerular filtration rate (eGFR).

Methods: We examined the association of daily DPI normalized to actual body weight (g/kg actual weight [AW]/day) ascertained by 24-hour dietary recall, with all-cause mortality among 27,604 continuous NHANES adult participants (1999-2010) stratified by low vs. normal eGFR (<60 vs. ≥60 ml/min/1.73m², respectively) in adjusted Cox models. We also examined the relationship between high biologic value (HBV) protein consumption with mortality.

Results: In participants with low eGFR (N=1999), high DPI ≥ 1.4 g/kg AW/day was associated with higher death risk, while lower DPI levels were not associated with mortality (ref: 0.6–1.0: HRs [95%CI] 1.09 [0.90, 1.32], 1.03 [0.82, 1.29], and 1.37 [1.02, 1.85] for DPI <0.6, 0.6–1.0, 1.0–1.4, and ≥1.4 g/kg AW/day, respectively). In those with normal eGFR (N=25,605), low DPI <0.6g/kg AW/day was associated with higher mortality, whereas higher DPI levels were not associated with death. In those with low eGFR, the highest two tertiles of HBV consumption were associated with higher death risk (ref: lowest tertile), whereas no association of HBV intake with mortality was observed in those with normal eGFR.

Conclusions: In participants with low eGFR, higher DPI and HBV consumption were associated with higher mortality, whereas lower DPI was associated with higher mortality in those with normal eGFR. Further studies are needed to elucidate the specific pathways between higher DPI and HBV consumption and mortality in those with CKD.

Funding: NIDDK Support
Decline in Renal Function After Withdrawing Ketoanologue Supplementation: A Randomized Clinical Trial

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Background: Studies have reported preservation of renal function and nutritional status in patients with a low protein diet supplemented by ketoanalogues. Our group reported preservation of renal function and nutritional status in patients who were supplemented with ketogenic diets. The aim of the study was to evaluate if the renal function is maintained after withdrawing ketogenic supplementation despite continuing on the same diet.

Methods: Forty CKD patients were randomized into two groups: Group 1 (Intervention) patients were supplemented with 6 tablets of ketogenic diet for 10 months. Patients were advised very low protein diet 0.4 g/kg/day. Group 2 (Control) patients were given conservative treatment with 0.6 g/kg protein restriction. Dietary assessment was done at visit 1 and at visit 2 (10 months). Nutritional assessment was evaluated with SGA score. GFR and serum albumin were evaluated at baseline and at 10 months. After 10 months ketoanologue supplementation was stopped and patients were followed up for four years with same dietary intake.

Results: At baseline, the GFR was higher in controls (51.14±15.1 ml/minute). In supplemented group serum albumin decreased from 3.8±0.90 g/dL to 3.09±0.38 g/dL. In supplemented group the GFR and albumin remained stable at 47.79±13.2 ml/minute and 4.11±0.43 respectively. In ketoanologue group patients did not comply to low protein diet, in stead they consumed normal protein diet 0.6±0.24 g/kg/day. In supplemented group serum creatinine decreased from 1.61±0.52 to 1.4±0.52 but increased to 2.2 mg/dL after stopping ketoanologe. After stopping supplementation at 10 months patients were followed up for four years. Gradual decline was observed in GFR (47.79±13.2 to 28.0±3.6 ml/minute) and albumin (4.11±0.43 to 3.6±0.46). Some patients progressed to ESRD. After stopping ketoanalogues, the dietary intake remained the same.

Conclusions: Low protein diet supplemented with ketoanalogues preserves renal function and nutritional status in predialysis patients. However, a rapid decline in renal function is observed after stopping ketoanologue supplementation.

Funding: Commercial Support - Panacea Biotech

Metabolomics of Dietary Protein Sources and CKD Progression in Children

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Background: Recent evidence suggests that source of dietary protein may influence kidney disease risk. We aimed to characterize the plasma metabolome of plant and animal sources of protein and to determine whether dietary protein-related metabolites were associated with CKD progression in children.

Methods: Metabolites were measured using an untargeted platform (Metabolon) in baseline plasma specimens from 488 Chronic Kidney Disease in Children (CKiD) participants. We assessed the cross-sectional association between protein source (plant, animal) and metabolites using linear regression adjusted for age, sex, BMI, glomerular proteinuria, anemia, hypertension, and serum albumin in addition to the same covariates in the cross-sectional analysis.

Results: A total of 94 (9.9% of 949) known serum metabolites were significantly associated with animal protein and 45 (4.7% of 949) metabolites were significantly associated with plant protein. Only one metabolite was significantly associated with both animal and plant protein: phenylaceta. For the prospective analysis, 23 animal protein-related metabolites (24.5% of 94) and 8 plant protein-related metabolites (17.8% of 45) were associated with CKD progression, including 21 lipids, 3 amino acids, 3 cofactors and vitamins, 2 xenobiotics, 1 peptide, and 1 nucleotide (p<0.05; Table).

Conclusions: An untargeted metabolomics platform identified multiple blood metabolites that were associated with animal and plant protein consumption and CKD progression. These findings could inform more nuanced dietary recommendations for children with CKD regarding protein source.

Funding: NIDDK Support
**SA-PO799**

**Diabetes Results from the CKD Observational Database (CKDOD) in China**

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**Background:** Protein restricted diets (PRD) with or without ketoanalogue (KA) supplementation are an established dietary treatment option in chronic kidney disease (CKD). The aim of this study was the evaluation of specific types of protein restriction for management of CKD in China and assessment of associations between different nutritional protein interventions and estimated glomerular filtration rate (eGFR) changes over time.

**Methods:** 733 non-dialysis CKD patients were observed for median 1.1 year in this registry from routine care in China. Demographics and dietary prescriptions were analyzed descriptively. A mixed-effects model adjusting for demographics, CKD stage, and primary cause of CKD was used for longitudinal analysis of eGFR changes.

**Results:** Time since diagnosis of CKD was 1 [8; 3.1] years. 15% of patients were in stage 1-2, 35% stage 3, 20% stage 4, and 24% stage 5. PRD were mainly used in stages 3 and 4 (Figure 1A), with 90% of these patients receiving an advice for target of protein intake of 0.6-0.8 g/kg/d (LPD). Higher protein recommendations (0.8-1.0 g/kg/d, intermediate protein diet (IPD)) were more common in earlier CKD stages, e.g., in stage 2, 58% received advice for PRD with 25% of these for IPD. KA was prescribed more frequently with lower dietary protein intake (72% LPD, 38% IPD, p=0.001). Mixed effects regression suggested that lower protein intake is associated with slower eGFR decline compared to IPD or normal protein intake (Figure 1B).

**Conclusions:** In this select Chinese population cohort, the use of protein restricted diets with or without KA supplementation in advanced stages of chronic kidney disease might be associated with a trend towards slower eGFR decline.

**Funding:** Commercial Support - Fresenius Kabi

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**SA-PO800**

**Low-Protein Diet for Patients Older Than 70 Years with CKD due to Benign Nephrosclerosis Is Effective in Suppressing Its Progression Without Causing Sarcopenia and Frailty**

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**Background:** Restriction of protein intake delays or stops the progression of CKD. However, the effect of low-protein diet (LPD) in the elderly CKD patients is not well understood because of risk for malnourishment and other concerns. We studied the effect of LPD on them.

**Methods:** Patients with CKD stage 3-4 due to benign nephrosclerosis (BNS) were studied. All of them were 70 years old or older. Nutritional guidance of energy 30-35 Kcal/kgBW/day, protein intake 0.6-0.8 g/kgBW/day, salt intake 6g/day was given to patients. Protein intake was evaluated using the Maroni's formula by 24-hour urine sample. For patients on immunosuppressive therapy were excluded. We included 135 patients with an eGFR between 20 and 60 ml/min/1.73 m² who started LPD (0.6-0.7g/kg/d) between 2015 and 2017 and retrospectively collected clinical history (diabetes status and RAASi therapy), serum eGFR (CKD-EPI), proteinuria, and urinary phosphorus. Dietary energy intake was >30Kcal/Kg/d. eGFR and 24h proteinuria were collected at the time of LPD initiation and at 6 and 12mo before and after LPD initiation. These time points were used to generate eGFR slopes before and after starting LPD. Adherence to LPD was estimated based on phosphaturia at 6mo after starting LPD. Patients on immunosuppressive therapy were excluded.

**Results:** There was a significant decrease in the rate of eGFR decline after LPD initiation (eGFR slopes: -0.35 ± 0.007 vs. -0.42 ± 0.003 ml/min/1.73/m²/month before vs. after LPD; p=0.0007) (Fig. 1), though proteinuria did not significantly change. Univariate analyses showed that phosphaturia was the only variable significantly (p = 0.05) associated with rate of eGFR change, while diabetes status, RAASi therapy, and proteinuria at baseline were not. In a multivariate analyses, phosphaturia retained an independent association. The adherence to LPD was estimated based on phosphaturia at 6mo after starting LPD. Patients on immunosuppressive therapy were excluded.

**Conclusions:** In this retrospective, single center study shows that adherence to LPD is independently associated with ameliorated kidney function decline. These data support strategies to increase patient adherence to LPD. Further studies are needed to elucidate mechanisms by which LPD exerts renoprotection.

**Fig. 1. Average eGFR at different time points before and after low-protein diet initiation.**

Grey dots represent single patients.
SA-PO802
High Plasma Branched-Chain Amino Acids Are Associated with Higher Risk of Post-Transplant Diabetes Mellitus in Renal Transplant Recipients

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Background: Post-transplant diabetes mellitus (PTDM) is a serious complication in renal transplant recipients (RTR). Branched-chain amino acids (BCAAs) are involved in the pathogenesis of insulin resistance and may predict new onset diabetes in the general population. Here, we prospectively determined the association of plasma BCAAs which comprise the amino acids valine, leucine, and isoleucine, with PTDM in RTR.

Methods: Adult RTR (n=18) recruited between November 2008 and May 2011 with a functioning graft for ≥1 year were eligible. Plasma BCAAs were measured in 518 RTR using nuclear magnetic resonance spectroscopy. We excluded RTR with a history of diabetes, leavin 368 non-diabetic RTR eligible for analysis. Cox proportional hazards analysis was used to assess the association of BCAAs with the development of PTDM.

Results: In 368 non-diabetic RTR (mean±SD age: 52.7±13.0 y, 53.7% men), fasting plasma BCAA was 377.6±13.0 μM. During median follow-up of 5.3 years (IQR, 4.2-6.0) y, 38 (9.8%) RTR developed PTDM. Total BCAAs were associated with a higher risk of developing PTDM (HR: 1.42, 95% CI 1.08-1.89) per SD change (p<0.01), independent of age and sex. Adjustment for other potential confounders did not significantly change these associations.

Conclusions: High concentrations of plasma BCAAs are associated with developing PTDM in RTR.

SA-PO803
High Circulating Concentrations of Very-Long-Chain Saturated Fatty Acids Are Associated with Low Risk of Premature Mortality in Renal Transplant Recipients

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Background: Recent epidemiological studies indicate that high exposure to very long chain saturated fatty acids (VL-SFA), present in peanuts and canola oil, is associated with low risk of premature mortality in RTR.

Methods: We included 680 stable RTR with a functioning graft ≥1 year. Plasma VL-SFA is inversely associated with mortality and to estimate mortality risk across tertiles of VL-SFA concentrations.

Results: Age was 53±13 years, 57% were male and eGFR 52±16 mL/min/1.73m². VL-SFA concentrations of C22:0 and C24:0 were measured by Agilent gas chromatography with flame ionization detector. Dietary data were collected using a Food Frequency Questionnaire. Correlations between dietary intake and C22:0 and C24:0 were analyzed by Spearman’s Rho. Cox regression was used to analyze the association of VL-SFA on mortality and to estimate mortality risk across tertiles of VL-SFA concentrations.

Results: During median follow-up of 5.4 years, 146 (22%) RTR died. Mortality risk according to tertiles of C22:0 and C24:0 was inversely associated with mortality in RTR. Increasing intake of foods containing VL-SFA, such as peanuts, may improve patient survival in RTR.
SA-PO806

High Circulating Concentrations of Marine-Derived N-3 Polyunsaturated Fatty Acids Are Associated with Low Risk of Premature Mortality in Stable Renal Transplant Recipients

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Background: Cardiovascular disease contributes significantly to high rates of premature mortality in renal transplant recipients (RTR). Plasma marine derived omega-3 poly-unsaturated fatty acids (N-3 PUFA) have been shown to have a positive effect on cardiovascular risk in the general population. The benefit of marine derived N-3 PUFA in RTR is unclear as most studies relied on intake derived from food frequency questionnaires rather than on plasma concentrations.

Methods: We included 680 stable RTR with a functioning graft ≥1 year. Plasma EPA and DPA were measured by Agilent gas chromatography with flame ionization detector. We used linear regression analyses to investigate the association of plasma EPA+DHA with log-transformed plasma concentrations of N-terminal Pro Brain Natriuretic Peptide (NT-proBNP). Cox regression analyses were used to analyze the prospective association of EPA+DHA on mortality.

Results: RTR were 53 ± 13 years old, 386 (57%) were male and mean eGFR was 52 ± 20 ml/min/1.73 m². Mean plasma concentrations of EPA+DHA were 0.28 ± 0.12 μmol/L. Median NT-proBNP concentrations were 249 [IQR 105-625] ng/L. EPA+DHA was inversely associated with NT-proBNP; independent of potential confounders, including age, sex and eGFR (β [-0.080, P=0.02]). During 5.4 years of follow-up, 146 (22%) RTR died. In prospective analyses, we observed EPA+DHA was inversely associated with risk of premature mortality, independent of potential confounders (HR 0.24; 95%CI 0.06-0.98, P=0.047).

Conclusions: High circulating concentrations of marine derived N-3 PUFA (EPA+DHA) are associated with low circulating concentrations of NT-proBNP, consistent with beneficial effects on cardiovascular health and low risk of premature mortality in RTR. These results support advances for increased intake of N-3 PUFAs in RTR.

SA-PO807

The High Dietary Polyunsaturated Fatty Acid Level Is Associated with Lower Prevalence of CKD: A Population-Based Cohort Study

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Background: There have been steady interests in the effects of polyunsaturated fatty acid (PUFA) on health and several studies have proved PUFA is associated with lower risk of hypertension and diabetes. However, the effect of dietary PUFA on renal function in general population has been relatively unexplored, yet. Therefore, we aimed to evaluate the relationship between dietary PUFA intake and renal function in a nationwide nutritional survey.

Methods: Data were retrieved from the Korea National Health And Nutrition Examination Survey (KNHANES). Among 39,225 subjects collected from 2013 to 2017, 22,079 subjects were included in final analysis, after exclusion of those who were under 18 or whose baseline data were missing. PUFA intake (EPA fraction of PUFA among dietary fat intake) was defined as percentage of daily PUFA intake (g) relative to daily total fat intake (g). The subjects were categorized into quintiles according to the PUFA Primary outcome was defined as a prevalent chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) by Korean version of CKD-EPI ≤ 60 ml/min/1.73 m² and composite outcome was eGFR < 60 ml/min/1.73 m² or the presence of proteinuria, defined as 1+ by dipstick urine test.

Results: The mean age and eGFR of the subject were 51.1 ± 10.0 %. Interestingly, the subjects in higher PUFA group tended to be older and have slightly lower eGFR compared to those in lower PUFA group. Moreover, they had lower daily fat intake and higher prevalence of HTN, DM and dyslipidemia. Total 899 subjects were found to have prevalent CKD and 1,106 subjects had composite outcomes. Multivariable logistic regression analyses revealed that the risk of CKD was lower in the group with the highest PUFA compared to the lowest PUFA group after adjustment for confounding factors [odds ratio (OR) 0.71, 95% confidence interval (CI) 0.58-0.88, P = 0.002]. This finding was consistent in terms of composite outcome (OR 0.75, 95% CI 0.62-0.90, P = 0.002).

Conclusions: The risk for CKD was lower in the subjects with the high dietary PUFA. Fraction of PUFA among dietary fat may affects renal function in healthy population.

SA-PO808

The Effects of Omega-3 Fatty Acids on Proteinuria Among Diabetic Patients: A Meta-Analysis of Randomized Controlled Trials

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Background: Long-chain omega-3 fatty acids including eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA) have been the focus of experimental studies in humans. There are clinical trials studying in various types of kidney diseases including IgA nephropathy and lupus nephritis. However, the effects of omega-3 fatty acids on diabetic kidney disease have not been studied in depth into the focal lipid profile of CKD. We performed a focal lipodics study of patients receiving hemodialysis (HD).

Methods: We conducted electronic searches in Pubmed, Embase and Cochrane Central Register of Controlled Trials from January 1960 to April 2019 to identify RCTs, which examined the effects of omega-3 fatty acids on proteinuria, eGFR and metabolic biomarkers among diabetic patients.

Results: Ten RCTs with 344 participants were included in our meta-analysis. Omega-3 fatty acids reduced the progression of proteinuria among type 2 diabetes mellitus (type 2 DM) and type 1 diabetes mellitus (type 1 DM). This association was only significant among type 2 DM (SMD = -0.29 (95% CI: -0.54, -0.03; p = 0.03). Only studies with duration of intervention of 24 weeks or longer demonstrated a significant decline in proteinuria comparing omega-3 fatty acids to placebo group (SMD = -0.30 (95% CI: -0.58, -0.02; p = 0.04). There was a slower decline in eGFR for both type 1 and type 2 DM groups, however, the effect was not statistically significant. Regarding, serum LDL-cholesterol and HbA1C, there was no significant difference comparing omega-3 fatty acids to placebo group. There was a non-significant systolic blood pressure reduction in the omega-3 fatty acids supplementation group compared to placebo.

Conclusions: Omega-3 fatty acids could help diminish proteinuria among type 2 DM who received omega-3 supplementation for at least 24 weeks without adverse effects on HbA1C and serum LDL-cholesterol.

SA-PO809

Lipidomics of Feces in Hemodialysis Patients and Some Potential Biomarkers

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Background: Earlier studies have demonstrated that chronic kidney disease (CKD) results in profound changes in lipid. Serum lipid profile of CKD patients has been determined at many studies, but few studies have measured fecal lipid profile of CKD patients in the clinical setting. The principal component analysis (PCA) and orthogonal-partial least squares analysis (OLPS-DA) were used for multivariate statistical analysis to screen potential biomarkers related to diseases.

Results: A total of 478 lipid species were identified from positive and negative ion modes. Out of 478, 52 identified lipid species were significantly altered in patients with ESRD compared with the healthy controls. TG(18:1/18:1/22:0)+NH4, TG(18:1/18:1/18:1)+NH4 and TG(18:1/18:2/22:0)+NH4 were all decreased in ESRD patients compared with the healthy individuals. TG(18:1/18:2/22:0)+NH4 and TG(18:1/18:2/22:0)+NH4 are all triglycerides which participate in pathways including fat digestion and absorption, vitamin digestion and absorption and regulation of lipid in adipocytes that could be searched at the KEGG website. DG (18:0/19:3) +NH4 is diglyceride involved in adipokine signaling pathway which is correlated with leptin production.
Conclusions: Facial lipodiscomics uncovered the lipid metabolism disorder of HD patients with CKD. These associations could be potential markers of ESRD. As reported, the incidence rate of cardiovascular and cerebrovascular diseases (CCDs) is now increasingly high in CKD patients and high cholesterol is closely related to CKD. Our study indicated that ESRD patients had lower triglycerides and diglycerides in their blood compared to healthy controls. We considered that CKD patients may absorb more glycides which promote to the development of CCDs. However, the exact mechanism still needs to be studied further.

SA-PO810
Diploid Gene Deletion of Transient Receptor Potential Canonical 1 (TRPC1) Channel Produces Metabolic Syndrome (MetS) but Prevents Further Liver Steatosis and Dyslipidemia Induced by a High-Fat Diet (HFD) Muhammad B. Mahmood, 1 Bonnie Eby, 1 Lindsay Barron, 2 Alexander Lau, 2 Meghan M. Pantaila, 2 Usman A. Khan, 1 Chris D. Skaggs, 1 Kai Lau, 1, 2

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Background: There is growing evidence for the role of TRPC1 in regulating glucose & lipid metabolism. Secretion of insulin, leptin & adiponectin is sensitive to cell free Ca++. TRPC1 may mediate the effects of leptin in anorexigenic hypothalamic neurons. TRPC1 was found low in diabetes & we recently found hyperglycemia in null mice. We tested if TRPC1 deficiency produces MetS if it 45% HFD x 3 mon aggravates it.

Methods: In unstretched TRPC1 +/- and +/- mice we measured glucose & lipids using standard methods & insulin, leptin, & adiponectin by mouse ELISA. We did glucose tolerance test (GTT) by IP glucose (2 mg/kg) after 13 h fast.

Results: From 4-30 week, null mice ate & weighed more than +/- & wt. At 4 mon, HOMA-IR was up 60% & HOMA was down 40%. By 12 mon, HOMA IR was up fold. At 7 mon, by GTT, both TRPC1 +/- & +/- mice were diabetic. In null, adiponectin was down 11% but leptin up 77%. At 2 mon, total cholesterol was 85% higher in null, their liver 36% higher, & triglyceride content (TG) 47% higher. Liver echinocytosis was up by 50-150% at 7, 11, & 22 mon, confirmed by 140% higher liver TG. At 12 mon, only null mice had hyperlipidemia (cholesterol up 30%, LDL up 60%, & TG up 200%). In +/- & wt, lipids, liver density at 12 & 19 mon, & liver TG at 12 mon were all normal. Fasting glucose was high only in null from 1 through 16 mon. TRPC1 null mice had hyperglycemia (p<0.05) vs wt & +/- mice. TRPC1 deficiency produced higher FV intake and urinary albumin–to-creatinine ratio (ACR).

Conclusions: TRPC1 deficiency produces MetS & if 45% HFD x 3 mon aggravates it.

Funding: Other U.S. Government Support

SA-PO811
Higher Fruit Intake Is Associated with Albuminuria in a Nested United Kingdom Biobank Case Control Cohort Gareth J. McKay, Euan N. Paterson, Alexander P. Maxwell. Queen’s University Belfast, Belfast, United Kingdom.

Background: Fruit and vegetable (F&V) consumption is associated with better renal function and lower risk of CKD. These associations may be explained by the protective effects of antioxidant vitamins and phytonutrients, nitric oxide precursors, and other active substances present in F&V. The potential negative consequences of increased fruit intake on renal health however have not been extensively studied. Fruit is an important dietary source of the monosaccharide fructose that has been implicated as an environmental toxin increasing the risk of metabolic syndrome and incident ESRD using a fine-gray competing risk model with age as time scale and cardiovascular mortality as the competing event. We adjusted for age, sex, socio-economic status (SES), total caloric intake, meat and fish intake, A1C, systolic BP, baseline eGFR, and urinary albumin-to-creatinine ratio (ACR).

Conclusions: Average fruit intake in quintile 1 (fewest servings of FV per day) was more likely to have lower SES; those in highest quintile (most servings of FV per day) were more likely to have DM and hypertension. 120 participants (11.1%) developed ESRD during follow-up. Compared to quintile 5, those in quintile 1 had a greater risk of ESRD for quintile 4: relative hazard (HR), 95% CI) = 1.75 (1.10-2.76), for quintile 3: 1.11 (0.89-1.36), for quintile 2: 1.56 (1.18-1.98) and for quintile 1: 1.39 (1.10-1.72). Sex modified the estimated effect of FV quintile (p-interaction=0.03), the RH for the lowest vs highest quintile was 2.10 (1.71-2.64) for women and 1.24 (0.90-1.71) for men.

Conclusions: Fewer servings of FVs per day, with a threshold value corresponding to servings less than quintile 3 (4-5 servings/day in men and women), is independently associated with a higher risk of ESRD. Since dietary restrictions in the setting of CKD result in a lower intake of FVs, a randomized trial to evaluate potential benefits and harms of higher FV servings may provide a feasible effective dietary recommendation.

Funding: Other U.S. Government Support

SA-PO813
Cycles of a Fasting Mimicking Diet Restore Renal Function in a Rat Model of PAN Nephrosis Laura Perin, 1 Valentina Villani, 1 Camille H. Nicolas frank, 2 Roberta Buono, 2 Charmi Dedhia, 1 Valter Longo, 1, 2 Children’s Hospital Los Angeles, Los Angeles, CA; 1The Saban Research Institute, Los Angeles, CA; 2USC, Los Angeles, CA.

Background: A major hallmark of end-stage renal disease (ESRD) is the irreversible loss of the glomerular filtration barrier, the structure in charge of the blood ultrafiltration. The only treatment options for ESRD are dialysis or transplantation. To date, no cure is available to restore kidney function in ESRD patients. While dietary recommendations are currently given to patients with kidney disease to minimize the burden of the disease itself and slow down its progression, no diet has proven effective in restoring renal function. Animals have evolved adaptive mechanisms to fasting that are associated with stress resistance, reduced inflammation, longer lifespan. The fasting mimicking diet (FMD) was developed to induce similar metabolic changes as observed during fasting and FMD has been clinically proven to be extremely efficient in various human disease settings (including diabetes and cancer) by activating endogenous regenerative mechanisms.

Conclusions: We tested the effect of FMD to treat kidney disease. Sprague Dawley rats were injected with purymycin aminonucleoside (PAN) to induce chronic nephrosis. Multiple cycles of FMD have been applied to PAN-induced rats to determine their effect on renal function and structure. Rats were monitored for renal physiological parameters, histological and WB analysis of glomular and tubular structures were performed.

Results: We observed amelioration of proteinuria and reduced levels of BUN in rats undergoing 6 cycles of FMD compared to the PAN group. The effect was sustained long term up to 6 weeks after the last dietary cycle. Histological characterization showed preservation of the renal structure including tubular and glomerular structures in rats treated with FMD in contrast to PAN-induced rats. Podocyte number in FMD treated rats was comparable to that of healthy animals, while a significant reduction was noted in the PAN group. WB also revealed mitochondrial function protection measured by the level of mitochondrial membrane potential expression ( mitochondrial transcription factor A) associated with the post re-feeding time after only one cycle of diet.

Conclusions: These results support the application of multiple cycles of FMD to restore renal function and as a possible treatment of chronic kidney disease.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**SA-PO814**

**Skipping Breakfast and Dinner and Incidence of Proteinuria: A Retrospective Cohort Study**

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**Background:** Chronic kidney disease (CKD) characterized by proteinuria and low glomerular filtration rate (GFR), is one of the major risk factors of end-stage kidney disease, cardiovascular disease (CVD), and mortality. Recent studies showed that skipping breakfast was associated with type 2 diabetes (T2D) and CVD. Regarding CKD, little information is available about a clinical impact of skipping breakfast on CKD. The aim of the present study was to assess an association between breakfast frequency and incidence of proteinuria in a retrospective cohort study, along with lunch and dinner frequency.

**Methods:** The present study included 7,881 employees of Osaka University, one of the largest national universities in Japan, who underwent their annual health checkups between April 2004 and March 2013, and had negative or trace result of dipstick urinary protein and estimated GFR (eGFR) ≥60 ml/min/1.73m² at their baseline visit. Main exposure of interest was self-reported frequency of breakfast, lunch and dinner at their baseline visit: almost every day vs. irregularly. The associations of irregular breakfast, lunch, and dinner with the incidence of proteinuria defined as 1+ or more of dipstick urinary protein, using a Cox proportional hazards model adjusting for clinically relevant factors.

**Results:** Baseline clinical characteristics of 7,881 employees: age, mean ± SD 39 years; body mass index, 21.6 ± 2.6 kg/m²; main exposure of interest was self-reported frequency of breakfast, lunch and dinner at their baseline visit: almost every day vs. irregularly. The associations of irregular breakfast, lunch, and dinner with the incidence of proteinuria defined as 1+ or more of dipstick urinary protein, using a Cox proportional hazards model adjusting for clinically relevant factors.

**Conclusions:** Skipping breakfast and dinner were risk factors of proteinuria in females, not males.

**SA-PO815**

**Dietary Oxalate Ingestion, Urinary Oxalate Levels, and Response to Reloxaliase in Three Phase 2 Studies**

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**Background:** Over-absorption of oxalate from dietary oxalate can lead to hyperoxaluria (HOx) in patients with malabsorptive gastrointestinal (GI) conditions (enteric HOx (EH)). Reloxaliase is an oral enzyme that degrades oxalate within the GI tract, resulting in less oxalate absorbed and lower urinary oxalate (UOx) excretion. We hypothesized that patients with greater baseline levels of UOx may show increased responsiveness to a therapy that degrades dietary Ox. Data on patients with EH in three phase II trials were analyzed to examine this hypothesis.

**Methods:** A composite analysis of data from three Phase 2 studies of reloxaliase was performed to include: an uncontrolled study with 5 EH subjects treated for 4d (NCT02997555), an RCT with 3 EH subjects treated for 28d (NCT02547805) and an ongoing open label study in EH patients with advanced CKD (NCT03391804). Ox intake was assessed via dietary recall in studies 396 and 713. UOx levels were assessed serially as part of the respective protocols.

**Results:** There was a consistent effect seen in EH subjects with higher UOx levels across three Phase 2 clinical trials. All EH patients demonstrated an average reduction of at least ≥30 mg/d across all three studies. On average, patients who had a ≥50 mg/d baseline UOx, demonstrated a ≥30 mg/d or ≥24% reduction in UOx across all studies. The results of these Phase 2 studies support the design of the ongoing Phase 3 program for UOx in EH.

**Conclusions:** Consistent with the mechanism of action of reloxaliase, patients with higher baseline UOx appear to benefit from a therapy that degrades oxalate in the GI tract before systemic absorption.

**Funding:** Commercial Support - Allena Pharmaceuticals Inc

**SA-PO816**

**Association Between Probiotic Intake and Inflammation in CKD Patients**

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**Background:** Little is known about the effect of probiotics on inflammation in chronic kidney disease (CKD) and results are inconsistent. Our study aims to investigate the association between probiotic intake and inflammation in patients with CKD.

**Methods:** This study is based on 900 patients with moderate or advanced CKD from the French CKD-REIN cohort. The intake of both dietary supplements and yoghurts was assessed from a food frequency questionnaire, and divided in 3 classes: probiotics (yoghurts or dietary supplement), regular yoghurts (which contains 2 regulated bacteria strains), and none. Inflammation was defined as CRP≥5mg/l. Multivariable logistic regression was performed to assess the cross-sectional association between probiotic intake and inflammation.

**Results:** Patients’ median (IQR) age was 70 (63-78) years, eGFR, 31.1(22.8-40.7) ml/min/1.73m², CRP, 3.0(1.6-7.2) mg/l and 34% had inflammation. 30% consumed <5% regular yoghurts and 12% none. Compared to non-consumers, patients consuming probiotics or regular yoghurts were less likely to have inflammation, although it did not reach significance [OR (95% CI): 0.64 (0.40;0.91), P = 0.05, and 0.75(0.49;1.15), P = 0.2, respectively]. After adjustment for co-morbidities, socio-demographics and nutritional intake, probiotic intake was associated with a significant decrease in the risk of inflammation [0.57 (0.35;0.94); P = 0.03], while the association was weaker and non-significant for regular yoghurts [0.67(0.43;1.04); P = 0.08].

**Conclusions:** Probiotic intake, but not regular yoghurts, was found to be associated with lower odds of inflammation.

**SA-PO817**

**Dietary Fiber Intake Is Associated with Indoxyl Sulphate in Hemodialysis Patients**

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**Background:** Gut microbiota imbalance is a common complication in chronic kidney disease (CKD) patients. This dysbiosis is linked to increased gut-derived uremic toxins production such as indoxyl sulphate (IS), involved with inflammation and oxidative stress in these patients. Lifestyle modifications may have significant favorable effects on reduction of uremic toxins from the gut microbiota, as increased fiber intake, which seems to be associated with gut microbiota modulation and reduction on uremic toxins production. The aim of this study was to verify a possible relationship between fiber intake and IS plasma levels in hemodialysis (HD) patients.

**Methods:** In this cross-sectional study, 50 HD patients were evaluated. Indoxyl sulphate plasma levels were measured by Reverse-Phase High-Performance Liquid Chromatography (HPLC) and, the food intake was assessed using a 3-day 24-hour dietary recall.

**Results:** Table 1 shows the characteristics and food intake parameters of the HD patients evaluated. The IS plasma levels were negatively correlated with fiber intake (r = -0.32, p = 0.02). One HD patient.

**Conclusions:** Our results suggest that increasing dietary fiber intake the IS plasma levels can be reduced in hemodialysis patients, probably due the gut microbiota modulation.

**Funding:** Government Support - Non-U.S. Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Table 1. Characteristics and food intake parameters of the HD patients.

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<th>Parameter</th>
<th>Placebo (N=8)</th>
<th>TZD (N=7)</th>
<th>Placebo (N=8)</th>
<th>P AUC (C)</th>
<th>P B V (G)</th>
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<tr>
<td>hsCRP (ng/mL)</td>
<td>1.9 (1.0, 3.2)</td>
<td>2.9 (1.5, 5.5)</td>
<td>4.7 (4.0, 11.5)</td>
<td>0.16 0.03</td>
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<td>Delta hs CRP</td>
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<td>-2.1 (2.6, 42.3)</td>
<td>1.34 (27, 67)</td>
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<td>IL-6 (pg/mL)</td>
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<td>2.5 (1.7, 7)</td>
<td>1.9 (0.9, 2.8)</td>
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<td>IL-8 (pg/mL)</td>
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<td>0.0 (0.1, 1.0)</td>
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<td>WBC (cells/μL)</td>
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<td>3.8 (3.4, 4.5)</td>
<td>4.0 (6.0, 4.1)</td>
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<td>Albumin (g/dL)</td>
<td>0.2 (0.1, 0.6)</td>
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<td>0.0 (0.1, 0.1)</td>
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<td>Creatinine (mg/dL)</td>
<td>1.5 (1.0, 2.0)</td>
<td>1.6 (1.0, 2.0)</td>
<td>1.5 (1.0, 2.0)</td>
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<td>GFR (mL/min/1.73m2)</td>
<td>61.6 (49.9,65)</td>
<td>55.8 (40.3, 66)</td>
<td>52.7 (45.5, 68)</td>
<td>0.12 0.81</td>
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</table>
| Median and IQR values for baseline and after 8 weeks of intervention.

SA-PO818

Resistant Starch Supplementation Attenuates Inflammation in Hemodialysis Patients

Denise Mafra,1 Bruna Paiva,¹ Marta Esgalhado,1 Natália A. Borges,2 Julie ann Kemp,1 Ludmila F. Cardozo,3 Jessyca S. Brito,2 Paulo emilio C. Leite,3 Renata D. Macedo,3 Gutenberg G. Alves.4 Nutrição em Nefrologia ¹Federal University Fluminense, Rio de Janeiro, Brazil; ²Universidade Federal Fluminense, Rio de Janeiro, Brazil; ³Federal Fluminense University, Niterói, Brazil; ⁴Fluminense Federal University, Rio de Janeiro, Brazil; INMETRO, Rio de Janeiro, Brazil.

Background: Dysbiosis in chronic kidney disease (CKD) is linked to oxidative stress and inflammatory response. Researchers have investigated strategies capable of reestablishing the symbiosis of the gut microbiota in CKD, and suggested that resistant starch (RS) can promote many benefits, including immunomodulatory effects. The aim of the study was to evaluate the impact of RS supplementation on levels of some inflammatory markers in hemodialysis (HD) patients.

Methods: A double-blind, placebo-controlled, randomized trial was conducted with sixteen HD patients [53.3 ± 10.0 years, BMI, 25.9 ± 5.4 kg/m², 56]% men, an on dialysis 38.9 ± 29.2 months] that were equally divided in RS (16 g of RS HI-MAIZE 260, Ingredion®) or placebo (mancin flour) groups, to receive alternately 9 cookies/day (dialysis days) and 1 sachet/day (non-dialysis days) for 4 weeks. Cytokines and growth factors plasma levels were evaluated by XMap-labeled magnetic microspheres based multiparametric immunoassay (LuminexCorp, USA), before and after supplementation.

Results: After RS supplementation there was a reduction of Normal T Cell Expressed and Secreted (RANTES) (p<0.001), Platelet-derived growth factor two B subunits (PDGF-BB) (p=0.014) and Interferon-inducible protein 10 (IP-10) (p=0.027) (Fig 1). The other parameters did not change significantly.

Conclusions: The results of this randomized study suggested that supplementation with prebiotic, specifically RS, was able to minimize the inflammation in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO819

Effects of Anti-Inflammatory and Insulin Sensitizing Agents on Markers of Inflammation and Protein Turnover in Maintenance Hemodialysis (MHD) Patients

Ascel Alsouqi,1 Serplie mugue Deger,4 Adriana Hung,2 Edward D. Siew,2 Talat Alp Ikizler,1 1Vanderbilt University Medical Center, Nashville, TN; 2Y & Vanderbilt University, Nashville, TN; 3Vanderbilt University School of Medicine, Nashville, TN; 4Vanderbilt University Faculty of Medicine Department of Nephrology, Nashville, TN.

Background: Systemic inflammation and insulin resistance are associated with increased protein catabolism leading to protein energy wasting in MHD patients.

Methods: We studied the metabolic effects of a PPAR-gamma agonist (pioglitazone-TZD 30 mg daily, N=9) and an Interleukin-1 receptor antagonist (anakinra subcutaneous injections 3 times weekly during hemodialysis, N=7) versus placebo (n=8) over 3 months in MHD patients through a randomized placebo-controlled trial. Whole body and skeletal muscle protein turnover, inflammatory markers and body composition were measured at baseline and 12 weeks after intervention in all patients (Total N = 24). The primary outcome was change in whole-body protein balance (WBPB) measured by stable isotope technique. Inflammatory markers and lean body mass (LBM) were secondary outcomes.

Results: There were no significant demographic or clinical differences at baseline between groups. There were no statistically significant differences in whole-body protein balance between groups over 3 months (Table 1). Patients in the pioglitazone group demonstrated a significant decline in HsCRP concentrations compared to placebo (p<0.03), but there were no statistically difference in changes in IL-6 for either group. There were no statistically significant differences between groups regarding changes in in total body mass or fat mass in any of the study groups.

Conclusions: In this pilot mechanistic trial, we were not able to demonstrate a significant change in whole-body protein balance and body composition. In this study, our analyses could be limited by relatively small number of subjects and duration of intervention.

Funding: NIDDK Support, Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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SA-PO820
Low Dietary Fiber Consumption Contributes to Gut Dysbiosis with Increased Fecal Indole and Circulating Indoxyl Sulfate in CKD Patients
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Background: Recent advances in the understanding of the role of gut microbiota and its function and composition in health and disease have revealed previously unappreciated effects of CKD-associated colonic pathology on the development of uremic complications. We aim to investigate the relationship between dietary content, gut microbiota, fecal bacterial metabolites, and circulating gut-derived uremic toxins in CKD patients.

Methods: We obtained dietary frequency questionnaires, blood, and stool samples for patients in CKD stage 5, and healthy controls. We examined and analyzed their gut microbiome by 16S RNA sequencing and fecal indole amount. Also, we successfully developed a method for quantification of the indole level in human fecal samples.

Results: We enrolled 62 patients, among which 40 patients were CKD stage 5. Compared to healthy controls (n = 22), and we found a distinct gut microbiome between groups. Next, we stratified subjects into age-matched subgroups, and we found that though the most dominant phylum was Bacteroides within each group, its relative abundance in the CKD group was much higher than the other two control groups. Second, three genera Faecalibacterium, Sheranella, and Erwiniella were present in the CKD group, but not in the others (Fig. 1). Besides, in contrast to the sum of relative abundance of the common top 10 genera in the control groups and the top 10 genera within individuals, the microbial composition of the fecal community were much diverse in the CKD patient than the non-CKD patient. Also, we also found that dietary fiber consumption is less, and fecal indole is higher in CKD patients (Fig. 3). Interesting, through combining FFQ and nutrient quantification, we identified that the circulating levels of total p-cresol sulfate negatively correlated with fiber-rich and ascorbic acid-rich diet intake.

Conclusions: Vegetables and fruits are enriched with dietary fibers but were instructed to be restricted in patients with advanced CKD to avoid hyperkalemia. Our data proved that such fiber-restricted diet creates an intestinal environment which is unfriendly for beneficial microbial flora with subsequent local and systemic inflammation as evidenced by increased fecal indole and increased the circulating level of indoxyl sulfate.

Funding: Government Support - Non-U.S.

SA-PO821
Effect of Cranberry Extract (Vaccinium macrocarpon) on Inflammation, Oxidative Stress, and Uremic Toxins in CKD Patients
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Background: Chronic kidney disease (CKD) patients present many complications that potentially could be linked to increased cardiovascular risk such as inflammation, oxidative stress and high levels of uremic toxins from gut microbiota. Bioactive compounds from food may help reduce these complications, such as polyphenols present in fruits like cranberry, which have antioxidant, anti-inflammatory and prebiotics properties.

Methods: In this randomized, double-blind, placebo-controlled study, 30 non-dialysis CKD patients were randomized to receive cranberry dry extract (1000 mg/day containing 72mg of proanthocyanidins) or placebo (1000mg/day of corn starch) for 2 months. Blood samples were collected at baseline and after intervention. The mRNA expression of factor erythroid 2-related factor 2 (Nrf2) and nuclear factor-kappa B (NF-kB) in PBMCs were assessed at baseline and after cranberry dry extract intervention. The CRP, TNF-alpha, IL-6, IL-10, sICAM-1 and sVCAM-1 plasma concentrations were measured at baseline and after cranberry dry extract intervention. The immunostaining for ICAM-1 in the kidney cortex and medulla were assessed at baseline and after cranberry dry extract intervention.

Results: Twenty-seven patients concluded the study: 13 patients in the cranberry dry extract group (55.7 ± 5.7 years, 49 males) and 14 in the placebo group (57.7 ± 5.7 years, 4 men). Treatment adherence was above 96% in both groups. There was no significant difference in NF-xB or NF2 mRNA expression after cranberry supplementation [0.91 (0.62 – 1.19) to 1.20 (0.75 – 1.80), p=0.21 and 1.31 (0.59 – 2.95) to 0.99 (0.61 – 1.25), p=0.57, respectively]. TBARS levels also did not change after cranberry supplementation. The uremic toxins plasma levels also did not change [CRP: 2.97 (1.28 – 4.42) mg/L to 2.88 (1.32 – 4.14) mg/L, p=0.53; PCS: 14.94 mg/L (7.12 – 23.53) to 17.63 (7.54 – 23.50) mg/L, p=0.04; IAA: 758.99 mg/L (605.5 – 1237.4) mU/L to 664.5 (500.5 – 1592.3) mU/L, p=0.58]. There were no significant differences in the placebo group.

Conclusions: Short-term cranberry dry extract supplementation does not appear to influence inflammation, oxidative stress and uremic toxins in non-dialysis CKD patients. Long-term studies with different doses are needed to determine whether cranberry dry extract may affect these markers in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO822
Effect of the Dietary Antioxidant Supplement Alpha Lipoic Acid on Nuclear Reduced Glutathione Levels in Kidney Cortex and Medulla from Young Rats
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Background: Supplementation with antioxidants, such as alpha lipoic acid, are thought to be beneficial since they can increase the level of reduced glutathione (GSH) inside cells. GSH is the major antioxidant inside cells and provides protection against damage by free radicals produced as a consequence of oxidative metabolism. Previous studies have reported that GSH levels in mitochondria from kidney, liver and heart are significantly increased with alpha lipoic acid supplementation in old rats, but not in young rats. This suggest that dietary antioxidant supplementation may not always be beneficial in young rats. The purpose of this study was to determine whether the nucleus in kidneys from young rats does respond to alpha lipoic acid supplementation with an increase in GSH levels.

Methods: Young female Experimental Lewis rats (3 months of age; n=7) received alpha lipoic acid (100 mg/kg) via i.p injection for one week. Age-matched Control rats (n=4) did not receive any supplementation. The kidneys were harvested from anesthetized rats, and the cortex and medulla were separated and homogenized. The nuclear fractions were isolated using differential centrifugation. The GSH and total glutathione (Tot GLUT; GSH plus oxidized GSH) were measured with a spectrophotometric assay. The GSSG (oxidized GSH) levels were determined from the difference between Tot GLUT and GSH levels, and then divided by 2. Comparisons were done using a Student’s T Test.

Results: There was a significant increase in nuclear GSH levels in the kidney cortex and medulla with dietary supplementation with alpha lipoic acid. This was accompanied by a significant decrease in nuclear GSSG levels. Nuclear Tot GLUT levels did not change or were decreased following supplementation.

Conclusions: The nucleus in kidney cells from young rats does respond to alpha lipoic acid supplementation with an increase in GSH levels.

Effect of Alpha Lipoic Acid on Nuclear GSH Levels in Young Rat Kidney

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>182 ± 21</td>
<td>262 ± 21*</td>
</tr>
<tr>
<td>Medulla</td>
<td>180 ± 17</td>
<td>231 ± 19*</td>
</tr>
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</table>

All data shown as X +/- SEM. * Significantly different from Control at p<0.05.

SA-PO823
Changes in Metabolic Syndrome Components Affect the Incidence of ESRD in the General Population: A Nationwide Cohort Study
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Background: Few studies have investigated the impact of a change in metabolic syndrome (MetS) components on clinical renal outcomes in the general population.

Methods: Using nationally representative data from the Korean National Health Insurance System, 13,310,924 subjects without chronic kidney disease who underwent two health examinations over 2 years and were free from end-stage renal disease (ESRD) from 2009 to 2012 were followed to the end of 2016. The subjects were divided into four groups according to the change in MetS components between the two visits over 2 years: no MetS (–/–), post-MetS (+/+), pre-MetS (+/-), and both MetS (+/+).

Results: The proportion of patients in the no-MetS (–/–), post-MetS (+/+) , pre-MetS (+/-), and both MetS (+/+), groups was 61.3%, 10.8%, 8.3%, and 19.5%, respectively. After a median follow up of 5.11 years, 18,822 incident ESRD cases were identified. In the multivariate adjusted model, the hazard ratio (HR) and 95% confidence interval (CI) for the development of ESRD in the both-MetS (+/+) group compared with the no-MetS (–/–) group was 5.65 (95% CI, 5.42–5.89), which was independent of age, sex, and baseline estimated glomerular filtration rate. Additionally, the HR for the pre-MetS (+/-) group versus the no-MetS (–/–) group was 2.28 (2.15–2.42). In subgroup analysis according to renal function, the impact of a change in MetS on the incidence of ESRD was more pronounced in individuals with advanced renal dysfunction.

Conclusions: Subjects with resolved MetS components had a decreased risk of ESRD, similar to that as low as those that never had MetS components. This provides evidence supporting the strategy of modifying MetS in the general population to prevent the development of ESRD.

Funding: Government Support - Non-U.S.
SA-PO824
Abdominal Fat, Physical Function, and Their Associations with Insulin Resistance, Inflammation, and Adipokines in CKD

Background: Adiposity and physical inactivity are major drivers of cardiometabolic risk, and may confer differential metabolic risk profile in CKD. We examined the associations of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and physical function with inflammation, insulin resistance, adipokines in those with CKD.

Methods: We obtained MRI of the abdomen and pelvis, and 400m walk test to assess the relationships between VAS, VAT and SAT using four 419 CRIC study participants using a standardized protocol. We also measured markers of inflammation (IL-β, IL-6, TNF-R1, and TNF-R2), insulin resistance (HOME-R), and adipokines (adiponectin total, and HMW, resistin, and leptin). We evaluated the associations between VAT, SAT volume and physical function, and individual markers (log-transformed values) adjusting for relevant confounders.

Results: Mean age of the study population (n=419) was 64.3 years; 40% were females, and the mean eGFR was 57.7 (±18.4) ml/min/1.73 m². Over 85% of them were overweight or obese, and 39% were diabetics. Each SD higher VAT and SAT were associated with lower levels of total and HMW adiponectin, and higher levels of leptin and insulin resistance [Figure]. However, higher 400m walk was associated only with higher levels of plasma IL-6 and TNF-R1 [Figure].

Conclusions: The observations that greater adiposity is associated with altered adipokine profile and insulin resistance, while lower levels of physical function are related to enhanced inflammation in CKD are intriguing. A deeper understanding of the reasons for these differential associations may lead to new approaches to management of patients with KD.

Funding: NIDDD Support

SA-PO825
Associations Between Visceral Obesity and Renal Impairment in Medical Checkup Participants
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Background: Obesity has been reported to be a risk factor for chronic kidney disease, which is now considered one of the most important public health issues worldwide. We aimed to evaluate the relationships between obesity indicators (visceral fat area [VFA], body mass index [BMI], waist circumference, waist-to-height ratio, and visceral-to-subcutaneous fat ratio) and cardiovascular disease risk factors (blood pressure, total cholesterol, glucose, and triglycerides).

Methods: Setting: Retrospective cohort study. Participants: Subjects who underwent VFA measurements during medical checkups in 2012 at Takeda Hospital Group Medical Examination Centers were included. The follow-up period was from April 2012 to March 2018. Exposures: Obesity was defined using a separate baseline value of each indicator: VFA ≥100 cm², BMI ≥25 kg/m², waist circumference ≥85 cm for men and ≥90 cm for women), waist-to-height ratio (≥0.5), and VSR (≥0.4). Main outcomes measures: Changes in estimated glomerular filtration rate (eGFR), and time to new-onset proteinuria were measured. Statistical analysis: The relationships between obesity indicators and eGFR, were evaluated using a linear mixed effects model. The relationships between obesity indicators and new-onset proteinuria were evaluated using Poisson regression analysis.

Results: Analysis was performed on 2,753 subjects (mean age 50.3 years [standard deviation 10.0], 1,419 men, 1,334 women). The VFA ≥100 cm² group exhibited a significantly larger difference in the annual change in eGFR, (-0.24 ml/min/1.73 m²/year) than the <100 cm² group. Furthermore, there was a significant difference in the proteinuria incidence ratio, which was 1.54 times higher in the VFA ≥100 cm² group (95% confidence interval: 1.01 to 2.35). Significant correlations were not observed with any of the obesity indicators.

Conclusions: VFA ≥100 cm² was significantly associated with a greater annual decline in eGFR, and the higher incidence of new-onset proteinuria. VFA is suggested as the most sensitive obesity indicator for the decline in kidney function and new-onset proteinuria.

Funding: Government Support - Non-U.S.

SA-PO826
The Effect of Bilateral Nephrectomy on Gene Expression of Hypothalamic Neuropeptides Regulating Feeding Behaviors
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Background: Anorexia is one of the most widespread eating disorders that appears to contribute to malnutrition in patients with advanced kidney dysfunction. Previously, many neuropeptides synthesized in the hypothalamus have been shown to regulate feeding behavior. Several mechanisms underlying uremic anorexia have been proposed, the hypothalamic neuropeptides that regulate feeding in the hypothalamus of patients with kidney dysfunction are poorly understood.

Methods: The gene expressions of hypothalamic neuropeptides controlling feeding behaviors were evaluated after bilateral nephrectomy, which is a model of acute kidney dysfunction, by in situ hybridization histochemistry. Adult male rats received bilateral nephrectomy or a sham operation under anesthesia. The rats were decapitated at 6, 12, and 24 h after treatment. The gene expression of corticotrophin-releasing hormone (CRH) in the paraventricular nucleus (PVN), proopiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART), neuropeptide Y (NPY), agouti-related peptide (AgRP), and melanin-concentrating hormone (MCH) and orexin in the lateral hypothalamic area were quantified by in situ hybridization histochemistry. After treatment, cumulative food intake, water intake, and body weight were measured.

Results: Food consumption decreased markedly in bilateral nephrectomized rats. The mRNA levels of CRH, POMC, CART, which suppress feeding behavior, were significantly higher in bilateral nephrectomized rats than in sham-operated rats. On the other hand, the mRNA levels of NPY, AgRP, MCH, and orexin, which promote feeding behavior, were significantly lower in bilateral nephrectomized rats than in sham-operated rats.

Conclusions: The results suggest that hypothalamic neuropeptides regulating feeding behaviors may be involved in the development of anorexia in bilateral nephrectomized rats. This report is the first step to elucidating the physiological mechanisms of anorexia in patients with kidney dysfunction.

SA-PO827
Obestatin Response to a Meal and Association with Subsequent Appetite Sensations in Hemodialysis Patients
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Background: Obestatin, a physiological opponent of acylated ghrelin, linked to the regulation of appetite reducing food intake in mice but its anorexigenic property in human is controversial. We aimed to investigate a potential role of obestatin in dietary intake regulation by examining response to a meal in maintenance hemodialysis (MHD) patients.

Methods: In this case-control study we have investigated the response of obestatin around a fixed calorie meal (500 kcal) in 21 MHD patients (age 69.2±13.1 years, 10 women, with body mass index 27.2±5.5 kg/m²). Parallel changes in serum obestatin and insulin levels and subjective scores of appetite (visual analogue scales for hunger, satiety, fullness and prospective food consumption) were recorded on fasting and 30, 60 and 120 min after meal.

Results: In a linear mixed effects model controlling for baseline demographics and clinical parameters including serum insulin concentrations, postprandial levels of obestatin did not change significantly from baseline to response to the meal. The response was the same in MHD patients treated with high or low flux dialyzers. However, postprandial obestatin levels were associated with the rate of change in sensation of fullness (linear estimate: 11.60 (95% confidence interval 0.17 to 23.04, P=0.05). The remained sensations of appetite did not correlate with postprandial obestatin levels in time.

Conclusions: Obestatin levels do not change acutely with food administration in MHD patients, but associate with the changes in sensation of fullness. This supports the possible role of obestatin in the long-term regulation of appetite in MHD population.
SA-PO828

Protective Effect of Leuconostoc in Renal Damage Induced by Obesity
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Background: There is enough evidence showing that obesity promotes kidney damage. Probiotics might help in improving several diseases. Mexican honey water contains bacteria known as Leuconostoc that have anti-obesity activity. However, its role in prevention of renal injury induced by obesity still unknown.

Methods: Forty three C57BL6 male mice were divided into four groups: control diet, 3.41 Kcal/g (n=10), probiotic control, 2x10⁹ CFU, IG, (n=10), hypercaloric diet, 4.9 Kcal/g, (n=11), and hypercaloric diet/probiotic (n=12). The groups were studied for 3 months and a half. Weekly measurements of weight and caloric intake were made. At the end of the follow-up, the determination of body fat and water was carried out using nuclear magnetic resonance (NMR). Urine was collected to analyze renal function and biomarkers. Tissue was stored for molecular analysis and the other kidney was fixed for histopathological analysis.

Results: At the end of the study, the hypercaloric diet induced a significant increase by 52.1% in body weight (BW) and by 3-fold in body fat (BF), with a reduction in lean mass by 27.4%. Also renal damage was observed that was characterized by a significant increase in: albuminuria, oxidative stress and KIM-1 levels, as well as, kidney inflammation, and TGF-b up-regulation. Leuconostoc administration significantly reduced the increase in albuminuria, oxidative stress, and KIM-1 levels in the hypercaloric/probiotic group were similar to control groups. Effects that were accompanied by restoration of IL-6, TNFa, albuminuria, oxidative stress, and KIM-1 levels, as well as, kidney inflammation, and TGF-b up-regulation.

Leuconostoc in: albuminuria, oxidative stress and KIM-1 levels, as well, kidney inflammation, and TGF-b up-regulation. Leuconostoc administration significantly reduced the increase in albuminuria, oxidative stress, and KIM-1 levels in the hypercaloric/probiotic group were similar to control groups. Effects that were accompanied by restoration of IL-6, TNFa, albuminuria, oxidative stress, and KIM-1 levels, as well as, kidney inflammation, and TGF-b up-regulation.

Conclusions: These results show that hypercaloric diet induced metabolic and renal alterations. While, Leuconostoc was efficient in preventing weight gain, renal injury, and oxidative stress, as well, as, probiotic and inflammatory pathways activation. Therefore, this probiotic seems to be a feasible and useful tool for the treatment of renal injury induced by obesity; however, controlled clinical studies are required to prove this hypothesis.

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SA-PO829

Noninvasive Measures of Visceral Adiposity and Risk of Kidney Function Decline
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Background: Measures of visceral obesity are better markers of adverse outcomes than body mass index (BMI) and waist circumference (WC). Lipid accumulation product (LAP) and visceral adiposity index (VAI) are novel, non-imaging markers of visceral adiposity calculated by using BMI, WC and serum lipids. We hypothesized that LAP and VAI will be associated with adverse kidney outcomes independent of traditional risk factors.

Methods: Using data from Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, we evaluated the association of LAP, VAI, BMI and WC with (a) 1127 cases of incident CKD, defined as reaching an eGFR <60ml/min/1.73m²; (b) 1452 cases of >30% eGFR decline using logistic regression; and (c) 353 cases of incident ESRD using Cox regression.

Results: Mean age was 65 years, 54% were women, and 41% were African American. The median time between visit 1 and 2 was 9.4 years. After adjusting for confounders, the top quartiles of VAI, LAP, BMI and WC were associated with higher odds of incident CKD and progressive eGFR decline compared to bottom quartiles. VAI and LAP were associated with an increased risk of ESRD after demographic and risk factor adjustment (HR 1.94; 95% CI, 1.37 to 2.76) but this association was no longer significant after adjusting for baseline eGFR and albuminuria.

Conclusions: Adiposity assessed by measures of generalized and visceral obesity is associated with higher risk of incident CKD and eGFR decline. VAI and LAP are not more strongly associated with CKD and eGFR decline compared to BMI and WC. However, for incident ESRD, VAI and LAP may be valuable for providing useful information beyond BMI and WC (in the models that do not include eGFR/ACR).

SA-PO830

Comparative Study on the Prognostic Value of Body Composition Parameters in Hospitalized Patients with Dialysis
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Background: Body composition is essential to the prognosis of dialysis patients, but comparison of prognostic value of different nutritional and fluid load parameters in the hospitalized patients with dialysis is limited.

Methods: We conducted a prospectively observational study to assess the association of different parameters in body composition with all-cause mortality in dialysis inpatients. The body composition was measured by bioelectrical impedance within the first 3 days after admission and hemodialysis patients should be measured before dialysis session. The parameters in fluid volume included overhydration (OH), the ratio of OH to extracellular water (OH/ECW), the ratio of extracellular water to body cell mass (ECW/BCM), the ratio of extracellular water to intracellular water (ECW/ICW); the parameters in nutritional status included fat tissue index (FTI), lean tissue index (LTI) and body cell mass index (BCM).

Results: Of the 832 study patients, 191 (23.0%) died during a median follow-up of 31 months. In multivariable adjusted Cox models, higher ECW/BCM (adjusted hazard ratio per 1-SD, 1.30; 95% CI, 1.09 to 1.54) were associated with a significantly greater risk of death, as were lower LTI (adjusted odds ratio per 1-SD, 0.70; 95% CI, 0.59 to 0.83) and BCM (adjusted hazard ratio per 1-SD, 0.72; 95% CI, 0.62 to 0.84). BMI, FTI and BCM/weight were also associated with death, but the magnitude of the association was greatest for ECW/BCM, LTI and BCM. When ECW/BCM, LTI and BCMI were added to the fully adjusted model, only LTI improved the predictability for all-cause mortality (net reclassification index =0.15, P=0.04; integrated discrimination improvement =0.02, P=0.01).

Conclusions: ECW/BCM was the most relevant to mortality in fluid volume indices, and LTI and BCM were most two relevant to mortality in nutritional status indices. Higher LTI was significantly associated with a lower risk of death and exhibited a stronger association with mortality than ECW/BCM, BCM and other body composition parameters in dialysis inpatients.

SA-PO831

Effect of Age and Gender on the Relation Between Body Fat Area and Kidney Outcomes in Patients with CKD
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Background: Increase in body fat area has been noted as a risk factor for progression of chronic kidney disease (CKD) as well as cardiovascular disease and death. Similarly, obesity has been shown to be associated with CKD progression, but this association might be interacted with patient’s characteristics. Here, we examined obesity assessed by body fat area is related to kidney outcomes in patients with CKD with possible interaction by age and gender.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We included 367 patients who completed CKD educational program between January 2011 and February 2017. Patients were classified into four groups: male patients under 75y (n=164), female patients under 75y (n=52), male patients 75y or older (n=98), and female patients 75y or older (n=53). Body fat area was measured at the level of the umbilicus using an CT-image analysis system. Kidney outcomes was defined as initiation of renal replacement therapy or incidence of 50% reduction in estimated glomerular filtration rate.

Results: The overall mean age of the patients was 73.0 (65.0-78.0) years old, of whom 262 patients (71.4%) were male, and the median estimated glomerular filtration rate based on plasma cystatin C (eGFRcys) was 28.9 mL/min/1.73m². During the observation period [median 1.7 year (0.7-3.5)], 187 patients reached kidney outcomes. In both univariate and multivariate Cox regression analysis, VFA and SFA were not associated with increased kidney outcome in overall population. However, in males under 75y, multivariate Cox regression analysis showed SFA but not VFA as significant risk for kidney outcomes (SFA: HR 1.06, 95% CI: 1.02-1.11). In turn, VFA but not SFA was significantly associated with decreased kidney risk in female under 75 y (VFA: HR 0.83, 95% CI: 0.71-0.97). Moreover, in patients 75y or older in both sex, multivariate Cox regression analysis failed to show the significant association with kidney outcomes in both VFA and SFA.

Conclusions: Obesity as assessed by body fat area was not a significant risk for CKD progression in very old patients with CKD. In younger patients with CKD, high SFA in men and women was a significant risk factor for CKD progression, whereas high VFA in females was a significant renoprotective factor. When we consider obesity as a potential risk for CKD progression, we need to consider age and gender.

SA-PO832
Change in Glomerular Filtration Rate After Bariatric Surgery Varies by Baseline Kidney Function
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Background: It is unclear whether GFR decreases after bariatric surgery in individuals with lower baseline GFR who may lack renal functional reserve.

Methods: GFR was measured by plasma isohex clearance in 27 adults at multiple research visits before and after bariatric surgery (twice pre-surgery, ~6 and 12 months post-surgery). We examined whether changes in GFR after bariatric surgery varied by pre-surgery GFR using generalized estimating equations, clustered by individuals.

Results: Pre-surgery, mean values of body mass index (BMI) and body surface area (BSA) were 49.4 kg/m² and 2.42 m². Mean unindexed and indexed GFR were 117.3 mL/min (range 57.4 to 206.0) and 84.1 mL/min/1.73m² (range 44.3 to 138.0), respectively. Six months after surgery, BMI decreased by 13.9 kg/m² (95% CI: -15.9, -11.8) and BSA decreased by 0.30 m² (95% CI: -0.34, -0.27). Post-surgery changes in GFR varied by pre-surgery GFR (p<0.001 for interaction). Those in the middle tertile of the umbilicus using an CT-image analysis system. Kidney outcomes was defined as initiation of renal replacement therapy or incidence of 50% reduction in estimated glomerular filtration rate.

Changes in GFR after Bariatric Surgery, by Baseline Tertile of GFR

Unindexed GFR
Indexed GFR

Conclusions: Baseline kidney function may be a significant factor to consider when performing pre-operative risk assessment.

SA-PO833
Dietary Zinc Amount Is Associated with Incident CKD in General Population
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Background: Previous study suggests that zinc is associated with diabetes. No studies have undergone the association of incident chronic renal disease (CKD) and zinc consumption amount in a preserved renal function population. Data from the Korean Genome and Epidemiology Study (KoGES) community-based cohort study were used to assess the between the zinc consumption amount and incident CKD.

Methods: Zinc consumption amount was calculated by a 24-hour dietary recall Food Frequency Questionnaire and converted into relative zinc consumption amount with energy-adjusted method. A total 7821 participants were analyzed with a primary of incident CKD that defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m².

Results: The mean age was 52.1 ± 8.8 years, 47.5% were male, and mean eGFR was 92.1 ± 16.1 mL/min/1.73m². The mean daily zinc consumption amount was 8.6 ± 3.4 mg. During a median follow up of 11.5 (1.6 – 13.0) years and 74177 person-year observation, CKD developed in 1428 (18.3%) participants. When the participants were categorized into quartiles according to energy-adjusted zinc intake, the lowest quartile was significantly associated with the development of incident CKD compared to third lowest quartile group in multivariable cox hazard analysis (Hazard ratio; 1.19; 95% Confidence Interval 1.02 – 1.39; p = 0.027) and this finding was consistent after further adjustment. The U shaped hazard association was noted between zinc consumption and incident CKD in restricted cubic spline analysis.

Conclusions: Thus, low zinc consumption was associated with the increased risk for CKD.

SA-PO834
Low Serum Zinc Concentration Is Associated with Infection Events in CKD Patients
Yosuke Saka, Tomohiko Naruse. Department of Nephrology, Kasugai Municipal Hospital, Kasugai, Aichi, Japan.

Background: Zinc plays an important role in immune function. Several studies reported the association between zinc deficiency and infection. Infectious disease is one of major complications in CKD patients. We investigated whether serum zinc concentration is associated with infection risk in stage 5 CKD patients.

Methods: We retrospectively analyzed 232 patients in whom serum zinc concentration was measured to evaluate renal anemia before January 2013 and December 2016. Of the 232 patients, 9 patients receiving zinc supplementation at the time of measurement were excluded. We followed up the remaining participants after enrollment. The endpoint was infection-related hospitalization. The length of infection-related hospitalization was also analyzed. Participants were divided into two groups according to the median of serum zinc concentration, categorized as low or high (Zn ≤ 50 and > 50 μg/dl, respectively). Data were analyzed using the Kaplan-Meier method and Cox hazards models.

Results: The median follow-up period was 36 months. During follow-up, 40 patients were hospitalized due to infection. Low serum zinc concentration was associated with a higher rate of infection-related hospitalization (low vs. high: 23.3% vs. 12.6%; p=0.042), and also associated with long-term hospitalization (more than 20 days) due to infection (low vs. high: 17.9% vs. 7.2%; p=0.016). After adjustment in Cox hazards models, low serum zinc concentration remains an independent risk factor for infection-related hospitalization (HR 2.11, 95% CI 1.06-4.21, p = 0.034).

Conclusions: Patients with low serum zinc concentration are at high risk of infection-related hospitalization, which also causes long-term hospitalization.

SA-PO835
Impact of Sodium Bicarbonate (NaHCO3) on Systemic and Urine Metabolites in Patients with and Without CKD
Julia D. Scialla,1 Jennifer L. Modlinski,1 James R. Bain,1 Michael Muehlbauer,1,3 Olga Ilkayeva,1,3 Shirin Pourafshar,1 Crystal C. Tyson,1 Laura P. Svetkey,1 David L. Corcoran,1 Pao-Hwa Lin.1 Duke University, Durham, NC; 2University of Virginia, Charlottesville, VA; 3Duke Molecular Physiology Institute, Durham, NC.

Background: Net acid excretion (NAE) falls in early stages of CKD, yet systemic metabolic acidosis (MA) occurs in late CKD. Homeostasis may be maintained by OAs and potential consequences for systemic metabolism after alkali in a cross-over trial.

Methods: The Acid-Base Compensation in CKD Study was a cross-over trial evaluating 7-days of NaHCO3 vs. 7-days of NaCl supplementation in the setting of fixed diet in adult, non-diabetic patients with (n=8) and without CKD (n=6). 24h urine, and fasting and 90-minute postprandial plasma were collected at the end of each period. We reported the association between zinc deficiency and infection. Infectious disease is one of major complications in CKD patients. We investigated whether serum zinc concentration is associated with infection risk in stage 5 CKD patients.

Results: The median follow-up period was 36 months. During follow-up, 40 patients were hospitalized due to infection. Low serum zinc concentration was associated with a higher rate of infection-related hospitalization (low vs. high: 23.3% vs. 12.6%; p=0.042), and also associated with long-term hospitalization (more than 20 days) due to infection (low vs. high: 17.9% vs. 7.2%; p=0.016). After adjustment in Cox hazards models, low serum zinc concentration remains an independent risk factor for infection-related hospitalization (HR 2.11, 95% CI 1.06-4.21, p = 0.034).

Conclusions: Patients with low serum zinc concentration are at high risk of infection-related hospitalization, which also causes long-term hospitalization.
Acidosis Is Associated with Failure to Thrive and Fractures and Falls in Patients with CKD

Background: Metabolic acidosis causes muscle-wasting and bone loss in experimental animal and human studies. However, its association with clinical outcomes in epidemiological studies is unknown. Here we assess the role of metabolic acidosis as an independent predictor of adverse muscle, bone and functional outcomes in patients with non-dialysis CKD.

Methods: De-identified electronic medical records (Optum® EMR), 2007–2017 were queried to identify non-dialysis CKD patients with ≥2 consistent serum bicarbonate test values 28–365 days apart, ≥3 eGFR values >10 and ≤24 mL/min/1.73m2 and ≥2 years of post-index date or until death. Patients were followed for 2 years for adverse outcomes using ICD codes: failure to thrive (muscle/functional outcome); composite of hip, spine, pathological fractures and falls (bone outcome); metabolic acidosis and normal serum bicarbonate groups were defined by two serum bicarbonate values between 12 and <22 mEq/L and 22-29 mEq/L, respectively. Logistic regression was used to examine serum bicarbonate as an independent predictor of 2-year outcomes and possible demographic and comorbidity confounding factors.

Results: 51,558 patients qualified for this longitudinal observational study. The incidence of adverse outcomes was significantly higher in patients with metabolic acidosis during the 2-year follow-up compared to patients with normal serum bicarbonate: muscle outcomes: 6.5%, vs. 1.9%, p<0.0001; bone outcomes: 17.3% vs. 11.6%, p<0.0001, respectively. Serum bicarbonate was a significant predictor of both types of outcomes; odds ratios for failure to thrive, 0.883, CI: 0.869-0.898, and for fracture/fall, 0.948; CI: 0.939-0.956, independent of age, sex, race, eGFR, diabetes, hypertension, heart failure, coronary artery disease, peripheral vascular disease, hemoglobin and serum albumin. Each 0.939-0.956, independent of age, sex, race, eGFR, diabetes, hypertension, heart failure, coronary artery disease, peripheral vascular disease, hemoglobin and serum albumin. Each 1 mEq/L increase in serum bicarbonate was associated with a 12% decrease in failure to thrive and a 5% decrease in fracture/fall risk.

Conclusions: In this analysis of >51,000 non-dialysis CKD patients followed for 2 years, metabolic acidosis was independently associated with increased incidence of failure to thrive and the composite endpoint of fractures (hip, spine, or pathological) and falls.

Funding: Commercial Support - Tricida, Inc.
SA-PO839

Evaluation, Classification, and Identification of CKD Progression in Rhesus Macaques

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Background: Chronic kidney disease (CKD) is characterized by progressive reduction in kidney function, and with accelerated cardiovascular disease and increased mortality. The goal of the present study was to characterize naturally occurring CKD in rhesus monkeys in comparison to the CKD of humans, to explore the relationship between CKD and CVD, and to evaluate the response of rhesus monkeys with combined CKD-CVD to the angiotensin receptor blocker, Valsartan.

Methods: Plasma biomarkers (Creatinine (Cr), Cystatin-C (CYS C), and Blood Urea Nitrogen (BUN)) were measured in 1198 adult rhesus monkeys (Macaca mulatta, 7-22 yrs). Four hr urine collections were obtained from 100 of these monkeys in order to measure urine albumin and urine creatinine for calculation of the urine albumin/creatinine ratio (UACR). Monkeys with eGFR (CKD-EPI) 30-59 ml/min/1.73m² and/or UACR >10mg/g were defined as having CKD (Grade G3a-3b). Blood pressure and cardiac function were measured, monkeys with LVF<50%, e'<8 cm/s and E/e'>10 were defined as having CVD. A colony of 37 adult male monkeys received medical examinations and direct GFR measurements (Iohexol clearance). Eight monkeys with combined CKD-CVD were enrolled in the validation study and divided into the Valsartan group (n=4) and the vehicle group (n=4). Cardiac function, blood pressure and UACR were measured before and after 8 weeks treatment. Cr, CYS C, BUN and eGFR were measured every other week.

Results: Among the 1198 adult rhesus monkeys studied, 52 monkeys (4.3%) had eGFR 30-59 ml/min/1.73m² and/or UACR >10mg/g. Among the 52 monkeys with CKD, 30 monkeys had confirmed CVD. With Valsartan treatment, average eGFR increased by 23.1% in CKD, eGFR increased by 76.45%, and average SBP decreased by 14.40%. All of these biomarkers differed significantly compared to the vehicle group (p<0.05). The cardiac ultrasound parameters remained stable.

Conclusions: The 4.3% incidence of CKD in adult rhesus monkeys was similar to that in adult humans, and 58% of those with CKD also had CVD as in patients. Valsartan increased eGFR, and also decreased UACR and BP in monkeys. The extent of change in rhesus monkeys was similar to that observed in clinical trials. These monkey models, therefore, provide important new opportunities to understand the pathogenesis of CKD and predict the human response to new therapeutic agents.

SA-PO840

Use of Kidney Disease Progression Model Care Planning Report Associates with Lower Dialysis Catheter Rates at the Initiation of Hemodialysis

Yue Jiao,1 Nelson P. Kopyt,2 Ravindra Bollu,2 Kyleene Casey,2 Sam Gopal,2 John W. Larkin,1 Peter Kotanko,2 Yuedong Wang,4 Jeffrey L. Hynes,1 Len A. Usvyat,1 Franklin W. Maddux,1 Fresenius Medical Care North America, Waltham, MA; 2Acumen Physician Solutions, Durham, NC; 3Renal Research Institute, New York, NY; 4University of California - Santa Barbara, Santa Barbara, CA; 5Valley Kidney Specialists, A Division of Kidney Care Specialists, Allentown, PA.

Background: Approximately 80% of end stage kidney disease (ESKD) patients use a central venous catheter (CVC) at the initiation of hemodialysis (HD) (USRDS 2018). A healthcare organization developed a CKD Forecaster Tool for nephrologists to use for prognostic clinical decision support and patient education in care planning for the transition from CKD to ESKD. We assessed CVC rates at the initiation of HD based on the nephrologists’ level of utilization of the CKD Forecaster Tool.

Methods: We used data from CKD patients treated by nephrology practices using Acumen Electronic Health Record system who progressed to ESKD during April 2018 to October 2019. The CKD Forecaster Tool uses an artificial intelligence modelling of historic eGFR values to predict the trajectory of eGFR values in the future. We assessed CVC rates at HD initiation in patients who progressed to ESKD stratified by the frequency of their nephrologist accessing the CKD Forecaster Tool. Only nephrologists with ≥15 CKD patients who transitioned to ESKD were used for the analysis. Frequent users accessed the tool on >1% of their CKD patients, occasional users accessed the tool on 0.1-1% of their CKD patients, and non-users did not use the tool.

Results: Among a population of 106,915 CKD patients treated by 309 nephrologists, we analyzed data on 6,917 patients who progressed from CKD to ESKD (this includes only nephrologists with ≥15 CKD patients who transitioned to ESKD). A total of 30 nephrologists were frequent users of the CKD Forecaster Tool, 39 were occasional users, and 240 were non-users. Patients treated by nephrologists who used the CKD Forecaster Tool exhibited 1% to 2% lower CVC rates at HD initiation (Figure 1).

Conclusions: Nephrologists who used the CKD Forecaster Tool had slightly less patients transitioning to HD with a CVC. Further assessments are needed to determine if greater adoption and consistent use of the CKD Forecaster Tool over time is associated with larger improvements.

Funding: Commercial Support - Fresenius Medical Care North America

SA-PO841

Added Value of Census Tract Measures of Socioeconomic Status to Identify Patients at High Risk of CKD in the Twin Cities Metro Area

Lama Ghazi, Paul E. Drazin. University of Minnesota, Saint Paul, MN.

Background: CKD is associated with low socioeconomic status (SES); however, guidelines do not recommend screening low SES patients for CKD. Our objective was to assess whether adding census tract level SES status to the traditional CKD screening approach improves our ability to detect patients with CKD.

Methods: Electronic health records of 256,212 patients with outpatient serum creatinine ≤1.5 mg/dL were examined. Patients with ≤3260 ml/min/1.73m² or ≥60 ml/min/1.73m² were defined as having CKD by eGFR (CKD-EPI) and/or UACR ≥300mg/g. We computed 5 approaches for screening: (1) traditional screening, (2) adding SES to traditional screening, (3) adding diabetes (DM), hypertension (HTN), CKD-EPI, or SES to traditional screening, and (4) adding SES to all 5 approaches. We computed sensitivity, specificity, positive and negative predictive value (PPV and NPV) for each approach. We compared performance of the approaches with McNemar's test.

Results: In our cohort, 34,489 patients had CKD. Adding low census tract SES (Approach 2A and 2B), significantly increases the sensitivity of detecting CKD (Table1). Number needed to screen to detect 1 CKD case was 4, 5, 5, and 7 for Approaches 1, 2A, 2B, and 3B, respectively.

Conclusions: Adding an individuals’ residence SES status to traditional risk factors improved our ability to detect individuals at risk of CKD who may benefit from interventions to reduce risk of cardiovascular disease and progression of CKD.

Table 1. The sensitivity, specificity, positive predictive and negative predictive value of the screening approaches for detecting CKD.

<table>
<thead>
<tr>
<th>Approach</th>
<th>Number of CKD cases detected</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
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<tbody>
<tr>
<td>Approach 1</td>
<td>12,137</td>
<td>50</td>
<td>77</td>
<td>56</td>
<td>80</td>
</tr>
<tr>
<td>Approach 2A</td>
<td>10,769</td>
<td>54</td>
<td>69</td>
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<tr>
<td>Approach 2B</td>
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</tr>
<tr>
<td>Approach 3</td>
<td>3,890</td>
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<td>12</td>
<td>87</td>
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<tr>
<td>Approach 4</td>
<td>4,420</td>
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</table>

SA-PO842

Outcomes from Development of a Unique Statewide Platform to Improve CKD Care

Andrea K. Fasson,1 Nadia M. Alquirini,6 Nishank Jain,1 John M. Arthur,2 Manishika Singh,3 Nephrology, UAMS, Little Rock, AR; 1University of Arkansas For Medical Sciences, Little Rock, AR; 2Little Rock VA Hospital, Little Rock, AR; 3University of Arkansas for Medical Sciences, Little Rock, AR.

Background: The division of Nephrology at University of Arkansas for Medical Sciences (UAMS) and Arkansas health department faculty co-investigated a pilot project identifying barriers to chronic kidney disease (CKD) awareness in the State of Arkansas (AR). These included a lack of infrastructure and patient and provider education. To address these barriers, our core investigators reached out to potential stakeholders. We invited a multidisciplinary team of health-care professionals to partner with non-profit organizations and CKD patients, creating the platform of the Arkansas State CKD Advisory Committee (ARCKDAC), with a mission to increase CKD awareness, detection and education through community engagement activities. We also provided baseline AR data to improve systems of care and generate tract SES-housing quartile 1 of the median value of owner occupied housing units; Approach 2B, DM, HTN, or low census tract SES-housing education (quartile 1 of percent of residents ≥ 25 years with complete college education); Approach 3A, screening patients with low census tract SES-housing; Approach 3B: screening patients with low census tract SES education.

Results: In our cohort, 34,489 patients had CKD. Adding low census tract SES (Approach 2A and 2B), significantly increases the sensitivity of detecting CKD (Table1). Number needed to screen to detect 1 CKD case was 4, 5, 5, and 7 for Approaches 1, 2A, 2B, and 3B, respectively.

Conclusions: Adding an individuals’ residence SES status to traditional risk factors improved our ability to detect individuals at risk of CKD who may benefit from interventions to reduce risk of cardiovascular disease and progression of CKD.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
The Relationship Between County-Level Contextual Determinants and Risk of CKD

Yan Xia,1 Benjamin C. Bowe,1 Yan Yan,2 Hong Xian,2 Ziyad Al-Aly,3 1VA Saint Louis Health Care System, Saint Louis, MO; 2Saint Louis University College for Public Health & Social Justice, St. Louis, MO; 3Washington University School of Medicine, Saint Louis, MO.

Background: Multiple studies described geographic variation in the burden of chronic kidney disease (CKD) in the United States, and evidence suggests that this variation cannot be fully explained by individual level risk factors. We aimed to examine the relationship between county-level contextual determinants and individual risk of incident eGFR<60 ml/min/1.73 m².

Methods: We built a cohort of 2,456,853 US veterans with eGFR>60 ml/min/1.73 m² and followed for up to five years. Contextual determinants were curated from County Health Rankings databases. High dimensional propensity score method was used to estimate prognostic score for CKD based on individual level risk factors. Logistic regression analyses were conducted to examine the association between contextual determinants and incident eGFR<60 ml/min/1.73 m², controlling for individual risk factors.

Results: Within 38 contextual determinants, the top 5 determinants which have strongest univariate association with incident eGFR<60 ml/min/1.73 m² included physical inactivity, injury deaths, some college or above degree, heart care costs and median household income. After controlling for sumarized prognostic score, physical inactivity, injury deaths, heart care cost and median household income associated with eGFR<60 ml/min/1.73 m² independent of individual risk factors (table). Interaction analyses suggested that association between individual risk factors and incident eGFR<60 ml/min/1.73 m² was modified by county level contextual determinants including physical inactivity, health care costs and median household income.

Conclusions: Contextual determinants are associated risk of eGFR<60 ml/min/1.73 m² independent of individual risk factor. In addition, they could modify the relationship between individual risk factors and eGFR<60 ml/min/1.73 m². Contextual determinants may play important role in burden of CKD; their role should be reflected in the national discussion about reducing CKD burden.

Funding: Veterans Affairs Support

SA-PO843

Housing Insecurity and Healthcare Engagement Among People with CKD

Tessa K. Novick,1,2 Dingfen Han,1 Delphine S. Tuot,2 Elizabeth A. Jacobs,3 Alisa Zemere,1 Michele K. Evans,2 Desira C. Crews,4 Johns Hopkins University, Baltimore, MD; 3University of California, San Francisco, San Francisco, CA; 4University of Texas Dell Medical School, Austin, TX; 5Johns Hopkins University School of Medicine, Baltimore, MD; Intramural Research Program, NIA, NIH, Baltimore, MD; 6National Institutes of Health/National Institute on Aging, Baltimore, MD.

Background: Housing insecurity is characterized by high housing costs or unsafe living conditions. Among persons with CKD, we examined whether housing insecurity was associated with postponing medical care.

Methods: We performed a cross-sectional analysis of data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study (Baltimore, MD) during study visit 4. We used multivariable log binomial and Poisson regression with robust estimate of variance clustered on neighborhood to quantify associations between housing insecurity (self-report of inability to afford a suitable home or difficulty paying rent/mortgage payments) and self-report of postponing medical care that was felt to be needed among individuals with CKD (eGFR<60 ml/min/1.73 m² or albumin-to-creatinine ratio ≥30 mg/g).

Results: Among 355 HANDLS participants with CKD, 135 (38%) reported housing insecurity. Individuals with housing insecurity were younger (median [SD] age 57.8 [9.1] years versus 61.1 [8.3] years), more likely to be male (48.9% versus 38.6%), less likely to have a high school degree (60.5% versus 72.2%) and more likely to lack health insurance (6.7% versus 4.1%) than stably housed persons. Overall, 35 (23.9%) participants reported postponing medical care that was felt to be needed. Housing insecurity was associated with increased risk of postponing medical care even after adjusting for demographics, household income status, health insurance status, CKD awareness, food insecurity and education level (Table).

Conclusions: Individuals with CKD experiencing housing insecurity may be more likely to postpone medical care, which could increase their risk of poor clinical outcomes.

Funding: Other NIH Support - National Institute on Aging, National Institute of Health

SA-PO845

Documenting CKD in the Primary Care Electronic Health Record

Clauudine T. Jurkowitz,1 Sarahafey Dolman,2 Richard Caplan,1 Ruben K. Irani,3 Sidney J. Swanson,1 Christiana Care Health System, Newark, DE; 2MedStar Health Research Institute, Washington, DC; 3AstraZeneca, Newark, DE.

Background: The KDOQI guidelines recommend 2 measurements of glomerular filtration rate (GFR) <60 ml/min/1.73 m² or evidence of kidney damage at 3 months intervals or more to establish the diagnosis of chronic kidney disease (CKD). We examined whether the diagnosis of CKD in an outpatient primary care setting was documented in the Electronic Health Record (EHR) according to the CKD-based KDOQI criteria.

Methods: We used the CKD-Epi equation to assess GFR from the serum creatinine records of patients seen in a network of primary care offices from 2011 to 2015. Our study population was defined as patients ≥18 with at least one GFR<60 and at least one followup visit. We excluded patients with an initial GFR<15, those on renal replacement therapy and those with a known CKD diagnosis. Followup began at the time of the first GFR<60. We calculated the time interval between the first GFR<60 and the second GFR and stratified patients into 3 categories according to their first GFR<60, ≥30, >30–45, ≤45. We used the Systematized Nomenclature of Medicine (SNOMED) codes to ascertain documentation of CKD.

Results: Our final study population included 7098 patients. Of those, 37% were male, 84% white, 15% black, 3% and 78% had a first GFR<30, 30–45 and 45–60 respectively. Mean age was 70. Overall 63% had a second GFR<60. A total of 4669 patients did not have a CKD diagnosis during followup. Of those, 65% met the KDOQI criteria and CKD should have been documented in the EHR. Of the 2429 patients assigned a CKD code, 41% met the KDOQI criteria, 12% had a second GFR<60, 27% were given the diagnosis prior to the second GFR measurement, 20% had a second GFR measured within 3 months. Of our study population (n=7098), 43% met the KDOQI criteria but did not receive a documented diagnosis and 20% had a documented diagnosis but did not meet KDOQI criteria.

Conclusions: CKD diagnosis was not appropriately documented in a large number of patients. Algorithms used to identify CKD patients for population health management should not rely only on diagnosis codes but also include measurements of GFR. More resources should be developed to assist primary care physicians to enter the appropriate code in the EHR. The lack of albuminuria information in our dataset limits the interpretation of the apparent over CKD coding of those who did not meet the GFR-based KDOQI guidelines.

Funding: Other NIH Support - NGMS-US4-GM104941

SA-PO846

Kidney Disease Knowledge, Health Literacy, and Self-Care in CKD

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Background: Research is needed to better understand the links between health literacy and kidney disease knowledge in order to guide interventions to improve self-care in chronic kidney disease (CKD).

Methods: Among study participants with CKD stage 1-5, validated surveys assessed level of health literacy ( Rapid Estimate of Adult Literacy in Medicine [REALM]), perceived kidney disease knowledge (Perceived Kidney Knowledge Survey [PKKS]), objective kidney disease knowledge (Kidney Disease Knowledge Survey [KiKS]), and self-care behaviors (modified Summary of Diabetes Self-Care Activities Assessment [SDSCA]). A summary score of self-care was constructed utilizing the DSICA scoring code. Multivariable adjusted linear regression models were performed to examine the association between health literacy and self-care behaviors with health literacy (inadequate vs. adequate, determined by REALM score ≤59 vs. >59, respectively) and PKKS and KiKS scores (per SD). Health literacy was also explored as a potential effect modifier.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Of the 401 participants: mean age was 57 years; 47% female, 38% diabetes; 77% CKD stage 3-5. The prevalence of inadequate health literacy was 18%. The median KiKS score (range 0-1) was 0.7 (interquartile range [IQR] 0.6-0.8), and median PiKS score (range 0-4) was 2.6 (IQR 2.1-3.0). After full adjustment, a PiKS score was positively associated with self-care scores (β = 1.0, 95% confidence interval: 0.3-1.7). Health literacy and KiKS scores were not associated with self-care. There was evidence of effect modification by health literacy; a KiKS score appeared to positively associate with self-care scores only among those with inadequate literacy, but this did not reach statistical significance (Figure).

Conclusions: Objective kidney knowledge is likely necessary, but not sufficient for self-care, and may be particularly helpful to those with inadequate health literacy. Perceived kidney knowledge has a strong positive association with self-care, and may be particularly helpful to those with inadequate health literacy. A strong positive association with self-care scores (β = 1.0, 95% confidence interval: 0.3-1.7). Health literacy and KiKS scores were not associated with self-care. There was evidence of effect modification by health literacy; a KiKS score appeared to positively associate with self-care scores only among those with inadequate literacy, but this did not reach statistical significance (Figure).

SA-PO848

Predicted Risk of Renal Replacement Therapy at Time of Referral for Arteriovenous Fistula Placement in CKD

Ken J. Park,1 Jose G. Benuzillo,2 Erin Keast,4 Micah L. Thorp,1 David Mosen,1
Eric S. Kramer.2 1Kaiser Permanente, Salem, OR; 2Northwest Permanente, Portland, OR; 3Kaiser Permanente Northwest, Portland, OR; 4Kaiser Permanente Center for Health Research, Portland, OR.

Background: The complexity in predicting which and when patients with chronic kidney disease (CKD) will progress to renal replacement therapy (RRT) contributes to 80% of patients starting hemodialysis without a functioning permanent access. This has been associated with higher mortality, morbidity, and cost. A prediction model developed at Kaiser Permanente Northwest may help guide timing of AVF placement.

Methods: 398 CKD stage 4 patients followed by nephrology were classified into AVF referral group (n = 199) and non AVF referral group (n = 199). The non-referral group was randomly selected and matched 1:1 on age, gender, and eGFR. Patients were followed for up to two years and censored if they died or discontinued coverage. Survival analyses were performed for overall hemodialysis initiation.

Results: The average age was 68.5 years in the AVF referral group and 68.1 years in the non AVF referral group. The mean eGFR among the AVF referral group was 16.8 mL/min and 17.2 mL/min in the non AVF referral group. The average 2-year predicted risk of progression to RRT was 47.7% in the AVF referral patients and 44.1% in the matched controls. Hemodialysis initiation occurred at a significantly higher rate in the AVF referral group than in the non AVF referral group (43.7% vs. 23.6%, HR = 1.9, p < 0.001). The AVF referral group was stratified into quartiles based on predicted risk of progression to RRT. The lowest quartile (average risk 17.6%) had a 78% lower risk of hemodialysis initiation than the highest quartile (average risk 84.3%); HR = 0.22, p < 0.001.

Conclusions: In patients with CKD stage 4, a computer-generated risk score identified a subgroup of AVF referred patients with a low predicted risk to RRT that may have been referred too early.
SA-PO850

Developing a Clinical Decision Support Software to Monitor and Tailor Treatment of CKD Patients
Ulla T. Schultheis,1,2 Michael C. Altenbuehinger,2 Kai-Uwe Eckhardt,1,3 Peter J. Oefinger,4 Wolfram Gronwald,1 Anna Kortgen,2 Johannes Rafler,4 Helena U. Zacharias,5 GCKD investigators 1Department of Nephrology and Medical Intensive Care, Charité – Universitätsmedizin Berlin, Berlin, Germany; 2Institute of Functional Genomics, University of Regensburg, Regensburg, Germany; 3Institute of Genetic Epidemiology, Medical Center - University of Freiburg, Freiburg, Germany; 4Institute of Bioinformatics and Systems Biology, Helmholtz Center Munich, Neuherberg, Germany; 5Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany.

Background: CKD is a complex disease with several therapeutic challenges: silent onset; different: etiopathologies, progression patterns, prognosis and comorbidities; polypharmacy. Clinical decision support (CDS) software may improve CKD management.

Methods: Within the German Chronic Kidney Disease (GCKD) study, a multi-center, prospective, observational CKD stage 3 cohort study, demographic, phenotypic, and clinical parameters of 5,217 Caucasian patients have been collected. We will model these data and variable dependencies by state-of-the-art machine learning methods to predict the risk of adverse endpoints, to interpret the results in the context of current biomedical knowledge, and to use the estimated models as a backbone for a CDS software, which will be provided as a user-friendly app to nephrologists (CKDNapp).

Results: CKDNapp, based on mathematical models and enriched by state-of-the-art machine learning methods to predict the risk of adverse endpoints, will be available for presentation at ASN Kidney Week 2019.

Funding: Government Support - Non-U.S.

Figure 1 Schematic workflow of the development and application of CKDNapp.

SA-PO851

The Keeping Kidneys Program: Baseline Results from a New Model of Care for Community Kidney Health
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Background: Intervention in early-stage CKD slows rate of progression. First contact healthcare providers like general practitioners (GPs) are at the forefront of detection and management of the early stages of CKD. Keeping Kidneys (KK) was implemented in 2018 to augment kidney care skills of GPs in a less-privileged socio-economic area of Queensland, Australia, where access to specialized kidney care was not available. Here we describe the characteristics of patients recruited to this program.

Methods: Two GPs were recruited and trained in a specific subset of CKD skills. Training included didactic knowledge acquisition and clinical detailing by a nephrologist. Demographic and clinical data were extracted from electronic medical records; patient-reported outcomes (CKD knowledge and self-management) were completed at KK entry. Data were analysed descriptively (frequency distributions and mean/median as appropriate).

Results: 140 patients were referred to KK in the first 8 months. Median age was 76 years (67-81). Most patients were in CKD stage 3B (54%) or 3A (22%). Hypertension and diabetes were the leading CKD causes but 35% had no aetiological diagnosis at entry. Most patients had low-average scores for CKD knowledge (13±28/116) and CKD self-management (4±6/116). Median Charlson comorbidity score was 7, predicting survival of <10 years. Mean haemoglobin (Hb) was 12.6±2 g/dL and 5% of patients had Hb<10g/dL. Mean parathyroid hormone, calcium (Ca++) and phosphate (PO4) were respectively 94±81 pg/ml, 9.6±0.5 and 3.4±0.5 mg/dL. Prevalence of hypoCa++ and hyperPO4 were respectively 1% and 2%. Mean urinary albumin:creatinine ratio was 38 (12-75) mg/g. One patient was referred for renal biopsy and one for bone marrow biopsy. Patients travelled, on average, 25 minutes less for their appointments, with 72% seen within 15 km of their homes.

Conclusions: KK focuses on the interface between patients, GPs and specialists. Trained GPs were capable of staging severity of kidney disease, initiating the work-up of the cause(s) of the kidney disease and screening for complications. They managed a cohort of patients with CKD that were elderly, had immediately advanced CKD and complex co-morbidities in their communities.

Funding: Other U.S. Government Support

Figure
SA-PO853
Physician Practice Characteristics Associated with Quality of CKD Care
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Background: Improving the quality of CKD care has important implications for delaying disease progression and preventing ESKD. Understanding physician practice characteristics associated with high quality CKD care is critical to provide insight into effective care delivery for CKD.

Methods: We performed a serial cross-sectional study of visits to office-based ambulatory care practices for adults with diagnosed CKD using National Ambulatory Medical Care Survey data. Our predictors were physician practice characteristics, geographic region, metropolitan area, solo practice, type of specialty, practice ownership, employment status, and physician compensation. Outcomes were quality indicators: 1) uncontrolled hypertension and diabetes; 2) ACEI/ARB use; and 3) self-reported age at time of use if age ≥50. Using multivariable logistic regression, we determined the association of physician practice characteristics with quality indicators, adjusting for patient age, sex, race, and comorbidities (hypertension, diabetes, congestive heart failure, and coronary artery disease).

Results: In 2006-2014, there were 9554 unweighted visits for CKD patients representing 232,899,670 weighted visits. Patients seen in medical specialty vs. primary care had nearly 2-fold odds of uncontrolled diabetes (95% CI: 1.11–2.86). Patients in metropolitan vs. non-metropolitan areas had higher odds of ACEI/ARBs (AOR 1.83, p=0.021), but there was no statistically significant association in adjusted analyses. CKD patients aged ≥50 seen in non-solo vs. solo practice had lower odds of statin use (AOR 0.81, 95% CI 0.66–0.99). Those seen in practices owned by insurance companies or health plans had 1.5-fold odds of statin use (95% CI 1.03–2.08), compared with patients with ownership by physicians with ownership by physicians with other ownership. Practice characteristics were otherwise not associated with CKD quality indicators.

Conclusions: In a nationally representative subset of outpatient visits for patients with diagnosed CKD, we found that few physician practice characteristics were associated with CKD quality indicators. Further studies are needed to determine optimal care delivery models based on practice-level characteristics. 

Funding: NIDDK Support

SA-PO854
Utilising Mobile and Web-Based Technology for Capturing Patient-Specific Information: Methods from the DISCOVER CKD Program
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Background: Chronic kidney disease (CKD) is a global health problem associated with cardiovascular complications, impaired health-related quality of life (HRQoL), and high mortality. New technologies allow capturing patient experiences and burdens of disease settings outside of the clinic through mobile or web-based technology are becoming more widely used, but not within CKD real-world data.

Methods: DISCOVER CKD is an enriched hybrid observational study utilising a novel cloud-based IT platform to integrate retrospective and prospective data from patients with estimated glomerular filtration rate (eGFR) <75 ml/min/1.73 m² to end stage kidney disease from the UK, US, Italy, Denmark, Sweden, China and Japan. Prospective data will be captured over a 3-year period from >1,000 CKD patients. Data collected by validated instruments including HRQoL (SF-36), physical activity (RAPA), weight, diet (WPDA), and diaries, and other patient-reported outcomes will be captured in a bespoke mobile/web-based application to be completed by the patient before, during or after their routine clinical visit. The application will be available, validated and user-tested in multiple languages.

Results: Capturing patient-reported information outside of the clinic setting provides an innovative patient-centric approach for understanding the burden and journey of CKD from a patients’ perspective. Initial results are anticipated in 2020.

Conclusions: Utilising mobile/web-based technology to collect patient experiences has the potential to increase the understanding of a disease, with easier communication, minimising burden of data collection in the clinic from a patient, physician and eCRF perspective while improving the consistency and validity of data that patients enter.

Funding: Commercial Support - AstraZeneca

SA-PO855
Where Patients Get Their CKD Information: Perceptions Vary by Individual Demographics
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Background: Patient education is a critical first step in the pathway to improved outcomes. Little data is available about sources of CKD information that patients perceive as most useful, and whether perceptions vary with patient characteristics.

Methods: Adults with CKD Stages 1-5 were enrolled in a cross-sectional survey. Eleven questions assessed patient ratings (1-not at all helpful to 5—extremely helpful) of specific sources of kidney information (e.g. healthcare providers, peer mentors, internet). Patients also answered questions about their perceptions of communication with healthcare providers and how well they thought providers communicate with each other (0—do not communicate at all to 4—outstanding communication). Associations between patient demographics and summarized patient ratings were examined using linear regression.

Results: 245 patients enrolled with a mean age of 60 years, mean eGFR of 34 ml/ min/1.73m², 49% were men, 80% White, 15% African American, 5% other and/or multiple races. Summarized patient ratings for each source of kidney information were: Kidney doctors (mean 4.7, SD 0.9), PCPs (3.4, 1.5), nurses (2.8, 1.9), diabetics (2.6, 2.1), Internet (2.2, 1.9), healthbulletins/news (1.8, 1.6), social workers (1.6, 1.9), family/friends (1.2, 1.7), classes (1.1, 1.7), news (0.9, 1.2), peer mentoring (0.7, 1.3). Most patients reported it was NOT difficult to talk with their doctors about CKD (213, 92%), and rated overall communication fair (mean 2.9, SD 1.1). In analyses adjusted for age, sex, race, education, income, eGFR the following were significantly associated with summarized patient ratings: 1. Women rated kidney doctors higher compared to men (β 0.26, p<0.03), higher eGFR predicted lower ratings for diabetics (-0.02, 0.01), higher income predicted lower ratings for social workers (-0.20, 0.01), Non/hite race predicted higher ratings for family/ friends (0.78, <0.01) for brochures/handouts (0.36, 0.02) and a trend for peer mentors (0.26, 0.07), older age predicted lower ratings (-0.03, <0.01) and more education higher ratings (0.20, 0.03) for Internet.

Conclusions: Patient perceptions of the usefulness of information from different sources vary significantly by patient demographics. More work is needed to explore reasons for, and interventions to improve, disparities in these perceptions.

Funding: NIDDK Support

SA-PO856
No Independent Relationship Between Socioeconomic Status and CKD Progression in South Korea: Results from the KNOW-CKD Cohort Study
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Background: Socioeconomic status (SES) has long been conjectured to be associated with the incidence and progression of chronic kidney disease (CKD). However, prospective studies from Asian data for impact of SES on renal progression were less. We revealed the association between SES and renal progression in CKD patients especially in South Korea where medical insurance is well established.

Methods: Data were collected from the KNOW-CKD Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD, NCT01630486, http://www.clinicaltrials.gov). SES was characterized based on monthly income which was divided into three strata; a>$4,500, $1,500-4,000, <$1,500. Patients who underwent baseline tests but did not have follow-up visits thereafter or who did not respond to questionnaires regarding SES were excluded. The outcome was a composite of estimated glomerular filtration rate (eGFR) halving or the onset of end-stage renal disease (ESRD). ESRD was defined as the initiation of maintenance dialysis or kidney transplantation. Cox or time-dependent cox regression analysis were conducted as appropriate. Age, sex, cause of CKD, baseline eGFR by CKD-EPI (cr) equation, hemoglobin, albumin, uric acid, calcium, phosphorus, mean blood pressure, 24hr sodium intake calculated by 24hr urine sodium was included as covariates in multivariable analysis.

Results: Total 1,732 patients were enrolled in this study. Mean age was 52.9 ± 12.0 years and 51.5% were men. Higher monthly income was associated with higher educational attainment (P for trend <0.001). There is an incremental tendency of CKD progression according to lower monthly income level ($1,500 to $4,500, adjusted hazard ratio [HR] 1.55, 95% confidence interval [CI] 0.86-2.77, P=0.144, <1,500, adjusted HR 1.75, 95%
CI 0.93-3.29, P=0.080; α≤4,500 group as reference), but the statistical significance was not observed, even after subgroup analysis according to age ≥50 years or below.

**Conclusions:** In the Korean CKD population, there is no definite association between SES classified by monthly income level and renal progression. We speculate that this is because health care accessibility is high regardless of the SES in Korea due to Korean National Health Insurance Service. Further studies are needed to confirm this phenomenon.

**Funding:** Government Support - Non-U.S.

**SA-PO857**

**Development and Initial Analysis of a Nationwide Multicenter Electronic Health Record Database of CKD in Japan (J-CKD-DB)**

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**Background:** Chronic kidney disease (CKD) is not only a precursor of end stage renal disease but also a strong risk factor for various adverse outcomes like cardiovascular disease and dementia. To collect clinical data from CKD patients in Japan, the Japanese Society of Nephrology in collaboration with the Japan Association for Medical Informatics has embarked on the Japan Chronic Kidney Disease Database (J-CKD-DB) project.

**Methods:** J-CKD-DB is a large-scale, nation-wide registry based on electronic health record (EHR) data from university hospitals in Japan. Using a standardized exchangeable information storage (the Standardized Structured Medical Information Exchange) J-CKD-DB succeeded to efficiently compile clinical data of CKD patients across hospitals despite their different EHR systems. CKD was defined as dipstick proteinuria ≥1+ and/or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² based on both out- and in-hospital laboratory data.

**Results:** As an initial analysis, we analyzed 40,409 CKD outpatient patients from 7 university hospitals and observed that majority of them were older than 65 years old, with the most prevalent age category 70-79 years in both sexes. Median age was 71 years (IQR 62-79), 54.8% were female. Median eGFR was 50.2 mL/min/1.73 m² (42.6-57.5). The number of patients with a CKD stage G1, G2, G3a, G3b, G4 and G5 were 929 (2.3%), 3,972 (9.8%), 23,333 (57.7%), 8,357 (20.7%), 2,710 (6.7%) and 1,108 (2.7%) respectively. Although proteinuria data were available in 19,725 cases (48.8%) of all patients, the number of patients with a CKD stage A1 [dipstick proteinuria (±)], A2 [dipstick proteinuria (+)] and A3 [dipstick proteinuria (≥1+)] were 10,360 (52.5%), 3,049 (15.5%) and 6,316 (32.0%) respectively. Younger CKD patients in J-CKD-DB tended to be at more advanced stages than older patients.

**Conclusions:** In the present study, we have constructed the J-CKD-DB which is a comprehensive nationwide CKD database. This registry will be a platform for a number of analyses, for example, mortality and morbidity risk, by clinical diagnoses, lab data, or medication data and may be able to fill important knowledge gaps surrounding CKD care.

**Funding:** Government Support - Non-U.S.

**SA-PO858**

**Detecting Lifestyle Risk Factors for CKD with Comorbidities: An Association Rule-Mining Analysis**

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**Background:** The results suggest that the lifestyle modification of CKD varies among different comorbidities. For example, the lifestyle modification of CKD with cardiovascular disease (CVD) focuses on increasing cardiovascular capacity by improving muscle strength or functional ability. For CKD patients with chronic pulmonary disease (CVD) or rheumatoid arthritis (RA), lifestyle modification should be high dietary fiber intake and participation in moderate-intensity exercise. Meanwhile, the management of CKD patients with diabetes should focus on exercise and weight loss recommendations.

**Conclusions:** We have demonstrated the use of ARM to identify lifestyle risk factors for CKD with common comorbid chronic conditions using data from BRFSS 2017.
SA-PO861

Urine Testing of Community Residents in a Region of Nicaragua with a High Burden of Mesoamerican Nephropathy Reveals That Background Systemic Inflammatory Signs Rapidly Increase in Younger Ages

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Background: A large and ongoing epidemic of kidney disease of unknown etiology affects the rural poor from Mexico to Panama and has resulted in greater than 50,000 deaths. Mesoamerican nephropathy (MeN) is a devastating and rapidly progressing disease that affects primarily young agriculture workers who are otherwise healthy and lack traditional risk factors for kidney disease. Very little is known about renal function in the community-at-large, especially among children.

Methods: Urine specimens were collected from individuals of all ages at health fairs in 4 rural, agricultural communities in the Pacific lowland areas of Nicaragua, a region heavily affected by MeN and where morbidity and mortality due to the epidemic has more than quadrupled since its emergence. Semi-quantitative dipstick and microscopic analysis were performed on fresh specimens. We generated descriptive statistics and tested for differences by age and community by Chi-squared and ANOVA in Stata 15.

Results: Urine from 471 community residents, ages 3 months to 89 years (median 21 years) were analyzed. Almost all individuals (99%) were shedding leukocytes, many (21%) with ≥ 5 per field. Renal cell shedding (11%), hemat尿 (13.4%) were also noted. Proteinuria was rare (3.2%). Hematuria and leukocyturia varied bylocale (p<0.05).Leukocyturia was more common in adults than children (p<0.05).Leukocyturia increased with age, which was different by age group 12-23 vs ≥24.

Conclusions: In this community-based sample, clinical urine specimens indicate an underlying prevalence of markers of impaired renal function. These markers increase in adolescence and young adulthood. Further investigations into MeN should target populations other than agricultural workers and should specifically look at renal function in children. Geographic differences in clinical indicators may also point to the highest risk communities.

SA-PO862

CKD Detection Might Benefit from an Ethnic-Specific Screening Approach: Results from the HELIUS Study


Background: Screening for chronic kidney disease (CKD) is currently recommended for patients with a history of diabetes mellitus, hypertension or cardiovascular disease (CVD). This approach may not identify all individuals with CKD. Ethnicity, age and socioeconomic status (SES) have been described to affect CKD risk and these factors may influence CKD detection in the general population. We studied whether the addition of criteria for age and socioeconomic status may improve CKD detection in a multietnic population.

Methods: Baseline data from the HELIUS study, a multietnic cohort study conducted in the city of Amsterdam, were used. Analyses were conducted among 21,617 participants (mean age 44 years, 43% male). The traditional approach (i.e. screening when a history of diabetes mellitus, hypertension or CVD was present); the traditional approach combined with age >50 yr; and the traditional approach with SES criteria improved detection in Turkish and Moroccan participants. Detection success of approach I among the ethnic groups varied from 38.8 to 70.3%. Detection improvement by using approach II and III showed ethnic specific differences.

Conclusions: Addition of age and SES criteria to the currently advised screening criterion improved detection in Turkish and Moroccan participants. Our results may prompt development of a different set of CKD screening criteria in a multietnic population.

SA-PO864

Automated Urinary Albumin Creatinine Testing in Stage 3 CKD and Effect on Prescriptions of ACE Inhibitors and ARBs

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Background: Kidney Disease Improving Global Outcomes recommends assessing for albuminuria annually in patients with chronic kidney disease (CKD). Despite this recommendation, many patients with CKD do not undergo annual testing for albuminuria. We were interested in whether automated testing in CKD for annual urinary albumin creatinine (ACR) testing improved ACR testing and prescribing of ACE inhibitors and ARBs.

Methods: We defined a CKD 3 cohort registry in April 2018 in Kaiser Permanente Northwest. We compared ACR testing and filled ACE inhibitor and ARB prescriptions in the year before and after April 2018 after implementing a quality improvement project targeting patients with stage 3 CKD based on eGFR criteria or ICD-10 codes. A web-based tool examined the registry and ordered an ACR in those patients that did not have an ACR checked within the past year. In those patients not on an ACE inhibitor or ARB who had a renal indication, primary care providers received an alert in the electronic health record (EHR) which recommended initiation. Renal indications for an ACE inhibitor or ARB were hypertension and an ACR > 30 mg/g with diabetes mellitus (DM) or an ACR > 300 mg/g without DM.

Results: There were 11,229 patients in the initial CKD registry with index date of April 2018. Average age was 72.7 years, 37.4% had DM, 79.4% had hypertension, and average eGFR was 46.8 ml/min. One year after implementation of the usual ACR testing, the registry decreased to 10,934. Average age was 73 years, 37.1% had DM, 79.4% had hypertension, and mean eGFR was 47.4 ml/min. One year after implementation of ACR testing, rate of ACR testing increased from 25.1% to 83% (p<0.001). In patients with renal indication, ACE inhibitor or ARB use increased from 77.4% to 80.2% but was not significant (p=0.07). Maximum dose ACE inhibitors or ARB use increased from 26.8% to 32.1% (p=0.02) in patients with A3 grade albuminuria and hypertension.

Conclusions: In patients with stage 3 CKD, a population-based tool that automated testing of ACR linked with EHR alerts resulted in a significant increase in ACR testing but did not result in a significant increase in ACE inhibitor or ARB prescriptions in patients who had a renal indication. However, prescribing of maximum dose ACE inhibitors or ARBs did increase in patients with A3 grade albuminuria and hypertension.

SA-PO865

The Association of Physical Activity with Poor Health Outcomes in Patients with Advanced CKD

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Background: Chronic kidney disease (CKD) disproportionately affects older adults, and is known to be associated with low physical activity levels. In the general population, low physical activity level is associated with an increased risk of all-cause mortality and other adverse outcomes. This association also exists in patients with moderate CKD and those on dialysis; however this has yet to be explored in patients with advanced CKD (G4-G5). The primary aims of this study were to determine the association of physical activity level with all-cause mortality, as well as the association with progression to dialysis and future fall risk in patients with advanced CKD.

Methods: Individuals with advanced CKD (G4-G5) were identified from the CanFIT cohort, a multicenter, prospective study of frailty, between October 2012 and July 2018 (n=592). Self-reported physical activity was assessed at baseline by the Physical Activity Scale for the Elderly (PASE). PASE scores were stratified by tertiles (0-40 (Low Activity); 41-90 (Light Activity); >90 (Moderate-High Activity)). Baseline clinical characteristics and comorbidities were obtained through chart review. Our primary outcome of all-cause mortality and secondary outcome of progression to dialysis were analyzed using Cox proportional hazard models. Logistic regression was performed for our secondary outcomes of future fall risk.

Results: We had 121 participants die during the study (mean follow-up 1193 days) and 215 participants progressed to dialysis (mean follow-up 896 days). Compared with low physical activity level, higher levels of physical activity were associated with a reduction in all-cause mortality (HR 0.56 [95% CI: 0.33-0.94]) when adjusted for age, sex, and SES. Of 447 participants with follow-up, 72% reported a fall event. Level of baseline physical activity did not predict progression to dialysis or future falls.

Conclusions: In advanced CKD, higher levels of physical activity were associated with a 50% reduction in all-cause mortality. Although progression to dialysis and future fall risk were not associated with baseline physical activity level, the impact in the change of physical activity level on these outcomes requires further investigation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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The SGE program included participatory small group discussions on the attendees’ remaining risk factors. The primary outcome of this study was the change in eGFR per year.

Results: The changes in eGFR in examinees who attended the SGE program (n = 209, +2.9 mL/min/1.73 m²/year [95% confidence interval (CI) +1.9–+3.9]) significantly improved compared with control (n = 383, +1.2 mL/min/1.73 m²/year [95% CI +0.5–+1.9], p = 0.006). Attending an SGE program was independently and positively related to the changes in eGFR at 1 year after attendance, after adjusting for classical covariates (β = 1.55 [95% CI 0.37–2.73], p = 0.01). In subgroup analysis, attending an SGE program was effective for the examinees with a lower eGFR compared with those with only proteinuria.

Conclusions: Our SGE program showed the beneficial effects of preventing the development of CKD, independent of classical factors. The type of SGE program that is more effective for preventing development of CKD should be investigated in a long-term analysis.

SA-PO866

CKD Awareness Among US Adults by Future Risk of ESKD, 1999-2016

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CKD Surveillance Team

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Background: Individuals with chronic kidney disease (CKD) are often unaware of their disease. Efforts to improve CKD awareness would have the most benefit if focused on individuals at highest risk of progression to end-stage kidney disease (ESKD). Therefore, we examined CKD awareness by future risk of ESKD in a representative sample of US adults.

Methods: We assessed the prevalence of CKD awareness among non-pregnant adults (≥ 20 years) with CKD stages 3-4 who participated in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2016 (n = 3,668). CKD awareness was defined by a “yes” answer to the question, “Have you ever been told by a doctor or other health professional that you had weak or failing kidneys?” The 5-year probability for ESKD was estimated by the 4-variable Kidney Failure Risk Equation. ESKD risk was categorized as minimal (<2%), low (2% to <5%), intermediate (5% to <15%), or high (≥15%). Unadjusted and adjusted trends in prevalence of CKD awareness by ESKD risk group were computed using logistic regression with complex sample survey methods.

Results: Unadjusted CKD awareness was less than 10% among adults with mild or high and was higher in the intermediate and high ESKD risk groups (approximately 45% and 50%, respectively). CKD awareness within each risk group was stable over time. Similar results were obtained when adjusted for age, sex, race, hypertension status, and diabetes status, and when analysis was limited to the subgroup with hypertension (Figure). Among adults with diabetes, awareness within each risk group was greater but was also stable over time.

Conclusions: Among adults with CKD stages 3-4 with over 15% 5-year risk of ESKD, approximately half were unaware of having kidney disease. CKD awareness was stable over time, demonstrating the need for intensified efforts to increase CKD awareness.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO867

Technology Use, Interest in Mobile Health Technology, and eHealth Literacy in CKD

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Background: Mobile health (mHealth) technologies improve patient-provider communication and increase information accessibility. eHealth literacy is needed to effectively find and appraise health information from electronic sources. Using a mixed methods approach, we assessed technology use, mHealth interest, and eHealth literacy among those with CKD.

Methods: We utilized data from Chronic Renal Insufficiency Cohort Study participants who completed a technology survey (N = 424) and an eHealth Literacy Scale (eHEALS) (N = 633). We report technology use (Internet/email/smartphone), interest in mHealth (Internet/email/smartphones/mHealth applications [apps]), and level of eHealth literacy, determined by the eHEALS score. We examined the association of participant characteristics with technology use, mHealth interest, and eHealth literacy by estimating prevalence ratios (PRs) and 95% confidence intervals (CI). We conducted a thematic content analysis of open-ended survey responses to augment the quantitative findings.

Results: Study participants (N = 932): mean age 68 years, 59% male, mean eGFR 54 mL/min/1.73 m². About 70% currently use Internet/email/smartphones; only 27% had adequate eHealth literacy (eHEALS score ≥ 32). Participants < 65 years (vs. older), White (vs. non-White) race, and with high school education (vs. lower) had more Internet/email use. Those of non-White (vs. White) race had more interest in mHealth apps (see Table for more results). Three themes emerged from the content analysis: opposing views on using mHealth, concerns about losing the patient-provider face-to-face interaction, and barriers to mHealth use.

Conclusions: Many people with CKD currently use and are interested in mHealth, but few have adequate eHealth literacy. Leveraging mHealth represents a potential opportunity to engage individuals with CKD, especially minorities since they had more interest in mHealth apps, compared to non-minorities.

Funding: NIDDK Support

Patient Characteristics and Technology Use, Interest, and eHealth Literacy. Prevalence ratios (PR) and 95% CI reported.

<table>
<thead>
<tr>
<th>Internet/Email</th>
<th>Smartphone</th>
<th>Interest in</th>
<th>mHealth literacy</th>
</tr>
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<tbody>
<tr>
<td>Current Use</td>
<td>Current Use</td>
<td>Internet/Email</td>
<td>Smartphone Use</td>
</tr>
<tr>
<td>Age &lt; 65 vs ≥ 65</td>
<td>0.68 (0.60–0.77)</td>
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<tr>
<td>White vs Non-White</td>
<td>1.23 (1.13–1.34)</td>
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SA-PO868

The Role of Renal Pharmacists in the Management of Patients with Renal Conditions

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Background: The review of the renal pharmacist role in assisting in the management of CKD is not clear. Our review is the first evaluation in the United States that tests the renal pharmacist as part of the interdisciplinary team in the management of patients with renal conditions.

Methods: This retrospective study assessed the clinical outcomes after the intervention of our renal pharmacist in the Nephrology clinic at the Miami VA Medical Center. The patients were initially evaluated in the outpatient clinic by the nephrologist and the renal pharmacist; medications were changed to decrease the progression of CKD, for management of hypertension (HTN), immunosuppression and CKD complications. The renal pharmacist followed the patients according to the changes in medical care.

Results: Fifty-six patients were assigned to the renal pharmacist in a 3-month period. Fifty patients (89%) were male; six patients (11%) were female. In 20 patients (35.7%) that had CKD III, HTN, and proteinuria, ACEIs or ARBs were started with close monitoring of the renal function, electrolytes, and proteinuria. In 10 patients (17.9%) that had uncontrolled HTN and CKD, BP medications were added and adjusted. In 9 patients (16.1%) that had a kidney transplant, tacrolimus dosages needed modification to achieve levels. In 11 patients (20%) that had CKD IV and V with a creatinine, erythropoietin stimulating agent dose was adjusted to reach appropriate hemoglobin (HB) levels. In 2 patients (3.6%) that had hypomagnesemia, magnesium supplements and amiloride were added to their medication regimen with close follow up of electrolytes and renal function. The interventions that were made in the 56 patients were successful (Proteinuria decreased, BP was controlled, tacrolimus levels achieved goal, HB levels reached goal), and patient adherence increased

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Conclusions: The intervention from renal pharmacists has improved the quality of care. We note not just the monitoring of potential adverse effects from therapies, but also by improving BP goals, electrolyte management, and medication adherence. These changes may reduce the progression of CKD, improve cardiovascular outcomes, lower hospital admissions, and decrease the risk of death.

SA-PO869
Screening and Recognition of CKD in Primary Care Clinics in the VA Health Care System and Its Impact on Delivery of Care
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Background: The successful implementation of interventions targeted to improve kidney disease outcomes requires early identification of CKD. Early identification involves screening at-risk population as well as recognizing CKD. We determined CKD screening and recognition rate in at-risk veterans enrolled in Vertically Integrated Service Network (VISN) 17, and evaluated the impact of CKD awareness on processes of care.

Methods: We interrogated VISN 17 corporate Data Warehouse for Veterans seen at least twice in primary clinics with ICD-9 codes for hypertension (HTN) and diabetes (DM). The final cohort of 220,229 subjects (55.6% HTN, 6% diabetes and 38.4% both) was examined for serum creatinine/eGFR reported at least twice 90 days apart, urine protein and ICD-9 for CKD. Presence of CKD was defined as eGFR <60 mL/min at least twice 90 days apart and/or urine albumin creatinine ratio (uACR) >30 mg/g. BP readings from last two visits were averaged to evaluate HTN control. Prescription rate for statins and non-steroidal anti-inflammatory agents (NSAIDs) were assessed.

Results: Overall, 173,966 (79%) patients had one or other screening procedure done. Patients with isolated hypertension were less likely to have any screening procedure (72.8%) as compared to DM (81.1%) or both conditions (87.6%). Only 40.3% of total patients had urine protein in the chart, worse in HTN (18.3%) compared to DM (62.6%) or both (68.5%). Of 173,966 patients, 73,965 (42.5%) had lab evidence of CKD. However, only 19,317 (26.1%) did have a documented ICD-9 CKD diagnosis. Many of these unrecognized CKD patients (30.5%) had CKD based on uACR criteria. There was no clinically significant difference between recognized vs. unrecognized CKD groups in terms of age, sex and race. Moreover, blood pressure control and statin prescription rates were also not different. Of note, patients with BP >140/90 mmHg consistently had high rates of uACR >300 mg/g irrespective of CKD documentation. Diuretics prescription was higher (66.7% vs 58%) and NSAIDs was lower (11.4% vs 22.9%) in documented vs undocumented CKD groups.

Conclusions: While overall CKD screening rate was 79%, identification of albuminuria was suboptimal and despite screening procedures the recognition of CKD was low in VISN 17 population with HTN and DM. Early awareness of CKD may improve processes of care.

Funding: Veterans Affairs Support

SA-PO870
Renal, Cardiac, and Safety-Related Events with Alpha Blockers in Patients with CKD
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Background: Alpha-blockers (ABs) are commonly prescribed as add-on therapy for blood pressure (BP) control in patients with and without chronic kidney disease (CKD). However, the association between AB use and renal, cardiac, mortality, and safety-related outcomes by CKD stage remains unknown.

Methods: Population-based, retrospective cohort study of Ontario (Canada) residents ≥66 years old with a diagnosis of hypertension from 2007 to 2015. Patients newly prescribed an AB (doxazosin, terazosin, prazosin) were matched to patients newly prescribed a non-AB BP-lowering medication using a high dimensional propensity score. Outcomes by CKD stage were also not different. Of note, patients with BP >140/90 mmHg consistently had high rates of uACR >300 mg/g irrespective of CKD documentation. Diuretics prescription was higher (66.7% vs 58%) and NSAIDs was lower (11.4% vs 22.9%) in documented vs undocumented CKD groups.

Conclusions: While overall CKD screening rate was 79%, identification of albuminuria was suboptimal and despite screening procedures the recognition of CKD was low in VISN 17 population with HTN and DM. Early awareness of CKD may improve processes of care.

Funding: Veterans Affairs Support

SA-PO871
Nephrotoxin Exposure After Hospital Discharge Predicts Development of CKD Among AKI Survivors
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Background: Survivors of acute kidney injury (AKI) are at high risk of progression to chronic kidney disease (CKD). A potentially modifiable risk factor for subsequent CKD is exposure to drugs with potential nephrotoxicity. The objective of this study was to evaluate the association between the prescription of potentially nephrotoxic medications in AKI survivors at hospital discharge and the subsequent risk of new or worsening CKD, readmission with AKI or death.

Methods: We conducted a population-based cohort study of adult Olmsted County, MN residents who developed AKI while hospitalized between 1/1/2006 and 12/31/2014 using data from the Rochester Epidemiology Project (REP). The REP links medical records across care providers in Olmsted County, making population-based studies possible. The cohort included those with a hospitalization complicated by AKI who survived to discharge. Discharge medication lists, prescription records, and clinical notes were queried for prescription of potentially nephrotoxic medications over the 3 years after discharge. New or worsening CKD was identified by both diagnosis codes and calculated estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m2. Cox proportional hazards models were fit to evaluate the association between exposure to potentially nephrotoxic medications and the study outcomes. A validated CKD risk prediction score was used to adjust the Cox models for the baseline risk of CKD following AKI.

Results: Among 2,894 AKI survivors, 2,143 (74%) received a potentially nephrotoxic medication at discharge. Those that received these drugs experienced a significantly higher risk of new or worsening CKD during 3-years of follow-up (cumulative incidence 71% vs. 57%; HR: 1.44; 95% CI 1.28, 1.63). Patients prescribed potentially nephrotoxic medications after discharge also experienced a significantly greater risk of the composite endpoint of AKI, AKI readmission, or death within 3 years of discharge (HR: 1.32; 95% CI 1.20, 1.46).

Conclusions: In this population-based cohort study, we observed that AKI survivors prescribed potentially nephrotoxic medications at hospital discharge were at significantly greater risk for CKD development, AKI readmission, and death in the 3 years following hospitalization.

Funding: Private Foundation Support

SA-PO872
Baclofen and the Risk of Encephalopathy in Older Adults with CKD: A Population-Based Cohort Study
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Background: Importance: Baclofen, a popular muscle relaxant, undergoes renal clearance and can accumulate in patients with low kidney function. Over 30 case reports involving baclofen use lead to the development of risk factors for encephalopathy. The objective of this study was to examine the association between the prescription of potentially nephrotoxic medications and the study outcomes. A validated CKD risk prediction score was used to adjust the Cox models for the baseline risk of CKD following AKI.

Results: Among 2,894 AKI survivors, 2,143 (74%) received a potentially nephrotoxic medication at discharge. Those that received these drugs experienced a significantly higher risk of new or worsening CKD during 3-years of follow-up (cumulative incidence 71% vs. 57%; HR: 1.44; 95% CI 1.28, 1.63). Patients prescribed potentially nephrotoxic medications after discharge also experienced a significantly greater risk of the composite endpoint of AKI, AKI readmission, or death within 3 years of discharge (HR: 1.32; 95% CI 1.20, 1.46).

Conclusions: In this population-based cohort study, we observed that AKI survivors prescribed potentially nephrotoxic medications at hospital discharge were at significantly greater risk for CKD development, AKI readmission, and death in the 3 years following hospitalization.

Funding: Private Foundation Support
Inpatient Admissions Account for the High Medical Costs of CKD

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Background: Chronic kidney disease (CKD) results in high medical costs typically attributed to renal dialysis but excess costs begin to accumulate in earlier CKD stages. Better understanding of medical costs and its determinants may help to optimize patient care in resource-constrained settings. We evaluated annual medical costs in patients with CKD across types of care and in subgroups of patients with and without diabetes, cardiovascular disease, and heart failure.

Methods: We used the electronic medical records of Kaiser Permanente Northwest to identify 21,252 patients with CKD in 2016 or 2017 and examined non-mutually exclusive groups according to presence of comorbidities. We used an annual follow-up data to calculate the annual outpatient, inpatient, emergency, pharmaceutical, dialysis, and total medical costs by KDIGO-defined stages of CKD adjusted for age, sex, non-white race, and within subgroups of patients with selected comorbidities.

Results: Inpatient costs accounted for 42%, 50%, and 29% of total costs for stages G3a, G3b, and G4, respectively (figure). Nearly 30% of all hospitalizations were CVD-related. Patients with CKD 1 or more comorbidities incurred 2.4 to 4-fold greater medical costs than those with no comorbidities. Inpatient costs accounted for 35%-66% of the total in stages G3a, G3b, and G4, and 23%-37% in stage G5.

Conclusions: Inpatient costs consistently accounted for over 40% of the total costs of care for CKD patients prior to reaching end-stage kidney disease regardless of the presence of comorbidities. Considering the significant economic burden evident in early CKD stages, development and implementation of effective measures to reduce the need for inpatient care is critical.

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SA-PO873

Immunosuppressive Agents for Treating IgA Nephropathy: An Updated Cochrane Review

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Background: IgA nephropathy (IgAN) is the most common glomerular disease worldwide. High certainty evidence for effective interventions has been impeded because of the rarity of patient-centred endpoints such as end-stage kidney disease (ESKD) and heterogeneity in clinical progression and disease severity. As several recent trials have reported, we updated the Cochrane review evaluating the benefits and harms of immunosuppression for the treatment of IgAN.

Methods: A Cochrane systematic review with meta-analysis was updated to include randomized controlled trials in which adult and children with biopsy-proven IgA nephropathy were randomly allocated to immunosuppressive agent versus placebo, no treatment/standard care, or other non-immunosuppressive agent. Treatment effects were estimated by random-effects meta-analysis. Evidence certainty was adjudicated using GRADE methodology.

Results: 54 studies (3730 patients) were included. Median follow-up was 24 months. Risk of bias was generally high or unclear. Steroid treatment probably prevents progression to ESKD (RR 0.41, 95% CI 0.26-0.65; moderate certainty evidence) and annual GFR loss (MD -5.40 ml/min/1.73m2, 95% CI -2.25 to -8.55; moderate certainty evidence), and may reduce risk of ESKD (RR 0.41, 95% CI 0.26-0.65; moderate certainty evidence) and annual GFR loss (MD -5.40 ml/min/1.73m2, 95% CI -2.25 to -8.55; moderate certainty evidence), and may induce complete remission (RR 1.76, 95% CI 1.03-3.01; low certainty evidence). The addition of cytotoxic therapy to steroids had uncertain effects as did regimens containing mycophenolate mofetil (MMF), or calcineurin inhibitors as monotherapy on background steroid treatment. Adverse effects of treatment, especially infections, were uncertain due to a lack of data and heterogeneous results in studies.

Conclusions: Steroid therapy probably prevents progression of ESKD and annual GFR loss and may induce complete remission. The effects of other treatments for treating IgA nephropathy were very uncertain and adverse events are poorly understood.

SA-PO875

Predictors of Hyperkalemia in Patients with Advanced CKD

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Background: Identifying predictors of hyperkalemia will help clinicians in managing patients with advanced CKD at a greater risk for future hyperkalemia events.

Methods: In 20,657 US Veterans with eGFR <30 ml/min/1.73m2 and with ≥1 year of follow-up prior to dialysis initiation, we identified predictors of plasma potassium ([K+] >6.0 mEq/l using multivariable logistic regression models with backward-selection based on Akaike’s information criterion, adjusted for demographics, comorbidities, vital signs, laboratory tests and medications. The sample was split (70%30%) into training set (n=14,463) and test set (n=6,194). We conducted model cross validation using the leave one out cross validation method (LOOCV). We assessed model predictive discrimination using the area under the receiver-operator curve (AUC).

Results: The mean (SD) age of the patients was 67 (10) years; 98% were male, 29% were African American, with a mean (SD) baseline K+ of 4.6 (0.6) mEq/l, and baseline eGFR of 23.6 (4.7) ml/min/1.73m2. At least one event of [K+] >6.0 mEq/l was experienced by 7.4% of the patients. Our final model included 16 predictor variables. The AUC (95% CI) estimates for training, test, and LOOCV were 0.765 (0.751-0.780), 0.761 (0.738-0.784), and 0.762 (0.749-0.774), respectively (Figure). Baseline K+ (OR [95%CI], 3.09 [2.83-3.39]), baseline Na polystyrene sulphonate use (2.51 [2.16-2.93]), and age (0.97 [0.96-0.98]) were the strongest predictors of hyperkalemia.

Conclusions: We developed and tested a prediction model with good discrimination ability to identify future hyperkalemia in patients with advanced CKD. Accurate prediction of future hyperkalemia could help implement preventive measures and may have a beneficial impact on outcomes.

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SA-PO876
Plasma Potassium Trajectories and Associated Post-Transition Mortality in Patients with Advanced CKD Transitioning to ESRD
Ankur A. Dashputre,1 Keiichi Sumida,1 Praveen Kumar Potukuchi,1 Suryatapa Kar,2 Yoshitsugu Obi,2 Fridthjof Thomas,1 Miklos Z. Molnar,1 Elani Streja,1 Kamyr Kalantar-Zadeh,1 Csaba P. Kovessy,1 University of Tennessee Health Science Center, Memphis, TN; 2University of California Irvine, Irvine, CA; Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 4University of California Irvine, School of Medicine, Orange, CA.

Background: Potassium (K⁺) homeostasis is impacted by reduced kidney function, but the pre-ESRD trajectory of plasma K⁺ concentration and the associated post-ESRD mortality is unknown.

Methods: In 34,167 US Veterans who transitioned to dialysis between 2007-2014 and had ≥1 K⁺ measurement in each year over the last three years prior to dialysis initiation, we examined K⁺ trajectory (slope) for both the entire three-year and for each of the three one-year pre-ESRD periods, using linear mixed effects models adjusted for fixed (age, sex, race, diabetes and congestive heart failure) and time-varying (RAAS inhibitor, sodium-polyaspartate salt, loop diuretics and mineralocorticoid receptor antagonist use, and eGFR) covariates with patient as the random effect. Quadratic spline and Cox regression models were used to assess the multivariable adjusted association between K⁺ slope and all-cause mortality within 6 months of dialysis initiation.

Results: The mean (SD) age of the cohort was 67 (11) years; 98% were male, 29% were African American, and 77% were diabetic. The unadjusted mean (95% CI) K⁺ slope was 0.008 (0.006, 0.011) mEq/l/year, which reversed after multivariable adjustment, especially for eGFR levels (adjusted mean [95% CI] K⁺ slope, -0.10 [-0.13, -0.07] mEq/l/year). Most of the change over time in plasma K⁺ was observed in the last year prior to dialysis. A reverse J-shaped association was observed between K⁺ slope and mortality (Figure).

Conclusions: The average intraindividual plasma K⁺ trajectory is remarkably stable in patients nearing ESRD, likely as a result of physiologic mechanisms and therapeutic interventions which counteract the progressively limited ability of the failing kidneys to excrete K⁺. A declining slope, but not an increasing slope, is associated with higher mortality risk.

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SA-PO877
Higher Discharge Serum Creatinine Is Associated with CKD Among Survivors of AKI
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Background: Despite many studies showing patients have higher risk of developing chronic kidney disease (CKD) after a hospitalization with acute kidney injury (AKI), data on the prognostic value of discharge serum creatinine (SCr) are limited. The aim of this study is to explore the association between discharge SCr and CKD risk among survivors of AKI.

Methods: From January 2011 through December 2011, patients hospitalized with AKI in the First Affiliated Hospital, College of Medicine, Zhejiang University without known CKD were screened. The primary endpoint was CKD progression within 5 years. The association between discharge SCr and CKD was assessed by multivariate logistic regression. The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) statistics were applied in statistical analysis.

Results: 673 patients was enrolled and 526 (78.1%) progressed to CKD in 5 years’ follow-up. After adjusting for age, gender, stage of AKI, diabetes, hypertension, coronary heart disease, proteinuria and baseline SCr, the odds ratio (OR) rose with the increase of discharge SCr. Multivariable model showed prognostic significance, with the area under the receiver operating characteristic curve (AUC) of 0.77. The addition of discharge SCr to established risk factors improved risk prediction of CKD (AUC of 0.841; NRI of 18.18%; 1.61, all P < 0.01).

Conclusions: Higher levels of discharge SCr were associated with increased risk of CKD among survivors of AKI, indicating that discharge SCr could be a predictor independent of established conventional risk factors.

Table 1. Discharge SCr concentrations prediction of CKD with AUC.

<table>
<thead>
<tr>
<th>End point</th>
<th>Discharge SCr</th>
<th>Risk factors</th>
<th>Risk factors with discharge SCr</th>
<th>Incremental area (ID)</th>
<th>NRI (%)</th>
<th>IDI (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>0.769</td>
<td>0.041</td>
<td>0.007</td>
<td>18.18%</td>
<td>0.13</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Established risk factors including age, gender, stage of AKI, diabetes, coronary artery disease, hypertension, proteinuria and baseline SCrs.

SA-PO878
Pre-Operative Biomarkers and Risk for CKD After Cardiac Surgery
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Background: The associations between various biomarkers and long-term kidney outcomes after cardiac surgery are unknown.

Methods: In patients undergoing cardiac surgery who were enrolled in the TRIBE-AKI study, we assessed the associations of 32 plasma and 8 urine biomarkers measured pre-operatively with the composite kidney endpoint of incident CKD or progression of existing CKD. The cohort was separated into exploration (Canada, n=613) and replication (USA, n=310) cohorts due to differences in outcome ascertainment and lack of data integration of the two cohorts. In the exploration cohort, top biomarkers were identified from the 40 candidate biomarkers. Results were confirmed in the replication cohort, thereby reducing reclassification and model selection biases. Estimates were pooled for biomarkers that were statistically significant in both the derivation and replication cohorts. Cox proportional hazard regression models adjusted for age, sex, AKI stage, pre-op albumin, pre-op SCr, discharge SCr estimated the relationship of the biomarkers with the CKD outcome.

Results: After a median (IQR) follow-up of 5.6 (4.3-5.8) years, a total of 172 (28%) patients experienced the CKD endpoint. 7 plasma and 0 urine biomarkers were independently associated with the CKD endpoint in the exploration cohort, of which 4 biomarkers retained statistical significance in the replication cohort and upon pooling. The pooled HRs (95% CI) per natural log increase were as follows: TNFR1 2.3 (1.6, 3.2), TNFR2 1.7 (1.2, 2.3), KIM1 1.8 (1.3, 2.4), NT-proBNP 1.2 (1.1, 1.3) (Table).

Conclusions: Pre-operative plasma TNFR1, TNFR2, KIM-1 and NT-proBNP were associated with incidence and progression of CKD several years after cardiac surgery. As in other clinical settings, these biomarkers may provide prognostic value for long-term kidney outcomes after cardiac surgery.

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SA-PO879

Plasma Potassium Variability and Associated Post-Transition Mortality in Patients with Advanced CKD Transitioning to ESRD

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Background: Both higher and lower plasma potassium (K+) levels are associated with increased mortality, but it is unclear if a propensity for higher plasma K+ variability (i.e. more frequent or extreme deviations in plasma K+) prior to dialysis initiation is associated with post-ESRD adverse outcomes independent of baseline K+ levels.

Methods: In 34,167 US Veterans who transitioned to dialysis between 2007-2014 and had ≥1 plasma K+ measurement in each year over the last three years prior to dialysis initiation, we examined the association of plasma K+ variability (PPVs) defined as the standard deviation of intra-individual K+ values over the three-year study period and expressed as quartiles) with all-cause mortality within 6-months after dialysis initiation, using Cox proportional hazard models with adjustment for baseline K+, demographics, comorbidities, cumulative length of hospital stay, medications, and average eGFR and number of K+ measurements (median [IQR]: 19 [8-35]) over the three-year study period.

Results: The mean (SD) age of the cohort was 67 (11) years; 98% were male, 29% were African American, and 77% were diabetic. After adjusting for potential confounders, higher PPV quartiles were consistently associated with increased risk of all-cause mortality within 6 months of dialysis initiation (adjusted HRs [95% CI] for quartiles 2-4 [vs. quartile 1]: 1.09 [1.01-1.18], 1.12 [1.03-1.22], and 1.19 [1.09-1.30] in model 5; Figure). Conclusions: Greater pre-ESRD PPV is associated with higher all-cause mortality within 6 months of dialysis initiation. Clinical trials are needed to determine if measures used to stabilize plasma K+ can improve patient outcomes.

Funding: NIDDK Support

SA-PO881

The Impact of Prevalent Stroke at Critical Junctures in the Care for Patients with Kidney Disease

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Background: Chronic kidney disease is an independent risk factor for stroke in the general population. The impact of a prior stroke on important outcomes for CKD patients is less well characterised. We examined associations between prior stroke and clinical outcomes in a large UK CKD cohort at study recruitment and at time of dialysis commencement.

Methods: 3060 participants of the Salford Kidney Study (a large UK CKD longitudinal epidemiological cohort study recruiting since October 2002) were included in the analysis. Multivariable cox regression survival analyses, adjusted for competing risks, was performed to examine the effects of prevalent stroke on endpoints of death, end stage renal disease (ESRD) and non-fatal cardiovascular events (NFCVE). Similar methodology was used to examine the impact of prior stroke on survival in patients who commenced dialysis.

Results: Of 3060 study recruits 227 had suffered a stroke prior to recruitment (table 1). Stroke was independently associated with mortality (HR 1.20 95%CI 1.0-1.43, p=0.05), reaching ESRD (HR 1.34 95%CI 1.06-1.69, p=0.02) and future NFCVE (HR 1.54 95%CI 1.12-2.11, p=0.01) after adjustment for age, gender, eGFR, diabetes, hypertension, myocardial infarction, heart failure, atrial fibrillation, smoking history and peripheral vascular disease. 579 patients reached ESRD and commenced dialysis. Stroke prior to dialysis commencement (N=48) was significantly associated with mortality (HR 1.47 95%CI 1.01-2.14 P=0.05) after adjustment for the same factors (except eGFR) over median 25 months follow up.

Conclusions: Stroke prior to study recruitment was independently associated with mortality, ESRD and future NFCVE. Similarly, stroke was independently associated with mortality in patients who commenced dialysis. This large observational study indicates that stroke alters cardiovascular risk in CKD patients and emphasises the importance of kidney brain crosstalk.

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Underline represents presenting author.
Pattern of Care for Lipid Management in CKD Stage 3-5 Patients: Results from CKDopps

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Background: Current KDIGO guidelines recommend conducting a lipid profile upon diagnosis for chronic kidney disease (CKD) and treating patients ≥50 years with a statin ½ ezetimibe. However, these guidelines do not provide target lipid levels for treatment. Thus, we aimed to evaluate current nephrologist care practice patterns for lipid management, including perceptions of target levels of LDL-cholesterol (LDL-C), statin/ezetimibe prescription, and achieved LDL-C using the CKD Outcomes and Practice Patterns Study (CKDopps).

Methods: We analyzed patient-level treatment and LDL-C levels and nephrologist-specified target LDL-C upper limits from CKDopps clinics in Brazil, Germany, and the United States (2013-2018). Patients were ≥18 years old with eGFR <60 ml/min at enrollment. P-values were obtained from a logistic model of the prevalence of treatment with statins ½ ezetimibe by age (< or ≥50), country, and CKD stage; and a linear model of mean LDL-C by treatment, country, and CKD stage. Both models used generalized estimating equations to account for patient clustering by clinic.

Results: Statin/ezetimibe treatment was more prevalent among CKD patients ≥50 years-old (p<0.0001) and differed significantly by country (p=0.0001; Figure 1a). LDL-C was lower among treated patients (p=0.0001) and differed significantly by country (p<0.0001; Figure 1b). Neither patient-level outcome varied significantly by CKD stage (p>0.2). Between 7–23% of untreated patients in each country had LDL-C ≥160 mg/dL. Only 7–17% of nephrologists believed that LDL-C should be <70 mg/dL.

Conclusions: There is no uniform pattern regarding lipid-lowering therapies across countries, but not across CKD stages. Treated patients appear to benefit with regard to LDL-C lowering, yet a significant proportion of hyperlipidemia patients are not receiving treatment.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

SA-PO883
SA-PO884
Treatment Preferences of Patients with CKD in Acute Coronary Syndrome: A Discrete Choice Experiment
Todd Wilson,1, Glen Hazlewood,1 Stephen B. Wilton,1 Tolulope Sajobi,1 Pantera Amin Javaheri,1 Juli Finlay,1 Winnifred (winnie) E. Pearson,2 Carol Connolly,3 Matthew T. James,1 Alberta Provincial Program for Outcome Assessment in Coronary Heart Disease (APPROACH) and Can-SOLVE CKD Network project team 1University of Calgary, Calgary, AB, Canada; 2Alberta Health Services, CALGARY, AB, Canada; 3Can-SOLVE CKD Network, Calgary, AB, Canada.

Background: Chronic kidney disease (CKD) is associated with a high incidence of acute coronary syndrome (ACS) and related morbidity and mortality. Treatment choices for patients with CKD involve tradeoffs in potential benefits and harms of invasive management options.

Methods: To design, pilot and field a discrete choice experiment (DCE) to quantify preferences of patients with CKD towards invasive heart procedures. Attributes of invasive versus conservative treatment for ACS were identified through semi-structured qualitative interviews. Levels for each attribute were determined from CKD subgroup analyses of early invasive versus conservative management clinical trials and cohort studies. The DCE was co-developed with physicians and patient input. Eligible patients for the study included those with CKD over 18 years of age, recruited from two multidisciplinary CKD clinics in Calgary, Alberta. Patients were recruited for the pilot study from September to November 2018 and the full study commenced in January 2019. Average importances for treatment attributes were quantified using Hierarchical Bayes estimation, and scaled on a 0-100 scale to reflect their relative importance.

Results: Among 64 patients who provided consent to participate in this full study, 59 (92%) completed the survey. Participants had an average age of 67 years, with 41% female, and mean eGFR 50 ml/min/1.73m². The most important attributes were risk of death within one-year (32.0, 95% CI [28.6, 35.4]) and end stage renal disease (20.5, 95% CI [17.3, 23.7]). The attributes AKI requiring dialysis, risk of another heart attack within one year and invasive procedures (versus conservative management) were less important (17.2, 95% CI [14.8, 19.7]; 15.8, 95% CI [14.2, 17.5]; and 14.5 95% CI [11.0, 18.0], respectively).

Conclusions: These results demonstrate the feasibility of conducting a DCE to quantify preferences of patients with CKD. Preliminary findings suggest patients with CKD are most risk averse towards death, however, end-stage kidney disease is a strong consideration. Measurement of these patient preferences can be used to inform the strength of clinical guideline recommendations and to improve shared-decision making approaches for cardiovascular disease for patients with CKD.

Funding: Private Foundation Support

SA-PO885
Statin Prescription in CKD Patients Aged ≥50 Years Without Prevalent Coronary Heart Disease
Jung-Im Shin,1 Yao (Lucy) Qiao,1 Lesley Inker,1 Jose’F Coresh,1 Alex R. Chang,2 Morgan Grams,3 1Johns Hopkins University, Baltimore, MD; 2Geisinger Medical Center, Danville, PA; 3Tufts Medical Center, Boston, MA.

Background: According to the 2013 Kidney Disease Improving Global Outcomes (KDIGO) guideline, statins are recommended in adults aged ≥50 years with chronic kidney disease (CKD) stages 3-5, not on dialysis. Our objective was to examine whether there was a change in prescription prevalence after publication of the KDIGO guideline in November 2013 in two real-world populations.

Methods: We created one-year period prevalence cohorts for each year in the Geisinger Health System (2004-2016) and Johns Hopkins Medicine (2013-2016), including patients with CKD stages 3-4 (to be conservative so as not to inadvertently include end-stage kidney disease), age ≥50 years, and without prevalent coronary heart disease (another indication for statin use that could confound interpretation).

Results: At Geisinger (N=54,788, mean age 72 years, 65% female, 99% white, mean eGFR 50 ml/min/1.73m²), statin prescription increased from 28% to 41% from 2004 to 2007 (p<0.001), but then remained relatively stable (Figure). There was no significant change in statin prescription after the KDIGO guideline was published; prevalence of statin prescription in 2016 was 47%. At Hopkins (N=19,682, mean age 70 years, 61% female, and mean eGFR 50 ml/min/1.73 m²), statin prescription did not change after the KDIGO guideline; prevalence of prescription in 2016 was 52%.

Conclusions: Despite the 2013 KDIGO’s recommendation that all adults with CKD aged ≥50 years should be prescribed statins, nearly half of the patients were not prescribed for statin of diabetes in 2016 in two real-world settings. We need to understand better why adherence to KDIGO guideline on statin use is low in this high-risk population.

Funding: NIDDK Support

SA-PO886
Hospitalization with Major Infection and Incidence of ESRD: The Atherosclerosis Risk in Communities (ARIC) Study
Junichi Ishizami,1 Logan T. Cowan,2 Ryan Demmer,1 Morgan Grams,3 Pamela L. Lutsey,1 Jose’F Coresh,1 Kunihiro Matsushita,1 Johns Hopkins School of Public Health, Baltimore, MD; 2Georgia Southern University, Statesboro, GA; 3Johns Hopkins University, Baltimore, MD; 4Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; 5University of Minnesota, Minneapolis, MN; 6Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

Background: Animal studies have suggested deleterious impacts of infection on the kidney. Whether incidence of infection increases long-term risk of incident ESRD has not been systematically evaluated in the general population.

Methods: In 10,293 participants of the ARIC Study who attended visit 4 (1996-1998), we evaluated the association of incident hospitalization with major infection (pneumonia, urinary tract infection, bloodstream infection, and cellulitis/osteomyelitis) with subsequent risk of ESRD. Hospitalization with major infection was entered into multivariable Cox models as a time-varying exposure to estimate the HRs.

Results: The mean age was 63 years, 56% were female, 22% were white, and 7% had eGFR < 60 ml/min/1.73m². During a median follow-up of 17.4 years, there were 2,910 incident hospitalizations with major infection and 279 cases of ESRD (209 cases of CKD: Pharmacoepidemiology

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Kidney C.A.R.E Program, Veteran Affairs Medical Center, University of
Male, 23% Black, mean age was 72 (standard deviation/SD 9). Mean eGFR was 39 (SD 6.18) compared to those without (HR, 2.06 [1.57-2.72]).

Conclusions: Hospitalization with major infection was independently and robustly associated with CKD outcomes as assessed by ESRD, and the risk of adverse outcomes of infection have beneficial impacts on kidney outcomes may deserve future investigations.

Funding: NIDDK, Support, Other U.S. Government Support

The hazard ratios for incident ESRD

Model 1 adjusted additionally for incident CVD.

SA-PO887
Proton Pump Inhibitor Use in Ambulatory Care Setting in Patients with
To assess PPI use in the absence of a clear indication. There were several subsequent deprescriptions.

Of those on PPI, 68% did not have an indication to be on it. Average duration of PPI prescription was 434 (SD 145) days in the indicated group compared to 482 (SD 266) days in the deprescribed group. Knowing the adverse outcomes associated with PPI use, 68% CKD patients were on PPI despite lack of a clear indication. There were several subsequently missed opportunities to de-prescribe these non-indicated medications. A concerted multidisciplinary program to de-prescribe PPI in high-risk CKD patients can improve patient safety and outcomes.

SA-PO888
Association Between Proton-Pump Inhibitors and CKD in Japanese Patients

Characteristics and Symptom Severity of Patients Reporting CKD in the PatientsLikeMe Online Health Community

SA-PO889
Identification of Symptom Clusters and Their Association with Clinical Characteristics and Quality of Life Outcomes in CKD: A Multicenter Study

Background: Renal patients suffer from an overwhelming symptom burden including fatigue, dysnea, sleep problems and depression. Research into symptom clusters (co-occurrence of symptoms) is emerging although primarily limited to end stage renal disease. Whilst individual symptoms are established contributors to poor quality of life (QoL), no research has investigated the role of symptom clusters on these outcomes.

Funding: Commercial Support - AstraZeneca

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

SA-PO890
Identification of Symptom Clusters and Their Association with Clinical Characteristics and Quality of Life Outcomes in CKD: A Multicenter Study


Background: Renal patients in the PLM community are broadly consistent with the usual US CKD population, although the percentage of females is slightly higher. PLM provides a unique source of real-world information on the patient experience beyond the clinical environment that can be utilized to improve understanding of the patient-level impact of CKD.

Funding: Commercial Support - AstraZeneca

Poster/Saturday

1848 patients met the inclusion criteria. The median age at registration was 56 years (IQR 45-64), most patients were female (60%), and US residents (87%). The 1234 patients who recorded race were predominantly Caucasian (80%) and African-American (9%). Median age at diagnosis was 47 years (IQR 33-56, N=578) and the median age of first symptom onset was 43 years (IQR 28-54, N=378). Most patients (74%, N=1574) reported at least one comorbidity (median 3 (IQR 0-4), the most common being type 2 diabetes (57%), hypertension (48%), hypercholesterolemia (32%) and diabetic neuropathy (27%). Less than half of patients (41%) entered any symptom within 30 days of registration. General symptoms were reported by 487 patients and rated as moderate or severe by 72% for fatigue, 58% for pain, 48% for insomnia, 41% for anxious mood, and 41% for depression. Most of the 13 symptom clusters reported by more than 15% of patients and rated moderate or severe by >30% were problems concentrating, nerve pain, and feet tingling (N=315-338). Treatments were reported by 1369 (74%) patients, the most common for diabetes (51%) and hypertension (27%).

Conclusions: Characteristics of CKD patients in the PLM community are broadly consistent with the general US CKD population, although the percentage of females is slightly higher. PLM provides a unique source of real-world information on the patient experience beyond the clinical environment that can be utilized to improve understanding of the patient-level impact of CKD.

Funding: Commercial Support - AstraZeneca

Poster/Saturday

Self-reported symptoms of 876 CKD pre-dialysis patients (44% females, 86% CKD patients were on PPI despite lack of a clear indication. There were several subsequently missed opportunities to de-prescribe these non-indicated medications. A concerted multidisciplinary program to de-prescribe PPI in high-risk CKD patients can improve patient safety and outcomes.

Conclusions: Knowing the adverse outcomes associated with PPI use, 68% CKD patients were on PPI despite lack of a clear indication. There were several subsequently missed opportunities to de-prescribe these non-indicated medications. A concerted multidisciplinary program to de-prescribe PPI in high-risk CKD patients can improve patient safety and outcomes.

SA-PO889
Characteristics and Symptom Severity of Patients Reporting CKD in the PatientsLikeMe Online Health Community

Elisabeth Nyman, Glen James, Jonatan Hedberg, Cathy E. Emmas. AstraZeneca, Cambridge, United Kingdom.

Background: Online health communities and research networks such as PatientsLikeMe (PLM) may provide important insight into understanding the real-world experiences of patients with chronic diseases, including chronic kidney disease (CKD).

Methods: Retrospective cross-sectional observational study using the PLM online health network database. Inclusion criteria were registration with PLM between 2011-2018, aged ≥18 years at registration, with self-reported CKD within 30 days of registration and not receiving dialysis. Information reported by patients within 30 days of registration was used to build a symptom network. The network was calculated using the Lancichinetti-Falkerson method, an algorithm used to calculate the network of the 13 symptom clusters.

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QoL (using the EQ5D index; $\beta$ $\sim$ $-0.465$, $P < 0.001$) and physical function ($\beta$ $\sim$ $-0.407$, $P < 0.001$). Cluster 3 was least predictive of poor QoL ($\beta$ $\sim$ $-0.108$, $P = 0.044$) and cluster 4 least predictive of physical function ($\beta$ $\sim$ $-0.079$, $P = 0.015$), although both significant. Worsening of eGFR was associated with cluster 2 symptoms only ($\beta$ $\sim$ $-0.142$, $P < 0.001$). Higher inflammation (CRP) was associated with cluster 1 symptoms ($\beta$ $\sim$ $-0.181$, $P = 0.340$).

Conclusions: We identified 4 unique symptom clusters in patients with non-dialysis dependent CKD. QoL was primarily affected by physiological symptoms relating to muscle and joint pain, dynapenia and dyspnea. Routine clinical assessment and management strategies targeted at cluster level could have synergistic effects in reducing the burden of CKD symptoms.

Funding: Private Foundation Support

SA-PO891
Disability and Its Association with Chronic Diseases, Especially Early CKD
Dong-Young Lee, Hyojeong Kim. VHS Medical Center, Seoul, Republic of Korea.

Background: In older people muscle weakness, defects in the organs of the body are common, and in severe cases help is needed for daily life. In addition, vision, hearing are reduced, walking disorders occur, and in this condition, they are called disabled. People with disabilities need continued support from family and community people, and people with disabilities have a higher mortality rate. Disabilities are known to occur and worsen when accompanied by chronic diseases such as stroke, ischemic heart disease, arthritis, diabetes and hypertension. Plantinga et al reported that disability is also associated with chronic kidney disease (CKD) and it can be induced from early CKD. We evaluated the association between disability and various chronic diseases, especially CKD, in older Koreans.

Methods: The subjects of this study were 3rd KNHANES participants who were over 65 years old. 3rd KNHANES did not conduct a microalbuminuria test, so the definition of CKD was defined as estimated glomerular function rate $\leq$ 60 ml/min/1.73 m² regardless of urine test, and the CKD stage followed the KDIGO. Disabilities included abnormal activity of daily living (ADL.), instrumental ADL and vision, hearing, walking impairment.

Results: The prevalence of abnormal ADL in CKD stage 3a, stroke, arthritis, DM and hypertension were 52.2%, 42.6%, 20.1%, 25.3% and 18.7%, respectively (Table 1). The prevalence of CKD stage 3a for vision, hearing and walking impairment was significantly higher and as high as that of other chronic diseases. In multivariate logistic regression analysis, abnormal ADL was significantly associated with CKD 3a ($\beta$ effects, 1.78 [95% confidence interval, 1.03-3.09]).

Conclusions: CKD was associated with the disorder from the early state, and was as frequent as the previously known chronic diseases.

<table>
<thead>
<tr>
<th>Prevalence of disabilities between CKD and other comorbidities</th>
<th>Abnormal ADL (%)</th>
<th>Abnormal IADL (%)</th>
<th>Visual impairment (%)</th>
<th>Hearing impairment (%)</th>
<th>Walking impairment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>25.3</td>
<td>41.2</td>
<td>60.4</td>
<td>32.4</td>
<td>51.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16.7</td>
<td>39.2</td>
<td>52.6</td>
<td>23.1</td>
<td>43.9</td>
</tr>
<tr>
<td>Arthritis</td>
<td>28.5</td>
<td>31.7</td>
<td>54.2</td>
<td>39.3</td>
<td>52.4</td>
</tr>
<tr>
<td>Cancer</td>
<td>8.4</td>
<td>37.8</td>
<td>48.7</td>
<td>11.1</td>
<td>60.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>42.5</td>
<td>62.3</td>
<td>57.4</td>
<td>17.7</td>
<td>78.1</td>
</tr>
<tr>
<td>DKA</td>
<td>17.0</td>
<td>44.6</td>
<td>54.3</td>
<td>23.9</td>
<td>70.0</td>
</tr>
<tr>
<td>CKD 3a</td>
<td>57.0</td>
<td>47.0</td>
<td>61.0</td>
<td>34.7</td>
<td>57.0</td>
</tr>
</tbody>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO894
Cannabis Use and Its Association with Incidence of Ischemic Stroke in Advanced CKD Patients Transitioning to ESRD
Praveen Kumar Potukuchi,1 Keiichi Sumida,1 Miklos Z. Molnar,1 Abduzhappar Gaipov,2 Frank Park,3 Cameron M. Kaplan,4 Hamid Moradi,5 Fridjof Thomas,1 Justin Gatwood,1 Yoshitsuji Obi,6 Elani Streja,7 Kamyr Kalantar-Zadeh,1 Csaba P. Kovessy,1 2University of Tennessee Health Science Center, Memphis, TN; 3National Scientific Medical Center, Astana, Kazakhstan; 4University of California Irvine, Irvine, CA; 5Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 6University of California Irvine, School of Medicine, Orange, CA; 7University of Tennessee Health Science Center College of Pharmacy, Memphis, TN.

Background: The risk of stroke is especially high in patients with CKD/ESRD. The effects of cannabis use on incidence of stroke in patients with advanced CKD are unclear.

Methods: We examined 3,615 US veterans who transitioned to dialysis during 2007-2014 and had undergone urine toxicology tests up to one year prior to dialysis. We compared patients whose toxicology tests were positive for cannabis alone (N=202) with those whose tests were negative for all drugs (N=3,413). We examined the association of cannabis use with incident ischemic strokes (defined using ICD-9-CM codes) using Cox proportional hazards model adjusted for sociodemographics, comorbidities, medications, vital signs and time dependent dialysis initiation. We applied conditional repeated measures in Cox regression (modeling the full time-course of the recurrent events) to handle the occurrence of multiple strokes in the same patient.

Results: The mean (SD) age of the cohort was 61.4 (10.3) years; 97% were male, 41% were African American, and 73% had diabetes. Ischemic stroke occurred in 18% of the cohort (N=661) with a median (IQR) follow up time of 2 (1-4) years (one stroke event N=311 and a 2 stroke events N=350). Cannabis use was associated with lower risk of stroke in unadjusted analysis [Figure]. However, the protective effect of cannabis use was attenuated in multivariable adjusted models [hazard ratio (95%CI): 0.88 (0.68-1.13)].

Conclusions: Cannabis use in advanced CKD patients is not significantly associated with the incidence of ischemic strokes.

Funding: NIDDK Support

SA-PO896
Extended and High-Dose Nonsteroidal Anti-Inflammatory Drug Use Is A Risk Factor for CKD Incidence
Kabir Jalal,1 Rocco C. Venuto,2 Andre F. Charest,3 1University at Buffalo, Amherst, NY; 2Erie County Medical Center, Buffalo, NY; 3UBMD Internal Medicine, Getzville, NY.

Background: The use of non-steroidal anti-inflammatory drugs (NSAIDS) and their risk for CKD progression is well known. However, risks for onset of CKD have not been definitively established. This study examined the extended use of NSAIDS and the extended use of high-dose NSAIDS among patients from a third-party insurer for risk of CKD development.

Methods: Serial observations from 2007 through 2017 were examined. Patients with valid serum creatinine measurements and complete supporting data, including other lab values (albumin, bilirubin, calcium, sodium, potassium, hemoglobin, glucose, chloride, and carbon dioxide), medication use (NSAIDS, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, proton pump inhibitors, hydralazine, and antihistamines), and comorbid conditions (diabetes, hypertension, cardiovascular diseases, congestive heart failure, proteinuria) were included for analysis. In addition to chi-squared tests of association between NSAIDS use and CKD development, Kaplan-Meier survival analysis of time to CKD onset was stratified by NSAIDS use and log-rank tests were performed on the log-rank difference of unadjusted and 1:1 matched sample patients with 1) NSAIDS use in over 50% (NSAIDS-50) of their prescription history matched to similar controls; and 2) evidence of high-dose oral NSAIDS usage (NSAIDS-H) matched to similar NSAIDS-50 controls.

Results: 80,619 patients qualified for the full data analysis, with 4,185 patients developing CKD, and 4,086 NSAIDS-50 patients (chi-sq p-value = 0.0001). In the NSAIDS-50 matched analysis, 514 of 8,172 patients developed CKD, 282 of which were NSAIDS-50 patients (chi-sq p-value = 0.0255). 755 patients were identified as NSAIDS-H patients with 54 developing CKD, while 34 of 755 controls developed CKD (chi-sq p-value = 0.0167). The full sample showed differences in log-rank test survival curves between NSAIDS and non-NSAIDS groups (p < 0.0001), as in the matched NSAIDS-50/ non-NSAIDS-50 sample (p = 0.0033) and the matched NSAIDS-H/non-NSAIDS-H sample (p = 0.0167).

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Underline represents presenting author.
Conclusions: While establishing firm dosing and exposure guidelines requires further research, this study suggests that extended and/or increased usage of NS-AID reduces the increased risk of CKD onset. Additional multivariate analysis to confirm the reliability and extent of these findings is underway and will be presented.

Funding: Other U.S. Government Support

SA-PO987

Emergency Department Utilization by Patients with Advanced CKD and Dialysis

Ruchi Chhibbar,1 Silvia J. Leon mantilla,1,2 Thomas W. Ferguson,1,2 Navdeep Tangri,1,2 Paul Komenda,1,2 Claudio Rigatto,1,2,4 Seven oaks General Hospital, Chronic Disease Innovation Center, Winnipeg, MB, Canada; 1Chronic Disease Innovation Centre, Winnipeg, MB, Canada; 2Department of Community Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada; 3Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, MB, Canada; 4University of California Irvine, Huntington Beach, CA.

Background: Chronic Kidney Disease (CKD) is a potent risk factor for kidney failure, cardiovascular events and all cause hospitalizations. In addition to higher outpatient resource use, patients with CKD may present more frequently to the emergency department (ED) and may be more likely to be admitted for hospitalization. In Manitoba, we previously demonstrated an 8-fold increase in the frequency of ED presentations by patients on dialysis as compared to a non-dialysis population. Comparable data on ED visits remain sparse for patients with CKD G3-G5, not on dialysis. Here, we aim to describe the frequency of ED visits and highlight differences in reasons for visit in patients with CKD stages G3-G5 and Those on dialysis when compared to a non-CKD population.

Methods: We performed a retrospective cohort study using administrative health data from the Winnipeg Regional Health Authority, Canada. We included all adults (≥ 18 years) with CKD stages G3-G5 and patients undergoing dialysis between January 1st, 2010 and December 31, 2014. Secular trends in the in the rates of ED visits were calculated for those with CKD, those on dialysis and in the non-CKD population.

Results: Over the study period, patients undergoing dialysis had the highest incidence of ED visits, followed by patients with CKD and those with normal kidney function (15.0 vs 106 vs 34 per 100 persons per year respectively). These rates were stable over the period studied. Among the non-CKD population, the most common reasons for an ED visit were musculoskeletal complaints (25.6%), followed by gastrointestinal (11.0%) and cardiovascular complaints (10.2%). In the CKD and dialysis cohort, ED visits were more commonly secondary to cardiovascular complaints (21.54% and 18.99% respectively), followed by respiratory and gastrointestinal complaints. Admission to hospital was higher in CKD and dialysis populations than in the non-CKD population (29.36%, 26.07% vs 10.61%, respectively).

Conclusions: Patients with CKD present frequently to the ED, and are often admitted after presentation. Cardiovascular and respiratory complaints are more common in the CKD population.

SA-PO989

Associations of Opiate Use and Mortality Risk by Estimated Glomerular Filtration Rate in the NHANES Cohort

Emily N. Batcheller,1 Taryn B. Benson-Hernandez,2 Rachel H. Pitt,1 Connie Khee,3 Elani Streja,1 1Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; 2Harold Simmons Center, Bishop, CA; 3BUHS, Big Pine, CA; 4University of California Irvine, Huntington Beach, CA.

Background: A previous study from the National Health and Nutrition Examination Survey (NHANES) cohort revealed that adults with chronic kidney disease (CKD) had a higher likelihood of having an active prescription for opioid medication. Although it is known that opioids are associated with a higher mortality risk, it is unknown if that risk differs according to estimated glomerular filtration rate (eGFR) or CKD stage. We sought to examine the association of opioid use with mortality risk across eGFR in the NHANES cohort.

Methods: We examined associations of opioid use with mortality risk in 42,041 NHANES adult participants between 1999-2014 using Cox proportional hazards models with adjustment for demographics, body mass index, albumin and indicators of comorbid conditions such as cancer, diabetes, and hypertension. eGFR was estimated from serum creatinine using the CKD-EPI equation. Data on mortality up to year 2015 were downloaded from the corresponding CDC website. Effect modification by continuous eGFR using restricted cubic splines were modeled.

Results: The mean±SD age of the cohort was 47±19 years and was comprised of 52% females and 21% non-Hispanic black patients. Patients reporting opioid use were slightly older and were more likely to have a lower eGFR or eGFR<60 mL/min/1.73m². Overall opioid use was associated with a 27% higher risk of mortality in fully adjusted models (HR: 1.27, 95%CI: 1.13, 1.42). Hazard Ratios for eGFR ≥60, 60–<90, and <90 were [HR:1.47, 95%CI: 1.20, 1.81; HR:1.32, 95%CI: 1.11, 1.58; HR: 1.06, 95%CI:0.87, 1.29], respectively in fully adjusted models (p-for interaction eGFR-category and opioid use: p=0.067). In both unadjusted and adjusted models, restricted cubic splines show that the risk estimates of opioid use with mortality risk decline with lower [GFR figure].

Conclusions: In the NHANES cohort, mortality risk with opioid use appears to decline with lower eGFR or worsening CKD. Further studies should investigate these relationships. OPIED-CRD compares with the ability to address potential confounding by indication, and impact of opioid dose, and opioid type.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: Analysis included 4,281,223 commercially insured members from Optum Clínicaformatics aged 20-64 years from 2006 to 2016. ICD-CM diagnosis codes were used to identify DM and CKD. Antidiabetic drug use by year was measured as the proportion of patients prescribed the specified medications. OLS model is used to compare changes in antidiabetic therapy between DM patients with and without CKD.

Results: Among patients with different severities of CKD, 25% to 23% in those without CKD (p<0.01). Insulin use slightly decreased after 2014, from 44% to 40% among those with and without CKD suggesting that other strategies may be needed to accelerate translation of evidence to practice.

Results: We assembled a 100% Medicare FFS sample (n=20,880,490) with 12-month Part A, B, and D coverage between 1/1/2016-12/31/2016 to examine patient factors associated with 2 opioid utilization outcomes. We used a two-part model to estimate the probability of opioid utilization in 2016 via logistic regression and the level of average daily dose (ADD) for morphine milligram equivalents (MME) via a generalized linear model with a gamma distribution and identity link in those with >1 opioid prescription. Beneficiary characteristics (age, disability, ESRD, dual eligibility, race and ethnicity, rurality, 16 chronic conditions) were adjusted.

Results: Beneficiaries who are vulnerable due to ESRD filled opioid prescriptions at higher rates than other beneficiaries and at ADDs ≥120 MME. Beneficiaries who were age-eligible without ESRD, beneficiaries were more likely to fill opioids if they were disabled with ESRD (odds ratio (OR)=2.57, 95% confidence interval (CI): 2.53, 2.61) or without ESRD (OR=1.43, 95% CI: 1.42, 1.44) than beneficiaries who were disabled with ESRD (OR=1.99, 95% CI: 1.96, 2.02), or eligible for ESRD alone (OR=2.31, 95% CI: 2.25, 2.37). Beneficiaries who were disabled without ESRD (OR=2.99, 95% CI: 2.95, 3.03) or with ESRD (OR=1.34, 95% CI: 1.29, 1.40) had higher odds of having ADDs ≥120 MME, while beneficiaries who were age-eligible with ESRD (OR=0.97, 95% CI: 0.96, 0.76) had lower odds compared to those age-eligible without ESRD.

Results: The protective effect of TRT on CKD progression in hypogonadal men. Testosterone deficiency is common in CKD but the benefits of TRT are disputed. Here we examined if TRT slows CKD progression, cardiovascular disease and all cause mortality in patients with established CKD.

Results: Data from a large cohort of veterans diagnosed with low total testosterone (n=57,985) were used to determine the effect of TRT on the CKD progression, cardiovascular disease and mortality in patients with CKD. Data were extracted using the Veterans Administration Informatics and Computing Infrastructure (VINCI), and analyzed using SAS. Propensity score matching was used to adjust for age, vascular disease and follow up time. Results were compared by means tests, frequency tables, odds ratio and p values (p<0.01).

Results: Of the 3,627 patients with CKD, 2,496 received TRT, and of the 54,358 controls without CKD, 41,965 received TRT. Mean baseline serum creatinine was 1.97 mg/dl in CKD and 0.98 mg/dl in controls. TRT reduced new cardiovascular accident (CVA) in CKD (OR 0.86, 95% CI 0.76-0.98), and in controls (OR 0.86, 95% CI 0.79-0.94), and reduced all-cause mortality in CKD (OR 0.749, 95% CI 0.66-0.85) and controls (OR 0.71, 95% CI 0.68-0.74). New myocardial infarction (MI) in CKD were higher with TRT (OR 1.37) and lower in controls (OR 0.79). Prior cardiovascular disease was more common with CKD (% difference CKD-Control), coronary artery disease (130), congestive heart failure (284), CVA (111), hypertension (92), MI (162), peripheral artery disease (265). Average follow up was 6.1 years.

Conclusions: The protective effect of TRT on CKD progression in hypogonadmic men appears to taper off in patients with established CKD. TRT is associated with a higher burden of cardiovascular disease. TRT reduces all-cause mortality in established CKD (and controls) but the beneficial effect on cardiovascular events is blunted in CKD, underscoring importance of early TRT.

Funding: Other NIH Support - NIA

SA-PO902

Opioid Utilization for Pain Management Among Medicare Fee-for-Service Beneficiaries with ESRD in 2016

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Background: Opioid misuse has raised concerns about opioid utilization under the Part D drug prescription benefit for Medicare beneficiaries. It is important to understand whether Medicare Fee-for-Service (FFS) beneficiaries with end-stage renal disease (ESRD) are more likely to utilize opioids compared to other beneficiaries.

Methods: We assembled a 100% Medicare FFS sample (n=20,880,490) with 12-month Part A, B, and D coverage between 1/1/2016-12/31/2016 to examine patient factors associated with 2 opioid utilization outcomes. We used a two-part model to estimate the probability of opioid utilization in 2016 via logistic regression and the level of average daily dose (ADD) for morphine milligram equivalents (MME) via a generalized linear model with a gamma distribution and identity link in those with >1 opioid prescription. Beneficiary characteristics (age, disability, ESRD, dual eligibility, race and ethnicity, rurality, 16 chronic conditions) were adjusted.

Results: 35% of FFS beneficiaries had 1 or more opioid prescription fills in 2016 and 1.5% had ADDs ≥120 MME. Compared to age-eligible beneficiaries without ESRD, ESRD beneficiaries were more likely to fill opioids if they were disabled with ESRD (odds ratio (OR)=2.57, 95% confidence interval (CI): 2.53, 2.61) or without ESRD (OR=1.43, 95% CI: 1.42, 1.44) than beneficiaries who were disabled with ESRD (OR=1.99, 95% CI: 1.96, 2.02), or eligible for ESRD alone (OR=2.31, 95% CI: 2.25, 2.37). Beneficiaries who were disabled without ESRD (OR=2.99, 95% CI: 2.95, 3.03) or with ESRD (OR=1.34, 95% CI: 1.29, 1.40) had higher odds of having ADDs ≥120 MME, while beneficiaries who were age-eligible with ESRD (OR=0.97, 95% CI: 0.96, 0.76) had lower odds compared to those age-eligible without ESRD.

Conclusions: Beneficiaries who are vulnerable due to ESRD filled opioid prescriptions at higher rates than other beneficiaries and at ADDs ≥120 MME. Based on recently endorsed opioid-related quality metrics and findings of rapid dispensing, these beneficiaries should be prioritized for opioid optimization strategies to balance pain management and adverse event risk.

Funding: Veterans Affairs Support, Other U.S. Government Support

SA-PO903

Acceptance Measured as Psychological Flexibility Protecting Against Depression Among Different Severities of CKD

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Background: Depression is associated with poor survival among chronic kidney disease (CKD) patients. Psychological Flexibility (PF) is conceptualized as “the ability to contact the present moment more fully (i.e., accept any physical or emotional experiences without controlling them) and to change, or persist in, behaviors to pursue identified values.” Although PF is often measured as acceptance in clinical settings and its reduction during dialysis therapy is associated with reduced depression in the general population, this concept has not been examined in CKD patients.

Methods: This multicenter cohort study included five hospitals in Japan and patients with non-dialysis stage 3-5 CKD or stage 5D CKD receiving hemodialysis or peritoneal dialysis. The main exposure was PF measured by a 7-item Acceptance and Action Questionnaire (AAQ-II). The inverse mean of its summation score was used (ranging from 1 [low PF] to 7 [high PF]). The outcome was depression defined as a Center for Epidemiologic Studies Depression (CES-D) questionnaire score of 16 points or higher.

Results: PF measured by the AAQ-II was associated with lower prevalence of depression among all CKD patients, and between PF and incidence of depression after one year among CKD patients without baseline depression were analyzed by logistic regression models, with adjustment for age, sex, performance status, primary renal disease, treatment modality, presence of family, work status, and comorbidity.

Results: The cross-sectional and longitudinal analyses included 433 and 195 patients, respectively. The means (standard deviations) of age, PF, and CES-D were 67.2 (13.8) years, 5.64 (1.14) points, and 13.4 (8.6) points, respectively. Higher PF was associated with lower likelihood of depression (per 1 point increase, adjusted odds ratio [AOR] 0.44, 95% confidence interval [95%CI] 0.35-0.55) and lower likelihood of developing depression (per 1 point increase, AOR 0.50, 95%CI 0.33-0.75) after one year.

Conclusions: PF measured by the AAQ-II was associated with lower prevalence and incidence of depression. Nonpharmacological interventions to improve PF, such as acceptance and commitment therapy, could be useful for preventing depression in patients with different severities of CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
SA-PO904
Cognitive Impairment, Vascular Dysfunction, and Sedentary Behavior Differ Between Older Adults with and Without CKD
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Background: Chronic kidney disease (CKD) is common in older adults and is associated with multiple health risks, including cognitive impairment and cardiovascular disease. But it is unknown how such health risks differ depending on the kidney disease status.
Methods: In a cross-sectional study, 48 older adults (24 with CKD, age 68.4 (5.6), eGFR 43.9 (11.0) mL/min/1.73 m2; 24 without CKD, age 68.5 (5.5), eGFR 82.7 (12.3) mL/min/1.73 m2) were evaluated for performance on a test of global cognition and executive function (Montreal Cognitive Assessment (MoCA)), vascular function via carotid-femoral pulse wave velocity (cfPWV)) and ultrasound (cardioselective Doppler, flow-mediated vasodilation), and sedentary behavior via actigraphy. Data was analyzed utilizing t-tests and OLS regression.
Results: Older adults with CKD had higher levels of cognitive impairment and vascular dysfunction and higher sedentary time. In regressions including CKD and the covariates of age, history of smoking, and gender, the variance was significantly explained for total MoCA score, MoCA executive function score, cfPWV, indicators of carotid compliance, and sedentary time per day.
Conclusions: Cognitive impairment, vascular function, and sedentary behavior in older adults with CKD are different compared to those without CKD. This represents a possible unique phenotypic presentation in this at-risk population.

Funding: Private Foundation Support

SA-PO905
Central Systolic and Pulse Pressures as Predictors of Cardiovascular Events: A Prospective Study
Florencia Larmarche,1 Louis-Charles Desbiens,2 Fabrice Mac-Way,3 Melsene Agharazi,2 Francois Madore,1 Remi Goupil.1 1Hopital du Sacre-Coeur de Montreal, Montreal, QC, Canada; 2University Laval, Quebec, QC, Canada; 3CHU de Quebec, Hotel-Dieu de Quebec Hospital, Quebec, QC, Canada; 4CHUQ-HDQ, Quebec City, QC, Canada.
Background: Central blood pressure (BP) is proposed as a better predictor of cardiovascular (CV) burden than peripheral BP. Nevertheless, its clinical value remains to be determined. This study aims to characterize the role of central BP in CV risk stratification.
Methods: We included 15,923 CARTaGENE participants with available central BP (SphygmoCor PX; type I device) and prospective data from an administrative healthcare registry. The associations between central and brachial systolic and pulse pressures (PP) and MACE rate, use of beta-blockers, renin-angiotensin system blockers, calcium channel blockers, sex, BMI, smoking, diabetes, known CV disease, HbA1c, LDL-c, eGFR, uric acid, heart failure with hospitalization and CV death. The associations between of brachial and central BP parameters with MACE were assessed using Cox regressions adjusting for: age, years of education, history of smoking, and gender. The variance was significantly explained for total MoCA score, MoCA executive function score, cfPWV, indicators of carotid compliance, and sedentary time per day.

Conclusions: Cognitive impairment, vascular function, and sedentary behavior in older adults with CKD are different compared to those without CKD. This represents a possible unique phenotypic presentation in this at-risk population.

Funding: Private Foundation Support

SA-PO906
Iohexol Renal Measurement In Uro-Oncological Patients: Ready to Quit Pandora’s Box?
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Background: An accurate assessment of renal function in urological and oncological practice should be mandatory to define the most appropriate urological surgery technique (nephron sparing vs radical nephrectomy) and to decide the correct dose for each type of chemo-immunotherapy. Unfortunately, the most used method to measure GFR in clinical practice is represented by the estimated glomerular filtration rate (eGFR) which harbours error in comparison to gold standards methods (mGFR). The objective of this study is to determine the extent of the error of eGFR in the oncological and urological pts category.
Methods: A prospective consecutive cohort of 91 pts affected by uro-oncological neoplasms was collected comparing eGFR with mGFR using iohexol renal measurement. Four estimated GFR formulas were used for this study: CKD-EPI, MDRD, MCF, FAS. The agreement them was evaluated taking in account Bias, expressed as median of percent difference between mGFR and eGFR and overall accuracy as P30 representing the percent of estimates within 30% of measured GFR.
Results: The agreement between formulas and mGFR was poor. The Bias for MDRD was -1%, for CKD-EPI was 0%, for FAS was 1% and for MCF was -19% indicating that, except for the latter, those formulas don’t harbour systematic errors. Different information was provided by the accuracy parameter: the P30 was 81% for CKD-EPI, 76% for MDRD, 82% for FAS and 58% for MCF.

Conclusions: In our cohort study we observed that formulas equally over or underestimate mGFR resulting in unbiased methods; however the magnitude of the over/underestimations is not negligible, at least a 20 mL/min/1.73 m², and could lead to errors in clinical management.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO907

Association Between Kidney Function and the Risk of Cancer: Results from the China Health and Retirement Longitudinal Study (CHARLS)

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Background: In chronic disease clinics, reducing the number of patients who are lost to recommended follow-up (LTFU) may improve outcomes. We designed a method to identify LTFU patients and trigger a procedure to schedule appointments. Using this system at our nephrology clinic, we reduced the number of LTFU patients from 24% to 3.8% in one year. MDs activated an electronic medical record (EMR) trigger indicating follow-up (FU) time frame for 77% of visits. We sought to explore reasons for incomplete EMR triggers used and persistent LTFU patients.

Methods: We generated a monthly LTFU report that identifies patients who did not return to clinic in the recommended FU time frame. Clinical staff called these patients and classified them into three groups: "scheduled" (appointment made successfully); "no need to return" (patients transitioned to dialysis, transferred to another nephrologist, declined appointment, or died); or "active" (i.e. actively trying to reconnect). We aimed to increase MD use of the EMR trigger by faculty meeting reminders and administrative assistant prompts. Lastly, we identified explanation categories for patients persisted on the "active" list.

Results: We had 5730 patient visits from 1/31/2018 to 3/31/2019. MDs successfully used the EMR trigger on 3598 (62.8%) of the visits. The most common barriers for using the EMR trigger were: rotating trainees not familiar with this system; MDs running behind on charting; and MDs short on time during clinic. We identified 460 (12.8% of total visits) LTFUs. Among these 252 (54.8%) were "scheduled," 114 (24.8%) were designated "no need to return," and 94 (20.4%) are "actively trying to reconnect." Among the 94 patients, reasons we were unable to reach included homelessness; inaccurate contact information; and having multiple stressors at home causing postponement of routine care.

Conclusions: Retention in care is associated with improved outcomes. Our team has identified a method by which patients LTFU were identified and reconnected. A future goal may be to make MD trigger activation mandatory via EMR validation point. For the difficult to reconnect patients who may be the most vulnerable, a team approach with case management may improve chances of reconnection. Limitations of our study are that we lack outcome data on patients who were LTFU and the development and implementation of the system is time-intensive.

SA-PO909

Continuous System Improvements to Reinstate Kidney Patients Lost to Follow-Up

Lowell J. Lo. UCSF Nephrology and Hypertension Faculty Practice Team Internal Medicine, University of California San Francisco, San Francisco, CA.

Background: In chronic disease clinics, reducing the number of patients who are lost to recommended follow-up (LTFU) may improve outcomes. We designed a method to identify LTFU patients and trigger a procedure to schedule appointments. Using this system at our nephrology clinic, we reduced the number of LTFU patients from 24% to 3.8% in one year. MDs activated an electronic medical record (EMR) trigger indicating follow-up (FU) time frame for 77% of visits. We sought to explore reasons for incomplete EMR triggers used and persistent LTFU patients.

Methods: We generated a monthly LTFU report that identifies patients who did not return to clinic in the recommended FU time frame. Clinical staff called these patients and classified them into three groups: "scheduled" (appointment made successfully); "no need to return" (patients transitioned to dialysis, transferred to another nephrologist, declined appointment, or died); or "active" (i.e. actively trying to reconnect). We aimed to increase MD use of the EMR trigger by faculty meeting reminders and administrative assistant prompts. Lastly, we identified explanation categories for patients persisted on the "active" list.

Results: We had 5730 patient visits from 1/31/2018 to 3/31/2019. MDs successfully used the EMR trigger on 3598 (62.8%) of the visits. The most common barriers for using the EMR trigger were: rotating trainees not familiar with this system; MDs running behind on charting; and MDs short on time during clinic. We identified 460 (12.8% of total visits) LTFUs. Among these 252 (54.8%) were "scheduled," 114 (24.8%) were designated "no need to return," and 94 (20.4%) are "actively trying to reconnect." Among the 94 patients, reasons we were unable to reach included homelessness; inaccurate contact information; and having multiple stressors at home causing postponement of routine care.

Conclusions: Retention in care is associated with improved outcomes. Our team has identified a method by which patients LTFU were identified and reconnected. A future goal may be to make MD trigger activation mandatory via EMR validation point. For the difficult to reconnect patients who may be the most vulnerable, a team approach with case management may improve chances of reconnection. Limitations of our study are that we lack outcome data on patients who were LTFU and the development and implementation of the system is time-intensive.

SA-PO908

Effect of Statins on Cardiovascular Complications in CKD Patients: A Network Meta-Analysis

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Background: It is well known that cardiovascular mortality and morbidity increase in advanced chronic kidney disease (CKD), and that mild to moderate CKD is also limited. Therefore, we aim to investigate the risk of kidney function and the risk of cancer.

Methods: Our study was based on a nationally representative sample of population aged 45 years or older from China Health and Retirement Longitudinal Study (CHARLS) conducted between June 2011 and March 2015. Altogether 17,708 participants were randomly chosen using a multistage sampling scheme. For the current analyses, 11,508 eligible individuals with measurement of kidney function and without cancer at baseline were included. The, 104 participants without follow-up and 392 died of causes unrelated to cancer during follow up were excluded. Estimated glomerular filtration rate (eGFR) was calculated using Chronic Kidney Disease Epidemiological Collaboration equation. Reduced kidney function was defined as eGFR <60 ml/min/1.73m2 was associated with the increased risk of cancer, with fully adjusted relative risk of 2.04 (95% confidence interval 1.20 to 3.46).

Results: Altogether 11,012 participants with an average of 58.6 years were included. Participants with eGFR≥90, 60 to 89, and <60 ml/min/1.73m2 accounted for 63.4%, 33.4% and 3.2% respectively. During 43,854 person-years of follow-up, 217 new cases of cancer were recorded. Compared to participants with eGFR≥90 ml/min/1.73m2, those with eGFR<60 ml/min/1.73m2 was associated with the increased risk of cancer, with fully adjusted relative risk of 2.04 (95% confidence interval 1.20 to 3.46).

Conclusions: Reduced kidney function is associated with a higher risk of cancer and therefore should be integrated into the risk-stratification of cancer management.

SA-PO906

Resistance Training in CKD: A Randomized Pilot Trial


Background: Resistance exercise training has been shown to improve vascular function and cardiovascular risk factors in healthy individuals, but studies in patients with chronic kidney disease (CKD) are lacking.

Methods: We randomly assigned adults with mild-to-moderate CKD to a 12-week resistance exercise training intervention (45-minutes sessions, twice per week) or to control (educational material regarding the benefits of physical activity). The primary outcomes were aortic pulse-wave velocity (PWV), carotid artery stiffness and systolic blood pressure (BP), measured at baseline, 6 weeks and 12 weeks. Intention-to-treat analyses with repeated measures ANOVA were used.

Results: Of the 32 individuals included in the analyses (15 randomized to the intervention group and 17 to the control group), mean (SD) age was 57 (1.8) years, 47% were male, 94% African American, and 27% had diabetes; mean (SD) eGFR was 42 (14) ml/min/1.73m2. Of those randomized to the resistance exercise intervention, 67% completed at least half of the training sessions. No adverse effects were observed with the intervention. There was a decrease in PWV, carotid stiffness and systolic BP among participants randomized to resistance exercise training, but these changes were not statistically significant when compared with controls (Table).

Conclusions: Resistance exercise training is feasible and safe among patients with CKD, and has the potential of improving vascular function in this population.

Funding: NIDDK Support
**SA-PO911**

Effect of Sodium Bicarbonate on Acid Excretion and BP in Patients with and Without CKD: The Acid-Base Compensation in CKD (ABC) Study

Laura Crystal and Without CKD: The Acid-Base Compensation in CKD (ABC) Study

Background: As kidney function worsens, net acid excretion (NAE) diminishes resulting in subclinical, then overt, metabolic acidosis (MA). Treatment with alkali may improve outcomes in CKD even when overt MA is not present. Our goal was threefold: 1) evaluate NAE and response to alkali in the setting of controlled diet acid load; 2) compare responses in those with and without CKD; and 3) evaluate change in 24h BP as a potential mechanism of benefit.

Methods: We enrolled 14 non-diabetic adults in a random order, cross-over feeding study; 8 had CKD and 6 did not. After a 3-day run-in, participants consumed a 7-day controlled acid load diet supplemented with NaHCO3 tablets (alkali: 31 or 39 mg/kg/day based on weight) and an identical 7-day diet supplemented with NaCl as table salt (control), in random order. We assessed NAE and other acidification markers from two 24h urines, and measured 24h ambulatory BP at the end of each period. We estimated the alkali effect using mixed models adjusted for CKD status, study period, and intervention order, and tested for interaction between alkali and CKD.

Results: Mean age was 68, 64% were women, and 57% were white. In the control period, mean NAE and urine citrate were lower for those with CKD (29.6±7.7 meq/L and 38±15 mg/dL) vs. non-CKD (40±18.6 meq/L and 687±5×18.6 mg/dL) on identical diets. Overall, alkali lowered NAE and urine ammonium and increased urine pH, HCO3 and citrate. Response in urine pH and citrate to alkali differed by CKD status. Alkali increased urine pH more in patients with vs. without CKD (p=0.017), whereas urine citrate was lower only among those with CKD (p=int=0.05). Alkali had no effect on 24h BP (Table).

Conclusions: Despite identical diets, NAE and urine citrate are lower in CKD vs. non-CKD suggesting that NAE in CKD has non-diet determinants. NaHCO3 decreases NAE; however, it increases, thereby restoring, lower urine citrate in CKD. Urine citrate may be a useful marker of early, subclinical acidosis in CKD that responds to therapy.

**Funding:** NIDDK Support

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**SA-PO912**

Nitrite, Isocqueretin, and Endothelial Dysfunction Trial (NICE trial): Design and Preliminary Data

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Background: Endothelial dysfunction may be an early etiology for chronic kidney disease (CKD) and cardiovascular disease in CKD. We studied the safety and efficacy of correction treatments with sodium nitrite and isocqueretin on endothelial dysfunction, inflammation and oxidative stress in CKD patients.

Methods: This double blind, randomized, placebo-controlled trial enrolled 70 CKD patients. 35 patients were randomly assigned to oral combination of immediate-release sodium nitrite (40 mg twice daily) and isocqueretin (225 mg, once daily) or placebo for 3 months. The primary endpoint was changes in flow-mediated dilation (FMD) from baseline. The secondary endpoints were changes in biomarkers of endothelial function, inflammation, oxidative stress, eGFR, and urine albumin. The follow-up rate was 97%. Mixed-effects models were used to assess the time-course of FMD changes.

Results: Baseline characteristics were similar between groups. FMD increased by 1.13% (95% CI confidence interval [CI], -0.07 to 2.32) vs. 0.34% (95% CI, -0.86 to 1.53) in treatment vs. placebo group (p = 0.035). The level of von Willebrand factor (vWF) decreased by 695 pg/mL (95% CI, 3793 to 2403) vs. increased by 2768 pg/mL (95% CI, 300 to 5518) in treatment vs. placebo group (p = 0.047). There were statistically insignificant reductions between treatment and placebo groups in other biomarkers of endothelial dysfunction (intercellular adhesion molecule-1, vascular adhesion molecule-1, E-selectin, and Endothelin-1), oxidative stress (oxidized low-density lipoprotein and nitrotyrosine), and urine albumin. Additionally, there were no differences in changes of inflammatory biomarkers (C-reactive protein, tumor necrosis factor-α, interleukin [IL]-6, and monocyte chemoattractant protein-1) except IL-17 (1.35 [95% CI, 0.87 to 1.82] vs. 1.98 [95% CI, 1.50 to 2.45] in treatment vs. placebo group, p=0.05). There was no significant change in vWF level between groups. Methemoglobin and side effects were not different between groups.

Conclusions: The combination treatment significantly reduces vWF and IL-17 and may potentially improve endothelial dysfunction, inflammation, oxidative stress, and proteinuria. Larger trial is warranted to confirm these findings.

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**SA-PO913**

Correspondence of Ankle-Brachial Index and Doppler Ultrasound Findings in Patients with CKD

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Background: Ankle-brachial index (ABI) is used to diagnose peripheral artery disease (PAD). ABI may be artificially high among patients with chronic kidney disease (CKD) due to increased arterial calcification and stiffness. It is not well studied how ABI and traditional ultrasound (TUS) correlate with more accurate diagnostic measures of doppler ultrasound in evaluating PAD in CKD.

Methods: We conducted retrospective chart review among pre-dialysis CKD patients in Tulane Hospital in New Orleans, Louisiana. Total of 251 were included in the study. Demographic and laboratory information, clinical measures, ABI, TBI, and additional ultrasound findings were extracted into the study forms. The correlations of ABI, TBI, doppler waveforms, and peak systolic velocity (PSV) were analyzed. PSV is calculated as percentage change of measured PSV from normal value.

Results: Among patients with ABI ≤ 0.9, 73% had normal US waveform, 24% had biphasic waveform, and 3% had monophasic waveform; 54% had TBI ≤ 0.7. Among those with ABI > 1.4, 77% had normal waveform, 23% had biphasic waveform, and 0% had monophasic waveform; 0% had TBI > 0.7. Among those with ABI 0.9 > 1.4 and TBI ≤ 0.7 were poorly correlated with a r2 of <0.10 <0.100 or a 100% increase in PSV.

Conclusions: These data indicate that the ABI and TBI diagnostic criteria for PAD need to be further evaluated in CKD. Larger study is warranted to confirm these findings.

**SA-PO914**

Correlation of Raised NT proBNP Levels and Left Ventricular Filling Pressure in CKD Patients with Acute Decompensated Heart Failure (ADHF)

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Background: Left ventricular filling pressures (LVPF) and N-Terminal pro brain natriuretic peptide (NT-proBNP), both of which are well known indicators of poor prognosis, are elevated in ADHF. The relationship of NT-proBNP with LVPF in CKD patients is not well documented. Therefore, the aim of our study is to find integrative utility of measuring NT-proBNP levels with LVPF in patients with acute dyspnea enabling their utilization as diagnostic and prognostic markers in the management of CKD patients with ADHF.

Methods: From 1st May, 2018 through 30th April, 2019, 450 patients who presented in Emergency department of Doctors Hospital Lahore with acute dyspnea and potential fluid overload were assessed. Out of these, 85 patients who underwent simultaneous echocardiography and NT-proBNP measurement were included in the study. Charts were analysed by a nephrologist and cardiologist. Both CKD(66) and non CKD(19) patients with reduced LV ejection fraction (LV EF <40%>HFIEF, Midrange (LV EF 40-50%>HFmEF) and preserved ejection fraction (LV EF >50%HFeEF) were included. eGFR was measured using the CKD-EPI (Chronic kidney disease Epidemiology collaboration) equation. Data was analysed using SPSS version 25.

Results: Echo parameters were compared between different NT-proBNP levels in the study group. The mean value of NT pro BNP was much higher in patients with ADHF as compared to non ADHF due to increased renal function. Additionally, there were no differences in changes of inflammatory biomarkers (C reactive protein, tumor necrosis factor-α, interleukin [IL]-6, and monocyte chemoattractant protein-1) except IL-17 (1.35 [95% CI, 0.87 to 1.82] vs. 1.98 [95% CI, 1.50 to 2.45] in treatment vs. placebo group, p=0.05). There was no significant change in vWF level between groups. Methemoglobin and side effects were not different between groups.

Conclusions: NT-proBNP is a rapid and reliable marker for accurate and early diagnosis of ADHF since it has a significant correlation with LVEF and LVPF in CKD patients with ADHF.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
SA-PO915
Effects of a 16-Week Physical Training on Mortality, Quality of Life, and CKD Progression: NEPHROS Post-Trial Follow-Up
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Background: The NEPHROS is a randomized controlled trial which applied a 16-week aerobic and resistance training to patients with chronic kidney disease (CKD) and high blood pressure and found an improvement in functional capacity, inflammatory status and metabolic profile, compared with usual care. The current report describes a long-term post-trial observational follow-up study, comparing survival, health-related quality of life (HRQoL) by estimated glomerular filtration rate (eGFR) changes from baseline in-trial intervention and control groups, and according to in-trial cardiovascular (CV) risk factors.

Methods: After three years of the original trial, the NEPHROS participants were recontacted and of 831 participants, 175 (21%) could not be recontacted or did not report. The main analysis was used to compare survival using data reported. Baseline in-trial eGFR (HR 0.95, 95% CI 0.92 to 0.98) and ABI (HR 0.03, 95% CI 0.002 to 0.43) were positive independent predictors for survival, Lower ABI (coef. 9.00, 95% CI 0.43 to 17.5) and higher systolic blood pressure (coef. -0.13, 95% CI -0.24 to -0.03) were independent predictors for eGFR decline.

Conclusions: We conclude that lower eGFR and ABI, and higher systolic BP were associated with poorer prognosis among CKD patients. A six-week exercise program had no long-term effect on survival, quality of life or glomerular filtration change in patients with CKD stages 2 to 4. This finding highlights the scant usefulness of long-lasting structured exercise interventions if not associated with long-term lifestyle changes.

SA-PO916
What Is the Best Predictable Subtraction for Cardiovascular Outcomes in Patients with CKD?
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Background: Dyslipidemia is an important parameter for prediction of cardiovascular disease (CVD). We aimed to investigate the most valuable subtraction of lipid for predicting CVD in patients with chronic kidney disease (CKD).

Methods: We retrospectively reviewed the National Health Insurance Service (NHIS) database for a people who received nationwide health check-up in 2009. The population had no long-term effect on survival, quality of life or glomerular filtration change in patients with CKD stages 2 to 4. This finding highlights the scant usefulness of long-lasting structured exercise interventions if not associated with long-term lifestyle changes.

Conclusions: The pattern and significance of lipid subtraction were different according to the grade of renal function. Thus, TG/HDL should be additionally considered with LDL as a target variable in patients with advanced CKD.

SA-PO917
Outcomes in Patients with Renal Impairment and Myocardial Infarction Identified by High-Sensitivity Cardiac Troponin Testing: A Prespecified Analysis of the High-STECAS Trial
Peter J. Gallacher, High-STECAS Investigators University of Edinburgh, Edinburgh, United Kingdom.

Background: Patients with renal impairment are at increased risk of myocardial infarction (MI), but the interpretation of cardiac troponin in this context is challenging. Using a high-sensitivity cardiac troponin I (hs-Ctnl) assay that has widely been adopted into clinical practice, we describe the diagnosis and outcomes of patients with MI, stratified by renal function.

Methods: In a pre-specified secondary analysis of a stepped-wedge cluster-randomised controlled trial, consecutive patients with suspected acute coronary syndrome (ACS), a hs-Ctnl concentration greater than the sex-specific 99th centile and renal impairment (defined as an estimated glomerular filtration rate [eGFR] of <60 mL/min/1.73m2) were identified between June 2013 and March 2016. Diagnoses of type 1 or type 2 MI were adjudicated and classified according to the 4th Universal Definition of Myocardial Infarction. The primary outcome of type 1 MI or cardiovascular death was compared in patients with and without renal impairment at 1 year.

Results: eGFR was available in 46,927 (97.1%) patients; 38,994 (83.1%) patients had an eGFR <60, 6,627 (14.1%) had an eGFR 30-59 and 1,306 (2.8%) had an eGFR <30. Plasma hs-Ctnl concentrations were raised in 47.9% of patients with and 16.2% without renal impairment. Patients with renal impairment were less likely to be diagnosed with type 1 MI (35.2% [1,336/3,800] vs 56.3% [1,556/3,311]) but more likely to be diagnosed with type 2 MI (12.6% [480/3,800] vs 9.8% [619/6,627]; P<0.001 for both) than patients with normal renal function. In patients with hs-Ctnl concentrations >99th centile, the risk of subsequent MI or cardiovascular death at 1 year was significantly increased in patients with renal impairment compared to those without it (24.9% [945/3,800] vs 12.0% [757/6,311]; adjusted hazard ratio [aHR] 1.56, 95% CI 1.34 to 1.82; P<0.001). This risk increased as eGFR declined: 30-59 mL/min/1.73m2 (23.2% [674/2,905]; aHR 1.51, 95% CI 1.28-1.78); <30 mL/min/1.73m2 (30.3% [271/895]; aHR 1.74, 95% CI 1.39-2.19) (P<0.001 for both).

Conclusions: Almost half of all patients with suspected ACS and renal impairment had a hs-Ctnl greater than the sex-specific 99th centile. This was associated with a poor prognosis, especially in those with an eGFR <30mL/min/1.73m2.

SA-PO918
A Cardiovascular Risk Mitigation Strategy on the Safety of Bardoxolone Methyl Post-BEACON
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Background: Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes (BEACON) was a multinational, randomized, double-blind, placebo-controlled Phase 3 trial that enrolled patients with type 2 diabetes (T2D) and stage 4 CKD. The BEACON trial was terminated due to a significant increase in the risk of heart failure occurring within the first four weeks of treatment with bardoxolone methyl (Bard). Post-hoc analyses identified a history of heart failure and elevated baseline serum concentrations of B-type natriuretic peptide (BNP) as risk factors for these events. Four subsequent clinical trials in other disease states have excluded patients with these clinical characteristics. Additionally, BNP and Nt-proBNP were measured as safety parameters over the course of these trials. Safety data from these trials will be presented.

Methods: Data from four studies were included: a 48-week, open-label Phase 2 study in patients with Alport syndrome (CARDINAL; NCT03191853); a 12-week, open-label Phase 2 study in patients with autosomal dominant polycystic kidney disease, IgA nephropathy, focal segmental glomerulosclerosis, or type 1 diabetes CKD (PHOENIX; NCT03366337); a 16-week, randomized, placebo-controlled, double-blind Phase 2 study patients with T2D and CKD in Japan (TSUBAKI; NCT02316821); and a 16-week, randomized, placebo-controlled, double-blind, global Phase 2 study of pulmonary hypertension (PH) (LARIAT; NCT02036970).

Results: A total of 423 patients were enrolled in four studies that were initiated after the termination of BEACON. There were no fluid overload-related serious adverse events in these studies. There were no deaths reported. These studies also were not associated with increases in mean blood pressure in any of these studies. Mean decreases in body weight were apparent by Week 12 of treatment with Bard and were more pronounced in patients with higher baseline BMI.
Increased Heart Rate Reflects Intrarenal Renin-Angiotensin System Activation in CKD Patients but Not in Subjects Without CKD

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Background: A higher heart rate is one of the risk factors for heart failure and cardiac remodeling during systolic and diastolic heart failure (HF). It is also associated with increased intrarenal renin-angiotensin system (RAS) activation. However, the association between heart rate and renal RAS activation remains unclear. We investigated the relationship between heart rate and urinary angiotensinogen (AGT) excretion, a surrogate marker for intrarenal RAS activity, in subjects with and without chronic kidney disease (CKD).

Methods: We measured heart rate during daytime and nighttime in CKD patients and in non-CKD subjects. Heart rate had a significant positive association with sCr levels during daytime and nighttime in CKD patients but not in non-CKD subjects. Moreover, although heart rate was not associated with urinary AGT excretion levels in non-CKD subjects during daytime (r = 0.29 and p = 0.34) and nighttime (r = 0.27 and p = 0.39), it was associated with urinary AGT excretion levels during daytime (r = 0.23 and p = 0.067) and nighttime (r = 0.45 and p = 0.01) in CKD patients. Multiple linear regression analysis revealed that heart rate had a significant positive association with the urinary AGT excretion levels during nighttime but not daytime, after adjustments for age, sex, body mass index, and sCr in CKD patients (β = 0.31 and p = 0.034).

Conclusions: Heart rate is associated with urinary AGT excretion levels, especially during the nighttime, in CKD patients but not in non-CKD subjects. Heart rate measurement may be a convenient surrogate marker for intrarenal RAS activation in CKD patients.

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SA-PO920
Comparison of Heart-Type Fatty Acid Binding Protein with Tropinin T for Prediction of Cardiovascular Events in the German CKD Study

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Background: Measurement of heart-type fatty acid binding protein (H-FABP) is more sensitive than high-sensitive troponin T (hs-TNT) in the early detection of myocardial injury. H-FABP also improves prediction of long-term cardiovascular (CV) outcomes in patients with CKD. H-FABP is more sensitive than high-sensitive troponin T (hs-TNT) in the early detection of myocardial injury. However, the association between heart rate and urinary AGT excretion levels during daytime and nighttime in CKD patients but not in non-CKD subjects. Heart rate had a significant positive association with sCr levels during daytime and nighttime in CKD patients but not in non-CKD subjects. Moreover, although heart rate was not associated with urinary AGT excretion levels in non-CKD subjects during daytime (r = 0.29 and p = 0.34) and nighttime (r = 0.27 and p = 0.39), it was associated with urinary AGT excretion levels during daytime (r = 0.23 and p = 0.067) and nighttime (r = 0.45 and p = 0.01) in CKD patients. Multiple linear regression analysis revealed that heart rate had a significant positive association with the urinary AGT excretion levels during nighttime but not daytime, after adjustments for age, sex, body mass index, and sCr in CKD patients (β = 0.31 and p = 0.034).

Conclusions: Heart rate is associated with urinary AGT excretion levels, especially during the nighttime, in CKD patients but not in non-CKD subjects. Heart rate measurement may be a convenient surrogate marker for intrarenal RAS activation in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO921
Peak Oxygen Consumption Is Reduced at All Levels of CKD in Chronic Heart Failure Patients

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Background: There is an increasing body of literature showing reduced Cardiorespiratory Fitness (CFR) in CKD. This is mainly proven in CKD stages 4 and 5, but increasing knowledge suggests that this is the case in earlier stages as well. Chronic heart failure (CHF) is characterized by the hearts inability to meet tissues blood demands, mainly during exercise. We wanted to see if CKD affected peak oxygen consumption (VO2peak) in CHF.

Methods: Participants were enrolled from two regional CHF clinics with similar access to different CKD stages and levels of renal insufficiency without any upper age limit. Cardiorespiratory performance was measured using the 6-minute walk test and the 3-stage graded exercise test (including VO2peak). Results: Of the 59 participants (22 male and 37 female), 14 patients were allocated to stage I and II diastolic dysfunction did not reach statistical significance.

Conclusions: Reduced renal function was associated with increased filling pressures depicted as Chronic Renocardiac Syndrome, whereas CHF caused by primary myocardial dysfunction display dilation of left ventricle with venous congestion leading to reduced renal perfusion in the Chronic Cardiorenal Syndrome. This heterogeneity in CRS complicates the study of its pathophysiology, and studies comparing echocardiographic features of diastolic function in CHF between CKD and non-CKD patients are scarce. Patients from two regional heart failure clinics were included if they had stable CHF and were medically optimized. Echocardiographic recordings, analyses and estimation of filling pressure and grade of diastolic dysfunction were based on latest recommendations. Estimated glomerular filtration rate (eGFR) was calculated based on creatinine, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Results: Mean age of the 67 participants was 68 (65-71.1) years (82 % male). eGFR(60 ml/min/1.73m2) was present in 46 %. Three patients were in dialysis and 1 had a renal transplant. NYHA class II and III was present in 77 % and 23%, respectively. Patients with elevated filling pressure had lower eGFR than patients with normal filling pressure (1.48 ± 1.73 ml/min/1.73m2, p = 0.03). Indexed left atrial end-systolic volume was significantly larger in HF patients with eGFR<60 ml/min/1.73m2 compared to those with better renal function (11 ml/min/1.73m2, p = 0.02). Patients with grade I diastolic dysfunction had a higher eGFR compared to grade II (18 ml/min/1.73m2, p = 0.01). The differences between grade I and II, and II and III diastolic dysfunction did not reach statistical significance.

Conclusions: Reduced renal function was associated with increased filling pressures and larger left atrial volumes in a general heart failure population. This shows a common trait in CKD-patients with CHF despite the otherwise heterogeneity in clinical presentation.

Funding: Government Support - Non-U.S.

SA-PO922
The Association of Diastolic Dysfunction with CKD in Patients with Heart Failure

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Background: Chronic Kidney Disease (CKD) is tightly connected to cardiac disease, including Chronic Heart Failure (CHF) through different Cardiorenal Syndromes (CRS). CRS can be triggered by hypertension and CKD often presents with left ventricular hypertrophy, stiffening and increasing filling pressures depicted as Chronic Renocardiac Syndrome, whereas CHF caused by primary myocardial dysfunction display dilation of left ventricle with venous congestion leading to reduced renal perfusion in the Chronic Cardiorenal Syndrome. This heterogeneity in CRS complicates the study of its pathophysiology, and studies comparing echocardiographic features of diastolic function in CHF between CKD and non-CKD patients are scarce.}

Methods: Patients from two regional heart failure clinics were included if they had stable CHF and were medically optimized. Echocardiographic recordings, analyses and estimation of filling pressure and grade of diastolic dysfunction were based on latest recommendations. Estimated glomerular filtration rate (eGFR) was calculated based on creatinine, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Results: Mean age of the 67 participants was 68 (65-71.1) years (82 % male). eGFR(60 ml/min/1.73m2) was present in 46 %. Three patients were in dialysis and 1 had a renal transplant. NYHA class II and III was present in 77 % and 23%, respectively. Patients with elevated filling pressure had lower eGFR than patients with normal filling pressure (1.48 ± 1.73 ml/min/1.73m2, p = 0.03). Indexed left atrial end-systolic volume was significantly larger in HF patients with eGFR<60 ml/min/1.73m2 compared to those with better renal function (11 ml/min/1.73m2, p = 0.02). Patients with grade I diastolic dysfunction had a higher eGFR compared to grade II (18 ml/min/1.73m2, p = 0.01). The differences between grade I and II, and II and III diastolic dysfunction did not reach statistical significance.

Conclusions: Reduced renal function was associated with increased filling pressures and larger left atrial volumes in a general heart failure population. This shows a common trait in CKD-patients with CHF despite the otherwise heterogeneity in clinical presentation.

Funding: Government Support - Non-U.S.

SA-PO923
Intraventricular Septum Thickness (IVST) Increases Depending on the Decline of eGFR in AL Renal Amyloidosis

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Background: In advanced AL amyloidosis, cardiac walls show thickening and cardiac function deterioration. It is unclear whether renal dysfunction and hypertension affect cardiac walls and functions in AL amyloidosis. We aimed to study the relationship between CKD progression and the ultrasound cardiac parameters in patients with AL amyloidosis.

Methods: The Amyloidosis Research Group, supported by funds from the Ministry of Health, Labour and Welfare in Japan surveyed the patients with AL amyloidosis in 2015. We collected clinical data concerning renal and cardiac functions from 353 cases.
SA-PO924

Right Coroanry Artery (RCA) Dominant Distribution of Coronary Artery Lesions in the Development of CKD Stage
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Background: It is reported that a more proximal lesions in RCA was observed in CKD patients compared with non-CKD patients (Kidney International (2009) 75, 80-87). This characteristic may affect the location and/or distribution of coronary atherosclerosis. The characteristics of coronary artery disease in CKD patients, however, have not entirely been clarified. We elucidate the relationship between the progression of CKD and the distribution of coronary artery stenosis diagnosed by coronary artery angiography.

Methods: Among the 13391 cases of coronary artery angiography performed in our hospital from 2003 to 2017, we characterized coronary artery lesions in predialytic phase of CKD patients. The inclusion criteria was the patients who had been treated with the first elective PCI. The patients with previous revascularization, acute myocardial infarction, unstable angina pectoris, coronary artery bypass imaging after coronary artery bypass grafting, or hemodialysis or unknown renal function were excluded in this study. Finally, 3268 CKD patients were enrolled in this study.

Results: The average age was 71 (64-79) years, and average eGFR was 65 (53-77) mL/min. A single lesion was observed in 2168 cases and multiple lesions were observed in 1085 cases. Location of the lesion was the right coronary artery (RCA) in 914 cases, left main trunk in 101 cases, left anterior descending artery (LAD) in 1832 cases, and left circumflex artery in 733 cases. The prevalence of RCA lesion significantly increases in parallel with the development of CKD stage, however this phenomenon disappeared in LAD and LCX lesion. In multivariate logistic regression analysis, odds ratios of RCA for parallel with the development of CKD stage, however this phenomenon disappeared in LAD and LCX lesion. In multivariate logistic regression analysis, odds ratios of RCA for

Conclusions: It is still unclear the mechanism, it is possibility that progression pattern of coronary artery disease in CKD patients differ from non-dialysis CKD patients.

SA-PO925

Maximisation of Renin-Angiotensin-Aldosterone System Inhibition (RAASI) in CKD Patients with Heart Failure (HF): Experience from a CKD-HF Clinic
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Background: CKD-HF patients suffer from high hospitalisation and mortality rates, which may improve with maximising RAASI - often avoided by physicians due to fear of worsening renal function and hyperkalaemia. This study reports impact of a novel multidisciplinary cardiology-nephrology clinic for RAASI maximisation in CKD-HF patients.

Methods: Clinical, biochemical data and medications were obtained from electronic patient records and clinical letters on 97 patients seen and followed up in CKD-HF clinic from 23/03/17 to 11/04/19. Daily doses of each medication were classified into None, Low (≤50%), Medium (>50% ≤90%) and Maximum dose groups and blood test results were compared between the first and last clinic visit.

Results: Patient characteristics were: median age 78.5 years (IQR 66.8-84.3 years), male 71.1%, diabetes mellitus 53.6%, mean ejection fraction (EF) 38.6±13.7%, HFrEF 48.5%, LFrEF 33.3%. Median follow up time was 302 days (IQR 176-479 days). 15 patients died during follow up. At the end of follow up: 78.4% patients remained same or milder CKD group. There was a difference in the number of RAASI were patients on, between first and last visit (p=0.02): none (41.2% vs 29.9%), one (45.5% vs 50.5%), both ACEi/ARB and MRA (13.4% vs 19.6%). ACEi/ARB dose was increased in 33.0% patients and MRA dose in 17.5% of patients. Proportion of patients on each dose category between first and last visit for ACEi/ARB was not different (p=0.11): none (45.4% vs 39.2%), low dose (26.8% vs 26.8%), medium dose (16.5% vs 20.6%), maximum dose (11.3% vs 13.4%); for MRAs, it was different (p=0.02): none (82.5% vs 71.1%), low dose (7.2% vs 13.4%), medium dose (10.3% vs 12.4%), maximum dose (0% vs 3.1%). There was no change in serum Na, K, creatinine in patients with ACEi/ARB or MRA dose increase between first and last visit. The change of eGFR was significant in patients with MRA dose increase (p=0.03), however, it was small (3.45 vs 32.1 ml/min/1.73m²). There was no significant correlation between RAASI dose and the likelihood of patients having CKD progression (p=0.64 for ACEi/ARB; p=0.66 for MRA).

Conclusions: A combined CKD-HF clinic was effective in maximising RAAS inhibition in a high-risk group of patients without clinically significant hyperkalaemia or deterioration in renal function.

SA-PO926

The Influence of Vascular Endothelial Dysfunction on the Prognosis of Cardiovascular Events and Its Possible Relationship to CKD: Results from KNOW-CKD Cohort
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Background: Vascular endothelial dysfunction may be involved in progression of renal fibrosis in CKD patients. Asymmetric dimethylarginine (ADMA) is an endogenous nitric oxide synthase (NOS) inhibitor, which plays an important role in the pathophysiological process of endothelial dysfunction. Elevated circulating ADMA level is one of the primary biomarkers of endothelial dysfunction. This study will explore the association factors leading to endothelial injury in CKD patients and the relationship between vascular endothelial dysfunction and CKD prognosis.

Methods: 77 adults in CKD stage 1–5 were enrolled. Baseline demographic data including age, gender and etiology of kidney disease were all recorded. Serum ADMA, α-klotho and phosphorus levels were measured and immunohistochemical staining was carried out. Patients were divided into two groups by the median serum ADMA level and were followed up for 6 years. The primary outcome was initiation of renal replacement therapy (RRT).

Results: The mean serum ADMA level of all patients was 64.3±36.4ng/mL. Serum ADMA level increased with declining renal function (r=−0.267, p=0.020). It was negatively correlated with serum α-klotho (r=−0.233, p=0.042) and positively correlated with phosphorus (r=0.243, p=0.037) levels. The expression of α-klotho in renal perfusion tissues of CKD patients was decreased by immunofluorescence staining. The expression of sodium-phosphorus synergistic transporter (NaPi) in renal tubules, which promoted phosphorus reabsorption and the expression of dimethylarginine-dimethylamine hydroxylase (DDAH), which regulated ADMA level, were significantly decreased, consistent with clinical results. Immunohistological analyses showed that the incidence of renal replacement therapy initiation in high ADMA group was significantly higher than that in low ADMA group (35.9% vs 13.2%, p=0.029, log rank test).

Conclusions: Serum ADMA level increased with deterioration of renal function and increased with stage of CKD. Lower serum α-klotho and high phosphorus levels were associated with increased circulating ADMA levels, which implies that they may be involved in the pathogenesis of endothelial dysfunction in CKD patients. High serum ADMA level predicts the occurrence of end-stage renal failure. Alleviating endothelial injury and improving endothelial dysfunction in patients with CKD may delay the progress of CKD.

SA-PO927

Incidence of Cardiovascular Events and Mortality in Korean Patients with CKD: Results from KNOW-CKD Cohort
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Background: There are lack of studies regarding the incidence of major adverse cardiovascular events (MACE) in Asian pre-dialysis population. This study was conducted to analyze the incidences of MACE and death in Korean chronic kidney disease (CKD) population, using the data from a multicenter prospective cohort study, entitled KNOW-CKD. Among a total 2,238 patients enrolled, 59 patients without follow-up data were excluded and, finally, 2,179 patients were included. MACE was defined as any of the cardiovascular events occurred during the follow-up. The composite outcome was defined as MACE and all-cause death.

Results: Mean age was 53.6±12.2 years and 38.7% were female. At enrollment, mean eGFR was 53.2±30.7 ml/min/1.73m² and the prevalence of cardiovascular disease and diabetes were 6.0% and 33.4%, respectively. During median 4.1 years of follow-up, the incidence of MACE, death and composite outcome were 9.6 and 2.45 per 1,000 patient-year (PY). All outcome incidences were higher in diabetic patients compared with non-diabetic patients. The incidence of MACE was significantly higher in patients with ≥3 cardiovascular risk factors (p=0.013) compared with those with <3 such risk factors.
Incidence of outcomes according to CKD stages

SA-PO928

Effect of Blood Pressure Variability and Arterial Stiffness for Renal Outcome in Patients with CKD Stage 3 or 4

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Background: Previous studies have reported that higher visit-to-visit blood pressure (BP) variability is higher risk of decreased renal function in hypertensive individuals. Arterial stiffness is associated with decline of renal function. We examined the association between BP variability and renal outcome in patients with chronic kidney disease (CKD) stage 3 or 4, and whether these renal outcomes were associated with arterial stiffness.

Methods: Among 2238 CKD patients in Korea in 2011 through 2017, 1241 patients who had CKD stage 3 or 4, and measured more than 3 times during follow-up period were included. BP variability was defined as standard deviation (SD) of systolic BP across 3 to 8 visits. SD was divided into quintiles. Composite renal outcome included a 50% reduction of eGFR, dialysis or transplantation. Arterial stiffness was measured with brachial-ankle pulse wave velocity (baPWV). We calculated adjusted hazard ratio (AHR) for composite renal outcome across SD quintile and analyzed the effect of baPWV.

Results: Mean age was 53±11.1 years, 37% were women, and mean estimated glomerular filtration rate was 36±12.2 ml/min/1.73m². Median follow-up was 3.0 years and 391 outcomes occurred. The AHR for composite renal outcome were 1.10 (95% confidence interval [95% CI]: 0.77-1.58), 1.19 (95% CI: 0.84-1.68), 1.30 (95% CI: 0.92-1.83), and 1.62 (95% CI: 1.15-2.28) for second through fifth versus the first quintile of SD. baPWV>15s was significantly higher risk for renal outcomes in fifth compared to the first quintile (AHR: 1.75, 95% CI: 1.08-2.80).

Conclusions: Higher visit-to-visit BP variability are associated with rapid deterioration of renal function. Furthermore, there are different association between BP variability and renal outcome depending on arterial stiffness such that higher BP variability has a strong association with CKD progression among patients with high arterial stiffness.

SA-PO992

Short-Term Systolic Blood Pressure Variability Predicts Renal Events in CKD: Results from the C-STRIDE Study

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Background: Whether short-term blood pressure variability (BPV) correlates with renal events across different clinical (CV) events is controversial in patients with chronic kidney disease (CKD).

Methods: A total of 1421 CKD stage 1-4 patients with ambulatory BP (ABP) data from the Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE) were enrolled in the present study. Short-term BPV was evaluated by calculating 24-hour standard deviation (SD) and the weighted SD of systolic BP (w-SD). The association of short-term BPV with CKD outcomes, including initiation of renal replacement therapy and CV events, was evaluated by Cox regression model. The adjustment included age, gender, smoking, diabetes, anti-hypertensive treatment, body mass index, serum albumin, estimated glomerular filtration rate, logarithm transformed low-density lipoprotein cholesterol and logarithm transformed uric acid.

Results: The mean age of the cohort was 49±13.7 years with 56% males. The average follow-up of 2.4±3 years, 236 renal events and 93 CV events occurred, respectively. Both 24-hour BP SD (hazard ratio [HR]: 1.04, 95% confidence interval [CI]: 1.01-1.06) and w-SD (HR: 1.05, 95%CI: 1.02-1.08) showed a greater hazard for renal events in fully adjusted model. Compared with the bottom tertile group, the risk for renal events was significantly increased in top tertile group for both 24-hour SBP and SD (HR:1.58, 95%CI:1.11-2.24) and w-SD (HR:1.48, 95%CI:1.07-2.06), respectively.

Conclusions: In CKD patients, short-term systolic blood pressure variability increases the risk for renal events independently.

SA-PO930

Clinical Burden of Complications Associated with CKD: A Novel Cardio-Renal Risk Tool

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Background: The prevalence of chronic kidney disease (CKD) is growing worldwide. CKD affects approximately 15% of Americans. CKD patients are a complex and comorbid population. Complications are frequent in people with CKD and represent an important component of the associated disease burden. This study aimed to synthesize evidence reporting associations between two common complications of CKD, hyperkalemia (HK) and anemia, and risk of adverse outcomes including death and cardiovascular (CV) events in a novel risk tool to encourage a holistic approach to evaluating the associated disease burden.

Methods: Systematic literature reviews were conducted to identify studies reporting risk of either HK or anemia in people with CKD including those receiving dialysis, and studies associating the incidence of HK or anemia with clinical outcomes including mortality, hospitalization and CV events. Reported evidence was then incorporated in a Cardiovascular Risk Assessment Tool development process to characterize the risks of HK, anemia and associated adverse outcomes in people with CKD.

Results: A total of 314 studies were identified that reported the risk of HK (n=123) or anemia (n=191), or the association between each complication and patient outcomes. For male patients aged 65 years with CKD stage 3b, the estimated 5-year risk of a HK event (potassium>5.5mmol/L) was 11.9%. Separately, the prevalence of anemia (Hb<11g/dL) was 35.0%. For a patient with HK the estimated relative risks (RR) of death, hospitalization and CV events were 1.50, 1.20 and 1.08, respectively. For a patient with anemia the corresponding RRs were 1.13, 1.47 and 1.12. Furthermore, risks were increased with the severity of each complication; RRs of death, hospitalization and CV events increased to 2.19, 1.73 and 1.14 for a patient with potassium>6.0mmol/L and to 1.13, 1.72 and 1.24 for a patient with Hb<10g/dL, respectively.

Conclusions: HK and anemia are both consistently and independently associated with increased risk of adverse outcomes in CKD patients. This study uniquely synthesizes the growing body of evidence on the burden and impact of complications such as HK and anemia in CKD patients. This novel risk tool can be used to communicate the importance of timely diagnosis and management of these conditions to reduce the burden of disease in this population.

Funding: Commercial Support - AstraZeneca

SA-PO931

Osteoprotegerin Is Associated with Development of Coronary Artery Calcification but Not Severity and Progression in Non-Dialysis CKD

Seon Ha Baek,1 Sun Ryoung Choi,1 Ja-Ryong Koo,2 Sejoong Kim,2 Ho Jun Chin,3 Dong-Wan Chea.3 1KNOW CKD group, Internal Medicine, Hallym University Dongan Sacred Heart Hospital, Hwasoeong-si, Gyeonggi-do, Republic of Korea; 2Seoul National University Bundang Hospital, Seongnam, GyeongGoo-Do, Republic of Korea.

Background: Coronary artery calcifications (CAC) are recognized as a predictor of all-cause and cardiovascular mortality in chronic kidney disease (CKD). Osteoprotegerin (OPG) could be a marker of vascular calcification presence and extent. The purpose of this study was to evaluate relationships between OPG levels and presence/severity/progression of CAC score in non-dialyzed CKD patients.

Methods: We prospectively enrolled 1974 CKD patients (1180 male/794 female, mean age: 53.2 years) who had OPG and electron beam computed tomography (CT) or multi-detector CT for CAC scoring at baseline. A CAC score of >400 Agatston unit (AU) was used to define severe CAC. In term of definition for CAC progression: among those with no baseline CAC, incidence was defined as an annual increase in CAC score ≥ 5 AU. Among those with baseline CAC, progression was defined as 15% annual increase.

Results: Mean serum concentrations of OPG amounted to 6.79±3.53 pmol/L. Among 1974 patients, 1011 (51.2%) had CAC score >0 and 209 (10.6%) had scores >400. Higher OPG levels were associated with the present CAC but not severe CAC at baseline. [LOP, presence: OR=-2.033, P=0.001; severe CAC: OR=-1.700, P=0.070]. Among 827 patients with 4-year follow up CAC scores, 22 (4.9%) participants without CAC at baseline had incident CAC and 243 (65.8%) participants with CAC at baseline had CAC progression. Among those with baseline CAC but not severe CAC at baseline progression. Among those without CAC at baseline, higher OPG levels were associated with incident CAC (LOP, OR = 5.045, P = 0.042). However, OPG was not associated with CAC progression among participants with CAC at baseline or in total.

Conclusions: Our results indicated that higher serum OPG levels are associated with the incidence and development of CAC non-dialyzed CKD patients. However, OPG does not seem to be involved in severity and progression of CAC.

Funding: Government Support - Non-U.S.
SA-PO932

Marijuana Use and CKD in an Urban Population
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Background: Marijuana is the most commonly used illicit drug in the US. Little is known about the relation of marijuana with kidney outcomes. We examined the association of marijuana use and CKD among a cohort of African American and white adults in Baltimore, Maryland.

Methods: We examined baseline data from the Healthy Aging in Neighborhoods of Diversity Across the Life Span study. Marijuana use was self-reported and defined as never, former or current. CKD outcomes were prevalent reduced kidney function (eGFR <60 ml/min/1.73m²) or prevalent albuminuria (urine albumin-to-creatinine ratio (ACR) >=30 mg/g). The association of marijuana use with CKD outcome was examined using multivariate logistic regression.

Results: Among 2352 participants, there were 56% never, 30% former and 14% current marijuana users. Current marijuana users were younger, with fewer yrs of education, and were more likely to be male, African American and use cigarettes, opiates and/or cocaine than never or former marijuana users, but were less likely to have hypertension or diabetes. Overall prevalence of reduced kidney function was 5.3%, with 6.1% of never, 4.6% of former and 3.4% of current marijuana users having reduced kidney function. Overall prevalence of albuminuria was 11.5%, with 12.2% of never, 10.9% of former and 9.7% of current marijuana users having albuminuria. There was no independent association of marijuana use with CKD outcome.

Conclusions: Marijuana use was prevalent among this urban population. We found no independent association of marijuana use with prevalent CKD. The effects of marijuana use on long term renal outcomes warrants further study.

SA-PO934

Effect of -55C/T Polymorphism of Uncoupling Protein 3 Gene on Risk for New-Onset Diabetes in Chinese Peritoneal Dialysis Patients: A Prospective Cohort Study
Yan Chen,1 Shuai Dai,1 Da Shang,2 Chun-Ming Hao,2 Tongying Zhu,2 Huashan Hospital, Fudan university, Shanghai, China; 3Huashan Hosp., Shanghai, China.

Background: Patients who have no history of glucose intolerance could develop diabetes mellitus after the initiation of PD therapy due to a high glucose load. Different genetic background may result in risk modulation. However, it has been rarely explored among PD patients. Uncoupling protein 3 (UCP3) belongs to a family of mitochondrial transporters and is associated with energy homeostasis. The aim of our study was to investigate the effect of polymorphism of the UCP3 promoter (-55C/T) on the risk of new-onset diabetes mellitus (NODM) in PD patients.

Methods: Non-diabetic patients newly started on PD therapy between May 2005 and March 2018 were recruited (n=190). The -55C/T polymorphism of UCP3 was genotyped in all participants at baseline. Patients were divided into two groups based on the genotype difference. The cohort was followed for up to 165 months (median: 60.1 months; interquartile range: 34.1 months). Cox regression models were used to analyze the impact of -55C/T polymorphism on risks of NODM. Association between glucose intolerance and genotypes was further ascertained in a second cohort of HOMA-IR low and high subjects.

Results: 62 patients (41.3%) had the genotype -55C/C (wild group), whereas 88 patients (58.7%) were T carriers (mutant group). During the follow-up, 14 NODM occurred in the mutant group while only 4 occurred in the wild group. Patients in the mutant group experienced significantly higher morbidity (HR: 3.324; 95% CI: 1.088 to 10.151; p = 0.035). Even after adjustments for age, body mass index, total cholesterol, triglycerides, and HOMA-IR, genotypes with T allele remained an independent predictor of NODM morbidity (HR: 5.804; 95% CI: 1.739 to 19.375; p = 0.004). In the mutant group, HOMA-IR values were higher. Frequencies of the T allele were 27.7% in the HOMA-IR low group compared with 42.1% (p=0.009) in the HOMA-IR high group. The variant of T allele was significantly associated with a higher HOMA-IR value (OR: 2.287; 95% CI:1.177-4.445; p=0.015).

Conclusions: The variant of T allele of UCP3 -55C/T polymorphism was associated with high insulin resistance and was an independent predictor of NODM in PD patients. Early identification of the genotype may provide scientific basis for clinic management of PD patients, improving the surveillance and prevention of diabetes.

Funding: Other NIH Support - National Natural Science Foundation of China (NSFC)

SA-PO935

GLP-1 Analogue Ameliorates Progression of Not Only Left Ventricular Hypertrophy But Also Atrial Volume in Patients with Type 2 Diabetes Mellitus on Peritoneal Dialysis
Takeyuki Hiramatsu, Konan Kosei Hospital, Konan Aichi, Japan.

Background: Diabetes mellitus (DM) is a progressive multifactorial disease associated with cardiovascular complications. Patients undergoing peritoneal dialysis also experience an increased incidence of cardiovascular disease. To prevent progression of systemic cardiovascular complications in DM patients, glycolytic control is important. Moreover, left ventricular mass index (LVMi) or left atrial volume index (LAVi) were known to be the predictive factors for mortality in dialysis patients. In this study, we examined the efficacy and safety of the glucagon-like peptide analogue (GLP-1) to treat type 2 diabetes mellitus patients undergoing peritoneal dialysis.

Methods: Thirty-four type 2 diabetes patients who underwent peritoneal dialysis were enrolled. Participants were divided in two groups (Group A; n=24, iraglutide 0.9mg daily, Group B; n=10, darulaglutide 0.75mg once a week). Prior to GLP-1 therapy, 16 patients used insulin, 8 used oral antidiabetic agents, and 3 used diet therapy. After iraglutide initiation, biochemical examination and echocardiography was examined at baseline and every 12 months for 36 months.

Results: In Group A, there were no differences in glycemic control before and after initiation of iraglutide. Nevertheless, medical adherence was improved after iraglutide use. After iraglutide use, brain natriuretic peptide (BNP) and human atrial natriuretic peptide (HANP) were significantly decreased. Moreover, echocardiographic finding showed LAVi and LAVi were significantly ameliorated instead of unchanged left ventricular end diastolic volume.

Conclusions: These findings suggest that GLP-1 analogue for type 2 diabetes patients undergoing peritoneal dialysis improved medical adherence and was effective for ameliorating left ventricular dysfunction. Moreover, it may ameliorate progression of diastolic function including E/e’ and LAVi.

Funding: NIDDK Support

Table. Clinical data change

<table>
<thead>
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<th>Group</th>
<th>Baseline</th>
<th>After 36 months</th>
<th>p-value</th>
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<td>171.3 ± 18.1</td>
<td>153.8 ± 13.1</td>
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<tr>
<td>LAVi (ml/m²)</td>
<td>47.7 ± 11.3</td>
<td>38.5 ± 8.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SA-PO936

Higher Neutrophil to Lymphocyte Ratio (NLR) Associates with Poor Clinical Outcome Independent of Traditional Factors in Peritoneal Dialysis Patients
Chen Zhihui,1 Abdal Rashid T. Qureshi,3 Fei Han,1 Xishao Xie,3 Peter Stenvinkel1 Bengt Lindholm,1 Xiaohui Zhang,1 Jianghua Chen,1 Kidney Disease Center, 1st Affiliated Hospital College of Medicine, Zhejiang University, Hangzhou, China; 2Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden; 3Karolinska Institutet, Huddinge, Sweden; 4First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; 5Kidney Disease Center, The First Affiliated Hospital, Medical School of Zhejiang University, Hangzhou, China; 6Karolinska University Hospital Huddinge, Stockholm, Sweden; 7Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; 8Zhejiang University, Hangzhou, China.

Background: Neutrophil to lymphocyte ratio (NLR) is an inexpensive and widely available biomarker of inflammation that predicts clinical outcomes in dialysis patients. However, the association between NLR and mortality among patients treated with peritoneal dialysis (PD) is not fully explored.

Methods: In 767 incident PD patients (median age 50 years, 57% males, 15% diabetes and 6% cardiovascular disease, CVD), baseline NLR and other metabolic biomarkers potentially linked to CVD were analysed in relation to mortality during follow up period of up to 60 months. All-cause and cardiovascular mortality risk associated with NLR were evaluated using competing-risk regression models with transplantation as competing risk, adjusting for all investigated covariats.

Results: Patients with highest tertile of NLR were older, had higher creatinine and higher cholesterol, and were more likely to have diabetes. In the highest tertile of NLR, 9% had diabetes, whereas 2% in the low tertile. NLR associated with white blood cell count (rho=-0.33, p=0.001), age (rho=0.10, p=0.01), calcium (rho=-0.10, p=0.01), iPTH (rho=0.09, p=0.001) and C-reactive protein (n=644; rho=0.10, p=0.01). Highest tertile of NLR associated with high all-cause mortality risk compared with low + middle tertiles, sub-hazard ratio (sHR) of 1.79 (95% CI, 1.18-2.73; p=0.006), and high CVD mortality risk, sHR 1.55 (95% CI, 0.85-2.85; p=0.01).

* p<0.01, ** p<0.05 vs at baseline

Funding: Other NIH Support - National Natural Science Foundation of China (NSFC)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
after adjusting for Framingham’s score, presence of CVD, circulating levels of uric acid, creatinine, calcium, phosphorus, Hb, iPTH, alkaline phosphatase, ALT and AST, and calendar year of recruitment.

Conclusions: In patients undergoing PD, higher NLR was associated with increased all-cause mortality risk, independently of Framingham’s risk score and additional confounders, suggesting that this biomarker of inflammation is a useful prognostic tool in PD patients.

SA-PO936
TH1 and TH2 Immune Response to External Stimuli in Patients on Peritoneal Dialysis
Arshi Rizwan, Sandeep Mahajan.

Background: Inflammation, Peritoneal Transport

Methods: PBMCs were isolated as per standard procedure and were seeded in tissue culture plates in a concentration of 1 x 10^6 cells/well. They were stimulated with phytohaemagglutinin (PHA, a potent T- and B-cell mitogen), peritoneal dialysate effluent (PDE) and fresh peritoneal dialysis fluid (PDF; Baxter, India). To evaluate the cytokine productions by stimulated PBMCs, ELISA was performed.

Results: In CAPD patients the expression of TH1 (IL-1β, TNFα, IFNγ), TH2 (IL-10, IL-4) cytokines from PBMCs stimulated by dialysate effluent was significantly lower compared with CKD5 (P<0.01, P<0.01, P<0.01, P<0.01, and P<0.001 P<0.004, respectively) and healthy controls (P<0.01, P<0.01, P<0.01, P<0.01, and P<0.01, respectively). TH1 (TNFα, IFNγ, IL-1β), TH2 (IL-4) and regulatory (IL-10) cytokines were significantly lower in PD patients when compared with healthy controls stimulated by dialysate effluent. PDE of PD patients stimulated by fresh fluid expressed reduced TH1 cytokines than those dialysed effluents. Cytokine immune response was significantly reduced when stimulated with PDE and dialysate effluent in PD patients as compared with CKD5 patients and controls. Cytokines values were significantly more with PHA followed by PDE and PDF for each group.

Conclusions: Polariization of helper T-cells in response to mitogenic stimulation was blunted in CAPD patients compared with controls and CKD 5 resulting in a significant decrease in both Th1 cells and Th2 cells. These studies suggest that the clinical presentation of the dialysis was influenced by the type of cytokine (Th1 and Th2) production.

Funding: Government Support - Non-U.S.

SA-PO937
T Regulatory Cells in Ureemia: Effect of the First Peritoneal or Hemodialysis Treatment
Carlotta Caprara, Valentina Corradi, Rahul Sharma, Elisa Scallotto, Massimo de Cal, Claudio Ronco, IRRIV, Vicenza, Italy; San Bortolo Hospital, Vicenza, Italy; University of Virginia, Charlottesville, VA; University of Padova, IRRIV, San Bortolo Hospital, Vicenza, Italy.

Background: A major challenge for the immune system is to preserve tolerance to self while maintaining the ability to fight foreign pathogens and infectious agents. This function is largely performed by the FOXP3+ T-regulatory (Treg) cells. In the literature, contrasting results have been reported about the influence of dialysis on Treg cells, in chronic kidney disease stage G5 (CKD G5) patients that show activated but impaired immune system. The aim of this study is to evaluate the changes in Treg cells numbers before and after the first dialysis treatment.

Methods: Peripheral blood samples for this pilot study were obtained from 21 CKD G5 patients not yet on dialysis (CKD G5): 8 started hemodialysis (HD, N = 8), 13 started peritoneal dialysis (PD, N = 13). Treg were studied by flow cytometry using CD3-PerCP; CD4-PE; CD25-FITC; CD127-PE and FOXP3-APC antibodies. Time point: T0 (before the first dialysis treatment); T1 (after 1 month). We performed Wilcoxon test for dependent samples to compare the mean percentage difference between T0 and T1 (%): (100×(T1-T0)/T0).

Results: The total cohort (8HD and 13PD, n = 21) included 88.9% and 77% males in HD and PD groups respectively. Mean age was 68 in HD group and 67 in PD group. The proportion of lymphocytes and T lymphocytes did not change before and after the first dialysis treatment (as evaluated 1 month after the start of dialysis) in PD and HD patients. Treg (considered either as CD25+ FOXP3+, Foxp3- or CD25-CD127+) and percentage of lymphocytes showed a statistically significant increase post-PD (median=35.92; P=0.0425 for CD25+ FOXP3+; median=30.85; P=0.0479 for FOXP3+ and median=23.71; P=0.0215 for CD25+ CD127+). The same populations did not change after the first HD session (median=0.07; P=0.843 for CD25+ FOXP3+; median=2.32; P=0.945 for FOXP3+ and median=6.09; P=0.742 for CD25- CD127-).

Conclusions: Our study is the first to evaluate the effect of PD or HD treatment on the status of T-regulatory cells to understand their role in immune homeostasis. PD was more effective in increasing Tregs levels when analyzed at one month post dialysis and may contribute to improvement of inflammatory status. Thus, PD may contribute to better outcomes for patients with renal dysfunction by not only restricting inflammation, but also maintaining homeostasis of peritoneal and renal tissues.

Funding: Private Foundation Support

SA-PO938
Implication of InflammamsosActivation in the Progression of Peritoneal Fibrosis in Mice
Hiroaki Kadoya, Yuji Sogawa, Minoru Satoh, Tamaki Sasaki, Naoki Kashihara. Kawasaki Medical School, Kurashiki, Japan.

Background: During peritoneal dialysis, the peritoneum is exposed to bio-compatible dialysate, which causes tissue fibrosis, which then limit the long-term effectiveness of peritoneal dialysis. Peritoneal fibrosis is the end result of chronic inflammation reactions induced by a variety of stimuli including peritonitis, allergic responses. Thus, understanding the molecular events that drive fibroproliferation and matrix deposition has been a favored area of investigation. However, the detailed mechanisms underlying peritoneal fibrosis are not well understood. The finding that activation of inflammasomes triggers chronic inflammation, which ultimately causes fibrosis. We investigated whether inflammasome activation causes peritoneal fibrosis.

Methods: We used ASC-deficient mice (ASCKO) to investigate the role of inflammasome, which ASC are critical components of the inflammasome. C57Bl/6 mice (WT) were used for control. Peritoneal fibrosis was induced by chlorhexidine gluconate (CG) into the peritoneal cavity of mice every other day for 4 weeks. VX-765 (100 mg/kg/day), an inhibitor of caspase-1 activity, was administered by gavage for 2 weeks. The mice were divided into the following groups: (1) WT-vehicle, (2) WT-CG, (3) ASCKO-vehicle, (4) ASKO-CG, and (5) WT-CG VX-765.

Results: After exposure to CG, WT-CG mice showed the progression of peritoneal fibrosis evaluated by Mason’s trichrome stain, and also been observed to enhance mRNAs expression of TGFB-1 in peritoneal tissue. Increased expression of inflammasome components, NLRP-3 and ASC, were demonstrated in WT-CG. Increased Caspase-1 activity and concomitant overproduction of IL-1β and IL-18 were also demonstrated in the WT-CG. These changes were suppressed in the ASCKO-CG and VX-765 injected mice. Furthermore, ASC-/- mice were merged with the immunofluorescent staining for the macrophage marker F4/80. Therefore, inflammasomes were mainly activated in the infiltrating macrophages.

Conclusions: Our results suggest that inflammasome activation plays a pivotal role in the development of peritoneal fibrosis in infiltrated macrophages. Thus, inflammasome activation and inflammasome macrophages could be a new therapeutic target for chronic inflammation-induced peritoneal fibrosis.

SA-PO939
Innate Immunity Dysfunction: A Prospective Study on Peritoneal Dialysis and Hemodialysis
Ana C. Figueiredo, Rita Leal, Helena O. Sa, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; Nephrology University Clinic, Medicine Faculty of University of Coimbra, Coimbra, Portugal; Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

Background: The immunological disorder associated with chronic kidney disease is complex since there is a coexistence of a proinflammatory state and immunological deficiency, both contributing to patients’ morbidity and mortality. The immune dysfunction observed in renal disease covers both innate and adaptive immunity, although disturbances in the innate branch are far better described in the literature. The aim of the present work is to study the innate immune system changes in patients undergoing hemodialysis and peritoneal dialysis, and if significant renal function influence innate immunity.

Methods: A prospective, case-control study was performed using peripheral blood samples from 21 patients undergoing PD, 20 patients undergoing HD and 12 healthy patients. Whole blood cells were analyzed and quantification of leucocyte subpopulations and surface molecules was made by flow cytometry using different fluorescent antibody conjugates.

Results: There was a significant decrease in monocytes and dendritic total cell counts in dialysis patients compared to healthy controls. Natural killer cells in hemodialysis patients, compared to peritoneal dialysis and controls, had enhanced expression of the receptors NKG3α, NKG4α, CD94/NKG2C, and IFNγ, indicating enhanced cytokine production, and increased expression of CD57. Hemodialysis patients also presented more pro-inflammatory markers in iNKT and gd T cells than peritoneal dialysis patients.

Conclusions: Our study suggests an innate immunity dysfunction in dialysis patients, more evident in hemodialysis patients that express a proinflammatory profile and chronic activation of the innate immune system.
Mean Corpuscular Volume Associates with Clinical Outcome in Incident Peritoneal Dialysis Patients

Chen Zhihim,1, 2 Abdul Rashid T. Qureshi,1 Xiaohui Zhang,4 Fei Han,4 Xishao Xie1; Bengt Lindholm,1 Peter Stenvinkel,3 Jianghua Chen.1 Kidney Disease Center, 1St Affiliated Hospital College of Medicine, Zhejiang University, Hangzhou, China; 2Division of Renal Medicine and Baxter Novum, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; 3Karolinska Institutet, Huddinge, Sweden; 4First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; 5Kidney Disease Center, The First Affiliated Hospital, Medical School of Zhejiang University, Hangzhou, China; 6Karolinska University Hospital Huddinge, Stockholm, Sweden; 7Kidney Disease Center, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; 8Zhejiang University, Hangzhou, China.

Background: Mean corpuscular volume (MCV), a measure of the average size of circulating erythrocytes, is used for differential diagnosis of anemia and for monitoring macrocytosis. While several studies revealed that MCV is associated with mortality in various clinical settings, it is unclear whether this association applies to PD patients. We investigated the relationship of MCV with all-cause and cardiovascular mortality in incident PD patients.

Methods: In 767 incident PD patients (median age 50 years, 57 % males, 15 % diabetes, DM, and 6 % cardiovascular disease, CVD), MCV and other metabolic biomarkers potentially linked to CVD were analyzed at baseline. We investigated associations (Pearson correlations) with MCV at baseline and during follow up period of up to 60 months analyzed the association of MCV with mortality risk using competing-risk regression models with transplantation as competing risk and adjusting for covariates.

Results: In univariate analysis, MCV associated with white blood cell count (rho=-0.01, p<0.001), age (rho=0.15, p<0.001), BMI (rho=0.15, p<0.001), gender (rho=-0.14, p<0.002), uric acid (rho=0.15, p<0.001), HDL cholesterol (rho<0.10, p<0.005), parathyroid hormone (rho=0.12, p<0.001), ASAT (rho=0.12, p<0.001) and DM (rho=-0.09, p<0.001). Compared with middle: high tertiles, the lowest tertile of MCV associated with decreased all-cause mortality risk, sub-hazard ratio (SHR) of 0.61 (95% CI, 0.42-0.89; p=0.01), and with decreased CVD mortality risk, SHR 0.50 (95% CI, 0.29-0.87; p=0.01) after adjusting for age, gender, DM, CVD and calendar year of recruitment.

Conclusions: In incident PD patients, after adjusting for age, sex, and presence of CVD at attributes, low MCV was independently associated with decreased all-cause and CVD mortality risk. These results suggest that monitoring of MCV may provide useful prognostic information in patients treated with PD.

Mean Corpuscular Volume Associates with Clinical Outcome in Incident Peritoneal Dialysis Patients

Chen Zhihim,1, 2 Abdul Rashid T. Qureshi,1 Xiaohui Zhang,4 Fei Han,4 Xishao Xie1; Bengt Lindholm,1 Peter Stenvinkel,3 Jianghua Chen.1 Kidney Disease Center, 1St Affiliated Hospital College of Medicine, Zhejiang University, Hangzhou, China; 2Division of Renal Medicine and Baxter Novum, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden; 3Karolinska Institutet, Huddinge, Sweden; 4First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; 5Kidney Disease Center, The First Affiliated Hospital, Medical School of Zhejiang University, Hangzhou, China; 6Karolinska University Hospital Huddinge, Stockholm, Sweden; 7Kidney Disease Center, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; 8Zhejiang University, Hangzhou, China.

Background: Mean corpuscular volume (MCV), a measure of the average size of circulating erythrocytes, is used for differential diagnosis of anemia and for monitoring macrocytosis. While several studies revealed that MCV is associated with mortality in various clinical settings, it is unclear whether this association applies to PD patients. We investigated the relationship of MCV with all-cause and cardiovascular mortality in incident PD patients.

Methods: In 767 incident PD patients (median age 50 years, 57 % males, 15 % diabetes, DM, and 6 % cardiovascular disease, CVD), MCV and other metabolic biomarkers potentially linked to CVD were analyzed at baseline. We investigated associations (Pearson correlations) with MCV at baseline and during follow up period of up to 60 months analyzed the association of MCV with mortality risk using competing-risk regression models with transplantation as competing risk and adjusting for covariates.

Results: In univariate analysis, MCV associated with white blood cell count (rho=-0.01, p<0.001), age (rho=0.15, p<0.001), BMI (rho=0.15, p<0.001), gender (rho=-0.14, p<0.002), uric acid (rho=0.15, p<0.001), HDL cholesterol (rho<0.10, p<0.005), parathyroid hormone (rho=0.12, p<0.001), ASAT (rho=0.12, p<0.001) and DM (rho=-0.09, p<0.001). Compared with middle: high tertiles, the lowest tertile of MCV associated with decreased all-cause mortality risk, sub-hazard ratio (SHR) of 0.61 (95% CI, 0.42-0.89; p=0.01), and with decreased CVD mortality risk, SHR 0.50 (95% CI, 0.29-0.87; p=0.01) after adjusting for age, gender, DM, CVD and calendar year of recruitment.

Conclusions: In incident PD patients, after adjusting for age, sex, and presence of CVD at attributes, low MCV was independently associated with decreased all-cause and CVD mortality risk. These results suggest that monitoring of MCV may provide useful prognostic information in patients treated with PD.

Genetic or Pharmacologic Blockade of Enhancer of Zeste Homolog 2 Inhibits the Progression of Peritoneal Fibrosis

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Background: Disruption of histone methyltransferase enhancer of zeste homolog 2 (EZH2) has been implicated in many cancers. However, the role of EZH2 in peritoneal fibrosis remains unknown.

Methods: We investigated EZH2 expression in peritoneal dialysis (PD) patients and assessed its role in peritoneal fibrosis induced by chlorhexidine gluconate (CHG) or high glucose peritoneal dialysis fluid (PDF) in mice by using 3-deazaneplanocin A (3-DZNeP), and assessment of EZH2 inhibition in fibrotic mouse models.

Results: An abundance of EZH2 was detected in the peritoneum of patients with PD-associated peritonitis and the dialysis effluent of long-term PD patients. EZH2 was also highly expressed in the peritoneum of mice after injury by CHG or PDF, and treatment with 3-DZNeP alleviated peritoneal fibrosis and inhibited activation of several pro-fibrosis mediators. Moreover, delayed administration of 3-DZNeP inhibited peritoneal fibrosis progression, reversed established peritoneal fibrosis and reduced matrix metalloproteinases-2 (MMP-2) and MMP-9 expression. Finally, EZH2-KO mice exhibited less peritoneal fibrosis compared with EZH2 WT mice. In cultured peritoneal mesothelial cells, EZH2 inhibition resulted in suppression of α-SMA and Collagen I and preservation of E-cadherin.

Conclusions: These results indicate that EZH2 is a key epigenetic regulator that promotes peritoneal fibrosis. Targeting EZH2 may have the potential to prevent and treat peritoneal fibrosis.

Nuclear Factor of Activated T Cells 5 Mediates Peritoneal Fibrosis via Modulation of Nod-Like Receptor 3 (NLRP3) Inflammation

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Background: NLRP3 is a multiprotein oligomer that promotes inflammation triggered by danger signals is mediated through a multiprotein complex called the NLRP3 inflammasome. The patho-physiological mechanisms of NLRP3 activation in the peritoneum could be a novel approach to protect peritoneal fibrosis in PD patients.

Methods: We investigated NLRP3 expression in peritoneal dialysis (PD) patients and assessed its role in peritoneal fibrosis induced by chlorhexidine gluconate (CHG) or high glucose peritoneal dialysis fluid (PDF) in mice by using 3-deazaneplanocin A (3-DZNeP), and assessment of EZH2 inhibition in fibrotic mouse models.

Results: An abundance of EZH2 was detected in the peritoneum of patients with PD-associated peritonitis and the dialysis effluent of long-term PD patients. EZH2 was also highly expressed in the peritoneum of mice after injury by CHG or PDF, and treatment with 3-DZNeP alleviated peritoneal fibrosis and inhibited activation of several pro-fibrosis mediators. Moreover, delayed administration of 3-DZNeP inhibited peritoneal fibrosis progression, reversed established peritoneal fibrosis and reduced matrix metalloproteinases-2 (MMP-2) and MMP-9 expression. Finally, EZH2-KO mice exhibited less peritoneal fibrosis compared with EZH2 WT mice. In cultured peritoneal mesothelial cells, EZH2 inhibition resulted in suppression of α-SMA and Collagen I and preservation of E-cadherin.

Conclusions: These results indicate that EZH2 is a key epigenetic regulator that promotes peritoneal fibrosis. Targeting EZH2 may have the potential to prevent and treat peritoneal fibrosis.
performed in the PD clinic via the liberDi’s PDPS™ under supervision of the PD team, followed by a one-month closed follow-up.

Results: Average drainage time was 10.7±2.3 min, filling time 8±2.6 min. Three patients noted mild abdominal discomfort at the end of the draining and start of filling (not unusual for them), while one patient showed slow drainage and shifted to a regular manual exchange. None of the patients developed peritonitis during the follow-up period. One patient died due to acute ST elevation myocardial infarction 5 days after the trial procedure, which was considered as unrelated to the procedure itself.

Conclusions: This first-in-human study showed the safety of liberDi’s PDPS device demonstrating its feasibility in a single automatic PD exchange. Its use seems to be convenient, easy and safe.

Funding: Commercial Support - liberDi

SA-PO945

The Significance of Mini-PET and Fibrosis-Related Factors in Effluents in Peritoneal Function

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Background: Peritoneal dysfunction characterized by peritoneal fibrosis is the problem of long-term peritoneal dialysis. Recent studies have reported that sodium sieving (ΔNa) in mini-PET was correlated with free water transport (FWT) and peritoneal fibrosis. We previously reported that lysophosphatidylcholine (LPC) signaling-dependent connective tissue growth factor (CTGF) was significant to peritoneal fibrosis. Therefore, we examined the association of mini-PET markers with fibrosis-related factors in effluents. In addition, we measured autotaxin (ATX), which is the enzyme of LPA production as well as assessed peritoneal function-related factors such as ANa and FWT. ANa was determined by the difference of sodium concentration in dialysate between 1 hr and 0 hr, and FWT by ultrafiltration volume except for the influence of sodium removal. In addition, we assessed peritoneal function-related factors such as ANa and FWT. We also performed standard-PET (4hrs-dwell) to assess D/P Cr and D/D0, and estimated the association of these values with mini-PET markers as well as the fibrosis-related factors.

Methods: ANa had the correlation with FWT (r=0.86, p<0.01), D/P Cr (r=0.28, p<0.05), D/D0 (r=0.40, p<0.01). In cases observed over the years (n=16), ANa at 1 year had the correlation with FWT (r=0.82, p<0.01) and D/P Cr (r=0.65, p<0.01) at 2nd year. The changes of ANa had the correlation with the change of ultrafiltration (r=0.61, p<0.05). Moreover, ANa had the correlation with ATX (r=0.80, p<0.01) and CTGF (r=0.75, p<0.01).

Conclusions: ANa and fibrosis-related factors in effluents have the possibility to be the predictive factors of peritoneal function.

SA-PO946

Nintedanib Attenuates the Development and Progression of Peritoneal Fibrosis

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Background: Nintedanib, a FDA approved triple tyrosine kinase inhibitor, has antifibrotic effects in idiopathic pulmonary fibrosis and renal fibrosis. Here, we examined the effect of nintedanib on the development and progression of peritoneal fibrosis.

Methods: Daily intraperitoneal injections of chlorhexidine gluconate (CG) induced peritoneal fibrosis in mouse and TGF-β1 was used to induce fibrotic changes in cultured human peritoneal mesothelial cells (HPMCs). The effects of nintedanib were determined by histochemical and immunofluorescence staining, immuno blot and ELISA analysis.

Results: Administration of nintedanib immediately after injury prevented the onset of peritoneal fibrosis and delayed administration of nintedanib (3 days after the onset of peritoneal fibrosis) halted fibrosis progression. Nintedanib treatment abrogated the increased phosphorylation of PDGFR, FGFR, VEGFR, Src, decreased the expression of extracellular matrix(ECM) protein (Fibronectin and type I Collagen), inhibited the expression if marker proteins of mesenchymal phenotype (α-SMA,β1 integrin) and transcription factors(Snail and Twist), increased expression E-Cadherin, blocked the phosphorylation of Smad3, STAT3, and NFKB during peritoneal fibrosis; it also inhibited the accompanying overproduction of proinflammatory cytokines (MCP-1, TNF-α, IL-1β, and IL-6) and the infiltration of macrophages (CD68-positive) to the injured peritoneum, and reduced the peritoneal increase of CD31-positive blood vessels after injury. Moreover, delayed administration of nintedanib significantly induced MMP-2 expression and inhibited TIMP-2 expression. Finally, nintedanib abrogated TGF-β1-induced the epithelial-to-mesenchymal transition, ECM protein overproduction and phosphorylation of aforementioned cell signaling molecules in cultured human peritoneal mesothelial cells.

Conclusions: These results demonstrate that nintedanib may inhibit epithelial-to-mesenchymal transition, extracellular matrix overproduction inflammation and angiogenesis, and improved extracellular matrix degradation, possibly through its blockage of PI3Ks and Src simultaneously. It suggests that nintedanib may have therapeutic potential in attenuating onset and progression of peritoneal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO947

Deletion of Matrix Metalloproteinase 10 Ameliorates Peritoneal Fibrosis

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Background: Peritoneal fibrosis is one of major characteristics of peritoneal membrane damage. Our group previously reported highly upregulated genes in the peritoneal membrane from chlorhexidine gluconate (CG)-treated peritoneal fibrosis mice compared with control in microarray analysis, one of which was matrix metalloproteinase-10 (MMP-10). MMP-10 was a proteasome protein degrading components of extracellular matrix (ECM) and was known to be associated with arteriosclerosis or tissue repair. Although deletion of MMP-2 and MMP-9, which were called gelatinases, ameliorated peritoneal fibrosis, the role of MMP-10 has not been elucidated in peritoneal fibrosis yet.

Methods: To investigate the role of MMP-10 in peritoneal fibrosis, we induced peritoneal fibrosis by intraperitoneal injection of chlorhexidine gluconate in wild-type (WT) and MMP-10 knockout (KO) mice. We administrated 0.01 mL/gBW of 0.1% CG in 15% ethanol and 85% phosphate-buffered saline (PBS) 3 times per week for 4 weeks. Control mice received intraperitoneal injection of PBS. Peritoneal sections were stained with Masson’s trichrome and were analyzed by immunohistochemical staining.

Results: We identified upregulation of MMP-10 by 8.6-times in the peritoneum from CG-treated WT mice by a microarray analysis. There were no histological changes in the peritoneum between PBS-treated WT mice and PBS-treated MMP-10 KO mice. CG-treated WT mice had a remarkable thickening of peritoneum, an increased number of CG-F4/80-positive cells in the peritoneum, and upregulation of MMP-10 mainly within the mesothelial cells and fibroblasts in the submesothelial area of the peritoneum. In contrast, CG-treated MMP-10 KO mice showed reduction of peritoneal thickness and accumulation of CG-F4/80-positive cells in the peritoneum. Furthermore, the peritoneal enhanced expression of Tgfb1, Col1a1, Ctgf, and Col2 (MCP1) in WT mice was remarkably reduced in MMP-10 KO mice.

Conclusions: These results indicate that MMP-10 is upregulated in mesothelial cells and fibroblasts in peritoneal injury and can aggravate peritoneal fibrosis. Therefore, inhibition of MMP-10 could become a therapeutic strategy in peritoneal fibrosis.

SA-PO948

Valsartan Ameliorates High Glucose-Induced Peritoneal Fibrosis by Blocking mTORC1 Signaling

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Background: Increasing evidences suggest that angiotensin II type 1 receptor (AT1R) blockers prevent peritoneal fibrosis (PF) under high glucose (HG) conditions. The study aimed to investigate the undefined mechanisms by which AT1R blocker valsartan on HG induced PF.

Methods: We used HG peritoneal dialysis solution (PDS) in a mouse peritoneal dialysis model to induce in vivo PF and HG in human peritoneal mesothelial cells (HPMCs) in vitro to stimulate extracellular matrix (ECM) accumulation.

Results: After the injection of 4.25% PDS for 4 weeks, mice showed typical features of PF, including markedly increased peritoneal thickness, excessive matrix deposition, increased peritoneal permeability, and higher expressions of ECM markers, such as α-smooth muscle actin (α-SMA) and collagen I. Valsartan significantly ameliorated these pathological changes at either week 6 or 8. These effects of valsartan were closely correlated with a decrease in the activation of mammalian target of rapamycin (mTOR) in the peritoneum. This was mediated through the down-regulation of protein expressions of phosphorylated-mTOR (p-mTOR), p-ekarystotic initiation factor 4E-binding protein 1 (p-4EBP1), and P-70 S6 kinase (p-S6K1). Further analysis showed the protein expression of α-SMA and collagen I in the peritoneum. In vitro, HG increased the protein expressions of α-SMA and collagen I in a dose dependent manner, while valsartan significantly inhibited HG-induced ECM accumulation in HPMCs. The effect was also accompanied by a decrease in the activation of mTORC1 pathway. Furthermore, mTOR agonist MIY1485 could reverse the downregulation of ECM components in HPMCs, even in the presence of valsartan.

Conclusions: We conclude that valsartan shows a protective effect on HG-induced PF by inhibiting the activity of mTORC1 pathway.

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SA-PO949

Pasp Deletion Mutation Reduced the Virulence and Pathogenic Ability of Pseudomonas aeruginosa

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Background: Pseudomonas aeruginosa is a very important conditional pathogen commonly existing in the environment, and it is the main pathogen of catheter-related infection in peritoneal dialysis. The formation of intraductal biofilm is an important reason, and the expression of PasP protein is increased in Pseudomonas aeruginosa, which is easy to form biofilm. It is intended to further explore the effect of PasP protein on the virulence of Pseudomonas aeruginosa.

Methods: The pasP gene of Pseudomonas aeruginosa PAO1 was knocked out by homologous recombination method, and the PAO1::pasP strain was constructed. The following parameters of parental bacteria and homologous recombinant bacteria were observed: colony morphology, biofilm forming ability, minimum bacterial concentration of common antibiotics to bacteria, tolerance of bacteria to temperature, determination of bacterial virulence (pyocyanin, protease, elastase). Difference analysis of protein spectrum were performed;

Results: the pasP gene of Pseudomonas aeruginosa PAO1 was successfully deleted, PAO1::pasP was successfully constructed by homologous recombination. The relative virulence of PAO1::pasP was weaker than that of parent bacteria, including the weakening of biofilm formation ability and the decreasing tolerance to temperature. The production of pyocyanin, protease, elastase were all decreased. The expressions of two-component reaction regulator, two-component sensor, ATP binding protein of ABC transporter, bacteriophage protein, purine binding protein, and the two-component reaction regulator, two-component sensor, ATP binding protein, bacteriophage protein and purine binding protein of PDX transporter decreased, Aer2 protein, type IV flagellan Flip and rhomnose glycose/transferase subunit A were significantly lower than in PAO1::pasP strain than in parental bacteria.

Conclusions: Pseudomonas aeruginosa pasP gene is involved in the biofilm formation and QS sensing system, and pasP gene deficient strains show weaker bacterial virulence and pathogenic ability.

SA-PO950

Effluent DcR2 Is a Novel Biomarker for Peritoneal Fibrosis in Peritoneal Dialysis Patients

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Background: Peritoneal fibrosis is the most severe complication of peritoneal dialysis (PD), but lack of noninvasive biomarkers for monitoring the rate of progression of peritoneal fibrosis. Decoy receptor 2(DcR2), a marker of senescence, has been used to evaluate the degree of differentiation of tumors. The aim of this study is to determine whether peritoneal effluent DcR2 could serve as a novel specific and sensitive biomarker for assessing peritoneal fibrosis.

Methods: 149 PD patients (PD duration>6 months) were enrolled in our unit from 2008 to 2018, free from acute infection and recent peritonitis. The fibrosis of peritoneal biopsy tissues were detected by Masson trichrome staining. Effluent and serum DcR2 levels were associated with Duration of PD, total glucose exposure, past peritonitis (%) and 4h D/P. The area of under curve was 0.74 for peritoneal fibrosis, Effluent DcR2-AR levels were associated with Duration of PD, total glucose exposure, past peritonitis (%) and 4h D/P. The area of under curve was 0.74 for peritoneal fibrosis, Effluent DcR2-AR levels were associated with Duration of PD, total glucose exposure, past peritonitis (%) and 4h D/P. The area of under curve was 0.74 for peritoneal fibrosis.

Results: There were 75 patients with peritoneal fibrosis and 74 without. Effluent and serum DcR2 levels had no statistical difference between two groups, but DcR2-AR levels were higher in patients with peritoneal fibrosis compared with normal peritoneum. Effluent DcR2-AR levels were associated with Duration of PD, total glucose exposure, past peritonitis (%) and 4h D/P. The area of under curve was 0.74 for peritoneal fibrosis, with a sensitivity of 73% and specificity of 76%, respectively. DcR2 was co-expressed with vimentin and colocalized with α-SMA and FN in peritoneal tissue.

Conclusions: Effluent DcR2 can potentially serve as a novel biomarker for peritoneal fibrosis and may reflect senescence of fibroblasts in PD patients.

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SA-PO951

Hepcidin, Iron Status, and Mineral Metabolism in Peritoneal Dialysis Patients

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Background: Few studies have examined the association between hepcidin, iron status, and bone mineral metabolism in peritoneal dialysis (PD) patients. The present study aimed to investigate the association of hepcidin with iron status and bone mineral metabolism in PD patients.

Methods: Patients who started PD at Seoul National University Hospital from January 2010 to August, 2018 and who had not received renal replacement therapy before and whose baseline serum samples were available were enrolled. Serum hepcidin levels were measured by enzyme-linked immunosorbent assay (ELISA) using Hepcidin 25 (bioactive) HS ELISA kits (DRG Diagnostics, Marburg, Germany), according to the manufacturer’s protocol. Multivariable linear regression analysis was used to identify the association of hepcidin with iron status and bone mineral metabolism.

Results: A total of 162 incident PD patients were analyzed. The patients were 45.4±13.6 years old and 78 (48.1%) were male. The median serum hepcidin level was 50.67 ng/mL (interquartile range, 25.34-83.61 ng/mL). Mean hemoglobin level was 10.4±1.3 g/dL. The prevalence of hemoglobin <10 and <11 g/dL were 40.1% and 67.9%, respectively. Hemoglobin (Pearson correlation, -0.19; P = 0.014) and ferritin (Pearson correlation, 0.59; P = 0.001) were associated with hepcidin in unadjusted analysis. In multivariable linear regression analysis with adjustment for multiple confounders, hepcidin was positively associated with ferritin (β=0.66; 95% confidence interval, 0.50-0.81; P< 0.001). There were no significant associations between hepcidin and markers of mineral metabolism: calcium (Pearson correlation, -0.01; P = 0.161), phosphorous (Pearson correlation, -0.05; P = 0.538), LogPTH (Pearson correlation, 0.05; P = 0.554), 25(OH)D3 (Pearson correlation, 0.04; P = 0.683). Hepcidin levels were not significantly different according to use of iron therapy, erythropoiesis stimulating agents or phosphate binders.

Conclusions: Hepcidin was positively associated with ferritin. There were not significant associations between hepcidin and markers of mineral metabolism in our PD patients.

SA-PO952

Prognostic Value of Serum and Dialysate APX-501 in Chronic Dialysis Patients

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Background: Patients on chronic dialysis are known to be in a chronic inflammation associated with increased oxidative injury, which results in increased morbidity and mortality. Recently APX-501 protein was identified to have regulatory role on oxidative stress. In the present study, we examined the clinical utility of APX-501 levels in serum and dialysate in chronic dialysis patients.

Methods: This study was a multicenter, prospective study that examined the level of serum and dialysate APX-501 in patients on chronic dialysis. Patients on dialysis (both peritoneal (PD) and hemodialysis(HD)) were enrolled between January 2016 to February 2018. Serum APX-501 level was measured using ELISA method. Time to overall mortality was recorded as the primary endpoint. For secondary endpoint, admission for major adverse cardiac events (MACE) and admission due to infection were recorded.

Results: Of 216 patients, patient on PD consisted of 136 patients. 37.5% of PD patients were enrolled initiating PD as the first dialysis modality (defined as new PD). During follow up period of 625±172.8 days, 15 patients died (6.9%), 27 experienced MACE (12.5%), 64 admitted to the hospital due to infection from any cause (29.6%). PD peritonitis event was reported in 35 patients (25.7% of PD group), of which 174/86% patients were who initiated PD for the first time. Serum APX-501 did not predict overall mortality, MACE or acute infection event during the follow up period. In PD patients, dialysate APX-501 level was increased in patients who were initiating PD, and those with increased level of baseline dialysate APX-501 were at an increased risk of incidence for infection including PD peritonitis.

Conclusions: Dialysate APX-501 level may help to predict the risk of infection, especially the risk of PD peritonitis. Whether it can predict imminent PD peritonitis should be studied.

Funding: Commercial Support - Fresenius Medical Care
SA-PO953

Systems Biology Analysis of Lithium-Mediated Cytoprotection in PD
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Background: Peritoneal dialysis fluids (PDF) harm peritoneal cells, leading to transmigration and cell death. Lithium chloride (LiCl), a clinically applicable kinase inhibitor, improved survival of immortalized mesothelial cells. Due to its availability and well-characterized pharmacological profile, LiCl could be a promising molecule to be used as local cytotoxic additive to PDF. The pleiotropic effects of LiCl on mesothelial cells, have not yet been investigated.

Methods: Here, we analyzed the protective potential of LiCl added to PDF in a systems biology approach which combined transcriptomics and proteomics analyses followed by validation in human samples and a chronic mouse model.

Results: PDF with LiCl caused significantly lower cell injury of primary human mesothelial cells in a dose dependent manner. PD-induced cell injury was associated with significantly differential expression of 478 genes and 92 proteins compared to control, LiCl in PDF altered 749 genes and 102 proteins. Pathway over-representation and molecular process enrichment tests showed a strong regulation of angiogenesis related pathways in response to PDF. Analysis of transcripts and proteins that were counter-regulated in PDF with LiCl compared to PDF alone, yielded candidates associated with the LiCl effect, with the small heat shock protein αB-crystallin as most strongly regulated candidate. αB-crystallin was significantly upregulated by PDF but close to control level with LiCl in the omics and targeted analyses. Modulated expression of αB-crystallin, which has been described as regulator of VEGF-mediated angiogenesis, confirmed its regulatory involvement in PD-induced pathomechanisms. Uremic as well as non-uremic mice showed significantly reduced peritoneal membrane thickening and transmigration with LiCl in the omics analyses. In the targeted analyses, we observed the long terms clinical outcomes.

Conclusions: The beneficial effects of LiCl in PDF may be explained by counter-regulation of the PD-induced angiogenesis via the novel target αB-crystallin. Reduction of cell damage and fibrosis suggests therapeutic potential of this intervention.

SA-PO954

Probiotics Decreased Concentrations of Indoxylsulphate in PD Patients
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Background: Clearance of protein-bound uremic toxins (PBUTs) by dialysis is a challenge in the treatment of uremic patients. P-cresylsulphate (PCS) and indoxyl sulphate (IS) are protein-bound urmic toxins which produced in the intestine by certain intestinal bacteria, and the productions of them are affected by various intestinal environmental factors. Quantitative and qualitative alterations in gut microbiome are noted in patients with end-stage renal disease (ESRD). The indol- and p-cresol-forming bacterial families were found more abundant while the formation of short-chain fatty acids was diminished. These changes in intestinal microbial metabolism may contribute to increased increased IS and PCS production. Treatment with probiotics may reduce serum/plasma PCS and IS levels, but there have been no randomised controlled trials to test the effects of probiotics on the serum PCS and IS levels in peritoneal dialysis(PD) patients.

Methods: We conducted a randomised controlled trial to evaluate the effects of probiotics on serum IS and PCS. Participants were randomized to probiotics or control group. Probiotics group received Bifid Triple Viable Capsules 0.42g orally 3 times daily as local cytoprotective additive to PDF. The pleiotropic effects of LiCl on mesothelial cells, have not yet been investigated.

Conclusions: The beneficial effects of LiCl in PDF may be explained by counter-regulation of the PD-induced angiogenesis via the novel target αB-crystallin. Reduction of cell damage and fibrosis suggests therapeutic potential of this intervention.

SA-PO955

Contribution of Proximal Tubular Solute Clearance in Residual Kidney Function
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Background: Residual kidney function (RFK) is associated with better health outcomes in end-stage kidney disease (ESKD). Current assessment of RFK relies on creatinine and urea clearance to estimate the glomerular filtration rate. Proximal tubular secretion is an essential intrinsic kidney function that is rarely measured in ESKD. We measured the kidney and peritoneal clearances of tubular secretory solutes in a primary cohort of incident peritoneal dialysis (PD) patients and determined association with uremic symptoms.

Methods: We enrolled 29 incident PD patients with RFK. We used liquid chromatography-mass spectrometry to quantify plasma, 24-hour urine, and dialysate concentrations of ten tubular secretory solutes. We calculated the kidney and peritoneal dialysis clearances of secretory solutes, creatinine, and urea standardized to 1.73m2. We created a composite secretory clearance score as the average of each solute clearance. We assessed symptom severity using the Dialysis Symptom Index.

Results: The mean age of our cohort was 55 years, mean dialysis duration was 4 months, and mean GFRurea+Cr was 7.8 mL/min/1.73m2. The kidney clearances of secretory solutes ranged from 1.3 mL/min/1.73m2 for p-cresol sulfate to 94.6 mL/min/1.73m2 for hippurate. The residual kidney clearance of each secretory solute was substantially higher than peritoneal dialysis clearance. Worse dialysis symptom severity was correlated with a lower composite secretory clearance score (r = −0.46; p = 0.01) and, to a lesser extent, lower GFRurea+Cr (r = −0.35; p = 0.06).

Conclusions: Among incident PD patients, tubular secretory solutes are more avidly cleared by residual kidney function than peritoneal clearance. Secretory solute clearance correlates more strongly with the severity of uremic symptoms compared with GFRurea+Cr.

Funding: NIDDK Support

SA-PO956

L-Carnitine Supplementation Preserves Residual Renal Function in Patients Undergoing Peritoneal Dialysis
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Background: Residual renal function (RF) is the most important factor to maintain well-being and quality of life in patients undergoing peritoneal dialysis (PD). Carnitine plays a central role in fatty acid b-oxidation and energy production by transporting long-chain fatty acids from the cytoplasm to the mitochondria. Furthermore, carnitine was reported to exhibit antioxidant effects. We previously reported that urine L-carnitine levels were significantly decreased in patients undergoing PD. Therefore, we investigated the impact of L-carnitine supplementation on peritoneal function and RF in these patients.

Methods: Total 24 PD patients with a mean age of 62.6 ± 9.5 years and a mean PD duration of 316.2 ± 316.2 months were randomly assigned to the L-carnitine (750 mg/day, n = 12) or control (n = 12) group and followed for 6 months. Serum free carnitine (FC) and acyl-carnitine (AC) levels were determined by enzyme cycling method. Additionally, the following parameters were measured before and after the treatment period: clinical chemistry, peritoneal function, RF, urine volume, urinary L-FABP, serum LPO, and serum MDA.

Results: Both serum FC and AC levels, which did not differ at baseline between the two groups, significantly increased in the L-carnitine group after treatment (4.7 ± 9.2, 128.2 ± 29.9 and 12.8 ± 3.3, 50.9 ± 16.6 μM/L, respectively). Both the Arenal KiV and Atrial volume, which decreased 6 months in the control group, were preserved in the L-carnitine group (0.46 ± 0.32 vs. 0.02 ± 0.22, p = 0.045; −367.1 ± 473.3 vs. 99.2 ± 316.2 mL, p = 0.010, respectively). The Aserum LPO levels were significantly lower in the
L-carnitine group (0.33 ± 0.81 vs -0.58 ± 0.67 mmol/mL, p = 0.007), whereas the Aurinur-L-Carn group showed a tendency to decrease by L-carnitine treatment (19.5 ± 53.7 vs -24.1 ± 65.0 ng/mL, p = 0.087, -0.02 ± 0.04 vs 0.06 ± 0.06 ng/mL, p = 0.177). Furthermore, there was an inverse correlation between Aurinur volume and AL-FABP (r2 = 0.585, p = 0.004) in the L-carnitine group.

**Conclusions:** L-carnitine supplementation is a promising therapeutic strategy for maintaining RRF by alleviating oxidative stress in L-carnitine-deficient patients undergoing PD.

**SA-PO957**

**Protective Effect of COMP-Angiopoietin 1 on Peritoneal Vascular Permeability and Peritoneal Transport Function in Uremic Peritoneal Dialysis Rats**

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**Background:** The angiopoietin-1 (Ang-1)/Tie-2 signaling pathway plays a crucial role in the maintenance of vascular stabilization and permeability.

**Methods:** Thirty-six male Sprague-Dawley rats were randomly assigned to the sham operation group, uremia group or uremia/PD group (each n=12). Then, COMP-Ang-1 adenovirus or vehicle adenovirus was injected into twenty other uremic PD rats via the tail vein (each n=10). A peritoneal equilibration test (PET) was performed to evaluate peritoneal transport function before the rats were euthanized. Peritoneal vascular permeability was assessed by measuring FITC-dextran (4 kDa) and FITC-BSA (69 kDa) leakage. The pericyte coverage rate was quantified by anti-CD31 and anti-Desmin immunofluorescence staining. Expression of endothelial junction proteins and Ang-1/Tie-2 signaling were examined by western blotting. The levels of proinflammatory adhesion molecules and cytokines in the peritoneum were measured by real-time quantitative polymerase chain reaction (PCR).

**Results:** Compared to the sham controls, uremic rats were characterized by decreased pericyte coverage, downregulated endothelial junction protein expression and increased FITC-BSA and FITC-dextran leakage, accompanied by increased levels of proinflammatory adhesion molecules and cytokines, increased D/Pcr and decreased ultrafiltration. After infusion of PDF for 4 weeks, more marked changes were noted. Peritoneal Ang-1 protein expression and Tie-2 phosphorylation were significantly lower in uremic rats than in sham controls and were significantly reduced in uremia/PD rats. After COMP-Ang-1 administration, phosphorylation of the Tie-2 receptor was significantly increased. Treatment with COMP-Ang-1 also significantly enhanced pericyte coverage, upregulated endothelial junctions expression and inhibited the leakage of FITC-BSA and FITC-dextran from the peritoneal vascularly induced during PD therapy, whereas these changes were accompanied by reduced peritoneal tissue levels of proinflammatory adhesion molecules and cytokines, decreased D/Pcr and increased ultrafiltration.

**Conclusions:** COMP-Ang-1 exerts a protective effect against damage-induced peritoneal vascular permeability and inflammation at least in part by enhancing pericyte coverage and endothelial junction protein expression, which subsequently significantly improves peritoneal transport function.

**SA-PO958**

**Cross-Omics Analysis of Transcriptome, Proteome, and Metabolome Dynamics During Peritoneal Dialysis**

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**Background:** Peritoneal dialysis effluent (PDF) presents a rich but underexplored source of molecular markers for the prediction of clinical outcome, therapy monitoring and investigation of deregulated molecular and cellular processes during PD. Novel PDF-Fluids (PDF) can be utilized to explore and understand the biological implications of PDF effluent. Alanyl-glutamine (AlaGln) has recently been shown to have beneficial effects in experimental and clinical PD. Modern high-performance methods allow monitoring of hundreds of analytes in parallel. In this study, we investigate the transcriptome, proteome and metabolome of PDF samples with or without AlaGln-addition to PDF.

**Methods:** Samples from a cross-over RCT, investigating AlaGln supplementation of PDF, were analyzed in a cross-omics analysis of effluent cells (RNAseq), soluble proteins (LC-MS) and metabolites in the PDF and plasma (targeted MS) to investigate the biological consequences of AlaGln in the 'ex-vivo' display of peritoneal cell populations and their response to PDF effluent. Peritoneal immune-compentence was analyzed by functional ex-vivo stimulated cytokine release of effluent cells. From each PD dwell, PDE was analyzed at multiple time-points. Peritoneal immune-competence was analyzed by functional ex-vivo stimulated cytokine release of effluent cells. From each PD dwell, PDE was analyzed at multiple time-points. Peritoneal immune-competence was analyzed by functional ex-vivo stimulated cytokine release of effluent cells. From each PD dwell, PDE was analyzed at multiple time-points. Peritoneal immune-competence was analyzed by functional ex-vivo stimulated cytokine release of effluent cells. From each PD dwell, PDE was analyzed at multiple time-points.

**Results:** We were able to quantify ~10,000 cellular transcripts, and 2,700 proteins and 300 metabolites in the PDF. Changes in the proteome could in part be explained by co-regulated biological processes observed on the transcript level. The remaining effects on the proteome might be due to changes in transport characteristics, supported by clinical findings in patients treated with AlaGln. These results correlate with restoration of suppressed peritoneal immune response by AlaGln. Bioinformatic analysis of proteome-metabolome interference was employed to discriminate local and systemic regulation and transport.

**Conclusions:** This combined investigation of proteomic and metabolomic properties of PDF represents the first cross-omics analysis of poorly understood molecular processes during PD and the obtained results enable a further step to unravel the beneficial effects of AlaGln-supplementation. Our data also suggest feasibility of multi-omics approaches to investigate pathomechanisms and interventions relevant in PD.
SA-PO961

Ionic Conductivity Uses on Evaluation of Peritoneal Transporter Type

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Background: Peritoneal equilibrium test (PET) was developed to evaluate peritoneal transport rate on peritoneal dialysis users, being the gold standard. Based on test results, peritoneal transport can be classified as: high, medium high, medium low and low. This classification has clear implications, since it allows making particular recommendations and patients individualized treatment. PET carries long realization time, given this, studies on ionic conductivity show good correlation with creatinine concentration ratio between dialysis product and plasma (D/PCreat), making it novelty on peritoneal function evaluation.

Methods: An analytic transversal study was made on 200 patients diagnosed with chronic kidney disease (CKD) on ambulatory continuous peritoneal dialysis (ACPD) from nephrology department at Unidad Medica de Alta Especialidad (UMAE) 1 of Instituto Mexicano del Seguro Social (IMSS) at Leon, Guanajuato. A modified PET was made, following standardized steps and classifying peritoneal transport, then cut point value of ionic conductivity was determined by under-the-curve analysis (UTC).

Results: Sensible cut values were found, which may allow using ionic conductivity as a suitable test to classify peritoneal transport as low, medium high and high, not so for medium low

Conclusions: Ionic conductivity test shows moderate accuracy to classify peritoneal transport.

SA-PO962

Uric Acid Clearance in Peritoneal Dialysis Patients

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Background: There’s a paucity of systematic study focus on the clearance of UA in peritoneal dialysis (PD). The aim of this study was to investigate the peritoneal UA transport and its influence factors in PD patients.

SA-PO963

Impact of Renal Replacement Therapies over Quality of Life of ESRD Patients

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Background: Renal transplant is generally considered as the ideal renal replacement therapy (RRT). Nonetheless, at the moment, hemodialysis and peritoneal dialysis remain as the main alternative treatment options for patients with end stage renal disease (ESRD). The negative impact of ESRD on the quality of life (QoL), has already been well described, and improvement of QoL could actually be translated into lower mortality.

Methods: Transversal, cohort, observational study, evaluating ESRD patients subjected to renal transplant (RT), undergoing hemodiafiltration (HDF) or automated peritoneal dialysis (APD). QoL was assessed using the Kidney Disease Questionnaire (KDQOL-SF), as well as Beck’s inventories for anxiety and depression. Additional factors like dialysis quality, body composition, and muscle strength were also assessed.

Results: 82 patients met the inclusion criteria: 32 RT patients, 26 on APD and 24 on HDF. 43% of them were in the age range between 31- 50 years. Lower phase angles and muscular strengths were measured in the HDF and APD groups when compared to RT patients (p<0.005) (p<0.0003). As for QoL, RT patients obtained better scores when compared to the other groups, however, statistically significant differences were only observed in five of the categories, which ultimately emphasized the importance of disease burden (p=0.0006) and effects of disease (p=0.0001). The HDF group had a slight tendency towards better QoL results than the APD group, without reaching statistical significance. Hydration status measured with bioelectrical impedance analysis revealed higher levels of overhydration in the HDF group, as expected, since measurement was performed pre HDF treatment (p=0.14). Higher levels of anxiety and depression were observed in the HDF group.

Conclusions: QoL of RT patients is superior to that of patients remaining on dialysis, yet on most of the categories assessed in the KDQOL-SF, no statistical significance was observed, suggesting QoL is acceptable, or even satisfactory, in patients on HDF and APD. As for these two dialysis modalities, there was no significant difference of QoL in our study group.
SA-PO964
Using Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA) on Pancreatic Lesions in Peritoneal Dialysis (PD) Patients
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Introduction: Any invasive procedure involving the abdominal or pelvic regions in a PD patient raises concerns for infection, bleeding, and peritoneal fluid leakage. EUS-FNA is a well-established minimally invasive GI procedure to diagnose and stage cancers of the pancreas, upper GI tract, and mediastinum. We report the pre-procedure preparation, peri-procedure precautions, and outcomes of 2 PD patients who underwent EUS-FNA for suspicious pancreatic lesions. These cases are the first to be reported in the literature.

Case Description: Patients performed the following to avoid complications and ensure the best outcome: 1-Performed additional dialysis daily for 3 days pre-procedure to optimize volume, electrolyte, and acid-base status as well as remove uremic toxins to improve platelet function. 2-Stopped any medications that would interfere with coagulation. 3-Reported to EUS-FNA with minimal PD fluid and received IV prophylactic antibiotics (ampicillin 1 gm and gentamicin 1 mg/kg) within 1 hr pre-procedure to minimize peritonitis risk. 4-Delayed restarting PD for 48 hrs to reduce peritonitis, bleeding and PD fluid leakage risks. 5-Monitored for abdominal pain, low blood pressure, fever, and GI symptoms such as nausea, vomiting, or diarrhea. During the EUS-FNA procedure, an endoscope with high frequency ultrasound capability examined the entire pancreas and the cystic lesion in the pancreas was sampled using a 22-gauge FNA needle. Samples were sent for pathologic evaluation. Patient-1’s findings were consistent with pancreatic pseudocyst. Patient-2’s findings were consistent with mucinous cyst, either side-branch intraductial papillary mucinous neoplasm or mucinous cystic neoplasm. PD risks (peritonitis and PD fluid leakage) and EUS-FNA risks (perforation, infection, iatrogenic pancreatitis, bile peritonitis, fistulization, and malignancy seeding) were not appreciated. Patient-2 noted bloody PD fluid on a manual exchange without hemodynamic compromise. PD fluid cleared after another rapid exchange.

Discussion: Take away lessons: EUS-FNA can be performed safely in PD patients with minimal short term complications. Appropriate measure should be taken to ensure peritonitis bleeding, and PD fluid leakage risks are minimized (see points 1-5 above). EUS-FNA can be used to evaluate pancreatic lesions and malignancies for diagnosis and staging.

SA-PO965
Elevated WBC Count in the Peritoneal Fluid After Transcatheter Arterial Chemoembolization and Microwave Ablation of Hepatocellular Carcinoma in a Peritoneal Dialysis Patient: A Case Report
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Introduction: Hepatitis C is a risk factor for hepatocellular carcinoma (HCC). The prevalence of Hepatitis C is high among end stage renal disease (ESRD) patients, and these patients are at high risk for developing HCC. In the past decade, transcatheter arterial chemoembolization (TACE) combined with microwave ablation (MA) have emerged as an effective therapy for HCC. These therapies can decrease the tumor burden while patients are on the liver transplant wait-list. Here we present an ESRD patient on peritoneal dialysis who developed a high white blood cell count in the peritoneal fluid following the TACE and MA procedures.

Case Description: A 63-year old male with ESRD on Peritoneal Dialysis (PD), and cirrhosis due to Hepatitis C was diagnosed with HCC. At the time of the HCC diagnosis, the patient was listed for a combined liver-kidney transplant. The patient underwent TACE and MA, but immediately following the procedure he developed fever (101°F) which subsided within 24 hours. As part of the fever workup, the peritoneal fluid was sent for white blood cell (WBC), gram stain and culture. The peritoneal fluid WBC was found to be elevated: 1131 (57% PMN, 19% lymphocytes), remaining elevated for more than a month. Notably, it was not accompanied by any associated signs or symptoms such as abdominal pain or cloudy peritoneal fluid. The peritoneal fluid gram stain and culture remained negative, and the patient was able to continue PD without any problems.

Discussion: TACE induces ischemic necrosis through arterial chemoembolization, and MA induces coagulative necrosis through thermal ablation. The most common complications of these therapies include fever and abdominal pain likely related to underlying tumor necrosis. It is important for Nephrologists to be aware of the complications related to these therapies, as was seen in our patient who developed an elevated WBC count in the peritoneal fluid. However, this persistent WBC elevation was not accompanied by abdominal pain, cloudy fluid, infection, and did not warrant PD catheter removal or cessation of PD. To the best of our knowledge, this is the first reported case of elevated WBC in peritoneal fluid in a PD patient following the TACE and MA procedure.

SA-PO966
A Quality Improvement Program to Reduce Avoidable Hospital Stays for Dialysis Patients Presenting to the Emergency Department
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Background: When an End Stage Kidney Disease (ESKD) patient presents to the ED, if the patient requires dialysis, this may result in a costly hospital stay. In Fiscal Year 2017 at the Hospital of University of Pennsylvania, 70% of ESKD patients who presented to the ED were admitted to an inpatient service or transferred to the ED observation unit (EDOU) and 31% of these hospital stays were <48 hours. We believe hospital stays <48 hours can be potentially avoidable.

Methods: A multidisciplinary team was formed with members from the departments of nephrology and emergency medicine (EM). We used Voice of the Customer to survey key stakeholders (RNs, advanced practitioners, residents, attendings, social workers, clinical resource coordinators, and representatives from large dialysis organizations). We performed a root cause analysis using the Ishikawa fishbone model. As a countermeasure, we developed a care pathway to standardize management of patients’ dialysis needs, with dialysis provided in the hospital before discharge or as an outpatient (introduced July 2018). A second plan-study-do-act cycle was performed in November 2018. New countermeasures included an alert identifying the patient as a dialysis patient with specific dialysis unit information and working with the hospitalist superutilizer program to identify additional dialysis patients appropriate for the program.

Results: After introduction of the care pathway, hospital stays <48 hours decreased from 31% to 22% and transferred from the ED to EDOU from 28% to 20%.

Conclusions: By utilizing QI tools and developing a care pathway as a countermeasure, we were able to decrease the percent of hospital stays <48 hours, which we believe represent potentially avoidable hospital stays.

SA-PO967
Reducing Hospitalizations with Artificial Intelligence and Clinical Decision Support: Lessons Learned
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Background: Artificial intelligence has the potential to improve healthcare. Previously, we created a model to predict which patients with kidney failure treated in outpatient dialysis clinics were at risk for all cause hospital admission in the next week. This model has an area under the receiver operating characteristic curve (AUROC) of 0.78 with a sensitivity of 69% and specificity 72%. Here we discuss lessons learned from implementing this model in a telephonic intervention.

Methods: Starting in December 2018, our analytics team partnered with a team of nurses who perform chart reviews and telephonic outreach to manage a large population of patients distributed across the United States. The goal of the outreach is to reduce the
number of hospitalizations. The workflow consists of pulling patients from a worklist, reviewing a chart, documenting any needed identified, and then calling the patient if warranted. Through the last few months, we have utilized agile techniques to iteratively improve each step of this process using observations, surveys, and data analytics.

Results: We deployed the predictive model as a worklist ranked by risk score through an excel sheet format. Initial review demonstrated that 1) excel sheets are difficult to use to display individual patient data, and 2) significant time was spent digging through electronic charts. To help mitigate these issues, we built a dashboard that showed the prediction-based prioritization worklist as well as an integrated patient view. Testing of the dashboard with 3 nurses increased the number of chart reviews by over 50%. We believe this is likely due to aggregating information from multiple electronic health records, reducing the time spent searching for information. Further, nearly every nurse who uses this new system has reported an increase in job satisfaction. To date, the existing workflow results in 70% increase in chart reviews per day with 250% increase in calls per day. Investigation of hospitalization rate is still underway.

Conclusions: Building healthcare predictive models is only part of the story for artificial intelligence to improve healthcare. Additional work must be conducted to understand how to fully integrate predictive models into existing and newly designed clinical workflows.

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SA-PO968
Impact of In-House Dialysis Schedule Change on Hospital Readmission Rate in Hemodialysis Patients
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Background: ESRD patients on Hemodialysis (HD) have high frequency of hospitalization and readmissions for multiple reasons. Often inpatient, they may not get HD treatments on their designated days (MWF or TTBS) due to various reasons, including nursing availability and patient condition. We hypothesized that changing HD schedule could impact readmission rate due to care coordination factors.

Methods: Data was collected from EMR at Stony Brook University Hospital for adult HD patients admitted from January 2019 to October 2019. First admission was taken as index admission, and dialysis days on index admission were noted as on or off-schedule. Patients who received ≥2 HD treatments on days other than their outpatient schedule were labelled as “off-schedule”. The readmission rate within 30 days and 6 months and baseline demographics was compared using Fisher’s exact test. Continuous variables were compared with t-test.

Results: In total, 46 patients were reviewed, of them 10 were labelled as “off-schedule” and 36 as “on-schedule”. Mean age of all patients was 60.8±18.6 years, 61% were male and 47% Caucasian, with no differences between groups. Both diabetes as cause of ESRD (70% vs. 44.4%), and history of CHF (80% vs. 50%) were more frequent among the off-schedule. Dialysis access between groups was not different. The 30-day readmission rate was not statistically significant (30% vs. 16.7%, p-value 0.3844) between two groups. However, six month readmission rate showed a trend towards significance in off-schedule vs on-schedule group (70% vs. 36%, p-value 0.0772, OR 4.128, 95% CI 0.9315-16.14).

There were no deaths in either group at 6 month follow up

Conclusions: Off-schedule inpatient dialysis had no effect on 30 day readmission rate. A trend towards increased rate of readmission within 6 months was observed. Future studies involving more patients and longer follow up are necessary to see the impact of off-schedule HD for hospitalized patients.

SA-PO970
Predictors of Need for Recurrent Emergency Medical Service Transport to an Emergency Department After Dialysis Initiation
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Background: Dialysis patients are frequently transported to the emergency department (ED) by Emergency Medical Services (EMS) due to acute illness. However, little is known about the predictors of recurrent transport to the ED (EMS-ED), based on characteristics at the time of dialysis initiation.

Methods: We analyzed a cohort of adult (≥18 years) patients affiliated with a large quaternary care center who initiated chronic dialysis from 2009-2013 (last follow-up: 2015). Data on patient characteristics at the time of dialysis initiation was linked to regional EMS data. Candidate predictors of recurrent EMS-ED transport included comorbid conditions, dialysis characteristics and frailty severity (using the first version of the clinical frailty scale score; CFS). Time to recurrent EMS-ED was analyzed using the Anderson-Gill counting approach, accounting for competing risks of death and transplant.

Results: A total of 455 patients were included in the study, 246 (54%) had one or more EMS-ED events, 90 (20%) never required an EMS-ED at last follow-up, and 15% and 12% experienced transplant or death as their first event, respectively. The mean age of the cohort was 62 ± 15 years, 89% were Caucasian, and 54% were of female sex. Patients were highly comorbid (48% had diabetes, 30% had coronary artery disease and 17% had peripheral vascular disease) and 97/381 with available data on frailty severity had a CFS score of ≥ 5 corresponding to “mildly to severely frail”. After adjustment, increasing CFS score (subdistribution hazard ratio (SHR) 2.41, 95% confidence interval (CI) 1.46-3.95 for CFS 3-4, and SHR 3.05, 95% CI 1.73-5.38 for CFS ≥5 relative to a CFS ≤2), Hematologic disease (SHR 5.4, 95% CI 1.04-2.29), end-stage renal disease (ESRD) secondary to polycystic kidney disease (SHR 2.00, 95% CI 1.11-3.59 relative to glomerulonephritis as cause of ESRD) and ≥3 months of nephrology follow-up prior to dialysis initiation (SHR 1.52, 95% CI 1.10-2.00) predicted recurrent EMS-ED.

Conclusions: Patients are at a high risk of EMS-ED after dialysis initiation. Frailty severity (at the time of dialysis initiation) is the strongest predictor of recurrent EMS-ED and this may be important to guide informed decision making and resource planning for dialysis patients.
High-Frequency, Distinctive Staffing and Outcomes: Improving the Dialysis Experience
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Background: Frequent dialysis has consistently improved patient outcomes. Professional staffing of dialysis affects patient care quality and safety. Requirements for physician presence during dialysis and for nurse staffing levels are highly varying worldwide. We have set up a 24-stations in-center short daily hemodialysis (SDHD) program whose all day long care is provided by two on-site nephrologists, certified nurses, renal dietitians and psychologists with fulltime dedication. This report outlines the impact of 10 years of combining daily hemodialysis with selected clinical enhancements.

Methods: Nephrologist schedule, patient to staff ratios, adverse events rates (hypotension, medication errors, patient falls), vascular access profile (type, infection rates), patient compliance (missed treatment rate), hospitalization (days per patient-year [ppy]), cumulative survival and kidney transplantation rates were assessed in 200 private-insured patients (122M±78F; mean age 58±0.185yrs, 18-96) receiving in-center SDHD (6-7 x/week; lasting 115.4±11.2min, 90-180; ultrapure dialysate and single-use high-flux dialyzer).

Results: From June 2006 to May 2019 four out 5 nephrologists shared equitable schedule 7 days/week, each one prescribing up to 24 patients in parallel and 2 sequential 6-hour workday. In 2009 we stopped hiring technicians and moved to 100% nurses staffing, reaching 21 fulltime certified nurses (up to 3:1 ratio). Additionally, 2 dietitians and 2 psychologists assist 80 current patients (40:1 ratios). In 2018 symptomatic hypotension occurred in 3% of 20,035 treatments, medication errors in 17 occasions (none critical) and no patients fell in the unit. Over the 10-year study period, arteriovenous fistula was used in 53% and tunneled catheter in 47% of prevalent patients, with bacteriemia rate of 0.15±0.50 events per 1,000 days. Missed treatment rate was 1.4% or 4.6 days ppy. Hospital length of stay was 2 days ppy, 5-year survival was 64% and average kidney transplantation rate was 7.5%. Duplicating nephrologist presence and replacing technicians with certified nurses doubled labor costs, largely offset by higher productivity (five-shift, 24-stations in-center short daily hemodialysis) and longer dialysis vintage.

Conclusions: This intensive dialysis modality delivered by a first-rate clinical staffing represents an unparalleled approach toward an optimal treatment.

Improvements in Quality of Care of Incident Hemodialysis Patients: An International Multicenter Study
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Background: The transition from predialysis care to initiation of hemodialysis (HD) has received increased attention, as this period is one of exceptionally high vulnerability. This analysis focuses on improvements in quality of HD care during the first 6 months. Methods: We included 3426 patients (mean age 65.9±4.1% females) on HD incident <90 days, n=603, prevalent >90 days, mean 55 months, n=2859) from 56 DaVita centers in Poland and Portugal. We compared all incident to all prevalent patients (t-test and Chi-2) and CCI showed that improvements in Kt/V at 6 months and a shift from CDC to AVF was observed similar Charlson comorbidity index (CCI): 6.9 vs 6.9 (p=NS); more use of central dialysis vs 11.0 g/dL ***; lower TSAT: 26% vs 31% ***; lower ferritin: 305 vs 541 ng/ml ***; lower inflammation. Conclusions: This intensive dialysis modality delivered by a first-rate clinical staffing represents an unparalleled approach toward an optimal treatment.

Pre-ESKD Nephrology Care and Employment at the Start of Dialysis
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Background: Employment is associated with improved sense of well-being in general population and higher quality of life in patients with kidney disease. Patients who receive nephrology care prior to onset of End-Stage Kidney Disease (ESKD) experience better health outcomes, perhaps due to smoother transitions to ESKD. We examine whether pre-ESKD nephrology care can also help patients to remain employed when starting dialysis.

Methods: We used a national ESKD registry to identify all patients in the United States between the ages of 18 and 54 who initiated dialysis from January 1, 2006 to December 31, 2014 and who were employed 6 months prior to ESKD. Using a multivariable (Modified Poisson) regression model, we examined the independent association between ≥ 6 months of pre-ESKD nephrology care and employment at the start of dialysis. Additionally, we measured geographic variation in pre-ESKD nephrology care by county-level population quintiles among patients who were excluded from the primary cohort due to age or pre-ESKD employment status. We then examined whether geographic variation in pre-ESKD care is associated with employment at dialysis initiation.

Results: Of the 75,700 patients included in study cohort, 36,940 (49%) reported receiving pre-ESKD care for ≥ 6 months. At the individual patient level, ≥6 months of pre-ESKD care was associated with a 21 % increase in the relative risk (RR) of remaining employed at dialysis initiation (95% CI: 20% to 23%). While geographic variation in pre-ESKD care was strongly correlated with a patient’s likelihood of receiving pre-ESKD care, there was no association between geographic measures of pre-ESKD care and the likelihood of employment at initiation of dialysis.

Conclusions: Despite there is a strong association between pre-ESKD care of ≥ 6 months and employment at the time of dialysis onset, geographic variation in pre-ESKD care is not associated with the likelihood of remaining employed. This suggests that while pre-ESKD care may be necessary for some patients to remain employed, it may not, by itself, be sufficient to foster employment.

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Anand System in Hemodialysis
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Background: Maintenance hemodialysis is a treatment that imposes clinical challenges and expenses to the health care system. Patients with end stage renal disease (ESRD) require disproportionately high use of health care in the USA, with <1% of the population using about 7% of the Medicare resource. Similar data have been reported in the other countries. The health care system have unchanged cost trajectories over the past 20 years, often neglecting one of the essential elements of successful innovation: a disciplined approach to meeting consumers’ needs. Evolving to new service models on hemodialysis (e.g. encouraging automation of process) may be important. Currently the dialysis service is organized in shifts counting on own teams (doctors, nurses, and cleaning staff). Waiting time between shifts is often long, resulting in an excessive number of working hours for the staff and poor quality of life for patients. Our aim was to minimize “waiting time” for patients on in-center HD, in southern Brazil through the Anand System, method pioneered in the Toyota Production System and part of the Lean approach.

Methods: This in-center HD takes care of about 130 ESRD patients, performing more than two thousand HD session/month. An external totem attached to an inward video monitor was installed to record the patient arrival and to allocate it in the queue. The patient is identified by the system through a barcode printed by the hospital. The admission process is done using the Andon method. The order of arrival is arranged on the computer screen from the hemodialysis room, sparing the staff work of calling the patient.

Results: Before implantation, the Lead time was one hour and thirty minutes. After the automation, the minimum transition time between HD sessions has been reduced to 30 minutes. Currently the unit starts working at 6 a.m., with the closing time around 9 p.m. (before the intervention it was 11 p.m.). Around one thousand and six hundred hours/year was spared, with an estimated savings of almost $8,000,000. Conclusions: Examining the patient needs rather than the available delivery-system resources lead to the exploration of different ways of providing the services. The wages of health-care professionals are a key contributor to the high cost of in-center HD. Turning the dialysis service into a continuous flow mapping can be a true innovation agenda in hemodialysis care.

Pairwise statistical analysis of quality of dialysis care over 6 months

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Hemodialysis and Frequent Dialysis - V
Poster/Saturday
Impact of National Payment Contracts on VA Spending and Access to Outpatient Community Dialysis

Virginia Wang,1,2 Shailender Swaminathan,3 Emily A. Comeau,3 Matthew L. Maciejewski,3 Amaal Treivedi,3 Ann M. O’Hare,3 Vincent Mor,3 Durham VAHCS, Durham, NC; 2Duke Univ, Durham, NC; 3VAMedical Center, Providence, RI; 3VA Puget Sound HCS, Seattle, WA; 3Brown Univ, Providence, RI.

Background: End-stage kidney disease (ESKD) is common among Veterans. VA’s limited capacity to deliver dialysis care means that VA relies heavily on community providers, making chronic dialysis the largest VA expenditure for outpatient community care. In the past, VA paid for non-VA dialysis on a local, ad hoc basis, with some payments exceeding Medicare rates. In 2011 the VA began implementing payment policies to standardize the process of pricing non-VA dialysis care, including use of the Medicare fee schedule and national dialysis contracts. This study examined the effect of VA’s standardized pricing policies on VA costs and patient outcomes.

Methods: We used an interrupted time series design and 2006-2016 VA, Medicare, and the US Renal Data System data to identify Veterans receiving VA-financed dialysis in the community from non-VA providers. Changes in price over time for non-VA dialysis were ascertained from >7M VA-paid community dialysis claims. We performed multivariable regression analyses, using differential trend and intercept shift models, to examine the effects of VA pricing policies on: VA treatment prices for non-VA dialysis, access to non-VA dialysis care (number of non-VA dialysis facilities, patient distance to non-VA dialysis care), and 1-year mortality, controlling for patient and facility fixed effects.

Results: The cohort comprised 24,130 Veterans who received ≥1 VA-financed community dialysis treatment in 2006-2016. Before implementation of national contracts, treatment prices for non-VA dialysis care varied widely across VA community from non-VA providers. Changes in price over time for non-VA dialysis were $36.40 to $60.33 and the average price per dialysis session dropped by 40% (p<0.001). Over the same time period, the average number of dialysis facilities providing VA-paid dialysis care grew from 19 to 37 and there were no changes in patient distance to non-VA dialysis facilities (p=0.81) or 1-year mortality (12% vs. 11%, p=0.98).

Conclusions: VA’s policy to standardize nationwide community dialysis contracts resulted in a substantial increase in the value of VA-financed community dialysis care by reducing spending with no adverse effect on Veterans’ access to care nor on mortality.

Funding: Veterans Affairs Support

ESRD Quality Incentive Program Payment Reductions, Mortality, Utilization, and Cost

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Background: The ESRD Quality Incentive Program (QIP) adjusts Medicare payments to dialysis facilities based on their performance on a set of quality measures. We assessed whether the magnitude of ESRD QIP payment reductions was associated with several important patient outcomes that are largely not an intrinsic part of the QIP measure set.

Methods: We compared mortality, utilization of healthcare services and Medicare payments per patient-year during 2015-2017 for facilities in each ESRD QIP payment reduction category corresponding to their QIP performance for the same year. The patient cohort consisted of Medicare fee-for-service beneficiaries receiving chronic dialysis for ESRD on the first day of each year. Patients were attributed to the first facility that provided treatment across individuals ($73.40 to $60.33) and the average price per dialysis session dropped by 40% (p<0.001). Over the same time period, the average number of dialysis facilities providing VA-paid dialysis care grew from 19 to 37 and there were no changes in patient distance to non-VA dialysis facilities (p=0.81) or 1-year mortality (12% vs. 11%, p=0.98).

Results: Most patients were treated in facilities that did not receive an ESRD QIP payment reduction category corresponding to their QIP performance for the same year. The patient cohort consisted of Medicare fee-for-service beneficiaries receiving chronic dialysis for ESRD on the first day of each year. Patients were attributed to the first facility that provided treatment across individuals ($73.40 to $60.33) and the average price per dialysis session dropped by 40% (p<0.001). Over the same time period, the average number of dialysis facilities providing VA-paid dialysis care grew from 19 to 37 and there were no changes in patient distance to non-VA dialysis facilities (p=0.81) or 1-year mortality (12% vs. 11%, p=0.98).

Conclusions: Mortality, utilization of healthcare services and Medicare payments per patient-year during 2015-2017 for facilities in each ESRD QIP payment reduction category corresponding to their QIP performance for the same year. The patient cohort consisted of Medicare fee-for-service beneficiaries receiving chronic dialysis for ESRD on the first day of each year. Patients were attributed to the first facility that provided treatment across individuals ($73.40 to $60.33) and the average price per dialysis session dropped by 40% (p<0.001). Over the same time period, the average number of dialysis facilities providing VA-paid dialysis care grew from 19 to 37 and there were no changes in patient distance to non-VA dialysis facilities (p=0.81) or 1-year mortality (12% vs. 11%, p=0.98).

Funding: Other U.S. Government Support

Expansion of the ESRD Payment Bundle and Dialysis Facility Closures in the United States

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Background: The inclusion of formerly separately billable injectable medications into the ESRD payment bundle in 2011 led to concerns that some facilities facing higher costs would close, disrupting care delivery and limiting access to care for some patients. We examined whether patients were more likely to be affected by dialysis facility closures following the 2011 payment reform, and whether factors that influence closures changed following the reform.

Methods: We identified all patients receiving in-center hemodialysis in the United States between 2005 and 2015 and tracked dialysis facility closures throughout this time period. We used an interrupted time-series regression model to examine immediate and longer-term changes in the odds of being at a facility that closed following enactment of the expanded ESRD payment bundle. We then included interaction terms in a series of logistic regression models to examine whether the associations among selected patient, facility, and geographic characteristics and facility closures changed after 2011.

Results: Dialysis facility closures were relatively uncommon throughout the study period, ranging from 92 facilities (2.0%) affecting 3,725 patients in 2005 to 32 facilities (0.2%) affecting 797 patients in 2014. In a model where we adjusted for changes over time in patient, geographic, and dialysis facility characteristics, the odds of being affected by a dialysis facility closure did not change significantly immediately after enactment of the expanded ESRD payment bundle. Over time, the odds of being affected by a dialysis facility closure decreased by 18% (OR 0.82, 95% CI 0.81 to 0.84) each year after 2011. Patients who were black and those in rural areas and hospital-based facilities experienced a relative increase in the likelihood of being affected by closures after 2011, while patients who were Hispanic, dual-eligible and at smaller dialysis facilities experienced a relative decrease in the likelihood of being affected by closures after 2011.

Conclusions: We did not find evidence that the 2011 expanded ESRD payment bundle was associated with an increased impact of facility closures on patients receiving outpatient dialysis. However, this likely led to the benefit of being affected by facility closures changed for some potentially high risk patient groups.

Funding: NIDDK Support

Dialysis Facilities with Recurring Payment Reductions Under the ESRD Quality Incentive Program (QIP)

Marc Turenne.1 Zhechen Ding,1 Alissa Kapke,1 Delia Houseal,2 Jeffrey Pearson,1 Eric W. Young.1,1Arbor Research Collaborative for Health, Ann Arbor, MI; 1Centers for Medicare and Medicaid Services, Woodlawn, MD.

Background: The ESRD QIP is designed to promote quality of care through financial incentives that reward improvement. It is not known whether a lack of improvement in certain aspects of quality care lead some facilities to consistently receive payment reductions under the ESRD QIP. We assessed the extent to which there are facilities continuing to receive payment reductions over time, whether this is more common among certain facility types, and whether this results from lower performance on certain ESRD QIP measures.

Methods: We studied 6,135 dialysis facilities eligible for the ESRD QIP in each payment year (PY) from 2017-19. Data sources include Medicare claims and CROWNWeb. We compared ESRD QIP measure scores among facilities with a payment reduction in 0, 1, 2, or 3 PYs. We used descriptive analyses and Poisson regression to examine factors associated with the number of PYs with a payment reduction.

Results: Among ESRD QIP eligible facilities during 2017-19, 60.5% had no payment reduction, 23.9% had a payment reduction in 1 PY, 10.6% had a payment reduction in 2 PYs, and 5.0% had a payment reduction in all 3 PYs. Payment reductions in all 3 PYs were more common among facilities that are independent (17.5%) or hospital-based (14.3%), treat ≥100 patients (6.1%), and in ESRD Networks 2 or 7 (13.8% and 11.2%). These findings were statistically significant based on Poisson regression. Facilities with recurring payment reductions had lower average scores for all clinical ESRD QIP measures (Table).

Conclusions: Dialysis facilities that receive recurring payment reductions under the ESRD QIP have lower performance across a range of quality measures. It is important to assess both outcomes and potential challenges for improvement among facilities with recurring payment reductions.

Funding: Other U.S. Government Support

Average facility measure score, ESRD QIP PYs 2017-19

Poster/Saturday
SA-PO979

Associations Between Mortality and Payment Reductions Under the Centers for Medicare & Medicaid Services (CMS) ESRD Quality Incentive Program (ESRD QIP)

Shannon Griffin,1 Jeffrey Mart,1 Andrew Breck,1 Dominick Esposito,1 Adébola O. Adeleye,1 Insight Policy Research, Arlington, VA; 2CMS, Woodlawn, MD.

Background: The implementation of CMS’ ESRD QIP in 2010 introduced financial incentives for certified dialysis facilities to provide high/adequate levels of care. Under the QIP, underperforming dialysis facilities receive a Medicare payment reduction of up to two percent. This study assesses how QIP penalties are associated with 1-year mortality during performance years (PY) and the likelihood of death in the years after each quality assessment.

Methods: We used Medicare claims, enrollment, and CROWNWeb data to examine mortality among outpatient dialysis patients enrolled in Medicare fee-for-service between 2010 and 2017. We used a Cox Proportional-hazards model to measure survival by payment reduction percentage and a difference-in-differences (DD) model to evaluate whether the gap in mortality between penalized and non-penalized facilities changed over time. We adjusted both models using facility and patient characteristics.

Results: Compared to facilities that received no penalty based on 2017 performance, 2017 mortality at penalized facilities was 9% higher (1.091 hazard ratio; p < 0.001). Mortality rates were also higher for facilities that received higher reductions: for PY2017, mortality at a facility with a 2% reduction was about 21% higher than at a facility with no reduction and 7% higher at a facility that received a 0.5% reduction (1.209 and 1.069 hazard ratios, respectively, p < 0.001). Results were similar for PY2010-2016. The difference in probability of death among patients at penalized facilities compared to non-penalized facilities decreased slightly after the performance year by up to 1 percentage point. DD model estimates varied in size and statistical significance across years and amount of time elapsed after each performance year.

Conclusions: Receiving an ESRD QIP payment reduction is correlated with same-year mortality among Medicare fee-for-service dialysis patients, and higher reduction amounts are associated with higher mortality rates. The differences in mortality between penalized and non-penalized facilities persisted after each performance year, though these differences decreased modestly in subsequent years.

Funding: Other U.S. Government Support

SA-PO980

Comprehensive Kt/V Measurement in the Medicare ESRD Quality Incentive Program: Including More Facilities and Recent Improvements in Pediatric and Home Dialysis

Alissa Kapke,1 Katherine Hanslits,1 Marc Turenné,1 Jeffrey Pearson,1 Delia Houseal,2 Amanda Szymanski,1 Alan B. Leichtman,1 Eric W. Young,2 1Archer Research Collaborative for Health, Ann Arbor, MI; 2Archer Research, Ann Arbor, MI; 3Centers for Medicare and Medicaid Services, Woodlawn, MD.

Background: In prior Payment Years (PY), facilities primarily treating pediatric patients were often excluded from QIP dialysis adequacy measures for not treating 11 or more eligible patients. In the PY19 QIP, to include more facilities treating pediatric patients, CMS introduced a Comprehensive Kt/V measure combining age groups and modalities.

Methods: Trends in Comprehensive Kt/V were retrospectively assessed using Medicare claims and CROWNWeb data from 2012-2018. Comparisons of Kt/V QIP scores among facilities eligible for the measure in PY19 to those eligible in the prior year used publicly available Performance Score Summary Reports. Pediatric facilities were defined as having more than 50% of period prevalent patients <18 years old; home dialysis facilities were defined as having more than 50% of period prevalent patients on home HD or PD.

Results: The national average Kt/V QIP score in PY19 was 8.0, an increase of 0.6 points over PY18. However, the average Kt/V score was lower for facilities newly eligible for the measure in PY19 compared to facilities eligible in both PY19 and PY18 (5.8 vs. 8.2). For pediatric facilities, the average score in PY19 was 4.0 (N=47), compared to 7.6 (N=8) in PY18. For home dialysis facilities, the average PY19 score was 5.6 (N=409), compared to 6.9 (N=287) in PY18. Performance rates for Comprehensive Kt/V were lowest among pediatric patients, but improved since initial data collection in July 2012 (Figure).

Conclusions: The change to the Comprehensive Kt/V measure in PY19 resulted in the inclusion of more pediatric and home dialysis facilities and lower Kt/V scores for these subgroups. Increases in Comprehensive Kt/V performance rates improved among pediatric PD and home dialysis patients in 2017 and 2018.

Funding: Other U.S. Government Support

SA-PO981

Clinical Quality Outcomes in Dialysis Facilities Performing Clinical Research

Kurt Mussing,1 Vladimir Rigodon,2 Lori Vienneau,1 Joanna Willette,1 Sheetal Chaudhuri,3 Marta Revierigo-Mendoza,1 John W. Larkin,2 Len A. Usvyat,1 Jeffrey L. Hymes,1 Robert J. Kossmann,1 Franklin W. Maddux,1 1Fresenius Medical Care, Waltham, MA; 2Frenova Renal Research, Waltham, MA; 3Fresenius Medical Care North America, Waltham, MA.

Background: Clinical research trials in kidney disease are underperformed compared to most chronic or acute disease states (Giovanni F, et al. JASN 2004). Barriers to stakeholders in clinical trials further impedes its advancement. Uncertainty regarding the impact of clinical trials on quality scores, star ratings, and related reimbursements might be contributing to such hurdles. We compared the profiles of clinical quality scores at a large dialysis organization (LDO) between clinics performing research trials vs those that did not.

Methods: We analyzed data from in-center hemodialysis (HD) patients treated at the LDO from 2016 to 2018. We performed a pooled analysis of the percent of patients achieving targets for the clinical quality measures for: albumin (≥7.4g/dL), mineral bone disorder (calcium ≥10.0mg/dL, phosphate 3.0-5.5mg/dL, and iPTH 100-600pg/dL), hemoglobin (10.0-11.0g/dL), adequacy (Kt/V≥1.2), diuretic foot checks, missed HD treatments, and catheter use.

Results: We included data from 252 and 2201 facilities with and without clinical research, respectively. We observed no remarkable differences in clinical quality scores for clinics that performed research trials, versus clinics without research (Figure 1).

Conclusions: Findings indicate there are no meaningful differences in clinical quality scores in dialysis facilities conducting research or not. These results are of importance to clinicians and providers considering involvement in clinical research, to advance care paradigms and the state of the art in nephrology.

Funding: Commercial Support - Fresenius Medical Care North America

SA-PO982

How to Reduce the Costs of Hemodialysis Treatment in Low-Income Countries

Malik Touam, Association RAMM-Paris-France Necker Hospital, Paris, France.

Background: We aimed to design a low-cost (~5000 €) dialysis monitor (LCDM) to increase access to hemodialysis (HD) in low-income countries.

Methods: LCDM is a hermetic tank with a volume of 64 L. The dialysate circulates in a closed circuit and in a single pass without mixing between the fresh dialysate and the spent dialysate. The experimental simulation setup was: 4-hour HD session; 70 kg body weight; variable dialysate flow rates (QD); blood flow rate (QB) of 300 ml/min; FX 100® pump. Samples from the inputs and outputs of the dialyzer were taken simultaneously by two operators.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value: Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UREA</td>
<td>205.21 (105.7)</td>
</tr>
<tr>
<td>CREATININE</td>
<td>10.72 (7.6)</td>
</tr>
<tr>
<td>TUBULAR ISCHEMIA</td>
<td>12.3 (8.4)</td>
</tr>
<tr>
<td>Mass Conservation Index</td>
<td>0.04 ± 0.01</td>
</tr>
<tr>
<td>Predialytic Volume (mL)</td>
<td>2069 ± 806</td>
</tr>
<tr>
<td>Duration (%)</td>
<td>0.81 ± 0.12</td>
</tr>
<tr>
<td>Uncertainty (mL)</td>
<td>15.52 ± 7.56</td>
</tr>
</tbody>
</table>

**Results:** Table 1 shows the quality of the removal of urea and creatinine with a QB of 396,200 yen for thrice-weekly HD. The mean age was 53.49 (±14.09) years. Mean BMI was 23.68 ± 0.1909 (93.1%) were on HD. Nearly 70% had dialysis vintage ≥ 1 year. Etiology wise, 801 patients (39.1%) had Diabetic Kidney Disease, and 3 evaluated peritoneal dialysis. All included studies were observational. 5 studies were published from start of database to date. Any study design was eligible, but we required the quality of life. Lack of vascular access is a major cause of morbidity and mortality as seen and more focus is required at this end. Adequacy parameters are fallaciously high as they are dependent on ultrafiltration volumes and body weight. A prime factor favouring twice weekly HD is economic and social factors in the form of cost of travel and distance/ time to reach dialysis centre.

**Funding:** Private Foundation Support

**SA-PO984**

**Characteristics and Effectiveness of Dedicated Care Programs for Patients Staring Systemic Infections**

Mina Attalla,1 Zoe Friedman,2 Samuel A. Silver.1 (Queen’s University, Kingston, ON, Canada; 2Queen’s University, Toronto, ON, Canada.)

**Background:** The transition period during dialysis initiation is associated with increased morbidity and mortality. Transitional care units are increasingly being used to reduce the risk of complications during this vulnerable period. The objectives of our systematic review were to determine the characteristics of existing transitional care programs and their effect on clinical outcomes.

**Methods:** We searched the Cochrane Library, Embase, PubMed, and MEDLINE. We included studies published after the start of date. Any study design was eligible, but we required the presence of a control group and patient-relevant outcomes (e.g. mortality, cardiovascular events, patient survival). We excluded studies that were published before 2013. We included studies published in English.

**Results:** The search strategy yielded 8575 studies. 32 full texts were evaluated, and 9 studies with 13,033 patients were included. 6 studies evaluated in-center hemodialysis and 3 evaluated peritoneal dialysis. All included studies were observational. 5 studies were rated as high quality, with scores of 8-9 on the NOQAS evaluated programs that provided transitional care followed by a significant decrease in mortality and cardiovascular events. Three high quality studies that were similarly structured to provide intensive education and patient monitoring at the start of dialysis suggested a trend towards reduction of mortality and use of central venous catheters. However, study heterogeneity precluded meta-analysis. No studies evaluated for an effect on home dialysis or transplant uptake, and few collected feedback from patients and staff on their sustainability.

**Conclusions:** Few high-quality studies have evaluated dedicated programs for patients new to dialysis, and most only measure an effect on mortality and vascular access. Further research is needed to design and evaluate these models of care before widespread implementation, with an emphasis on patient-relevant outcomes, such as home dialysis uptake, transplant, and quality of life.

**SA-PO985**

**Is Initiation of Twice-Weekly Maintenance Hemodialysis an Acceptable Option?**

Satish Mendoza, Devika Gupta. Nephrology, Army Hospital (Research & Referral), New Delhi, India.

**Background:** Twice weekly maintenance hemodialysis (HD) is not an acceptable form of renal replacement therapy primarily because there are not enough studies to prove its sustainability. However with the concept of incremental dialysis and residual renal function gaining ground this can definitely prove to be a good option for initiation of hemodialysis. The benefits of twice weekly hemodialysis at initiation are significant with respect to economic issues, patient quality of life, access longevity and preservation of residual renal function. We present a three year follow up of patients on twice weekly HD and outcomes.

**Methods:** This was a three year observational follow up of 88 patients initiated on twice weekly HD. Children, pregnant ladies, and patients being worked up for renal transplant were excluded from the study. Adequacy and basic cost effective hematological and biochemical parameters were studied monthly in each patient. In case of complications during the initiation forms of refeeding were given, uncontrolled hyperglycemia, secondary anemia, hyperphosphatemia and features of malnutrition, the patient was shifted to thrice weekly HD.

**Results:** 16406 sessions of HD were studied analysing adequacy, residual renal function, cardiovascular outcomes, mineral bone status and socioeconomic factors and vascular access. Majority of the patients had a urine output of 1176 ml at initiation with a RRF of 3.1ml/min. BP was controlled in 93.19% of patients and left ventricular hypertrophy was seen in 37.2%. SpKv was 1.75, eKv was 1.38 and Std KxV was 2.8. 1.91 Kgs with a mean ultrafiltration of 2600ml. There were 27.2% deaths during this period the commonest cause being cardiovascular causes and emergency HD was required in 0.24% of sessions.

**Conclusions:** Twice weekly HD at initiation is a favourable option with increments, in case of requirement, as majority of patients had a good urine output and RRF at commencement. It also preserves the residual renal function, reduces cost and improves the quality of life. Lack of vascular access is a major cause of morbidity and mortality as seen and more focus is required at this end. Adequacy parameters are fallaciously high as they are dependent on ultrafiltration volumes and body weight. A prime factor favouring twice weekly HD is economic and social factors in the form of cost of travel and distance/ time to reach dialysis centre.

**Funding:** Government Support - Non-U.S.

**SA-PO986**

**Planned Incremental Hemodialysis (PIHD) Is a Cost-Effective and Patient-Centered Renal Replacement Therapy (RRT)**

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**Background:** Hemodialysis (HD) in Japan is the highest quality of RRT in the world but its cost is increasing continuously. The conventional thrice-weekly regimen is a common way to introduce HD but not Incremental hemodialysis (HD) in Japan. When HD patients’ conditions are sufficiently managed by once-/twice-weekly HD with good adherence to their diet, its cost reduction effect can be expected.

**Methods:** We selected 279 patients on HD. Among them, 101 patients who were far from the ideal diet, we initiated PIHD considered residual renal function individually and careful follow-ups from 2013 to 2018. The average age was 63.7 (36 to 90), and 69.2% were men. Their causes of ESRD include chronic glomerulonephritis (38.5%), diabetic kidney disease (26.9%), nephroclerosis (23.1%), and others (11.5%) polyvascular kidney disease, chronic interstitial nephritis, Hypoplastic kidney. We also examined the cost of HD.

**Results:** Initiation of HD was performed as follows: 11 patients were treated once-weekly HD, and their mean eGFR was 4.49 and mean urine volume was 1510 mL/ week. 16 patients were treated twice-weekly HD, and their mean eGFR was 2.97 and mean urine volume was 1278 mL/day. At the end of 2018, six patients, who had been treated once-weekly for 8 months on average, were transited to twice-weekly HD. Five patients, who had been treated twice-weekly for 15.6 months on average, were transited to thrice-weekly HD. Three patients have continued once-weekly HD for 3 to 11 months. 13 patients have continued twice-weekly HD for 16.4 months on average. The overall 1-year survival rate of PIHD was 91.8%, and the 5-year survival rate was 88.3%. On January 2019, we have 27 (24.5%) once-/twice-weekly and 87 thrice-weekly HD patients(total 110 maintenance HD) in our clinic. The monthly costs of dialysis in January 2019 were as follows: 146,000 yen for once-weekly, 254,500 yen for twice-weekly, and 396,200 yen for thrice-weekly HD. The calculated one-year cost of 110 patients was reduced by 10.02% as
Hemodialysis and Frequent Dialysis - V
Poster/Saturday

SA-PO987
Hepatitis B Virus Vaccine Immune Response in Dialysis Patients and Mortality: A Meta-Analysis
Suwasisin Udomkarnjanan1, Kullaya Takkavatakarn,2 Kearsie Padrupinslip,1 Bertrand L. Jaber,2 Somchai Eiam-On9,2 Pawnsa Sansuriapithong.1
1Chulalongkorn University, Bangkok, Thailand; 2Division of Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 3St. Elizabeth's Medical Center, Boston, MA.

Background: Despite the effectiveness of the hepatitis B virus (HBV) vaccine in the general population, dialysis patients frequently do not develop a protective immune response. We performed a systematic review and meta-analysis to identify patient- and dialysis-related factors that are associated with HBV immune response in dialysis patients, and the association between the immune response to the HBV vaccine and mortality.

Methods: Electronic databases were searched for studies of dialysis patients that compared the characteristics of HBV vaccine responders and non-responders. Mortality was analyzed according to the vaccine immune response [NC1]. Random-effects meta-analyses were performed to compute a weighted mean difference (WMD), a pooled odds ratio (OR), and a pooled risk ratio (RR) between groups.

Results: We identified 63 studies (57 cohort studies and 6 clinical trials) with a total of 6,867 dialysis patients receiving the HBV vaccine, resulting in 4,764 (69%) responders and 2,103 (31%) non-responders. By meta-analysis, relative to non-responders, HBV vaccine responders were younger (WMD -4.6 years, P<0.001) and less likely to have diabetes mellitus (pooled OR 0.65, P<0.001), and they were less likely to carry the human leukocyte antigen (HLA) DR3 (pooled OR 0.38, P<0.001). HBV vaccine responders also had a higher serum albumin (WMD 0.12 g/dL, P<0.001), a higher normalized protein catalytic rate (WMD 0.12 g/dL/day, P<0.001), a higher hemoglobin (WMD 0.14 g/dL, P=0.048), a higher parathyroid hormone level (WMD 44 pg/mL, P<0.001), and a higher Kt/V (WMD 0.10, P<0.001). Compared to non-responders, HBV vaccine responders had a 36% lower risk for all-cause mortality (pooled RR 0.64, P<0.001), a 26% lower risk for cardiovascular-related mortality (pooled RR 0.74, P<0.001), and a 24% lower risk for infection-related mortality (pooled RR 0.76, P=0.29).

Conclusions: In dialysis patients, the lack of immune response to the HBV vaccine is associated with older age, diabetes mellitus, HLA-DR3 status, lower nutritional status, lower serum albumin, lower PTH level, and lower dialysis adequacy. Tackling some of the modifiable factors (e.g., nutritional status and dialysis adequacy) might improve the HBV vaccine immune response.

SA-PO988
Immune Response to Influenza Vaccination in Dialysis Patients: Analysis of Four Consecutive Seasons
Jaromir Eisich1, Daniel Rajdl2.1 Internal Dept. 1, Charles University, Plzen, Czechia; 2Dept. of Biochemistry, Plzen, Czechia.

Background: Hemodialysis (HD) is associated with the state of immune dysfunction. In our previous study we identified low antibody response to influenza vaccine as an independent predictor of mortality in HD population. In the present study we tried to determine the factors influencing the immune response to influenza vaccination.

Methods: We analyzed data of a total of 46 HD patients who were vaccinated against influenza in four consecutive seasons from 2015/16 to 2018/19 and completed the 4-year follow-up. Their post- and post-vaccine hemagglutination-inhibition antibody titres (HIA), iron status, C-reactive protein (CRP), albumin, parathyroid hormone and 25-OH vitamin D were measured each year at the time of vaccination. Post-vaccination seroprotection rates in consecutive seasons were compared using Cochran’s test with multiple comparisons. To identify variables associated with the immune response to vaccine, analyses were performed using Spearman’s correlation among post-vaccine rise in HIA, demographic data and the above mentioned biomarkers.

Results: Seroprotection rates changed during the 4-year follow-up, but >70% of seroprotection against all vaccine strains was achieved in all 4 years except H1N1 strain in a 2018/19 season. Results are summarized in table 1. We did not prove significant correlations among intensity of immune response to influenza vaccine and iron status, CRP, albumin, iPTH and 25-OH vitamin D.

Conclusions: The immune response to influenza vaccine varies from year to year in the HD population, but the percentage of seroprotection, with rare exceptions, is very high. We did not find a significant association between the potential factors of immunodeficiency (markers of inflammation / malnutrition, bone metabolism or iron status) and the level of seroprotection in HD patients.

SA-PO990
HCV Eradication Campaign in a Dialysis Clinic in Argentina: Nephrologists’ Role in Patient Care
Pablo E. Bevione, Fernando J. Perretta, Esperanza Berhongaray. Fresenius Medical Care, Pilar, Argentina.

Introduction: Hepatitis C (HCV) increases mortality in dialysis patients and carries a worse prognosis for transplant. Still outbreaks continue to be reported. Direct antiviral agents (DAA) open the door to HCV free units with individual benefits and overall patient security.

Case Description: In 2016 eleven HCV patients were transferred to our zero prevalence clinic. As Infection risk rises with the number of positive patients and DAA were recently available, medical decision was to start the fight against HCV. Whole staff participation was of key impact. Remote hepatologist advice was enough except for complex cases. ELISA III was used for screening. PCR and posterior genotyping were done as pangenotypic was available. Seven PCR + patients were genotype 1b and two 1a. Spontaneous viral clearance occurred in one of three 1b acutely infected patients. Three 1b patients were not treated due to their short life expectancy. One patient had Hepatitis B (HBV) and HCV 1b connectivity requiring hepaticologic surveillance. Cirrhosis did not developed but HCV activation occurred after HCV sustained virologic response (SVR). All Four HCV 1b patients were effectively treated with 90 day Vieka Pak Abbvie (Ombi/Pari/Rit/Dasa). Two HCV 1a patients were treated with Viekira Pak + Ribavirin needing ESA adjustment and weekly Hb check. Only one HCV 1a patient did not achieve response and is still supervised compliance. IRMIGYU was done and pangenotypic scheduled. No patient had cirrhosis nor was IV drug user. Functional isolation was applied while viremic, 

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Background: There is paucity of data on direct anti-viral agents (DAA) in patients on maintenance hemodialysis infected with HCV genotype 3. Sofosbuvir (SOF) based therapy leads to high rates of SVR with few side effects (18), however its use is restricted to patients with an eGFR of >30 ml/min per 1.73 m². The aim of this study is to evaluate DAA therapy in patients infected with HCV genotype 3 on maintenance hemodialysis (MHD).

Methods: In this prospective open label, parallel, non-randomized interventions trial, group 1 received 400 mg daily sofosbuvir/ 60 mg daily daclatasvir; while group 2 received thrice a week 400 mg sofosbuvir/ daily 60 mg daclatasvir for 12 weeks. Patients with compensated cirrhosis received therapy for 24 weeks. Patients were classified as having compensated cirrhosis based on clinical data, Child-Pugh score and abdominal imaging. FibroScan and EGD were performed when indicated. Baseline data were obtained before and after therapy. HCV viral load was assessed at week 4, 8, at end of therapy and 12 weeks after treatment. SVR was defined as undetectable viral load 12 weeks after completion of therapy.

Results: Eighteen patients were enrolled in each group. Mean age was 47.2±14.17 in group 1 and 53.89±14.11 in group 2. Mean duration of known infection was 4.61±1.84 years in group 1 and 3.55±1.92 years in group 2. Four (22.2%) patients in group 1, while six (33.3%) in group 2 had cirrhosis. Genotype 3 was most common with 12 (66.6%) in group 1, and 11 (61.1%) in group 2. Three patients (16.6%) had prior HCV treatment in group 1, while 02 (11.1%) in group 2. Three patients in group 1 left treatment (non-compliance) while left in group 2 (adverse effects – skin rash). All patients in both groups achieved undetectable viral load at 12 week. Overall 29/32 (90.62%) patients in group 1, while 02 (11.1%) in group 2. Three patients in group 1 left treatment (non-compliance) while one left in group 2 (adverse effects = skin rash). All patients in both groups achieved undetectable viral load at 12 week. Overall 29/32 (90.62%) patients in group 1, while 02 (11.1%) in group 2. Three patients in group 1 left treatment (non-compliance) while one left in group 2 (adverse effects = skin rash). All patients in both groups achieved undetectable viral load at 12 week.

Conclusions: DAA therapy using sofosbuvir and daclatasvir is highly effective and tolerable in patients with HCV genotype 3 undergoing maintenance hemodialysis, especially when given daily. Decreasing the dose or frequency of SOF may lead to decreased SVR or higher relapses.

SA-P0994
Exploring the History and Outcomes of Hepatitis B Core Antibody-Positive Hemodialysis Patients Focusing on Occult Hepatitis B Chandrika Chitturi, Sandeep S. Soman. Henry Ford Hospital, Dearborn, MI.

Background: Occult Hepatitis B (OHB) is defined as hepatitis B core antibody (HBcAb) positivity (pos) in the absence of surface antibody (HBsAb) or surface antigen (HBsAg). The reported incidence in hemodialysis (HD) patients (pts) is 3%-8%. Our study is among the first in the US to examine the history of OHB. This work is of interest in HD pts to estimate HepatitisB transmission risk.

Methods: A retrospective study of 352 HD pts was performed from 2010 to 2017. Primary outcomes were the development of HBsAb pos/(considered protective) or development of HBsAg pos or new HepatitisB viremia(adverse events). Univariate and multivariate regression analysis was used to study pertinent risk factors for the outcomes comparing OHB and NonOHB pts. Results: In our study 98 (27%) pts had OHB. Each group had similar baseline demographics, while OHB pts had a higher ALT, proportion of drug use and HepatitisC compared to nonOHB pts (Tab1). There were 15 adverse events (10 viremias) in the nonOHB group. Only 1 adverse event (viremia 19 copies/mL) was seen in the OHB group (Tab2). Conversely, OHB status was a statistically significant predictor of protective HBsAb development in follow up, occurring at a 7 fold increase compared to nonOHB pts. Univariate analysis showed that history of liver disease, HepatitisC and drug use predicted HBsAb development (Tab3). History of liver disease raises risk of adverse events in an univariate model (P<0.05) (Tab4).

Conclusions: OHB pts at our center tend to develop protective HBsAb titers over time rather than develop viremia/antigenemia in contrast to NonOHB pts. Our study finds that OHB confers minimal risk of potential transmission of HepatitisB among HDpts.
SA-PO995

A Study on Prevalence of Hepatitis C Virus Infection and Its Genotype Distribution Among Chronic Renal Failure Patients on Maintenance Hemodialysis: A Single-Center Experience

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Background: Hepatitis C virus (HCV) infection is a very common infection in chronic renal failure (CRF) patients on maintenance hemodialysis (HD). Genotype detection is crucial for management of chronic hepatitis C patients, prediction of prognosis, epidemiological study and also for vaccine preparation. Based on the sequence divergence, till date HCV strains are divided into 7 main genotypes and multiple subtypes (67 confirmed, 20 provisional).

Methods: The aim of this study was to find out single centre prevalence and distribution of HCV genotypes in CRF patients on maintenance haemodialysis (MHD). Genotyping was performed by nested reverse transcriptase PCR. Isolation of HCV RNA, reverse transcription and nucleic acid amplification of 5' UR was carried out. Biotinylated oligonucleotide primers were used to generate amplified product and reversely hybridized to type-specific probes on nitro-cellulose strips. Conjugate and substrate were added post-hybridization to observe the generated bands which were then matched with control bands. The genotypes studied were 1a to 1c, 2a to 2d, 3a to 3f, 4a to 4k, 5a and 6a.

Results: Out of 2550, 210 patients (12.14%) (Male: 166, Females: 44) were HCV positive. Genotype 1 was found in 179 (85.2%) and genotype 3 in 31 (14.8%) patients. The genotypes studied were 1a to 1c, 2a to 2d, 3a to 3f, 4a to 4k, 5a and 6a. No other genotypes were found.

Conclusions: HCV infection was found in 12.14 % CRF patients on MHD with genotype 1 (85.2%) being predominant followed by genotype 3 (14.8%) in our study.

SA-PO996

Impaired T Cell Functionality in ESRD Is Not Reversed by Immune Checkpoint Blockade

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Background: Polymotential T cells are critical for maintaining protection against pathogens. Patients with end-stage renal disease (ESRD) are at increased risks for infection but their pathogen-specific T cell function is not well understood.

Methods: 32 healthy individuals and 57 patients on maintenance hemodialysis were enrolled in this study. All the donors were seronegative for CMV. In addition to PMA/ionomycin, CMV peptide pools (IE1 and pp65) were used to stimulate PBMCs and four effector functions were measured by multicolor flow cytometry (IL-2, TNFα, IFNγ and CD107a) to identify polymotential T cells (cells capable of all four functions).

The statistical comparisons were performed using the Kruskal-Wallis equality-of-populations rank test.

Results: The age of the two groups was similar (mean, 60 years old). ESRD patients showed increased levels of T cell differentiation, including the decrease in CD4+ and CD8+ T+ cells and the increase in the CD4+ and CD8+ T+ cells. T cells from ESRD patients exhibited significant impairment in their effector functions in response to PMA/ionomycin, and such impairment is independent from differentiation status. While the cellular frequency of virus-reactive CD4+ and CD8+ T cells were similar, polyfunctional T cell response were dramatically reduced in the ESRD. The CD8+ CMV pp65 reactive polyfunctional profile showed the most dramatic reduction, 12.4% in healthy donors versus 0.8% in ESRD patients (p<0.001). We further identified that immune checkpoint molecules PD-1 and TIM-3 are upregulated on T cells from ESRD patients; nevertheless, immune checkpoint blockade therapy and regulatory T cell depletion did not reverse the dysfunction phenotype. Transcriptome analysis demonstrated pathway enrichment of advanced T cell differentiation in ESRD but did not demonstrate the enrichment of exhausted related genes in T cells from ESRD patients.

Conclusions: Renal failure patients are characterized by a dramatic loss of polyfunctional T cells and impairment in T cell effector functions, which might explain the increased risk for infection and cancer. Whether infection events before entering dialysis have a long-term negative impact on patients with advanced CKD who survive to permanent dialysis.

Methods: Using Taiwan National Health Insurance Research Database, we enrolled 62,872 patients with advanced CKD who transitioned to maintenance dialysis between January 1, 2004 and December 31, 2013. We identified 20,566 (32.7%) patients who had at least one infection episode during the pre-dialysis advanced CKD period. We used multivariable Cox models to determine the association of pre-dialysis infection exposure with all-cause mortality after starting dialysis. Furthermore, we analyzed the risk of post-ESRD mortality according to four quartiles based on the annual number of infection episodes during pre-dialysis advanced CKD.

Results: Compared with no infection during advanced CKD, the presence of infection exposure during that period was independently associated with a higher risk of first-year mortality (hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.35–1.50) and the increased risk still exists during entire follow-up period (HR 1.22, 95% CI 1.19–1.25). The risks also increased incrementally with higher annual number of infections during advanced CKD (P for trend <0.001).

Conclusions: Pre-ESRD infection events are associated with increased risk of early and late post-ESRD mortality in patients with advanced CKD transitioning to dialysis.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO997

Pre-ESRD Infection Event and Post-ESRD Mortality in Patients with Advanced CKD Transitioning to Dialysis

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Background: Accumulating evidence indicates that infection is a frequent event in patients in non-dialysis advanced chronic kidney disease (CKD) and that reduced estimated glomerular filtration rate(eGFR) is associated with a higher risk of subsequent infection mortality. However, it is unclear whether infection events before entering dialysis have a long-term negative impact on patients with advanced CKD who survive to permanent dialysis.

Methods: Using Taiwan National Health Insurance Research Database, we enrolled 62,872 patients with advanced CKD who transitioned to maintenance dialysis between January 1, 2004 and December 31, 2013. We identified 20,566 (32.7%) patients who had at least one infection episode during the pre-dialysis advanced CKD period. We used multivariable Cox models to determine the association of pre-dialysis infection exposure with all-cause mortality after starting dialysis. Furthermore, we analyzed the risk of post-ESRD mortality according to four quartiles based on the annual number of infection episodes during pre-dialysis advanced CKD.

Results: Compared with no infection during advanced CKD, the presence of infection exposure during that period was independently associated with a higher risk of first-year mortality (hazard ratio [HR] 1.42, 95% confidence interval [CI] 1.35–1.50) and the increased risk still exists during entire follow-up period (HR 1.22, 95% CI 1.19–1.25). The risks also increased incrementally with higher annual number of infections during advanced CKD (P for trend <0.001).

Conclusions: Pre-ESRD infection events are associated with increased risk of early and late post-ESRD mortality in patients with advanced CKD transitioning to dialysis.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO998

Implementation of Antimicrobial Stewardship (AS) in a Large Dialysis Organization

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Background: Fresenius Kidney Care (FKC) implemented an antimicrobial stewardship (AS) program to ensure blood cultures were drawn prior to antibiotic administration and to optimize the selection of empiric antibiotic therapy, timing of de-escalation of broad-spectrum antibiotics, and the duration of antibiotic therapy.

Methods: The FKC AS program consisted of the following: 1) a care pathway for catheter-related blood stream infection (BSI); 2) implementation of a software platform that allowed for real-time monitoring of blood cultures, prescription of IV antibiotics, and blood culture (BC) and sensitivity results; 3) a pharmacist to monitor BC results and IV antibiotic treatment; and 4) educational programs. Starting in 2018, a targeted deployment of the AS program was undertaken sequentially in four regions. To examine the effect of AS activities, we identified CKD patients (HD patients in FKC facilities between January 1, 2016, and March 31, 2019 and ascertained vascular access (VA) type in use at each HD session and positive BC results. To estimate effects of the intervention, blood culture (BC) and sensitivity results; 3) a pharmacist to monitor BC results and IV antibiotic treatment; and 4) educational programs. Starting in 2018, a targeted deployment of the AS program was undertaken sequentially in four regions. To examine the effect of AS activities, we identified CKD patients (HD patients in FKC facilities between January 1, 2016, and March 31, 2019 and ascertained vascular access (VA) type in use at each HD session and positive BC results. To estimate effects of the intervention,
we fit a series of Poisson regression models of BSI incidence, adjusted for region, VA type, secular trend, seasonality, and region-specific timing of the launch of the intervention.

**Results:** The cohort included 42,535 HD patients; 696,106 patient-months (80% with fistula/graft, 20% with catheter); and 3,747 BSIs (39% with fistula/graft, 61% with catheter). Among all 4 regions, the adjusted secular trend during the study era was 7% lower in BSI incidence per year. After accounting for this trend and seasonality, the adjusted relative rate (ARR) of BSI incidence after the launch of AS was 0.58 (95% CI 0.48-0.70), relative to expected incidence in the absence of the intervention. The ARR was 0.78 with fistula/graft and 0.48 with catheter; ARR varied among the regions (Table).

**Conclusions:** Implementation of AS was associated with a reduction in BSI incidence relative to modeled trends. However, outcomes differed by access type and region.

**Funding:** Commercial Support - Fresenius Medical Care North America

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**SA-PO1001**

**Microbiome in Tunneled Catheters of Patients Receiving Maintenance Hemodialysis**

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**Background:** Sepsis is one of the leading causes of morbidity and mortality in patients receiving maintenance hemodialysis via catheter. Bacteremia in dialysis patients generally results from contamination of the catheter lumen (biofilm). Dialysis catheter lumen is instilled with sterile heparin solution at the end of dialysis treatment and discarded prior to next treatment. The aim of our pilot study was to identify the presence and characteristics of microbiome in heparin fluid in tunnelled catheters.

**Methods:** For 20 hemodialysis patients with catheters, 3 ml samples of heparin (mixed with blood) in catheter lumen was collected. Bacterial DNA was isolated and amplified using multiple displacement amplification; 16S rRNA sequence analysis was used to identify and characterize the microbiome. Sample diversity of the sequence positive composition was quantified using the inverse Simpson and Chao indices.

**Results:** Among the 20 patients with a tunnelled hemodialysis catheter, median age was 54 (range 20-80 years), 50% were male, and race was African American in 50% and white in 20% and rest were Hispanic or Asian. Median catheter days was 127 (range 42 to 347 days). Seven of the 20 catheter fluid samples had greater than 200 reads. One specimen was dominated (greater than 50% reads) by the genera Lactobacillus. This patient with dominance of Lactobacillus species in the catheter microbiome was a young female with catheter duration of 344 days. The other 6 showed no dominant species and showed high diversity with inverse Simpson Index 6.25 (95% CI 4.34, 11.11) and Chao index of 35.22 (95% CI 27.42, 43.02).

**Conclusions:** The microbiome of heparinized fluid in tunnelled dialysis catheters does not appear to be sterile. Information on the catheter biome may be used to predict future bloodstream infections and/or to develop protocols for infection prevention.

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**SA-PO1000**

**Analysis of Dual-State Antibiotic Prescription Practices in the ESRD Population**

flavor Rishi,1,2 Sean Yaphe,3 Carly E. Munro,1 Aaron S. Stern,3,1 Teresa Lubowski,4 Ti-Kuang Lee,4 George N. Coridis,1 3Nephrology, Icahn school of medicine at Mount Sinai, New York, NY; 4Henry Ford Hospital, Royal Oak, MI; 5Elmhurst Hospital Center, Elmhurst, NY; 6Atlantic Dialysis Management Services, New York, NY.

**Background:** We previously analyzed outpatient oral antibiotic prescriptions (ABP) for end-stage renal disease patients on hemodialysis (ESRD) in New York State (NYS). Nearly 50% of ABPs had no associated infectious diagnosis. Here, we compare ABPs between NYS and South Carolina (SC).

**Methods:** 2018 NYS and SC Medicare part B and D data were collected and linked to ICD-10 diagnosis (DX) codes. Patients under 18 years of age, on peritoneal dialysis, or who had chronic kidney disease were excluded. ICD-10 codes were classified into 14 DXs. Chi-square analysis was used to compare data between NYS and SC.

**Results:** Table 1 presents the top 5 infection DXs. Incidence of ABPs was 619.9/1000 patients in NYS compared with 597.3/1000 patients in SC. In both states nearly 40% of ABP were categorized as nonspecific symptoms or had no DX. The top 10 ABPs were also similar between states (Table 2). Trimethoprim-sulfamethoxazole was prescribed often in both states despite not being recommended in ESRD.

**Conclusions:** Antibiotic selection and sources of infection were similar in both states, and indications are often not clear. This suggests that antibiotic guidelines in ESRD is a national problem. The number of skin infections may reflect access complications.

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**SA-PO1099**

**Bloodstream Infections in Relation to Environmental Cultures in 12 Dialysis Units in New York City**

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**Background:** Infections are an important complication of end-stage renal disease (ESRD) and represent a significant contribution to morbidity and mortality rates. Central venous catheters (CVC) contribute to bloodstream infections (BSI). We examine environmental cultures in 12 units of a small dialysis organization (SDO) in New York City in comparison to bloodstream infection surveillance data to discern whether a potential association exists.

**Methods:** Direct and non-direct care staff members and the dialysis unit environment (dialysis chair, dialysis machine, laptop, television remote, doorknobs, countertops, etc.) were cultured. Jewelry worn and method of hand hygiene were noted. Cultures that grew normal flora, or airborne contaminates were considered negative. This data was compared with the number of bloodstream infections in 2018 and standardized infection ratio (SIR) of CVC BSI.

**Results:** A total of 560 environmental cultures were collected: 349 from the dialysis environment and 211 from staff. Of the total cultures, 25% were positive, while 18.5% of staff cultures were positive. 56% of staff performed hand hygiene immediately prior to culture: 6.2% with alcohol-based sanitizer, 49.2% with soap and water; and 0.5% with both. 18.5% of staff also wore jewelry, namely non-direct care personnel. Table 1 displays the percentage of all positive cultures and positive direct-care staff cultures in each unit, as well as their associated number of BSIs and SIR.

**Conclusions:** The 12 units of this SDO have BSI rates that are lower than predicted. The cohort included 42,535 HD patients; 696,106 patient-months (80% with fistula/graft, 20% with catheter); and 3,747 BSIs (39% with fistula/graft, 61% with catheter). Among all 4 regions, the adjusted secular trend during the study era was 7% lower in BSI incidence per year. After accounting for this trend and seasonality, the adjusted relative rate (ARR) of BSI incidence after the launch of AS was 0.58 (95% CI 0.48-0.70), relative to expected incidence in the absence of the intervention. The ARR was 0.78 with fistula/graft and 0.48 with catheter; ARR varied among the regions (Table).

**Funding:** Commercial Support - Fresenius Medical Care North America

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**SA-PO10001**

**Microbiome in Tunneled Catheters of Patients Receiving Maintenance Hemodialysis**

Anuradha Wadhwa,1,2 Travis R. Jameson,1 Michael Zilliox,1 Kavitha Vellanki,1 Vinod K. Bansal,1 Benjamin Ling,1 Julia Schneider,1 Holly J. Kramer,1 Loyola University Medical Center, Maywood, IL; 2Hines VA Hospital, Chicago, IL.

**Background:** Sepsis is one of the leading causes of morbidity and mortality in patients receiving maintenance hemodialysis via catheter. Bacteremia in dialysis patients generally results from contamination of the catheter lumen (biofilm). Dialysis catheter lumen is instilled with sterile heparin solution at the end of dialysis treatment and discarded prior to next treatment. The aim of our pilot study was to identify the presence and characteristics of microbiome in heparin fluid in tunnelled catheters.

**Methods:** For 20 hemodialysis patients with catheters, 3 ml samples of heparin (mixed with blood) in catheter lumen was collected. Bacterial DNA was isolated and amplified using multiple displacement amplification; 16S rRNA sequence analysis was used to identify and characterize the microbiome. Sample diversity of the sequence positive composition was quantified using the inverse Simpson and Chao indices.

**Results:** Among the 20 patients with a tunnelled hemodialysis catheter, median age was 54 (range 20-80 years), 50% were male, and race was African American in 50% and white in 20% and rest were Hispanic or Asian. Median catheter days was 127 (range 42 to 347 days). Seven of the 20 catheter fluid samples had greater than 200 reads. One specimen was dominated (greater than 50% reads) by the genera Lactobacillus. This patient with dominance of Lactobacillus species in the catheter microbiome was a young female with catheter duration of 344 days. The other 6 showed no dominant species and showed high diversity with inverse Simpson Index 6.25 (95% CI 4.34, 11.11) and Chao index of 35.22 (95% CI 27.42, 43.02).

**Conclusions:** The microbiome of heparinized fluid in tunnelled dialysis catheters does not appear to be sterile. Information on the catheter biome may be used to predict future bloodstream infections and/or to develop protocols for infection prevention.
**SA-PO1002**

**Change in the Incidence and Pattern of Staphylococcus aureus Bacteraemia in Haemodialysis Patients: 12-Year Single-Centre Experience**

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**Background:** Patients on haemodialysis (HD) are greater risk of infection if they dialyse through lines, than with via arteriovenous fistulae or grafts. The most commonly implicated organism is *Staphylococcus aureus* (SA), which can cause metastatic infections e.g. endocarditis, osteomyelitis. There has been a focus on reducing the incidence of infections, especially methicillin resistant SA (MRSA). We looked at the incidence of methicillin sensitive SA (MSSA) and MRSA in HD patients with SA bacteraemia at our centre over the last 12 years.

**Methods:** Data were collected from the hospital’s microbiology database of all the SA bacteraemias in HD patients between 2007 and 2018.

**Results:** There were 261 bacteraemias in 1361 patients, from a total of 32,000 dialysis episodes. 62.8% were male. Median age was 67 years (range 18-96). Blood cultures grew MSSA - 71%, MRSA - 29%. 78% occurred in patients dialysing via lines. The incidence of infections fell from 50 in 2007 to 15 in 2018. The proportion of MSSA infections increased however.

**Conclusions:** There was a significant reduction in SA bacteraemias, but an increase in the proportion of MSSA bacteraemias. It is important not to allow the reduction in numbers (in particular of MRSA) to lead to complacency in the efforts to reduce the numbers of MSSA and other infections in this particularly vulnerable group of patients.

**SA-PO1003**

**A Clinical Nomogram for the Prediction of Early Mortality in Elderly Patients Initiating Dialysis for ESRD**

Masaki Yoshida, Kazue Ucki. Sanshikai TOHO hospital, Midori, Japan.

**Background:** The number of elderly patients (>80 years) with end-stage renal disease is rapidly increasing. The initiation of dialysis extends the duration of survival; however, the rate of early mortality—mortality within the first few months after the initiation of dialysis—is reportedly higher than the rate of late mortality.

**Methods:** We retrospectively studied a cohort of 300 patients, aged 80 years or older, in whom dialysis was initiated between January 1, 2010 and December 31, 2017. The rate of early mortality was assessed using the Kaplan-Meier method and the equivalence of survival curves was tested using log-rank tests. The univariate and multivariate analyses were performed using the Cox proportional-hazards model. To evaluate nomogram performance, we assessed both the discrimination and calibration of these models. Two hundred bootstrap resamples were used for internal validation of the accuracy estimates to reduce over-fit bias and to determine 95% confidence intervals

**Results:** The nomogram was built from eight predictors of initiation of dialysis by the temporary catheter (Hazard Ratio[HR]: 1.58, P=0.025), COPD (HR: 2.93, P=0.008), Peripheral vascular disease (HR: 2.82, P=0.019), Hemiplegia (HR: 1.87, P=0.011), Malignancy (HR: 5.37, P<0.001), Serum Albumin<3g/dl (HR: 1.48, P=0.061), Bone fracture by the fall within one year (HR: 2.52, P=0.010) and Performance status≥3(HR: 1.77, P=0.025). Nomogram to predict 3-, 6- and 12-month survival using eight easily available clinical characteristics. To use the nomogram, locate patient’s variable on the corresponding axis; draw a line to the points axis, sum the points, and draw a line from the total points axis to the 3-, 6- and 12-month survival rate axis.

**Conclusions:** We developed and validated a nomogram that predict early mortality in elderly patients starting dialysis for end-stage renal disease. Nomogram might help nephrologists make a shared decision with patients and families regarding the initiation of dialysis.

**SA-PO1004**

**Measurement of Dialysate Sodium: Beware of Assay Artifact**

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**Background:** Dialysate sodium is traditionally set at a constant in the range of 136 to 140 mmol/L. However, increasing dialysate sodium, either as a constant, or using sodium ramping, modelling, or using biofeedback systems, can decrease intradialytic hypotension, and symptoms. An individualised dialysate sodium prescription may decrease thirst, intradialytic weight gain and blood pressure. There are some reports that the measured dialysate sodium concentration may vary from the ordered sodium. This quality assurance study was conducted to measure the bias between machine reported conductivity and the actual delivered dialysate sodium and determine the factors associated with the bias.

**Methods:** We conducted analyses on 3 different dialysis machines by running patient-free dialysis sessions with varying combinations of sodium and potassium baths. With the different permutations of the 3 machines, sodium and potassium baths. The conductivity meters of the machines were validated prior to each run using a calibrated external handheld conductivity meter. Dialysate samples were sent for measurement of sodium (indirect ion selective [ISE] method) using the Siemens Vista 1500 analyzer in an accredited clinical laboratory, using serum and urine modes. Samples were obtained from the arterial dialyser port. The primary outcome was quantification of the bias between ordered and measured dialysate sodium, defined as the mean difference between the two. The secondary outcome was to measure the variation of the bias based on certain prespecified covariates.

**Results:** Overall data are available as 230 measurements from 85 sessions. Overall, there was a significant difference between ordered sodium level and measured sodium (mean ±5.6, standard deviation [SD] 1.8 mmol/L), with the delivered sodium being higher. There was no significant difference between the different machines, differing sodium ordered (135 or 140), K bath (2 or 3K), time (0, 1, 2 or 4 hours). However, there was a marked difference between using serum mode (+ 6.0 SD 1.6) and urine mode (mean 1.5, SD 2.9).

**Conclusions:** Since serum plasma is composed of 7% solids, the serum measurement includes the amount of proteins. In the case of the dialysate, using urine mode for measurement of sodium has a correction factor that should not be applied when measuring samples with lower amount of proteins. In the case of the dialysate, using urine mode for measurement of electrolytes corrects the apparent bias in delivered sodium.
Impact of the Serum Sodium and Chloride Difference on All-Cause Mortality in Japanese Hemodialysis Patients: The Miyazaki Dialysis Cohort Study

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Background: Few studies have examined the relationship between the acid-base balance and mortality in hemodialysis patients. In actual clinical settings, the regular collection of blood gas data is rarely conducted. In theory, the serum sodium and chloride difference (SCD) is equal to the anion gap plus bicarbonate, and we herein investigated whether SCD as a simple acid-base balance index affected the risk of mortality in maintenance hemodialysis patients.

Methods: Study design: Cohort study. Setting. Participants: Data from the Miyazaki Dialysis Cohort study, including 1113 hemodialysis patients aged ≥18 years, dialyzed sodium 140 mEq/L, with SCD pre- and post-dialysis. Predictors: Pre-dialysis SCD, ≤33, 33 to 35, 35 to 37, ≥37 (reference), and post-dialysis SCD <36, 36 to 37, 37 to 39, ≥39 (reference) according to quartiles. Outcomes: All-cause mortality during a 2-year follow-up. Measurements: The crude mortality rate in each group was assessed using a Kaplan–Meier analysis with the Log-rank test. Hazard ratios (HRs) were estimated using Cox’s model for the relationships between SCD categories and mortality, and adjusted for potential confounders. Patients in the higher group were set as our reference category.

Results: Among the 1113 patients in this cohort study (median age [interquartile range], age 69 [59-77] years, dialysis vintage 72 [34-141] months, and females 42.7%), 154 patients died during the follow-up. The Kaplan-Meier analysis showed that the survival rate was significantly lower in patients in the lowest SCD (<36) group post-dialysis than in those in the other groups (Log-rank test, P<0.01), whereas no significant differences were observed pre-dialysis (Log-rank test, P=0.26). Cox’s regression analysis showed that the lowest SCD (<36) group post-dialysis was independently associated with an increased risk of mortality (adjusted HR [95% CI] 2.01 [1.25-3.23]). No relationship was observed between pre-dialysis SCD levels and all-cause mortality.

Conclusions: Among Japanese maintenance hemodialysis patients, low SCD levels post-dialysis, but not pre-dialysis, increased the risk of mortality. The present results suggest that SCD post-dialysis is a predictor of mortality.

Comparing the Prognostic Value of eGFR and Residual Urine Volume in New Dialysis Patients

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Background: Residual renal function (RRF) is a pivotal predictor for long-time outcome of maintenance dialysis patients that can be assessed by simply measuring residual urine volume (RUV) or calculating estimated glomerular filtration rate (eGFR) at the start of dialysis. However, it remains unknown which one is better for prognostic evaluation as the substitution of RRF in new dialysis patients.

Methods: This is a multiple-center, retrospective cohort study. Patients who started dialysis between January1, 2008 and December 31, 2017 at the third affiliated hospital of Sun-Yat Sen University were eligible for the study with follow-up through June 30, 2018. The data was collected at the start of dialysis. All eGFR was calculated by eGFR-EPI equation. Main endpoint was all-cause mortality. The predictive accuracy and discriminative ability of the nomogram were determined by a concordance index (C-index) and calibration curve and were compared with eGFR-EPI and RUV. The results were validated with data from dialysis patients at the other two institution enrolled from 2008 to 2017.

Results: 612 patients were included in the primary cohort, while 236 patients were enrolled in the validation cohort. Compared with eGFR, RUV showed a better prognostic value for dialysis patients both in the primary and validation cohort either by K method or regression analysis. Independent risk factors derived from multivariable analysis of the primary cohort to predict mortality were age, diabetes mellitus, mean blood pressure, albumin, uric acid which were all assembled into the nomogram with RUV (nomogram B) or with eGFR (nomogram A). The calibration curve for the probability of mortality showed that the nomogram B (RUV) predictions were in better agreement with actual observations. The C-index of nomogram B (RUV) for predicting mortality was 0.680 (P=0.004), which was statistically higher than the C-index values of nomogram A (0.570). The results were confirmed in the validation cohort.

Conclusions: Our results show that higher residual urine volume at the beginning of dialysis was associated with lower risk of mortality, that indicates the RUV has a better prognostic value than eGFR at the beginning of dialysis for maintenance dialysis patients.

Impaired Secretory Clearance in the Residual Kidney of Hemodialysis Patients

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Background: Residual kidney function is associated with survival and better control of fluid and inorganic solutes in patients on hemodialysis (HD). This study assessed the extent to which the residual kidney maintains the ability to clear organic solutes by tubular secretion.

Methods: Plasma and timed urine were collected to measure kidney clearances for the secreted solutes hippurate (Hipp), indoxyl sulfate (IS), and p-cresol sulfate (PCS) in 10 patients on twice weekly HD with residual kidney function and in 10 control subjects. Clearance values were expressed as a % of the free, unbound solute levels. Clearances were normalized to the GFR (fractional clearances) to assess the degree to which solutes were secreted. GFR was calculated as the mean of the creatinine and urea kidney clearances.

Results: As expected, the GFR was much lower in the HD patients than control subjects (4.0±2.0 vs. 97±2.1 mL/min/1.73m2, p<0.001). Kidney clearances of HIP, IS, and PCS were also much lower in the HD patients. The fractional clearances of these solutes remained greater than 1 in the HD patients, confirming that they were cleared by secretion. The degrees to which secretory clearances of these solutes were maintained relative to GFR in the residual kidney, however, varied greatly. Fractional HIP clearance was preserved in the HD patients as compared to control subjects (15±10 vs. 19±5, p=0.35). Secretion of IS and PCS, however, declined to a greater degree than the GFR in the residual kidney of HD patients, so that their fractional clearances were markedly lower than the control subjects (IS: 9.2±6.1 vs. 31±18, p=0.001, PCS: 4.4±2.7 vs. 12.4±3.2, p=0.001).

Conclusions: Secretory clearances of organic solutes are variably impaired in the residual kidney of HD patients. Residual secretory function cannot therefore be assessed by measurement of a single solute. Further studies will be required to assess the residual kidney’s contribution to removal of medications and uricolic solutes which are cleared by secretion and guide adjustment of medication doses and dialysis prescriptions.

Funding: Veterans Affairs Support
Non-GFR Determinants of Endogenous Filtration Markers in Dialysis Patients

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Background: When kidney function declines, measurement of residual kidney function (RFK) becomes challenging, while the importance of precise measurement rises. We sought to understand the non-GFR determinants of endogenous filtration markers (Beta-2-microglobulin (B2M), Beta-Trace Protein (BTP), and cystatin C) in dialysis patients.

Methods: We measured GFR (mGFR; average of urinary urea and creatinine clearance) and estimated GFR (eGFR) from endogenous markers in patients from the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD) cohort. We used stacked generalized estimating equation (GEE) models to estimated associations of several factors with eGFR, including mGFR.

Results: 1107 patients were eligible for inclusion, of whom 224 without RFK. Mean age was 61 (± 15) years, and mean mGFR was 4.4 (± 3.2) ml/min/1.73m2. In those with RFK: B2M, BTP and Cystatin C were all associated with age. Only BTP was associated with race. All associations became smaller after accounting for mGFR. Compared to creatinine, the effect of age was significantly smaller for B2M and the effect of sex was significantly smaller for B2M and Cystatin C. After adjustment for age, sex and race associations dialysis modality was significantly less strong associated with BTP than with mGFR. Additional adjustment for mGFR resulted in a smaller associations for diabetes with cystatin C when compared to creatinine. However, diabetes was stronger associated with BTP than creatinine.

Conclusions: In dialysis patients, BTP, B2M, and cystatin C were mainly influenced by mGFR, but additionally by age and sex. Furthermore, diabetes and dialysis modality also influenced these results. Use of these makers for GFR estimation should account for these influences.

Funding: Government Support - Non-U.S.

SA-PO1010

Eliminating Routine Post-Dialysis Serum Urea Nitrogen Measurements in Hemodialysis: Testing a Proposed Method Using Conductivity Dialyzer Clearance to Determine Protein Catabolic Rate

John Howang, Andrew I. Chin. University of California Davis Medical Center; Sacramento, CA.

Background: Traditionally, pre and post-HD BUN measurements are used to determine Kt/V and normalized protein catabolic rate (PCRs). Timing and care of post-HD BUN sampling is critical for results to be accurate. A method of estimating PCRs without the post-HD BUN, utilizing conductivity clearance and only a pre-HD BUN, has recently been proposed. We tested this method in a cohort of patients in which online conductivity clearance monitoring (OCM) and clearance by usual formal kinetic modeling were measured.

Methods: We used a retrospective cohort of 39 patients totaling 271 HD treatments during which OCM and routine monthly laboratory tests with formal kinetic modeling for V. Output data of interest included the estimated post-HD BUN, spKt/V and PCRn based on these estimated values.

Results: The spKt/V by OCM underestimated that of formal kinetic modeling with a mean difference of 0.40, primarily driven by difference in V. The overall correlation of spKt/V was modest. Using pre-HD BUN with OCM to estimate PCRs as proposed by Daugirdas, we found a good correlation between PCRs by kinetic modeling and OCM method (Fig 1).

Conclusions: In this retrospective evaluation, the method using OCM without a post-HD BUN, as proposed by Daugirdas, appears to adequately estimate PCRs. The post-HD blood draw, subject to inaccuracies due to improper sampling technique, is potentially problematic in traditional determinations of HD adequacy and calculation of PCRs. OCM based calculations of Kt/V and PCRn remove this potential source of error. This process has practical applications and should be further validated.

Funding: Clinical Revenue Support

SA-PO1011

Relationship Between Phosphate Binder Type and Gut Microbiome-Derived Uremic Toxin Levels in Hemodialysis Patients

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Background: Phosphate binder choice may differentially affect gastrointestinal physiology (e.g. colonic transit time and gut microbiota composition). Interestingly, patients on saccorifere oxyhydroxide (SFO), Velphoro® have lower rates of constipation than those taking sevelamer carbonate (SEV; Renvela®). We hypothesized that phosphate binder choice may affect serum levels of gut microbiome-derived uremic toxins (UTOX). We examined the relationship between the type of prescribed phosphate binder and gut microbiome-derived UTOX levels in hemodialysis (HD) patients treated with either SFO or SEV.

Methods: Weekly blood samples and bowel movement diaries were collected from 16 HD patients during six consecutive weeks per subject. Stool types were categorized according to the Bristol Stool Chart. Nine substances including eight UTOX (7 gut microbiome-derived; 1 mammalian-derived) and tryptophan (TRP) were quantified in serum using liquid chromatography–mass spectrometry. For each substance, we calculated the median concentration per subject, then the median across all subjects. We also report the differences in median serum concentrations between the treatment groups and their respective 95% confidence intervals.

Results: Subject characteristics are shown in Table 1. The SEV group reported a 3.3-fold higher frequency of stool types 1 and 2 (constipation), while stool types 5 to 7 (diarrhea and urgency), indicating reduced colonic transit time, were 1.5-fold more frequent in the SFO group. Most gut microbiome-derived UTOX, including three protein-bound UTOX, showed a trend towards lower serum levels in the SFO group, while one mammalian-derived UTOX and TRP were higher in the SFO group (Table 2).

Conclusions: Compared to SEV, SFO may lower the serum levels of gut microbiome-derived uremic toxins, putatively by decreasing colonic transit time.

Funding: Commercial Support - Fresenius Medical Care

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO1012

Comparison of Actual Dietary Intakes in Hemodialysis Patients: A Prospective Observational Study

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Background: Although appropriate dietary adjustments in hemodialysis (HD) patients are important, most HD patients have difficulty adhering to dietary therapy due to the stress of a restricted food diet or loss of appetite, which eventually leads to malnutrition and other complications. The actual dietary intakes among HD patients stratified by nutritional status have not yet been studied.

Methods: In total, 111 HD patients from five dialysis centers were stratified into 2 groups based on subjective global assessment (SGA): the well-nourished group vs. the poorly-nourished group. The 7-day dietary intakes and food behaviors of the two groups were compared. Logistic regression analysis was performed to reveal the factors associated with the poorly-nourished status.

Results: The enrolled HD patients consumed an average of 23.44 kcal/kg/day and 0.92 g/kg/day of protein. However, they also consumed an average of 3285 mg/day of sodium, 1856.91 mg/day of potassium, and 760.61 mg/day of phosphorus. The poorly-nourished group ate out and ate fried food significantly more frequently than the well-nourished group. More frequent eating out, more frequent fried food consumption, and lower serum albumin level were significantly associated with the poorly-nourished status.

Conclusions: These findings demonstrate the differences in actual dietary intake patterns and food behaviors of well- and poorly-nourished HD patients. However, further research should be performed on HD patients to design customized nutritional education, consultations, and dietary management.

Table 1. 7-day dietary intake between the two groups stratified by the nutritional status

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Well-nourished</th>
<th>Poorly-nourished</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kcals/kg/day</td>
<td>23.44 ± 3.74</td>
<td>20.37 ± 3.23</td>
<td>0.015</td>
</tr>
<tr>
<td>Protein g/kg/day</td>
<td>0.92 ± 0.15</td>
<td>0.78 ± 0.12</td>
<td>0.033</td>
</tr>
<tr>
<td>Sodium mg/day</td>
<td>3285 ± 975</td>
<td>3965 ± 1235</td>
<td>0.001</td>
</tr>
<tr>
<td>Potassium mg/day</td>
<td>1856.9 ± 352</td>
<td>2102.6 ± 468</td>
<td>0.001</td>
</tr>
<tr>
<td>Phosphorus mg/day</td>
<td>760.6 ± 150</td>
<td>895.7 ± 184</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SA-PO1013

Dietary Advanced Glycation End Products Restriction Effects on Intestinal Bacterial Flora and Microinflammation State in Maintenance Hemodialysis Patients

Meng Wang, Hua Liu. First Affiliated Hospital of Medical College of Xi’an Jiaotong University, Xi’an, China.

Background: It has been found that dietary AGEs was related to markers of inflammation and oxidative stress in a population of end stage renal disease (ESRD) patients undergoing dialysis. This study was to explore the effects of dietary advanced glycation end products (AGEs) restriction on microinflammation state and intestinal bacterial flora in maintenance hemodialysis (MHD) patients.

Methods: Patients were randomized to normal group (n=10) continuing the same diet, and intervention group taking a dietary AGE restriction for one month (n=10). Blood and stool samples were collected before and after intervention. Highsensitive C-reactive protein and interleukin-6 were detected. The alteration of gut microbiota were analyzed by bacterial 16S DNA amplification and DNA pyrosequencing to determine the presence of bacteria.

Results: Plasma High-sensitive C-reactive protein and interleukin-6 levels were significantly reduced in dietary AGEs restriction group (P<0.05). The number of Bilobobacterium and Lactobacillus decreased whereas the number of E. coli and Enterococcus faecalis increased (P<0.05) in intervention group.

Conclusions: This study showed significant microbiota differences between two groups in MHD patients, might provide evidence for reducing uremic toxin from the view of gut microbiota, and play a role in improving life quality of patient. More research is needed.

SA-PO1014

Comparison of Three Nutritional Screening Tools for Predicting Mortality in Maintenance Hemodialysis Patients

Junzhi Chen. Min Liang. Nanfang Hospital, Guangzhou, China.

Background: There has been a great consensus that the key first step in the evaluation of nutritional status is to identify “at risk” status by using the validated nutritional screening tools. However, an effective and simple nutrition screening tool has not been identified in maintenance hemodialysis (MHD) patients. To the best of our knowledge, the comparison of mortality predictability between two objective scores of nutrition on dialysis (OSND) and the malnutrition-inflammation score (MIS) or the geriatric nutritional risk index (GNRI) has not been conducted in previous studies.

Methods: A cohort of 1,025 MHD patients were enrolled from 8 hospitals. The MIS, OSND, and GNRI were measured at baseline. All-cause mortality and cardiovascular (CV) mortality were the major study outcomes. Harrell’s C statistics were derived to examine the discrimination between three tools and mortality.

Results: The median follow-up duration was 28.1 months. The MIS (per standard deviation (SD) increase, HR =1.35, 95% CI: 1.18–1.55), the OSND (per SD decrease, HR =1.24, 95% CI: 1.09–1.42), and the GNRI (per SD decrease, HR =1.26, 95% CI: 1.10–1.43) were all significantly associated with the risk of all-cause mortality. More importantly, the mortality predictability of the MIS appears similar to the GNRI (P=0.182) and greater than the OSND (MIS vs. OSND: P=0.001; GNRI vs. OSND: P=0.045).

Conclusions: Each of the three nutritional screening tools was significantly associated with an increased risk of all-causes and CV mortality. The mortality predictability of the MIS was similar to the GNRI and greater than the OSND.

Results of Harrell’s C Statistic

<table>
<thead>
<tr>
<th>Nutritional Status</th>
<th>C Statistic (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIS</td>
<td>0.62 (0.58, 0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OSND</td>
<td>0.59 (0.52, 0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GNRI</td>
<td>0.61 (0.59, 0.64)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SA-PO1015

The Efficacy of Probiotic, Prebiotic, and Synbiotic Supplementation in Modulating Gut-Derived Circulatory Particles Associated with Mortality in Dialysis Patients: Systematic Review and Meta-Analysis

Daniel S. March,3 Arwel W. Jones,4 Nicolette C. Bishop,3 James Burton,1,2,3 University of Leicester, Leicester, United Kingdom; University of Lincoln, Lincoln, United Kingdom; Loughborough University, Loughborough, United Kingdom.

Background: There is accumulating evidence that modification of the microbiota through prebiotic, probiotic or synbiotic as an additional supplement. Primary outcomes were measures of circulating endotoxin, indoxyl-sulphate and p-cresyl sulphate.

Methods: Seventeen databases were searched, supplemented with internet and hand searching. Randomised controlled trials of adult end stage renal disease individuals receiving either haemodialysis or peritoneal dialysis were eligible. Trials were restricted to those which had administered a prebiotic, probiotic or synbiotic as an additional supplement.

Primary outcomes were measures of circulating endotoxin, indoxyl-sulphate and p-cresyl sulphate.

Results: Twenty-one trials were eligible (1152 randomised participants) of which 19 trials were considered to have a high risk of bias. The number of trials available for meta-analysis varied for each primary outcome. Synthesised data indicated that supplementation significantly reduced circulating levels of toxic metabolites. This systematic review and meta-analyses provide an up to date synthesis on the effects of supplementation on circulating levels of toxic metabolites, markers of uremia and inflammation, blood lipids and other clinical outcomes.

Conclusions: Supplementation reduces toxic metabolites associated with cardiovascular disease and mortality in individuals receiving dialysis. However, the majority of trials included were low in quality.
SA-PO1016

Association of Race/Ethnicity and Pre-ESKD Disease Duration with Subsequent Dialysis Mortality in U.S. Veterans with ESKD

Guofen Yan,1,2 Robert Nee,3 Keith C. Norris,4 Tom Greene,3 Mohammed N. Oliver,5 Wei Yu,3 Alfred K. Cheung,3,4 1University of Virginia, Charlottesville, VA; 2Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, UT; 3Walter Reed National Military Medical Center, Vienna, VA; 4UCLA, Marina Del Rey, CA; 5University of Utah, Salt Lake City, UT; 6Virginia Department of Health, Richmond, VA.

Background: The mortality rate of patients undergoing dialysis is exceptionally high. The role of disease duration before end-stage kidney disease (ESKD) on subsequent dialysis mortality is not clear due to lack of data on the accurate time of CKD onset. Using a national incident CKD cohort we recently constructed, we examined the association between disease duration prior to ESKD and dialysis mortality by race/ethnicity.

Methods: We first identified all subjects with new onset CKD (stage 3-5) in the U.S. Veteran Affairs database since 4/1/2002. CKD onset was determined by two eGFRs (based on CKD-EPI equation) <60 mL/min/1.73 m² at >90 days apart. We then extracted the subset of patients who started dialysis with at least one year of follow-up until 5/1/2016. Disease duration was determined as time from the date of CKD onset to the date of first dialysis. Hazard ratios for death were examined for duration of <1 year, 1-3 years, and 3-5 years as compared to duration of ≥5 years for each race/ethnicity, adjusted for covariates including age at ESKD onset, gender, last eGFR prior to first dialysis, and major comorbid conditions such as diabetes, hypertension, and cardiovascular diseases.

Results: Of 28,129 incident dialysis patients included, 8,874 were Black, 1,882 Hispanic, and 17,363 White. The median duration from CKD onset to ESKD onset was 2.7 years for Blacks, 2.8 for Hispanics, and 3.3 for Whites. More than half of Blacks (55%) and Hispanics (53%) developed ESKD within 3 years of CKD onset, compared to 46% of Whites. After adjustments, shorter disease duration before ESKD was significantly associated with greater mortality on dialysis for Blacks, but not for Whites and Hispanics (Table). P value for testing the differential associations across three racial/ethnic groups was 0.003.

Conclusions: Our findings suggest the association of disease duration before ESKD and dialysis mortality differed by race/ethnicity, prompting the need to delineate the factors responsible for these differential associations.

Funding: NIDDK Support

Adjusted hazard ratios (HR) by race/ethnicity

<table>
<thead>
<tr>
<th>Pre-ESKD duration (years)</th>
<th>% patients</th>
<th>HH (95% CI)</th>
<th>P value</th>
<th>% patients</th>
<th>HH (95% CI)</th>
<th>P value</th>
<th>% patients</th>
<th>HH (95% CI)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>19.6</td>
<td>1.32 (1.19, 1.46)</td>
<td>&lt;0.0001</td>
<td>20.3</td>
<td>1.35 (1.22, 1.50)</td>
<td>0.54</td>
<td>15.7</td>
<td>1.37 (1.25, 1.50)</td>
<td>0.75</td>
</tr>
<tr>
<td>1-3</td>
<td>34.9</td>
<td>1.15 (1.09, 1.21)</td>
<td>0.004</td>
<td>32.9</td>
<td>1.84 (1.71, 1.99)</td>
<td>0.43</td>
<td>90.1</td>
<td>1.86 (1.76, 1.98)</td>
<td>0.15</td>
</tr>
<tr>
<td>5-5</td>
<td>25.2</td>
<td>1.15 (1.04, 1.28)</td>
<td>0.006</td>
<td>22.0</td>
<td>0.85 (0.77, 0.93)</td>
<td>0.42</td>
<td>54.2</td>
<td>0.99 (0.96, 1.02)</td>
<td>0.58</td>
</tr>
<tr>
<td>≥5</td>
<td>22.3</td>
<td>1.00 (0.85, 1.18)</td>
<td>1.00</td>
<td>24.8</td>
<td>1.00 (0.85, 1.18)</td>
<td>1.00</td>
<td></td>
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</table>

SA-PO1017

Does Erythrocyte Stimulating Agent (ESA) Exposure Contribute to the Obesity Paradox?

Jeffrey I. Silberzweig,1,2 Thomas Parker,1 Kwan Kim,1 Daniel M. Levine,1 The Governing Body of The Rogosin Institute (The Rogosin Institute, New York, NY; 1Nephrology & Hypertension, Weill Cornell Medicine, New York, NY).

Background: Epidemiologic and retrospective data document a survival advantage for obese (BMI ≥ 30 kg/m²) patients treated by maintenance hemodialysis (HD). Prospective data suggest that higher ESA doses are associated with adverse clinical outcomes.

Methods: Our quality program reviews the proportion of patients with hemoglobin (hgb) between 10-11.5 g/dL and ESA dosing and costs. We sought to understand variations by comparing ESA requirements based on BMI.

Results: The facility with the lowest average patient weight has the lowest average ESA cost (See table). ESA exposure decreased as BMI increased (p<0.0001). Hgb levels did not vary with BMI. (See figures.) There is a trend towards longer survival among obese patients.

Conclusions: ESA exposure varies with BMI in our patient population; hgb does not. ESA costs and doses vary with BMI. We hypothesize that lower ESA exposure contributes to improved survival among obese patients with CKD treated by HD.

Funding: Clinical Revenue Support

Impact of Weight on ESA Cost per Treatment Q1 2019

<table>
<thead>
<tr>
<th>Facility</th>
<th>ESA Cost/Treatment ($)</th>
<th>Average Patient Weight (kg)</th>
<th>ESA Cost/Treatment (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.47</td>
<td>72.5</td>
<td>0.24</td>
</tr>
<tr>
<td>2</td>
<td>18.30</td>
<td>75.1</td>
<td>0.24</td>
</tr>
<tr>
<td>3</td>
<td>27.28</td>
<td>80.0</td>
<td>0.34</td>
</tr>
<tr>
<td>4</td>
<td>22.72</td>
<td>77.3</td>
<td>0.30</td>
</tr>
<tr>
<td>5</td>
<td>21.86</td>
<td>77.8</td>
<td>0.31</td>
</tr>
<tr>
<td>6</td>
<td>20.17</td>
<td>79.4</td>
<td>0.26</td>
</tr>
<tr>
<td>Average</td>
<td>19.98</td>
<td>79.3</td>
<td>0.25</td>
</tr>
</tbody>
</table>

SA-PO1018

Efficacy and Safety of CKD-11101 (Darbeponin-Alfa Proposed Biosimilar) Compared with Darbeponin Alfa in Patient on Hemodialysis

Yaein Kim,1 Yong-Lim Kim,2 Soo Wan Kim,3 Duk-Hee Kang,4 Kang Wook Lee,2 Won Suk An,2 Jung Pyo Lee,2 Kwon Wook Joo,2 Dong-jin Oh,2 Jun-Young Do1 Jin hyuk Paek,3 Woo Yeong Park,3 Kyubok Jin,4 Su-Kil Park,1 1Seoul National University Hospital, Seoul, Republic of Korea; 2Kyungpook National University Hospital, Daegu, Republic of Korea; 3Chonnam National University Medical School, Gwangju, Republic of Korea; 4Ewha University College of Medicine, Seoul, Republic of Korea; 5Chungnam National University Hospital, Daejeon, Republic of Korea; 6Dong-A University, Busan, Republic of Korea; 7Seoul National University Boramae Medical Center, Seoul, Republic of Korea; 8Myongji Hospital, Goyang, Republic of Korea; 9Yangnam University Hospital, Daejeon, Republic of Korea; 10Keimyung University School of Medicine, Daegu, Republic of Korea; 11Dongsan Medical Center, Daegu, Republic of Korea; 12Asan Medical Center, Seoul, Republic of Korea.

Background: Anemia is critical problem which is caused by deficiency of endogenous erythropoietin (EPO) synthesis in patient on dialysis. Darbeponin-alfa is a useful EPO with long elimination half-life. Herein, we aim to evaluate the efficacy and safety of intravenous CKD-11101 (biosimilar darbeponin-alfa) compared with darbeponin-alfa in patients undergoing hemodialysis.

Methods: The study group composed with 24 different institutes was divided by randomized, double-blinded, and prospectively. Follow-up duration was 24 weeks which was consisted with 20 weeks of maintenance and 4 weeks of evaluation period. All patients underwent the stabilization period to achieve target baseline hemoglobin (Hb) as 10-12 g/dL before randomization. After randomization, patients received EPO by weekly or biweekly with adjusted dose following the permitted rule of darbeponin alfa. First, we compared the efficacy of CKD-11101 to darbeponin-alfa. Secondly, we investigated the safety of CKD-11101.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

hgb by BMI

ESA exposure by BMI
Results: A total of 405 patients were randomized to two different groups during June 2015 and June 2017. Among randomized populations, 78 (19.35%) were dropped out due to major infarction or side effect, 325 (80.65%) patients completed the investigation. The average administered dose of EPO was not different in both groups; 74.90 ± 56.85 mcg and 61.96 ± 43.51 mcg in CKD-11101 and darbepoetin-alfa, respectively. During the study period, 148 patients with targeted Hb was 19.44% (28/144), and 20.95% (31/148) with CKD-11101 and darbepoetin-alfa, respectively (p = 0.750). There was no difference in rate of patients need to be changed the dose; 95.83% (138/144) and 93.24% (138/148) with CKD-11101 and darbepoetin-alfa (p = 0.331). There was only one patient who, due to transfusion, was lost to follow-up group.

Conclusions: The difference in change of the level of Hb, dose of EPO, and achievement rate to target Hb during study period was comparable between two groups. CKD-11101 is an equivalent therapeutic efficacy compared with the darbepoetin-alfa patient undergoing hemodialysis.

Study 2: EPO doses in both studies. In VIE after 3, 6, 9 and 12 months of treatment in both studies.

VIE. Administered EPO dose was recorded and blood samples withdrawn at inclusion and after 12-month period. Study participants included 21 hemodialysis patients who presented with chronic kidney disease patients on dialysis with low grade inflammation at the four major infarction or side effect, 325 (80.65%) patients completed the investigation. The average administered dose of EPO was not different in both groups: 74.90 ± 56.85 mcg and 61.96 ± 43.51 mcg in CKD-11101 and darbepoetin-alfa, respectively. During the study period, 148 patients with targeted Hb was 19.44% (28/144), and 20.95% (31/148) with CKD-11101 and darbepoetin-alfa, respectively (p = 0.750). There was no difference in rate of patients need to be changed the dose; 95.83% (138/144) and 93.24% (138/148) with CKD-11101 and darbepoetin-alfa (p = 0.331). There was only one patient who, due to transfusion, was lost to follow-up group.

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Coagulation and Circulating Heparin Profile in Patients with ESRD

Hemodialysis and Frequent Dialysis - VI

SA-PO1023

Undergoing Maintenance Hemodialysis

Emilie Bontekoe,1 Arjun S. Grewal,2 Jasdeep S. Bajwa,1 Fakhia Siddiqui,1 Vinod K. Bansal,1 Omer M. Iqbal,1 Debora Hopenstend,1 Jawed Fareed,1 1Loyola University Medical Center, Maywood, IL; 2Loyola University Chicago; 3University of Rochester, Mississauga, ON, Canada; 4University of Rochester, Wauconda, IL.

Background: Unfractionated heparin is widely used as an anticoagulant for maintenance hemodialysis in end-stage renal disease (ESRD) patients. Since these patients are administered with heparin repeatedly throughout treatment, it is hypothesized that detectable circulating levels of heparin may be present in their blood 48 hours post-dialysis session. The profiling of these parameters may provide the hemostatic status of patients in reference to circulating residual heparin in the pre-dialysis blood samples.

Methods: This study included 95 patients with ESRD undergoing maintenance hemodialysis, which was administered 3 times per week in 48-hour intervals. Plasma samples were analyzed utilizing clot-based methods including activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT). Employing a chromogenic assay, the circulating levels of heparin in each patient were measured. All of these samples were also analyzed for thrombin generation capacity using calibrated automated thrombogram (CAT, Diagnostica Stago, Paris, France).

Results: In the clotting assays, prothrombin time was elevated (16.4±20.3 sec.) in comparison to the normal control (11.1±2.2 sec.; p<0.05). Activated partial thromboplastin time was also prolonged (43.0±43.1 sec.) when compared to normal human plasma (32.5±2.2 sec.; p<0.05). The thrombin time values were markedly higher (44.6±8.31 sec.) in comparison to normal (31.2±2 sec.; p<0.001). Circulating heparin levels, measured by anti-Xa methods, were found to be 0.11±0.21 U/ml and anti-IIa levels being 0.25±0.27 U/ml (p<0.05). In the thrombin generation assay, the ESRD samples showed wide variation and a lowered thrombin generation value (107.55±2.52 nmol) in comparison to normal control (185±4.5 U/ml; p<0.05).

Conclusions: These results suggest patients undergoing maintenance hemodialysis exhibit a mild hypercoagulable state as determined by PT and aPTT methods. The circulating levels of heparin were lower in Anti-Xa compared to anti-IIa, suggesting the presence of higher molecular weight components of circulating heparin. These studies suggest that ESRD patients on maintenance hemodialysis exhibit a hypercoagulable state in which circulating residual heparin may contribute to the overall hemostatic deficit.

SA-PO1024

Measurement and Characterization of Circulating Heparin in Heparin-Naïve ESRD Patients on Maintenance Hemodialysis

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Background: In a cohort of 95 ESRD patients undergoing maintenance hemodialysis, 30 patients did not receive any exogenous heparin during their routine dialysis sessions. However, these patients showed an increase in their PT, anti-Xa, and anti-IIa assays, which were neutralized upon heparinase treatment indicating the presence of endogenous heparin. The objective of this study is to quantify and characterize the heparin in these samples.

Methods: Thirty heparin-naïve patients were identified through a chart review. Blood plasma samples collected at routine pre-dialysis sessions from 95 ESRD patients undergoing maintenance hemodialysis were analyzed for the presence of residual heparin utilizing standard laboratory methods such as aPTT, Anti-Xa and anti-IIa activities On a centrifugal analyzer (ACL-Elite: Instrumentation Laboratory, Bedford, MA). The levels of heparin were calculated in terms of units per ml relative to the US reference standard. Heparinase digestion was used to confirm the presence of heparin.

Results: Wide intra individual variations were noted in the different tests carried out on these samples. The pre-heparinase aPTT was 43.1±49.8 seconds whereas the post-heparinase clotting time was 31.1±10.2 seconds (P<0.0002). The mean anti-Xa activity pre-heparinase was 0.11±0.21 U/ml whereas the post-heparinase anti-Xa activity was 0.04±0.14 U/ml (P<0.0001). The mean anti-IIa activity for the pre-heparinase samples was 0.25±0.27 U/ml whereas the post-heparinase samples had a mean of 0.14±0.15 U/ml (P<0.0007).

Conclusions: The presence of residual heparin was demonstrated by both clot- and amidolytic assays in the plasma samples collected from ESRD patients prior to their next dialysis session. Since these samples were obtained 3 days following the last dialysis session the presence of significant levels of heparin was surprising. Upon heparinase treatment of these samples, the aPTT and the anti-Xa and IIa tests were restored to near normal levels. Our studies confirm the presence of residual heparin in pre-dialysis plasma samples collected from ESRD patients. The Anti-IIa activity was greater pre-heparinase and it was not decreased to the same extent as Anti-Xa after heparinase digestion. These results suggest that heparin found in ESRD patients plasma is of high molecular weight origin with delayed clearance.

SA-PO1025

Persistence of Circulating Residual Heparin in ESRD Patients Undergoing Maintenance Hemodialysis

Arjun S. Grewal,4 Jasdeep S. Bajwa,1 Emily Bontekoe,3 Debra Hopenstend,1 Omer M. Iqbal,1 Jawed Fareed,1 Vinod K. Bansal,1 1Loyola University Medical Center, Maywood, IL; 2Loyola University Chicago, Chicago, IL; 3University of Rochester, Mississauga, ON, Canada; 4University of Rochester, Wauconda, IL.

Background: ESRD patients who receive routine maintenance hemodialysis are administered with unfractionated heparin to prevent thrombotic complications. The hemostatic dysregulation along with detectable levels of circulating heparin may cause them to be in a hypocoagulable state. The purpose of this study is to determine the circulating levels of heparin in ESRD patients and its characterization using heparinase digestion methods.

Methods: Blood plasma samples collected at routine pre-dialysis sessions from 95 ESRD patients undergoing maintenance hemodialysis were analyzed for the presence of residual heparin utilizing standard laboratory methods such as aPTT, Anti-Xa and anti-IIa activities On a centrifugal analyzer (ACL-Elite: Instrumentation Laboratory, Bedford, MA). The levels of heparin were calculated in terms of units per ml relative to the US reference standard. Heparinase digestion was used to confirm the presence of heparin.

Results: Wide intra individual variations were noted in the different tests carried out on these samples. The pre-heparinase aPTT was 43.1±49.8 seconds whereas the post-heparinase clotting time was 31.1±10.2 seconds (P<0.0002). The mean anti-Xa activity pre-heparinase was 0.11±0.21 U/ml whereas the post-heparinase anti-Xa activity was 0.04±0.14 U/ml (P<0.0001). The mean anti-IIa activity for the pre-heparinase samples was 0.25±0.27 U/ml whereas the post-heparinase samples had a mean of 0.14±0.15 U/ml (P<0.0007).

Conclusions: The presence of residual heparin was demonstrated by both clot- and amidolytic assays in the plasma samples collected from ESRD patients prior to their next dialysis session. Since these samples were obtained 3 days following the last dialysis session the presence of significant levels of heparin was surprising. Upon heparinase treatment of these samples, the aPTT and the anti-Xa and IIa tests were restored to near normal levels. Our studies confirm the presence of residual heparin in pre-dialysis plasma samples collected from ESRD patients. The Anti-IIa activity was greater pre-heparinase and it was not decreased to the same extent as Anti-Xa after heparinase digestion. These results suggest that heparin found in ESRD patients plasma is of high molecular weight origin with delayed clearance.

SA-PO1026

Heparin-Free Dialysis: A Phase 2 Pilot Study Using Asymmetric Cellulose Triacetate (ATA) Dialyzers

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Background: Not all dialysis patients tolerate heparin anticoagulation. Heparin should be avoided in patients at high risk of bleeding. Strategies include saline infusion, citrate-containing dialysate, regional citrate anticoagulation and heparin-coated membranes. We recently studied the combination of a heparin-coated membrane and citrate-containing dialysate, with a success rate of 94%. Although this combination resulted in low rates of clotting, heparin-coated membranes are not ubiquitously available. The quest for easy to perform, safe and affordable heparin-free dialysis is on. Asymmetric cellulose triacetate (ATA) dialyzers have a low degree of platelet contact activation and might be an alternative to heparin-free dialyzers.

Methods: We performed a phase II pilot study in maintenance dialysis patients. The Strategies for Asymmetrical Triacetate dialyzer heparin-Free Effective hemodialysis (SAFE study) was a two-arm open-label cross-over study. In Arm 1, patients were dialyzed using a 1.9 m2 ATA membrane (Solacea™-19H, Nipro Corp., Japan) in combination with citrate-containing dialysate. In Arm 2, patients were dialyzed with the same 1.9 m2 membrane, in combination with high volume predilution hemodiafiltration. The primary endpoint was the success rate to complete 4 hours of hemodialysis without preterm clotting.

Results: We scheduled 240 dialysis sessions (120 per arm) in twenty patients. Ten patients were randomized to start in Arm 1, the others to Arm 2. All patients crossed to the other arm halfway the study. 232 (96.7%) study treatments were delivered. Overall, 23 clotting events occurred, 7 in Arm 1 and 16 in Arm 2. Success rate in Arm 1 (ATA + citrate containing dialysate) was 90.8 / 94.0 % (intention to treat/ as treated). Success rate in Arm 2 (ATA + predilution HDF) was 83.3 / 86.2 % (intention to treat/ as treated). TheraPy survival was borderline significantly better in Arm 1 (Mantel-Cox log rank P = 0.05).

Conclusions: Asymmetric cellulose triacetate (ATA) dialyzers have a low clotting propensity. In combination with citrate-containing dialysate, asymmetric cellulose triacetate (ATA) may be a suitable alternative to heparin-coated membranes for systemic heparin-free hemodialysis.

Funding: Commercial Support - Nipro restricted grant
**SA-PO1027**

Hemodialysis with a Citrate Containing Ca- and Mg-Free Dialysis Fluid: Exit Heparin?  

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**Background:** Hemodialysis (HD) with heparin increases mortality of bleeding. Regional anticoagulation with citrate (C) HD (infusion of C before dialyzer, Ca-, Mg-free dialysis fluid and Ca/Mg substitution after dialyzer) may decrease this risk, but is laborious. This study describes the effect of adding C to the Mg-, C-free dialysis fluid.

**Methods:** In 12 HD patients on anticoagulants (6 vit. K antagonist, 6 acetylsalicylic acid), 2 HD sessions with dialyzer (D) and 2 with C were performed. During D dialysis fluid contained Ca 1.5 and Mg 0.5 mmol/l. During C, a Ca-, Mg-free, 0.8 mmol/l C containing dialysis fluid was used. Ca 540/ Mg 240 mmol/l substitution was 35 ml/h.

Before, during and after HD, urea, ionized Ca (iCa), Mg, were tested and clotting tests (APTT, NATEM full blood CT ROTEM Delta, Tem-innovations Munich) were done. Clotting phenomena in venous airtrap and dialyzer were graded by visual inspection (grade 0-2 respectively 0-3). Data were analyzed using linear mixed models to account for repeated measurements.

**Results:** No HD was stopped prematurely. During C, clotting tests remained unaltered (APTT 31 vs 32 vs 32 sec; NATEM CT: 1079 vs 1052 vs 1048 sec). At D, clotting tests became significantly abnormal (APTT: 32 vs 42 vs 35 sec; NATEM CT: 1132 vs 2892 vs 1913 sec; p<0.001). Small clots in the venous airtrap were seen in 3/46 sessions (2C and 1D).

**Conclusions:** HD with a 0.8 mmol/l citrate, calcium- and magnesium-free dialysis fluid was slightly but clinically irrelevant inferior to HD with dialyzer without changing clotting tests in patients. Thus, citrate HD may probably prevent the increased risk of bleeding in patients already on maintenance anticoagulants.

**Funding:** Commercial Support - Werfen Benelux, Breda, The Netherlands

**SA-PO1028**

Effect of Taurodilute Citrate and Unfractionated Heparin Combination on Inflammatory Response and Dialysis Adequacy in Hemodialysis Patients  


**Background:** In hemodialysis (HD) patients, Catheter-related infections and dysfunction are a major health problem. In Egypt, recent data show that 6.6% of HD patients use catheters, of which short term catheters represent 59.6% and 40.4% with long-term catheters. In this study, we aim to assess the effect of using Taurodilute citrate and unfractionated heparin combination, as a lock solution for temporary dialysis catheters, on inflammatory markers, incidence of catheter related infections (CRIs) and dialysis adequacy in HD patients.

**Methods:** A randomized controlled clinical trial included 60 stable HD patients from Ain-Shams University Hospitals at the time of catheter insertion. Patients were randomized into 2 groups: Group 1: 30 Patients received taurodilute citrate (4%) and 500 i.u of heparin as a catheter lock after HD session. Group 2: 30 Patients received unfractionated heparin (heparin sodium 5000U/ml) as a catheter lock after HD session. Both groups were followed up for 1 month period and monitored for signs of CRIs. Also, Urea reduction ratio (URR) were measured weekly. Highly sensitive CRP and Interleukin 6 (IL-6) were measured at baseline and 1 month after using the lock solutions. Blood cultures were withdrawn in patients who developed signs of CRIs.

**Results:** Group 1 (mean age 39.5 ± 14. 46.7% males), Group 2 (mean age 39.3 ± 14. 60% males). As regard inflammatory markers, a significant difference was noted between the 2 groups one month after catheter insertion (P 0.001 and 0.018 for hsCRP and IL6 respectively), with the higher levels of inflammatory markers showed in group 2. Catheter performance determined by URR and blood flow rate between the 2 groups by the 4th weeks was significantly different in favor of group 1, suggesting better performance of the catheter (P 0.007 and 0.001 respectively). CRIs were demonstrated in 9 patients group 2 (30%) in contrast to 1 patient only in group 1 (3.3%) (P 0.006).

**Conclusions:** We may conclude that using Taurodilute citrate and unfractionated heparin combination as a lock solution for temporary dialysis catheters was associated with lower levels of inflammatory markers and lower incidence of CRIs when compared to the standard unfractionated heparin lock. Its use also was associated with better catheter performance.

**SA-PO1029**

Anticoagulation for People Receiving Long-Term Hemodialysis: A Cochrane Review and Meta-Analysis  

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**Background:** Hemodialysis requires safe and effective anticoagulation to prevent clot formation during the procedure. Low molecular weight heparin (LMWH) may provide more predictable anticoagulant effects and be simpler to administer than unfractionated heparin (UFH) but may increase risks of bleeding. This Cochrane review evaluates the benefits and harms of anticoagulation strategies for long-term hemodialysis.

**Methods:** We searched the Cochrane Kidney and Transplant Register of Studies for randomized controlled trials evaluating anticoagulant agents administered for hemodialysis treatment in adults with end-stage kidney disease (ESKD). Two authors independently screened citations for eligibility, extracted data, and assessed risk of bias using the Cochrane tool. Evidence certainty was evaluated using GRADE.

**Results:** Eighty-seven studies (5548 participants) were eligible. Median trial duration was 0.75 months (range 1 week to 24 months). Median trial age was 58.2 years (range 10.93 to 74 years). Methodological risks of bias were high or incomplete for most studies. Forty-three studies (2066 participants) compared LMWH with UFH. The certainty of the evidence for very low or low for all outcomes. Two of 43 studies reported for the extra corporeal dialysis circuit thrombosis, with one study reporting one or more events. LMWH had very certain effects on dialysis circuit thrombosis compared to UFH (very low certainty evidence). Four studies reported zero major bleeding events (very low certainty evidence). No study reported time to achieve dialysis vascular access hemostasis. LMWH had uncertain effects on all-cause mortality (relative risk [RR] 2.41, 95% CI 0.62, 9.33; low certainty evidence). A single study reported the effect of LMWH on dialysis adequacy, measured as KT/V, such that meta-analysis could not be performed. Treatment effects of other anticoagulants were very uncertain.

**Conclusions:** Evidence for different forms of anticoagulation for hemodialysis is of very low certainty due to methodological limitations in existing trials and paucity of trial data. This review suggests the need for a head-to-head trial of LMWH versus UFH is sufficiently powered to assess clinical outcomes such as bleeding, dialysis adequacy, mortality or cardiovascular events, or complications related to dialysis vascular access.

**Funding:** Commercial Support - Vifor Fresenius Medical Care Renal Pharma

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 1031
SA-PO1031

Impact of Hyperphosphatemia Severity on Serum Phosphorus Reduction with Sucroferric Oxyhydroxide: A Subgroup Analysis of the VERIFIE Study

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Background: Sucroferric oxyhydroxide (SFOH) is an iron-based phosphate binder indicated for the treatment of hyperphosphatemia in dialysis patients.

Methods: VERIFIE is a non-interventional, prospective, multicenter, European cohort study evaluating the real-world safety and effectiveness of SFOH in dialysis patients with hyperphosphatemia. This interim analysis, performed 24 months after study initiation, evaluated serum phosphorus (sP) changes during SFOH treatment in 4 subgroups of patients stratified according to their sP levels at baseline (>4.5 to ≤5.5 mg/dL; >5.5 to ≤7.0 mg/dL; >7.0 to ≤8.5 mg/dL; >8.5 mg/dL).

Results: In total, 874 patients who received ≥1 dose of SFOH and had effectiveness follow-up data available, were included in the subgroup analysis, which evaluated sP changes during the first 12 months of treatment. Approximately 40% of patients received concomitant phosphate binders (in addition to SFOH) during the study. Statistically significant (p<0.001) reductions in sP from baseline through Month 12 were observed among patients with baseline sP >5.5 mg/dL, >7.0 mg/dL, >8.5 mg/dL, or >8.5 mg/dL. Smaller reductions in sP were observed in the >4.5 to ≤5.5 mg/dL subgroup (Figure). Overall, reductions from baseline in mean sP were greater among patients with higher baseline sP levels.

Conclusions: This subgroup analysis demonstrated that treatment with SFOH can lower sP in real-world dialysis patients with hyperphosphatemia, regardless of their baseline sP levels, and these reductions were sustained over 12 months.

Funding: Commercial Support - Vifor Fresenius Medical Care Renal Pharma

SA-PO1032

Association of White Blood Cell Count and Cause-Specific Mortality in Incident Hemodialysis Patients

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Background: Previous studies have shown higher white blood cell (WBC) counts to be strongly and independently associated with all-cause mortality in incident maintenance hemodialysis (HD) patients. However, the association between WBC count and cause-specific mortality in incident HD patients is unknown.

Methods: In a retrospective observational cohort study of 109,767 HD patients from a large US dialysis organization (2007-2011), we examined cardiovascular (CV) and infectious mortality associations with baseline WBC. Using Cox models, we examined the associations with three hierarchical adjustments for cause-mix variables, albumin, and additional laboratory markers of malnutrition and inflammation (MICS).

Results: Mean patient age of the cohort was 65 ± 15 years; 44% of patients were female, 22% were African American, and 58% were diabetic. Patients with higher WBC levels (>8.0 x10³/mm³) had a higher CV and infectious mortality risk compared to the reference group (7<8.0 x10³/mm³) in baseline models, and across all levels of adjustment. In the fully adjusted models, compared to the reference, patients with WBC >10.0 x10³/mm³ had a 22% higher risk of CV mortality (hazard ratio [HR]: 1.22, 95% CI: 1.14, 1.30) and a 58% higher risk of infectious mortality (HR: 1.58, 95%CI: 1.38, 1.82) (Figure).

Conclusions: Among incident HD patients, higher WBC count is associated with higher CV and infectious mortality risk, independent of other markers of malnutrition and inflammation, including albumin. These data suggest that higher WBC may be indicative of stronger risk of infectious mortality outcomes but further studies are needed to ascertain its use as a predictive marker in HD patients.

Funding: NIDDK Support

SA-PO1033

Hypersegmented Neutrophils in Hemodialysis Patients and Cobalamin (B12) Requirements

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Background: Estimation of Nuclear Hypersegmentation of Neutrophils (HN) has been widely used as an indicator of Vitamin B12 (B12) or Folate (FO) deficiency. We chose to monitor the above as an indicator of functional deficiency of B12, since B12 supplementation, either for reducing the level of homocysteine (HC) or as factor decreasing erythropoietin (EPO) resistance in hemodialysis (HD) patients (pts), still remains a controversial issue.

Methods: Serum B12 levels were calculated from 57 HD pts prior to HD, after having received weekly intramuscular B12 injections (1000 µg Cyanocobalamine) for the past 15 years; 44% of patients were female, 32% were African American, and 58% were diabetic. Patients with higher WBC levels (≥7.0 x10³/mm³) had a 22% higher risk of CV mortality (hazard ratio [HR]: 1.22, 95% CI: 1.14, 1.30) and a 58% higher risk of infectious mortality (HR: 1.58, 95%CI: 1.38, 1.82) (Figure).

Conclusions: Among incident HD patients, higher WBC count is associated with higher CV and infectious mortality risk, independent of other markers of malnutrition and inflammation, including albumin. These data suggest that higher WBC may be indicative of stronger risk of infectious mortality outcomes but further studies are needed to ascertain its use as a predictive marker in HD patients.

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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6 months. All pts had smears of their peripheral blood examined to assess percentage of cells with HN, the finding consistent with B12 deficiency. Hgb, MCV, FO, HC, PTH levels, KiV and EPO requirements were also recorded. Testing was repeated 6 months after discontinuation of B12 supplementation and 6 months after re-challenging with B12. FO supplements were administered throughout the study. Ferritin levels were kept > 200 ng/mL for all patients except for one patient.

Results: Nuclear Hypersegmentation of Neutrophils was found in 55% of our patients to exceed the accepted level of 5% and reached 100% after stopping B12 supplementation along with a significant increase in EPO requirements, though B12 levels were well above the upper normal limit. Other tests returned to previous levels after re-challenge. With B12 HC and FO levels were unaffected. No difference in other parameters were observed.

Conclusions: In this study maintaining FO levels stable, we have demonstrated that despite high B12 blood levels, there is a functional deficiency which is reversed by B12 treatment. The optimal dose decreased significantly by -16.3 Udaly (p = 0.001). Moreover, no significant changes were observed in the area under the curve >70 ml/dL per 24 h (AOC>70) in CGM. Six cases of gastrointestinal disorders were reported; however, both the DTSQ treatment satisfaction score (p = 0.029) and DTR-QOL total score (p = 0.014) improved significantly. BMI and FM changes were -0.6 kg/m² (p = 0.001) and -2.6 kg (p = 0.029), respectively. SMM and IDWG did not significantly change.

Conclusions: Dulaglutide may help improve glycemic control, body composition, and QOL without increasing hypoglycemia in insulin-treated patients with T2DM on maintenance HD.

SA-PO1036 Impact of Diabetic Nephropathy on Morbidity and Mortality in a Large Cohort of Hemodialysis Patients in Saudi Arabia Ezzeddine Abderrahim,1 Aynan Sabri,2 Mahmoud A. Ahmad,3 Saud S. Alolbaii,4 Abderrahim A. Al prést,5 Ibrahim A. Al Omari,1 Wissam Al Omari,1 Davita Saudi Arabia, Riyadh, Saudi Arabia; Davita Care-KSA, Riyadh, Saudi Arabia.

Methods: The aim of this study was to evaluate the impact of diabetes as a cause of ESRD on morbidity and mortality in adult dialysis patients. Methods: All patients referred to Davita Saudi Arabia clinics to continue ESRD treatment with hemodialysis from October 2014 to December 2018 were included in this analysis. The study population was divided in Group 1, corresponding to patients referred with the diagnosis of diabetes as a cause of ESRD and, Group 2, in whom ESRD was attributed to other causes with or without diabetes as a comorbidity. Mortality and hospitalization rates were calculated by dividing the number of events by the cumulative period of follow-up. Logistic regression was used to identify parameters that were independently associated with mortality and hospitalization.

Results: The cohort included 3508 patients (54% men). Patients with diabetic nephropathy represented 40.3% of included patients (G1), their mean age was of 58.1 ± 14.5 years vs. 48.7 ± 17.4 in Group 2 (p<0.0001). There was a slight male predominance in both groups with a sex ratio of 1.20 in G1 vs. 1.16 in G2 (NS). The proportion of patients who were hospitalized was of 31.7% in G1 vs. 22.3% in G2 (p<0.001), corresponding to a rate of 38.8 per 100 patient-years (CI, 95%: [16.5-41.4]) in G1 vs. 21.8 per 100 patient-years (CI, 95%: [20.2-23.3]) in G2. Mean duration of hospital stay was of 4.8 days per patient in G1 (CI, 95%: [4.8-4.9]) vs 2.5 days in G2 (CI, 95%: [1.4-2.5]). The mortality rate was of 10.5 per 100 patient-years in G1 (CI, 95%: [9.10-11.86]) vs. 5.1 in G2 (CI, 95%: [4.3-5.83]). After adjustment for age, gender, type of vascular access and, time on HD, hospitalization, and mortality risks were of 1.61 (CI, 95%: [1.33-2.11]) and 1.47 (CI, 95%: [1.24-1.73]) compared to G2. Conclusions: Patients referred to Davita for ESRD related to diabetic nephropathy, are at a higher risk for the number of hospitalization, hospital length stay and, mortality in comparison to those hemodialyzed for other causes.

SA-PO1037 The Impact of Antidiabetic Drugs on Mortality in Diabetic Patients Undergoing Hemodialysis Yi-Ting Chen,1 Cheng chia Lee,2 Chih-hsiang Chang,1 Yu-yun Chou,1 Chang Gung Memorial Hospital, Taoyuan, Taiwan; ‘Chang Gung memorial hospital, Taipei, Taiwan.

Background: Diabetes mellitus (DM) is associated with an increased risk of morbidity and mortality in patients undergoing hemodialysis (HD). Insulin and other oral antidiabetic drugs (OAD) are currently used in HD patients. However, there has been little research that have analyzed the long-term effect of antidiabetic drugs on mortality rate. The aim of this study is to evaluate the impact of use of antidiabetic drugs on the risk of mortality in such patients.

Methods: This is retrospective cohort study, we identified 212 diabetic HD patients who continued using at least one kind of antidiabetic drugs for more than 6 months in Chang Gung Memorial Hospital between November 1, 2009 and November 31, 2016. We excluded patients that had dialysis duration less than 6 months (N=60) and follow-up time less than 6 months (N=90). Finally, the cohort comprised a total of 143 patients. Primary outcome was all-cause mortality. Hazard ratios (HR) were calculated by Cox proportional hazard regression models which were used to adjust for age, gender, laboratory data and time on HD.

Results: In all 143 patients, mean age was 60.8 ± 12.2 years, 43.4% of patients were male and mean dialytic duration was 45.1 months. 71 patients (49.7%) used insulin for glycemic control, 54 (37.8%) used Sulfonylurea, and 25 (17.5%) used Dipeptidyl peptide-4 inhibitors. After a median follow-up duration of 39.6 months, 60 patients died. The Cox proportional hazard variate analysis revealed only age (HR = 1.04, p = 0.0001), serum albumin (HR = 0.206, p = 0.001) and insulin users (HR = 2.39, p = 0.011) to be independent

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predictors of mortality. The finding persisted after adjusting for hemoglobin A1c level being treated as both a categorical variable or a continuous variable.

Conclusions: This study demonstrated that compared with non-insulin users, insulin users were associated with a higher risk of mortality in diabetic HD patients, independent of glycemic control.

Cox-multivariate analysis for all-cause mortality

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
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</tr>
<tr>
<td>Diabetes</td>
<td>3.219</td>
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</tbody>
</table>

Multivariate adjustments were made for gender, dialysis duration, hemoglobin, triglycerides, use of Sulfonylurea, Dipeptidyl peptide-4 inhibitors, and Hemoglobin A1c level.

SA-PO1038

Standardized Clinical Foot Examination in Prevalent Hemodialysis Patients: Association with Mortality and Hospitalization

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Background: Atherosclerosis, neuropathy and SHPT contribute to increased risk of peripheral vascular disease (PVD) and adverse outcomes (eg, ulcers, limb amputation, hospitalizations and mortality) in diabetic patients on HD. Both the ACC/AHA and KDIGO guidelines recommend screening of individuals at risk. This study analyzed the frequency of foot complications following implementation of a standardized foot examination in 345 prevalent diabetic HD patients in 12 DaVita centers in Poland (n=177 pts) and Portugal (n=168 pts). Hospitalizations and cause-specific mortality were documented during 24 months follow-up.

Methods: The protocol includes: history of the patient (ulcers, amputation), inspection of feet (skin, nails) and examination of the pedal pulses (a dorsalis pedis and in L and R a tibialis post) was found in 17% and 10% of patients, respectively. All other patients had weak or absent pulses. The Wagner score was 0 or 1 in 88% of patients, 2-3 in 6%, and 4-5 in 5%. All-cause mortality was 31% during the 2 year follow up. 71% of patients had at least one hospital stay. Cardio-cerebrovascular disease, PVD, and infection accounted for 76% of all mortality. In an unadjusted analyses presence of weak or absent pulses in a dorsalis pedis was significantly associated with all-cause mortality (R2.1 (CI 1.1-4.3); p<0.05). In adjusted models including age, sex, Hb, albumin, Kt/V, vascular access, phosphorus,PTH and Charlson score, only albumin was associated with mortality (RR 0.89, CI 0.84-0.94; p=0.001) and risk of hospitalization (RR 0.92, CI 0.89-0.96; p=0.001).

Conclusions: Implementation of a standardized foot examination protocol in diabetic patients on HD showed a high prevalence of clinically significant complications that warrant close attention. This clinical tool is suitable to identify patients at high risk of future complications and could be the basis of a program to improve overall health outcomes.

SA-PO1039

Epidemiology of Pericardial Effusions in Patients with ESRD on Hemodialysis

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Background: Cardiovascular disease, including pericardial disease, remains a prominent cause of morbidity and mortality in patients with end-stage renal disease (ESRD). The prevalence, clinical and prognostic significance of pericardial effusions (PE) in ESRD patients has not been well established. This study examines the epidemiology of PE in patients on chronic hemodialysis (HD).

Methods: This was an observational, retrospective study of chronic HD patients (> 2 months on HD) from Stony Brook University Hospital Kidney Center from January 1, 2010 to November 31, 2017 with analysis of transthoracic echocardiograms (TTE) along with corresponding clinical and demographic data. Effusions were classified by size: trivial (< 5 mm), small (5-10 mm), moderate (10-20 mm), or large (> 20 mm) echo-free space in diastole, as per European Society of Cardiology guidelines. Statistical analysis was conducted in SAS v9.4 using parametric and non-parametric tests as appropriate.

Results: A total of 185 TTEs from 82 patients on HD were analyzed. Twenty-nine (35.4%) patients had some degree of PE. Sixteen (19.5%) patients had trivial, thirteen (15.9%) had small, five (6%) had moderate and two (2.4%) had large (including one with tamponade physiology requiring pericardiocentesis) PE. Eighteen patients had multiple TTEs during the study period and were found to have varying degrees of PE (ranging from none to moderate). Patients with PE had a significantly lower median age compared to those who did not have PE (54 years old vs. 65 years old), with the moderate/large effusions primarily observed in relatively younger patients (median age of 46). Patients with lower serum albumin levels had significantly higher numbers of PEs, with the most severe PEs seen in the groups with the lowest albumin levels (3.2 g/dL). Patients with PE also had a lower mean hemocrit level compared to those without PE (29.6% vs. 32.7%). No significant association was found between the presence of PE and gender, ethnicity, cardiac ejection fraction, change in weight compared to dry weight, urea reduction ratio, or ktv.

Conclusions: Approximately one-third of patients on chronic HD therapy had some degree of PE. In this study, relatively younger age, lower levels of serum albumin and lower hemocrit were independently associated with increased prevalence of PE.
SA-PO1042
Dialysis Outcomes at 12 Months Among Patients Starting Hemodialysis in India
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Background: Hemodialysis (HD) is the dominant renal replacement therapy (RRT) in India. Despite a national free dialysis programme since 2016, outcomes in dialysis have received limited attention. 1000 incident HD patients were followed up to evaluate the determinants of outcomes. We describe the baseline socio-demographic and clinical characteristics associated with 12-month survival on HD.

Methods: 1000 participants were recruited from 2016 to 2018 at 16 dialysis facilities across 9 Indian states. Demographic, clinical, socioeconomic and quality of life parameters were collected through a secure online data collection platform. We examined the association of survival with age, gender, education, family income, OoP expenditure, insurance coverage, vascular access, hemoglobin and intradialytic weight gain. Chi-square and Fishers T tests were used to test for associations and a p value of <0.05 was deemed significant.

Results: The median age (IQR) was 58 (18) years, and 29% were female. 20% of the participants had education beyond school. 80% of the females worked within the home, while 44% of the males were retired or not working. Of those who had a job, 9% changed their occupation. Median monthly family income was US$ 500 (586). Median distance traveled for dialysis was 10 (15) kms. 75% funded dialysis out of pocket (OoP), with 44% of the males being insured. Of those who had a job, 9% had a regular commute. Median monthly OoP expenditure was US$ 360±220 for uninsured participants and US$ 180±140 for insured patients. At 12 months, 53.4% remained on HD, 18.5% had died, 14.9% withdrew from dialysis, 7.5% received a transplant, 2.9% switched to PD, and 2.8% were lost to follow-up. Survivors had shorter travel distance, higher family income, hemoglobin and lower intradialytic weight gain. In the QoL analysis, the highest decline of function was observed in the domain of self-care (16%) followed by mobility (15%).

Conclusions: In this national HD cohort, 64% continued on RRT at 12 months. Availing dialysis closer to home, adequate financial risk protection was associated with continuing on dialysis. Hemoglobin levels more than 10 g/dl and low Intradialytic weight gains were strongly associated with survival. Monitoring outcomes in dialysis provides an opportunity to identify modifiable factors to improve quality and inform policy.

Funding: Commercial Support - Baxter International

SA-PO1043
Survival in Patients Who Return to Dialysis with Kidney Allograft Failure: The Argentinian Dialysis Registry Study
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Background: The number of patients (Pts) who return to dialysis (Dx) after Kidney allograft failure (KAF) is increasing. The outcome of these Pts remain unclear. Some studies describe long-term survival in KAF Pts that is comparable to naive Pts dialysis (TNID) Pts. Our aim was to compare outcome of KAF versus Pts on waiting list (WL) and those with a kidney transplant contraindication (KTC).

Methods: We performed a retrospective observational study using data from the Argentinian Dialysis Registry between 2005 and 2016. We recorded demographics, laboratory markers and vascular access at entry. To compare mortality between the 3 groups Kaplan Meier, log rank test and Cox regression were used.

Results: This study included 75722 Pts of which 2734 (3.6 %) were KAF Pts. The TNID (n=72988) Pts were significantly older, included higher percentages of males, diabetic and hypertensive when compared with Pts who started Dx after KAF. Regarding Dx modality, 5.8 % of Pts initiated PD in KAF group vs 3.9 % in TNID group (p<0.0001). There was a high percentage of Pts starting HD with transient catheters, being 66.1% and 65.5 % in KAF and TNID group respectively. Overall mortality was 54.6 % during follow up. Death probability between the 3 cohorts (KAF:n=2734) vs WL (n=14630) vs KTC(n=58558) revealed a significant difference (log-rank test: 10734.5; P< 0.0001) indicating worse survival for KTC incident Dx Pts cohort and best survival for WL. We also performed a survival curve adjusting for covariates that were statistically significant for mortality in Cox multivariate analysis. We found that KAF Pts had as poor outcome as KTC Pts. Multivariate Cox analysis showed that age<65 years: HR: 1.247 (1.21-1.28) P < 0.0001, transplant catheter: HR: 1.303 (1.26-1.34) P < 0.0001, male sex: HR: 1.043 (1.01-1.07) P < 0.0002, diabetic: HR: 1.273 (1.22-3.1) P < 0.0001, hemodialysis modality: HR: 1.168 (1.07-1.27) P < 0.0004, hepatitis C: HR: 1.303 (1.26-1.34) P < 0.0001 and Albumin: HR: 1.247 (1.21-1.28) P < 0.0001 were strongly associated with mortality, while being on waiting list: HR: 0.285 (0.23-0.35) P < 0.0001 was found to be protective.

Conclusions: Patients who return to Dx after KAF have higher mortality than WL patients and similar to KTC patients.

SA-PO1044
A Comparison of Death Records Between the USRDS and a Large Health Care System
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Background: The accuracy of mortality data is important when determining the mortality rates for the end stage renal disease (ESRD) population and assessing interventions to improve survivability or quality of life. Little research has been done to examine the completeness and accuracy of the USRDS mortality reports. The purpose of this study is to compare mortality records from a large integrated health system with the USRDS registry.

Methods: A retrospective cohort study (1/1/2007-12/31/2016) of ESRD patients within Kaiser Permanente Southern California (KPSC), an integrated health system, was performed. Patients were linked to the USRDS death records and evaluated. KPSC mortality data are obtained from several sources, but primarily from California state death certificates. USRDS mortality data are similarly obtained from several sources, but primarily from CMS form 2746.

Results: A total of 4827 death records were found between 2007 and 2016. There were 4189 death records found in both USRDS and KPSC databases, 609 found only at KPSC and 29 found only at USRDS. An average of 12.7% of death records per year were captured at KPSC but missing from the USRDS database. Of the 4189 death records, 86.92% of KPSC death records had consistent dates of death (DOD) with the USRDS. A few death records had a DOD that differed by more than a week (1.03%) to more than a year (0.77%).

Conclusions: These data suggest that mortality information from the USRDS could be systematically under-ascertained. Researchers should use caution when using USRDS mortality data because of the potential for incompleteness of the data as currently collected. The use of additional sources of information may supplement and help overcome these challenges.

Funding: Government Support - Non-U.S.

SA-PO1045
Sex-Specific Survival Advantage In Patients Undergoing Hemodialysis: Ten-Year Outcomes of the Q-Cohort Study
Hiroaki Tsuchioka,1 Shunsuke Yamada,2 Hiroto Hiyamuta,3 Masatomo Taniguchi,2 Shigeru Tanaka,1 Kazuhiko Tsuyoutu,1 Kumiko Tortsu,1 Toshiaki Nakanoma,1 Takarai Kitazono,4 Kyushu University, Fukuoka, Japan; 2Fukuoka Renal Clinic, Fukuoka, Japan; 3Nara Medical University, Kashihara, Japan; 4Department of Medicine and Clinical Science, Fukuoka, Japan

Background: The survival advantage of females is observed in the general population. However, there is a controversy on the survival benefits of being females compared to males in patients undergoing hemodialysis. The aim of the study was to compare the risk for infection-related and all-cause mortality between males and females in patients undergoing hemodialysis.

Methods: A total of 3,504 Japanese hemodialysis patients aged ≥18 years were prospectively followed for 10 years. The primary outcomes were infection-related and all-cause deaths. Multivariable-adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) of these outcomes were calculated using a Cox proportional hazards model.

Results: During the median follow-up period of 5.3 years, 448 died of infection and 1736 patients died of any cause. Compared with males, the multivariable-adjusted HRs (95% CIs) for infection-related and all-cause deaths in females were 0.47 (0.41–0.55) and 0.34 (0.25–0.44), respectively. This relationship was remained significant even when propensity score matching or inverse probability of treatment weighting (IPTW) adjustment methods were employed. Furthermore, even when the competing events of non-infection-related deaths were taken into account, the infection-related mortality rate in females was significantly lower than that in males.

Conclusions: The current study showed that the female advantage in survival is observed in patients undergoing hemodialysis. Further study are necessary to confirm the survival benefit of females and its underlying mechanism in patients receiving hemodialysis.
SA-PO1046

**Rural vs. Urban Residence and Survival on Chronic Maintenance Dialysis in US Veterans**

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**Background:** Most of the VA dialysis centers are urban. Veterans receiving maintenance hemodialysis (MHD) care in non-VA rural facilities may have lower mortality. Hence, rural and urban disparities might explain the better survival of veterans initiating MHD within the VA.

**Methods:** We examined a national cohort of veterans who initiated MHD from May 2012 to May 2016 by combining United States Renal Data System data obtained from VA Information Resource Center and VA Corporate Data Warehouse data obtained via VA Informatics and Computing Infrastructure. We defined rural and urban residence by zip codes. We used USRDS data to define VA and non-VA dialysis facilities, dialysis quality metrics and time to death.

**Results:** 46,470 veterans were included. VA veterans were younger, less likely to be white, had lower income and higher prevalence of traumatic brain injury and PTSD. However, irrespective of rural or urban residence, veterans who received dialysis care within the VA had better 5-year survival than veterans who received care outside the VA (Fig).

**Conclusions:** Veterans who received dialysis care within the VA had better survival compared to those who received care outside of the VA regardless of rural or urban residence.

**Funding:** Veterans Affairs Support

**Baseline Characteristics**

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Residence, VA care and 5 year mortality

SA-PO1047

**Impact of Altitude on Dialysis Patient Characteristics and Outcomes**

Sheetal Chaudhuri, Hao Han, Marta Reviriego-Mendoza, Brian S. Ashi, Janice D. Lindsay, John W. Larkin, Len A. Usyut, Jeffrey L. Hymes, Robert J. Kossmann, Franklin W. Maddux. Fresenius Medical Care North America, Waltham, MA.

**Background:** Barometric pressure, oxygen pressure as well as ultraviolet radiation are environmental factors that vary by altitude and have the potential to impact outcomes. Patients undergoing hemodialysis (HD) tend to suffer from several chronic conditions and could vary depending on the elevation they reside in. We aimed to define the characteristics and outcomes of the HD population at a large dialysis provider (LDO) by the altitude of residence.

**Methods:** We used data from HD patients treated at the LDO in 2018. Patients were stratified by the average elevation of the state of residence extracted from the US Geological Survey. Average state elevations were defined as: high (>4000 feet), mid (1000 to 4000 feet), and low (<1000 feet). We defined patient demographics, comorbidities, clinical characteristics and outcomes in the different elevations.

**Results:** Among a population of 244720 HD patients, 59% resided at low elevation, 35% at mid elevation, and 6% lived at high elevation. The percentage of females varied from 41-43% in the three elevations, and age ranged from 60-74 years old. Low elevations had the lowest percentage of white and Hispanic patients (whites: 44% vs 55% and 68% at low, mid and high elevations respectively; Hispanics: 5%). Low elevations had the smallest percentage of patients with diabetes (66%, 69% and 70% at low, mid and high elevations), while it had the highest number of patients with heart diseases (congestive heart failure: 21% vs 19% and 13% at low, mid and high elevations; ischemic heart disease: 21% vs 19% and 12% for low, mid and high elevations; hypertension 66% vs 67% and 70% at low, mid and high elevation). Patients more commonly received an extra HD treatment in higher elevations (7% vs 8% and 9% at low, mid and high elevation). Low elevation also had the highest hospitalization rates (1.9 vs 1.8 and 1.7 at low, mid and high elevation).

**Conclusions:** HD patient characteristics and outcomes vary by elevation. In low elevations heart diseases were more prevalent, patients more often received an extra HD treatment, and patients had higher hospital admission rates. Diabetes was more prevalent in higher elevations in HD patients. Further adjusted analysis are needed to identify the influences of altitude on practice patterns and outcomes.

**Funding:** Commercial Support - Fresenius Medical Care North America

SA-PO1048

**Racial Differences Among Recipients of Staff-Initiated CPR in Outpatient Dialysis Clinics**

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**Background:** Sudden cardiac arrest is the leading cause of death among hemodialysis patients. Despite practice guidelines recommending basic life support training for all hemodialysis clinic staff, rates of staff-initiated CPR are sub-optimal. Little is known about whether patient and clinic characteristics are associated with lower rates of dialysis staff-initiated CPR.

**Methods:** We examined data in the Cardiac Arrest Registry to Enhance Survival, a national surveillance registry with data submitted from 23 statewide registries and 70 additional communities, along with dialysis clinic data from the Centers for Medicare & Medicaid Services to identify cardiac arrests in outpatient hemodialysis clinics as well as characteristics of the response between 2013 and 2017. Using multivariable logistic regression, we examined the likelihood of receiving dialysis staff-initiated CPR based on patient and dialysis clinic characteristics.

**Results:** Of the 1,581 patients who experienced cardiac arrest in hemodialysis clinics, 88.0% received staff-initiated CPR. 91.1% of White and 84.8% of Black patients received staff-initiated CPR (p=0.009). After accounting for patient age and sex, clinic characteristics, dialysis clinic neighborhood characteristics, and U.S. region (see Table), Black patients remained significantly less likely to receive staff-initiated CPR than White patients (aOR 0.45, 95% CI, 0.28 to 0.73). There was no relationship between patient race and dialysis staff automated external defibrillator application.

**Conclusions:** Black patients are significantly less likely than White patients to receive staff-initiated CPR during cardiac arrest in dialysis clinics across the US. Further understanding of resuscitation practices in dialysis clinics is necessary to address this finding.

**Funding:** NIDDK Support
Racial Disparities in Advance Care Planning in Patients Receiving Maintenance Dialysis

**Table: Multivariable Predictors of Dialysis Staff-Initiated CPR**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio (95% Confidence Interval)</th>
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<td>Age (per year increase)</td>
<td>1.00 (0.98-1.01)</td>
<td>0.461</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.97 (0.89-1.05)</td>
<td>0.553</td>
</tr>
<tr>
<td><strong>Rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.07 (0.94-1.22)</td>
<td>0.371</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>1.00 (0.85-1.19)</td>
<td>0.969</td>
</tr>
<tr>
<td><strong>Cardiac Arrest Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unwitnessed</td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>Witnessed</td>
<td>0.94 (0.84-1.05)</td>
<td>0.397</td>
</tr>
<tr>
<td><strong>Clinic Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility Type</td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>Other (non-profit, non-chain)</td>
<td>0.87 (0.72-1.06)</td>
<td>0.173</td>
</tr>
<tr>
<td>For-profit, chain-based clinic</td>
<td>0.86 (0.70-1.07)</td>
<td>0.217</td>
</tr>
<tr>
<td><strong>Number of Dialysis Patiens (per clinic increase)</strong></td>
<td>1.02 (1.00-1.04)</td>
<td>0.081</td>
</tr>
<tr>
<td><strong>Medicare Status</strong> (non-profit chain)</td>
<td>4.51 (2.04-9.98)</td>
<td>0.001</td>
</tr>
<tr>
<td>0-1</td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>1.12 (1.00-1.25)</td>
<td>0.077</td>
</tr>
<tr>
<td>4-5</td>
<td>1.20 (1.07-1.35)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Region (U.S.- Census Bureau)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>Midwest</td>
<td>0.73 (0.55-0.98)</td>
<td>0.041</td>
</tr>
<tr>
<td>South</td>
<td>0.97 (0.77-1.22)</td>
<td>0.846</td>
</tr>
<tr>
<td>West</td>
<td>0.77 (0.63-0.95)</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Dialysis Clinic Neighborhood/Consortia-Trust Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population Density (persons per mile)</td>
<td>0.81 (0.70-0.93)</td>
<td>0.006</td>
</tr>
<tr>
<td>0-10</td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>10-50</td>
<td>0.88 (0.77-1.01)</td>
<td>0.080</td>
</tr>
<tr>
<td>50-250</td>
<td>0.78 (0.66-0.92)</td>
<td>0.007</td>
</tr>
<tr>
<td>250-500</td>
<td>0.69 (0.59-0.82)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Proportion Black</strong></td>
<td>1.00 (ref)</td>
<td></td>
</tr>
<tr>
<td>0-10</td>
<td>0.89 (0.75-1.06)</td>
<td>0.171</td>
</tr>
<tr>
<td>10-19</td>
<td>0.70 (0.55-0.89)</td>
<td>0.005</td>
</tr>
<tr>
<td>19-39</td>
<td>0.55 (0.44-0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Median Household Income (per $10,000 increase)</strong></td>
<td>0.91 (0.90-0.92)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Results:**

- African American race (OR 0.56, CI 0.35, 0.92, p=0.02) and lack of prognostic discussions (OR 0.48, CI 0.27, 0.87, p=0.02) were associated with a lower odds of having any advance care planning document. Age >65 years (OR 2.1, CI 1.35, 3.26, p=0.001) and religiosity (OR 3.76, CI 1.52, 9.27, p=0.003) were associated with higher odds of completion of ACP documents.

**Conclusions:** Racial disparities exist in completion of ACP documents. Factors associated with lower odds of advance care planning include African American race and the absence of prognostic discussions. Future interventions are needed to mitigate racial disparities in completion of ACP and encourage prognostic discussion with dialysis patients.
Background: Population density associates with distinct profiles of health in the general population. Patients undergoing hemodialysis (HD) could be affected by the urbanicity level of their residence. We classified the characteristics and outcomes of HD patients at a large dialysis organization (LDO) by population density.

Methods: We analyzed 2018 data from HD patients. They were classified according to the county level population density defined by the Rural Institute, University of Montana: i) Metropolitan: ≥50,000 residents with integration to adjacent counties; ii) Micropolitan: ≥10,000-50,000 residents with integration to neighboring counties; iii) Rural: <10,000 residents. Median income data was obtained from the US Census database. We defined the profiles of demographics, clinical characteristics, and outcomes by level of population density.

Results: We analyzed data on 254,322 HD patients. Of those, 84% resided in a metropolitan county, 10% lived in a micropolitan county, and 6% resided in a rural county. Average age was 64 years old in all population densities. More females lived in an urban county (44% vs 42% and 42% in metropolitan, micropolitan and rural counties, respectively). White race varied from 49%-52% and was the highest in micropolitan and lowest in metropolitan counties. Micropolitan areas had the highest proportion of Hispanics (13% vs 7% and 5% in metropolitan, micropolitan and rural counties). Median income was the highest in metropolitan areas ($54,883 vs $43,606 and $40,200 in metropolitan, micropolitan and rural). In metropolitan to rural counties, the prevalence of comorbid conditions varied from 67%-69% for diabetes, 19-22% for congestive heart failure, and 19-23% ischemic heart disease. In rural counties, patients less commonly received an extra HD treatment each week (7%, 5%, and 5% in metropolitan, micropolitan and rural). Hospital admission rates were higher in metropolitan areas (1.8 vs 1.7 and 1.7 admissions per patient year in metropolitan, micropolitan and rural).

Conclusions: Our findings suggest the characteristics and outcomes of HD patients vary by the population density of their residence. Further analyses are needed to understand the influence of practice patterns, access to health care, and distinctions in demographics on patient outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

SA-PO1053
Association Among Primary Care Involvement, Death, and Hospitalization Costs of Patients Newly Started on Dialysis: A Population-Based Study from Ontario, Canada

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Background: The transition to dialysis is a vulnerable time, where patients may benefit from nephrology and primary care support. However, the role of primary care for patients on dialysis is poorly defined. We sought to determine whether primary care physician continuity and visits have opportunity costs for patients and economic costs for the healthcare system.

Methods: We used linked administrative databases in Ontario, Canada, we conducted a population-based study of patients who initiated chronic dialysis between 2005-2014 and survived at least 90 days. We defined persistent PCP involvement as both 1) high usual provider of care index in the 2 years before dialysis, an established measure of PCP continuity and 2) ≥1 visit with the usual provider in the 90-days after dialysis initiation. We used propensity scores to match patients 1:1 based on indicators of baseline health. The primary outcome was all-cause mortality and secondary outcomes included all-cause and disease-specific hospitalization.

Results: We identified 19,099 patients who survived for >90 days. There were 6612 patients (35%) with persistent PCP involvement who were matched 1:1 to 6391 patients without persistent PCP involvement. Persistent PCP involvement was not associated with a lower risk of mortality 2 years after cohort entry (14.5 deaths per 100 person-years vs 15.2 deaths per 100 person-years for patients with persistant PCP involvement) and survival at year 5 (HR 0.96, 95% CI 0.92-1.01). We found no difference in the rate of all-cause hospitalizations (HR 0.96, 95% CI 0.92-1.01), and persistent PCP involvement was not associated with a lower risk of any disease-specific hospitalization except for diabetes (HR 0.84, 95% CI 0.80-0.87).

Conclusions: Persistent PCP involvement during the transition to dialysis was not associated with a lower risk of mortality or all-cause hospitalization. These additional visits have opportunity costs for patients and economic costs for the healthcare system, suggesting primary care redesign may be needed to better support patients during this vulnerable period.

SA-PO1054
Trends in Outcomes for Patients Receiving Renal Replacement Therapy in Canada

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Background: Alternate renal replacement therapy (RRT) modalities offer different survival and quality-of-life outcomes for patients. Recent technological and process advances in dialysis treatments and transplantation offer the opportunity for better survival outcomes for patients. Longitudinal data from the Canadian Organ Replacement Register (CORR) for patients receiving RRT in Canada allows for national-level tracking of patient outcomes over time. We analysed patient data from the CORR to investigate the next-, mid- and longer-term survival outcomes for patients receiving RRTs including hemodialysis (in-centre and home), peritoneal dialysis and kidney transplantation (living and deceased donors).

Methods: The dataset comprised 74,108 patients registered in the CORR between 2003 and 2017 for all provinces excluding Quebec. We calculated graft and patient survival rates at 3 months, 1-, 3-, 5- and 10-years after start of dialysis and after transplantation. We calculated Kaplan–Meier survival rates for 10 years after start of dialysis and after transplantation, and we adjusted rates based on a direct-adjusted Cox model controlling for patient age, sex and primary diagnosis of renal disease.

Results: Crude 5-year patient survival rates was highest in the living-donor transplant group (94.6%), followed by the deceased-donor transplant group (88.3%), PD treatment group (51.3%) and HD treatment group (40.9%). Between 2003 and 2012, crude 5-year survival rates for dialysis patients have increased by 6.6% and 7.0 percentage points for HD and PD patients, respectively. Graft survival rates improved over the 10 years by 0.9 and 4.6 percentage points for those who received a donation from a living or deceased donor, respectively.

Conclusions: Crude survival rates have generally increased over time across all RRT modalities, with similar rank order of survival between modalities as previously reported. Improvements in survival rates may reflect improvements in technology, technique, and patient education and characteristics, and process improvements within dialysis and transplant programs in Canada. CORR national data allow measurement and reporting of this important outcome as a performance measure.

SA-PO1055
Inverse Relationship Between Waist Circumference and Body Mass Index on Risk for All-Cause Mortality in Hemodialysis Patients: A Nationwide Population-Based Cohort Study

Chang Sung Kim1 Hong sang Choi,1 Eun Hui Bae,2 Seong Kwon Ma,3 Soo Wan Kim.1 Chonnam National University Medical School, Gwangju, Republic of Korea; 2Chonnam National University Hospital, Gwangju, Republic of Korea.

Background: Obesity underlies a high risk of all-cause and cardiovascular mortality in patients with end-stage renal disease. We investigated that the association between waist circumference and mortality and patients undergoing hemodialysis through a nationwide large population-based study.

Methods: Using nationwide representative data from the Korean National Health Insurance System, 6,823,298 participants aged over 40 years with information for waist circumference and BMI were followed up during 4.5 years.

Results: The mortality rate is greater in hemodialysis patients with highest waist circumference category compared to those with lower BMI (3.83 per 100 person-years, < 80 in men and < 75 in women). However, participants with higher BMI showed lower mortality rate than those with lower BMI (3.83 per 100 person-years in a 30 kg/m² and 6.87 in < 80 kg/m²). Multivariable Cox regression analysis found that participants with highest waist circumference category had higher risk of all-cause mortality than those with waist circumference 85 to 90 in men and 80 to 85 in women (reference group) [adjusted hazard ratio (HR), 1.280; 95% confidence interval (CI), 1.057–1.550], while those with lowest waist circumference category showed significantly lower risk of mortality compared to reference group (adjusted HR, 0.819; 95% CI, 1.410–1.929). Inversely, BMI categories ≥ 23 kg/m² were associated with significantly lower risk for mortality compared to the reference group (18.3 to 23 kg/m²), with adjusted HR of 0.734 for BMI of 23 to 25 kg/m², 0.59 for BMI of 25 to 30 kg/m² and 0.530 for BMI ≥ 30 kg/m².

Conclusions: Central obesity measured by waist circumference is associated with all-cause mortality in hemodialysis patients, whereas body volume measured by BMI is an inverse relationship with this outcome.
Effect of Serum Uric Acid Level on Mortality Risk in Maintenance Hemodialysis Patients

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Background: There is still much controversy about the relationship between serum uric acid level and all-cause or cardiovascular mortality in hemodialysis patients.

Methods: A retrospective cohort study was conducted to enroll 201 MHD patients in the Third Affiliated Hospital of Sun-yat-sen University. The baseline data of clinical and laboratory examinations were compared. The correlation between serum uric acid level and clinical variables was analyzed by Pearson correlation coefficient. Kaplan-Meier and Cox proportional hazard regression model was used to examine the association between serum uric acid and all-cause and cardiovascular mortality in HD patients.

Results: The average age of patients was 56.9 ± 16.7 years, and the average baseline serum uric acid level was 531.1 ± 137.9 µmol/L. With 442 µmol/L and 620 µmol/L as the boundaries, the patients were divided into four groups according to the level of serum uric acid. The lowest quartile group was older and had more diabetes mellitus than the highest quartile group (P = 0.05). Compared to the highest quartile group, the serum albumin, serum phosphorus and serum creatinine were lower in the lowest quartile group, while the hyperensive C-reactive protein were higher (P < 0.05). Pearson correlation coefficient showed that uric acid level was positively correlated with albumin, serum phosphorus and serum creatinine. After a median follow-up of 49.8 months, 66 (32.8%) all-cause deaths and 37 (18.4%) cardiovascular deaths were recorded. Kaplan-Meier method showed that with the decrease of serum uric acid, all-cause mortality (Log Rank = 23.63, P = 0.000) and cardiovascular mortality (Log Rank = -23.10, P = 0.000) increased.

Conclusions: Low serum uric acid level increases the risk of all-cause mortality and cardiovascular mortality in MHD patients.

Funding: Government Support - Non-U.S.

Lactate Rising: The “Unconventional” Use of Continuous Renal Replacement Therapy in Metformin-Associated Lactic Acidosis


Introduction: Metformin is considered first-line therapy for many patients with type II diabetes mellitus (DM2). Metformin toxicity is a rare, yet potentially fatal complication of chronic metformin use with an incidence of ~4.2 cases per 100,000 patient years and a mortality rate between 30-50%. Extracorporeal treatment with intermittent hemodialysis (iHD) remains the modality of choice for severe metformin poisoning. However, patients with metformin-associated lactic acidosis (MALA) often present similarly to patients with septic or cardiogenic shock with severe hemodynamic instability making iHD treatment less desirable. I present a case of severe metformin toxicity treated successfully with continuous venovenous hemofiltration (CVVH).

Case Description: A 75 year old male with history of hypertension, DM2, and chronic kidney disease presented with altered mental status, nausea, vomiting, hypoglycemia and dyspnea. His home medications included metformin 1 gm twice daily and Lisinopril. The patient was intubated and found to have a mixed arterial pH of 6.8, severe bicarbonates of 4 mmol/L, potassium of 6.3 mmol/L, SCr of 8.1 mg/dL, white blood cell count of 23.3 x10^9/L and lactate of 20.5 mmol/L. He required maximal doses of both norepinephrine and vasopressin for hemodynamic support. An EKG demonstrated peaked T-waves; therefore, a temporary femoral dialysis catheter was placed and CVVH was initiated. Initial concern was for ischemic bowel versus septic shock, however, MALA was also considered. Lactate levels decreased over the subsequent 24 hours to <2.0 mmol/L and arterial pH increased to >7.4, and the patient was discharged from the hospital six days later. One week after discharge, the patient returned at 37 mg/L confirming the diagnosis of metformin toxicity.

Discussion: Metformin toxicity is a rare, but treatable condition that poses unique challenges to clinicians given its similar presentation to more frequently observed clinical ailments. Although iHD has been the preferred modality for treatment of MALA, this case demonstrates that not only is CVVH an acceptable alternative, but may be the safest modality given the diagnostic uncertainty initially present. More studies evaluating the utility of CVVH in MALA may be beneficial to determine the optimal modality of extracorporeal therapy in patients with this rare but fatal condition.

Presence of Bisphenol S in Haemodialysis Patients: Environmental and Dialysis-Associated Exposure

Alberto Ruiz,1 Sebastian Mas,2 Pedro Abigar,3 Javier Santos,2 Vanesa Camarero,2 Emilio E. Gonzalez-purra.4 Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain; 1Hospital Universitario de Burgos, Burgos, Spain.

Background: In recent years, many studies demonstrated the effects xenobiotic of BPA, as results of these evidences, the industries are replacing BPA for different analogues such as BPS. However, the chronic and natural analogues of BPA such as central quaternary carbon and central quaternary carbon have been replaced by a sulfone. Due to of this similitude structural between BPA and BPS further studies promote to investigate the bioavailability and toxicities of BPS, and especially in the renal patient because of neither there is no literature about this group. In this study, our objective is to determine the plasmatic levels of BPS in comparison with BPA in the terminal renal patient and the influence of dialysis membrane.

Methods: The concentration of total BPS, BPA and hippocamic acid (free, conjugated with sulfat or glucorurate, or bound to proteins) was determined by single reaction monitoring mass spectrometry (SRM-MS).

Results: BPA and BPS were measured in two groups: one of 10 healthy subjects (blood donors) and the other of 14 patients in hemodialysis (hemodialfiltration) which they were treated with dialyzers fabricated with polyanephron (CTA) or cellulose triacetate (CTA) membranes. In healthy controls were in almost all cases below LOD of 0.05 ng/mL, while in hemodialysis patients regardless of the membrane used was 0.32 ± 0.52 ng/mL. BPA in healthy controls range from 0.8 ± 0.7 ng/mL and 16.9 ± 58.7 ng/mL in renal patients. When membranes are compared, we found an increase of both after one dialysis session with polyanephron (BPA: 45.63 ± 54.58 ng/mL at pre-dialysis vs 49.41 ± 64.67 ng/mL at post-dialysis; BPS: 0.42 ± 0.35 ng/mL at pre-dialysis vs 0.56 ± 0.36 at post-dialysis). On the other hand, with the polysulphone membrane exist there is a greater increase in the accumulation of BPA compared with BPS (BPA 51.4 ± 60.31 ng/mL at pre-dialysis vs 62.86 ± 77.39 ng/mL at post-dialysis; BPS: 0.49 ± 0.82 ng/mL at pre-dialysis vs 0.58 ± 0.47 at post-dialysis).

Conclusions: Similar to BPA, BPS accumulates in the renal patient as a result of the excretion problems of these patients along with the contribution of the dialysis membranes itself. However, the quantities measured are an order of magnitude lower than those measured for BPA both in a single dialysis session as well as in long-term dialysis (3 months or more).

Funding: Government Support - Non-U.S.
Long-Term Effect of Particulate Matter on Mortality Risk of Patients with ESRD

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Background: Aerodynamic particulate matter (PM) significantly worsens morbidity and mortality in various diseases, especially in cardiovascular and pulmonary diseases. However, little is known for relationship between PM and mortality of end-stage renal disease (ESRD).

Methods: 5041 patients who began dialysis from August 2008 to February 2015 were prospectively enrolled in the Clinical Research Center for End-Stage Renal Disease cohort study. We assigned daily mean concentration of PM < 10 μm in aerodynamic diameter (PM10) to each participants for provincial-level divisions (si-do) by the location of station. Time-varying Cox proportional hazard models were used to investigate the relationship between PM10 and mortality of ESRD patients who have received dialysis. Stratified analysis was also conducted by potential confounders such as age, sex, smoking status, education, insurance, marital status, and social and familial support.

Results: During the follow-up period (mean 4.18 years), 1475 deaths occurred among 5041 participants. We found non-linear relationship between PM10 and mortality. Based on a threshold level at 44.15 μg/m³, although lower PM10 group had higher HRs for mortality with decrease in PM10 (HR 0.71, CI 0.69-0.74), higher PM10 group had higher HRs with increasing PM10 (HR 1.25, CI 1.22-1.28). Those who married and highly educated were at a higher risk in both groups, but opposite tendency was shown in each groups when stratified by potential confounders such as age, sex, smoking status, education, insurance, marital status, and social and familial support. Analysis was also conducted by potential confounders such as age, sex, smoking status, education, insurance, marital status, and social and familial support.

Conclusions: We found that the mortality of ESRD patients has contrary effects based on a threshold level of PM10. It may be caused by toxicity of PM and characteristics of behavior at the region with relatively low concentration of PM10.

The Effect of Dialysis on Aryl Hydrocarbon Receptor Binding Activities in Patients with CKD

So-young Lee, Eulji University Hospital, Seoul, Republic of Korea.

Background: Persistent organic pollutants (POPs) are well-known endocrine disrupting chemicals reported to be associated with various metabolic diseases. We hypothesized that POPs levels are increased in patients with chronic kidney disease or undergoing dialysis, thus further complicating the disease course. In this study, we measured serum POPs levels using a highly sensitive cell-based arylhydrocarbon receptor (AhR) dependent luciferase activity (CLARA) assay in end stage renal disease (ESRD) patients undergoing dialysis or not, and compared differences between patients.

Methods: Patients undergoing peritoneal dialysis(22), hemodialysis(38) for at least 36 months, and in intracellular ATP levels were measured and compared according to treatment modality. We performed a correlation analysis between AhR binding activities and ATP levels and various clinical parameters.

Results: AhR binding activities differed significantly between groups, AhR binding activity was higher in non-dialysis CKD patients, compared to patients undergoing dialysis, and higher in patients undergoing hemodialysis compared to peritoneal dialysis. AhR binding activities decreased after hemodialysis treatment in HD patients. ATP level was the higher in healthy controls, compared to pre-dialysis CKD patients, and patients with peritoneal dialysis and hemodialysis. AhR binding activities and intracellular ATP levels showed significant correlations with multiple clinical parameters associated with cardiovascular risk factors.

Conclusions: POPs were associated with chronic kidney disease, and ESRD, while dialysis treatment reduced POPs levels. Further studies are mandated to specify the AhR binding activities and to evaluate the exact role in patients with chronic kidney disease.

Cancer in Hemodialysis Patients

Jose F. Navarette. Emory University, Atlanta, GA.

Background: The incidence of cancer in hemodialysis patients. Describe the most common types of cancer in hemodialysis patients.

Methods: Incident hemodialysis patients enrolled in the Emory Dialysis program from 1/2011 to 12/2015 were followed. The diagnosis of cancer, death or censoring up to 12/31/2018. Time from initiation of dialysis to diagnosis of cancer and type of cancer was recorded.

Results: 902 patients were enrolled in the hemodialysis program. 25 (2.8%) patients with prior cancer were excluded from the analysis as well as 51 patients followed less than a month. The remaining 826 patients are the base of this report. 51 patients (6.2%) developed a new cancer. Cancer patients were older (65 vs 57). The cumulative risk of cancer is presented in figure 1 (11%). The most common cancers were urological (20%), paraneoplastic (17%), gastrointestinal (8%), lung (8%), breast (6%), gynecological (6%), liver (4%), skin (4%) and brain, adrenals and unknown primary with 1% (Figure 2).

Conclusions: The cumulative risk of cancer was 11% over 8 years. Cancer patients were older and had a lower hemoglobin, Urolith, paraneoplasias and other solid organ cancers represent the majority of cancer diagnosed and this information could be used to delineate strategies for early detection of cancer in hemodialysis patients.

Concomitant Prescription of Gabapentinoids and Opioids Predicts Mortality and Morbidity Among US Dialysis Patients

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Background: The opioid epidemic is a public health emergency and appropriate prescription of medications for pain symptom management remains a challenge. Increasingly, providers prescribe gabapentinoids (gabapentin and pregabalin) for pain despite limited evidence to support their off-label use and reports of abuse in combination with opioids. We sought to estimate the prevalence of concomitant gabapentenoid and opioid prescriptions and evaluate the effect of concomitant prescriptions on morbidity and mortality among end-stage renal disease (ESRD) patients in the US.

Methods: We used the United States Renal Data System to identify ESRD patients who were continuously treated with dialysis and had part A, B, and D coverage for all of 2010. Part D filled prescription claims were used to identify whether each patient had filled a prescription for opioids, gabapentin, and pregabalin in 2010. Patients were followed for all-cause death, discontinuation of dialysis, and hospitalizations.

Results: The study population included 153,738 ESRD patients who met inclusion criteria. Concomitant prescription of an opioid and gabapentin (15%) was more common than concomitant prescription of an opioid and pregabalin (4%). In adjusted analyses...
using Cox models, concomitant prescription of an opioid and gabapentin was associated with increased odds of death (HR=1.16, 95% CI= 1.12, 1.19), dialysis discontinuation (HR=1.14, 95% CI= 1.03, 1.27), and hospitalization (HR=1.33, 95% CI= 1.41, 1.53). Similarly, concomitant prescription of an opioid and pregabalin was associated with increased mortality (HR=1.22, 95% CI= 1.16, 1.28) and hospitalization (HR=1.37, 95% CI= 1.33, 1.41), but not dialysis discontinuation (HR=1.13, 95% CI= 0.95, 1.35).

**Conclusions:** Concomitant prescription of opioids and gabapentinoids among US dialysis patients is common and is associated with worse outcomes. We were unable to identify the reasons why drugs were prescribed. The mechanisms underlying adverse effects and concomitant use of these drugs, prospectively and identify safe alternatives for pain symptom management.

**SA-PO1064**

**Geographic Variation of Increasing Mortality Risk in Black Dialysis Patients with Medicare Fee-for-Service Coverage**

Eric D. Weinhandl,1,2 Debabrata Ray,1 Kristine Kubisik,1 Allan J. Collins,1 1Fresenius Medical Care North America, Waltham, MA; 2University of Minnesota, Minneapolis, MN.

**Background:** We recently reported that the weekly risk of death in black dialysis patients with Medicare fee-for-service coverage increased between 2014 and 2017, from 25.2 deaths per 10,000 patients per week to 27.1 deaths per 10,000 patients per week (Am J Nephrol 2019). We aimed to assess whether this increase was homogeneous across US Census Divisions.

**Methods:** Using Medicare Limited Data Sets, we identified all black patients with Medicare Part B claims documenting outpatient dialysis from January 2014 to December 2017. For each calendar week (Monday to Sunday), we identified patients who had at least one outpatient dialysis session and who were alive at the end of the week; we calculated the proportion of patients who died during the subsequent calendar week. From the time series of weekly death rates in each US Census Division, we fit an autoregressive integrated moving average model to assess secular trend.

**Results:** The cohort included 208,786 unique patients; 23,685,808 patient-weeks; and 62,200 deaths. Mean age was 59.2 ± 14.0 years, 53% were female, and 54% of patients were concurrently enrolled in Medicare and Medicaid. Weekly mortality rates among all black patients were 25.1, 26.3, 26.5, and 27.1 deaths per 10,000 patients per week in 2014, 2015, 2016, and 2017, respectively. Death rates per 10,000 patients per week, by Census Division, are displayed in the table. Weekly mortality rates increased both monotonically and significantly (P < 0.05) in the South Atlantic and East South Central regions, an area that stretches from the Mississippi and Ohio Rivers to the Atlantic Ocean.

**Conclusions:** Increasing mortality among black dialysis patients with Medicare fee-for-service coverage appears to be a unique feature of the southeastern part of the United States. The extent to which this trend reflects dialytic factors versus broader health and socioeconomic trends is unclear and merits detailed investigation.

**SA-PO1065**

**Effect of Probiotic Supplementation on Regulatory T Cells and Inflammatory Monocytes in Patients Undergoing Hemodialysis**

Eunho Choi,1 Jihyun Yang,1 Myeong soo Park,2 Sewon Oh,1 Myung-Gyu Kim,3 Sang-Kyung Jo.1 Korea University Anam Hospital, Seoul, Republic of Korea; 1BIFIDO Co., Ltd., Hongchun gun, Republic of Korea.

**Background:** Emerging evidence suggests that intestinal dysbiosis might contribute to systemic inflammation and cardiovascular diseases in dialysis patients. This study investigated the effects of probiotics supplementation on various inflammatory parameters in hemodialysis (HD) patients.

**Methods:** This study included 22 patients undergoing maintenance HD (IRB No. 2018AN0346). Patients received probiotics twice daily for 3 months (Ziginduk Bifidus Premium from BIFIDO Co, total 10 billion CFU of Bifidobacterium bifidum BGN4, Bifidobacterium longum BORI, Lactobacillus acidophilus AD031, and Enterococcus faecium BH06). The percentages of CD4+CD25+ Foxp3 regulatory T cells and CD4+/CD25+ regulatory T cells (Treg) were determined by flow cytometry. Serum levels of calprotectin and zonulin (novel biomarkers of intestinal inflammation), and cytokine response to lipopolysaccharide (LPS) challenge, as well as various clinical parameters were measured before and after probiotics supplementation.

**Results:** The percentage of Treg showed a significant increase after 3 months of probiotic supplementation compared with baseline levels (8.6% vs. 3.5%, P<0.001), and the event count of CD4+CD16+ proinflammatory monocytes decreased significantly over baseline counts (194 vs. 310 cell numbers, P<0.05). LPS stimulation-induced interleukin (IL)-10 and IL-6 levels increased significantly (1159 vs. 517 pg/ml, 3743 vs. 2763 pg/ml, respectively, P<0.05). Serum levels of calprotectin but not zonulin significantly decreased after probiotic supplementation.

**Conclusions:** These preliminary data suggest that probiotic supplementation may modulate systemic inflammation by expansion of Treg, suppression of proinflammatory monocytes, as well as reduction of gut inflammation in patients undergoing HD. Thus, targeting intestinal dysbiosis might be a new therapeutic strategy.

**Figure 1** (a) CD4+/CD25+ Treg percentage (b) Actual event count of CD4+/CD16+ proinflammatory monocyte subset * p<0.05, ** p<0.001

**SA-PO1066**

**Metabolic Changes in Peripheral Blood Mononuclear Cells Isolated from Dialysis Patients with Vascular Access Dysfunction**

Mehmet M. Altintas, Salvatore DiBartolo, Beata Samelko, Monnie Wasse. Rush University Medical Center, Chicago, IL.

**Background:** As numerous complex pathologies can stem from cellular energy dysfunction, we aimed to elucidate whether mitochondrial dysfunction contributes to arteriovenous fistula (AVF) and arteriovenous graft (AVG) failure in a cohort of dialysis patients. We used peripheral blood mononuclear cells (PBMCs) as the model system of disease monitoring for bioenergetic analyses.

**Methods:** The bioenergetics study was conducted using PBMCs and serum from dialysis patients with AVF or AVG (re)stenosis. PBMCs and serum were isolated from whole blood through the use of a density gradient centrifugation, aliquoted and frozen at -80°C until analysis. On the day of analysis, PBMCs from healthy controls and patients were thawed, diluted and counted before being seeded into Seahorse XF24 assay plate to detect changes in mitochondrial respiration. The bioenergetic analysis was performed in the presence of Seahorse XF medium (free of bicarbonate, pH 7.4) using mitochondrial stress test kit and Seahorse flux analyzer. In order to test the metabolic changes caused by patient serum, we used commercially available control PBMCs and treated those with 10% serum from healthy controls and patients in 6-well plates. After 24 hours, cells were harvested and loaded to Seahorse XF24 assay plates for the bioenergetic analysis.

**Results:** We developed a technique to measure mitochondrial oxygen consumption in PBMCs isolated from dialysis patients with AVF or AVG (re)stenosis and control PBMCs fed with patient’s serum for 24 h. In PBMCs of patients, we found a reduction in each of fundamental parameters of mitochondrial function such as basal respiration, ATP turnover, proton leak, maximal respiration and spare respiratory capacity. A similar trend was observed when the control PBMCs were cultured in the presence of 10% serum from patients for 24 h.

**Conclusions:** Our data demonstrates a correlation between mitochondrial oxygen consumption of PBMCs and end-stage renal disease (ESRD) in a case-control study of 30 patients. We propose a link between mitochondrial dysfunction and vascular access failure since PBMCs are exposed to metabolic and hemodynamic stimuli in the vasculature.

Our findings and the methodology may help identify individuals at risk for hemodialysis vascular access dysfunction.

**Funding:** NIDDK Support

**SA-PO1067**

**Evaluation of NATEM (ROTEM Delta) in Whole, Non-Citrated Blood in Hemodialysis Patients During Citrate and Deltaparin Anticoagulation**

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**Background:** Standard clotting tests are performed in citrated blood. To investigate clotting in a study comparing citrate vs delpaparin anticoagulation during hemodialysis (HD), a NATEM in whole blood was developed using non-citrated blood. This study evaluates this NATEM.

**Methods:** 12 HD patients on anticoagulants (6 vit. K antagonist; 6 acetylsalicylic acid), underwent 2 standard HD sessions with delpaparin and 2 sessions using a Ca/Mg-free, 0.8 mmol/l citrate containing dialysis fluid with Ca/Mg substitution at the venous needle. Before, during and after HD, blood was taken for NATEM (ROTEM Delta, Tem innovations Munich) in non-citrated (NC-) and citrated tubes (NC+). Clotting time (CT) and clot formation time (CFT) were measured. Clot formation time (CFT) is the time from CT until a clot firmness of 20 mm is reached. Alpha is the angle of tangent between 0 mm and the curve when the clot firmness is 20 mm. A10 and A20

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Underline represents presenting author.
describe the clot firmness after 10 and 20 minutes. Maximum clot firmness (MCF) is the greatest vertical amplitude. NC+ within 10 minutes of NC- were considered to be simultaneous measurements. Data were analyzed using linear mixed models to account for repeated measurements and using linear regression to assess bias between methods. Median (M) and interquartile range (IQR) are reported.

**Results:** NC- CT (n=130; M 1116, IQR 942 – 1455 sec) and NC+ CT (n=126; M 937, IQR 747 – 1281 sec) were correlated (Spearman rho 0.71; p<0.001). There was a constant and a proportional bias with NC- CT giving higher values than NC+ CT. After 45-60 minutes 2 duplicate NC+ were performed. The mean of these CT values (n=45; M 546, IQR 377 – 720 sec) showed a significant constant bias towards the initial NC+ indicating a decrease of CT in time. Spearman rho correlations between NC- and NC+ were for CT 0.44, alpha 0.53, A10 0.52, A20 0.58 and MCF 0.63 (p < 0.001).

**Conclusions:** (Anti)coagulation in citrate HD can be measured with NATEM in whole, citrated blood (NC+), NATEM (NC-) in whole, non-citrated blood can be done but is not necessary. However; results in NC+ change over time. This dictates that NC+ should be performed at a set time after sample collection.

**Funding:** Commercial Support - Werfen Benelux, Breda, The Netherlands


**Background:** Our aim was to analyze patterns and risks of hospitalizations in a large cohort of hemodialysis patients treated in 22 outpatient clinics all over Saudi Arabia (KA-SA).

**Methods:** The study included all patients admitted at Davita-KSA clinics to continue hemodialysis treatment during the period from October 2014 to December 2018. Overall and cause-specific hospitalization rates were calculated by dividing the number of hospitalizations by the cumulative period of follow-up. Logistic regression was performed to identify factors predisposing to hospitalization.

**Results:** 3508 patients were included (1897 males, 1611 females) with a mean age of 52.5 ± 16.9 years. During a cumulative follow-up period of 5584 years, 1576 hospitalizations were recorded in 26.1% of included patients, 38.7% of them had repeated admissions. Infectious causes, including those related to vascular access, accounted for 34.1% of all recorded hospital admissions vs. 18.8% for cardiovascular complications. The overall hospitalization rate was of 28.2% patient-years with an annual duration of 3.4 days per patient. Infectious complications, not related to vascular access, accounted for the highest rate with an annual rate of 6.73% vs. 5.32% for infectious causes and 4.83% for hospitalizations attributed to vascular access creation and complications. The median length of hospital stays 11.5 days (range: 2-244 days) with an annual rate of 3.39 days per patient. This rate ranged from 0.05 for hospitalizations related to vascular access to 0.70 and 0. for infectious causes. Predictors of hospitalization were: Female gender (RR: 1.34, 95%; CT: 1.15-1.56), Age ≥ 65 years (RR: 1.32, 95% CI: 1.11-1.58); time on dialysis (RR: 1.44 per year, 95% CI: 1.34-1.55) diabetic nephropathy (RR: 1.61, 95% CI: 1.38-1.89), and Catheter as vascular access (RR: 1.38, 95% CI: 1.17-1.63). Among all these factors, Diabetic nephropathy predisposed to a prolonged hospital stay.

**Conclusions:** Infectious complications were the leading cause of hospitalization among our hemodialysis patients and resulted in the longest hospital stay. Female gender, Age ≥ 65 years, Diabetic nephropathy, Catheter as vascular access and, time on dialysis were found as predisposing to hospitalization but only diabetic nephropathy is associated with prolonged hospitalization.

SA-PO1069 Profiles of Dialysis Recovery Time in Incident Home and In-Center Hemodialysis John Danziger,1 John W. Larkin,2 Yue Jiao,3 Marta Revirigco-Mendoza,3 Sheetal Chaudhuri,1 Andrew Long,1 Joanna Willetts,1 Dagan Maddux,1 Jeffrey L. Hymes,1 Len A. Usvyat,1 Ravi I. Thadhani,1 Franklin W. Maddux,1 1 Fresenius Medical Care, Waltham, MA; 2 Harvard Medical School, Brookline, MA; 3 Fresenius Medical Care North America, Waltham, MA; 4 Cedars Sinai, Los Angeles, CA.

**Background:** Home hemodialysis (HHD) includes frequent treatments typically 4-6 times per week and yields a higher adequacy and fluid removal. HHD associates to reductions in dialysis recovery time (DRT) compared to in-center HD (ICHID) in prevalent patients who switch to the modality. DRT is a measure of the perceived time after HD a patient feels they can return to performing normal daily activities. We characterized the profiles of DRT in incident patients treated with HHD and ICHID.

**Methods:** We used data from adult incident HD patients treated at a large dialysis provider who completed a DRT survey ≥810 days from the first date of dialysis (FDD) during 2014 to 2017. DRT survey is administered with the annual KDQOL questionnaire and asks: “How long does it take you to be able to return to your normal activities after dialysis treatment?” Categorical answers include: <0.5, 0.5-1, 1-2, 2-4, >4 hours. We calculated the percentage of patients in DRT categories for the HHD and ICHID groups.

**Results:** We analyzed data from 1091 HHD and 89616 ICHID patients who completed the DRT survey ≥810 days from FDD. A lower proportion of HHD patients reported DRT <1 hour compared to ICHID (Figure 1). About half of HHD patients (53.9%) and a quarter (25.2%) of ICHID patients reported a DRT <0.5 hour.

**Conclusions:** Incident HD patients treated by HHD appear to experience a shorter DRT compared to ICHID. These findings show consistent signals with the Frequent Hemodialysis Network trial results in prevalent HD (Garg Kidney Int. 2017). Patients who chose HHD modality may be younger and have distinct clinical presentations and adjusted analysis are needed to substantiate these findings.

**Funding:** Commercial Support - Fresenius Medical Care North America

SA-PO1070 Provision of Outpatient Backup Dialysis in a Home Hemodialysis Unit Claire Kennedy,1,2 Bourne L. Auguste,1,2 Michael Y. Girisberger,1,2 Tadhamon Srothongkul,1,2 Rosalyn J. Bowman,1,2 Christopher T. Chan,1,2 Nephrology, Toronto General Hospital, Toronto, ON, Canada; 3 Medicine, University of Toronto, Toronto, ON, Canada; 4 Toronto General Hospital, Toronto, ON, Canada; 5 University Health Network, Toronto, ON, Canada.

**Background:** Patients doing home hemodialysis (HHD) require support from the parent unit when medical, dialysis-related and psychosocial issues arise at home. It is important that each HHD program makes provision for timely clinical assessment and back-up hemodialysis (HD), although this need has not been well quantified previously.

**Methods:** This was a retrospective, single-center cohort study of a HHD unit with an open-door policy in terms of clinical assessment and back-up HD during weekday office hours. Back-up HD in the incenter HD unit was organized for outpatient situations that arose outside of these hours. Emergency situations were directed to the emergency department (ED). The HHD unit electronic and paper medical records were reviewed for a twelve-month period. The uptake of outpatient back-up HD was established and reasons for this need were summarized.

**Results:** There were 104 to 107 prevalent patients in the HHD program during the twelve-month period. 79 outpatients attended for back-up HD (167 separate issues requiring 254 back-up HD sessions). Back-up dialysis was performed most commonly for medical reasons; followed by vascular access issues, technical issues, respite HD and post-operative/post-procedure HD (Figure). The majority of these issues necessitated one back-up HD session, facilitated in the HHD unit during weekday office hours. Respite HD for psychosocial reasons accounted for a small proportion of provided back-up HD.

**Conclusions:** One to two staffed dialysis stations were required each weekday for back-up HD in this HHD program of 100+ patients. Prompt access to clinical assessment and back-up HD in the parent HHD unit may relieve pressure on the incenter HD unit, ED and inpatient ward, and may facilitate ongoing HHD technique survival.

Figure: The number of separate events necessitating back-up outpatient HD that arose in a twelve-month period, and the number of back-up HD sessions each issue required.
SA-PO1071
Barriers to Home Hemodialysis in Saskatchewan Canada: Results from a Provincial Survey
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Background: Home hemodialysis (HHD) offers similar, and perhaps even superior clinical outcomes to in-center hemodialysis (HD) at a fraction of the cost. HDH remains underutilized as remote HD patients in Saskatchewan often relocate or travel hundreds of kilometers weekly in order to receive dialysis related care. The purpose of this study was to determine the barriers to receiving HHD in our province.

Methods: We conducted a cross sectional survey of in center HD patients across the province of Saskatchewan. 740 in center HD patients (two academic sites, 7 satellite units) were approached by study coordinators. 421 patients (n=208 in the main units and n=153 in the satellite units) agreed to participate in the study. A five-point Likert scale survey was created to identify barriers to HHD with questions addressing HHD awareness and knowledge, accessibility, home constraints, impact on family members, and risks/ fears/beliefs surrounding HHD. Responses were anonymous and tabulated using a data collection tool.

Results: Only 76% of patients were aware of HHD. 46% of patients felt they had no understanding of the benefits or risks of HHD. Despite only 8% of patients being told they were unsuitable for HHD by their nephrologist, only 28% had ever considered it as a treatment option. Other prominent barriers to HHD were: satisfaction with in center HD (76%), medical supervision during HD (76%), opportunity to socialize with in center HD patients (73%), increase in utility payments (54%), and fear of having a major health event at home (51%). Other home constraints (space, inability to make modifications to the home) also figured prominently (35%).

Conclusions: In this study, we identified patient specific barriers to HHD in a prevalent cohort of HD patients. Several barriers were identified with a few consistent themes being identified, including deficiencies in knowledge and awareness, home constraints, and perceived benefits of in center care (satisfaction with current care, socializing with patients and staff, and fear of a catastrophic event at home). The most frequently reported knowledge barrier was a lack of understanding of the benefits and risks of HHD. While the study does not reflect views of all the patients, this information will be valuable in designing an educational program to improve adoption of HHD within our province.

SA-PO1072
Differences in Perceptions of Home-Based Dialysis Therapies Among the Renal Multidisciplinary Team
Krishna Poinen,1 Mark Canney,1 Lee Er,2 Michael A. Copland.1 1University of British Columbia, Vancouver, BC, Canada; 2BC Renal, Vancouver, BC, Canada.

Background: Patients with end stage renal disease are encouraged to pursue home-based dialysis therapy (HDT) with the aims of improving quality of life, increasing patient autonomy and reducing the cost to the health care system. In the multidisciplinary setting, patients have exposure to nurses, clinicians and allied health staff, all of whom may influence a patient’s modality choice. We aimed to evaluate the perceptions of HDT amongst multidisciplinary team members and identify avenues for further education.

Methods: An electronic survey was distributed over a 6-week period to 695 non-center HD patients across multiple renal centers in British Columbia, Canada. The survey contained questions about work environment, patient/ system factors in choosing HDT, perceived knowledge of HDT and the need for further education. Results were stratified by 5 categories of respondent: nephrologists, nurses in 3 clinical areas (facility hemodialysis, HDT, pre-dialysis), and allied health (pharmacists, social workers, dieticians).

Results: A total of 334 respondents were included (48% response rate). The majority of respondents in all categories stated that they would choose HDT if they were ever to require dialysis. The majority also recommended that a higher proportion of patients should receive HDT, especially patients who work or study. Facility nurses were believed to have the least impact on a patient’s choice of modality, yet they also perceived themselves as key patient educators. Facility and HDT nurses favored in-center dialysis and HDT respectively for patients with lower socioeconomic status, lower education or a language barrier. All respondents acknowledged the benefits of HDT for cost savings and improved patient satisfaction. The majority of nurses and allied health staff felt the need for further education in HDT, favoring practical over knowledge-based educational opportunities.

Conclusions: The majority of the renal multidisciplinary team members would welcome increased uptake of HDT due to benefits on the patient and healthcare system level. Nurses differed substantially in their perceptions of modifiable barriers to HDT depending on their primary area of work. Further HDT education has the potential to bridge these gaps and help patients make informed decisions about their dialysis modality.
with calcium ±0.1mg/dL, phosphate ±0.5–6.5mg/dL, and intact parathyroid hormone (PTH) ±150–600pg/mL, and 10% central venous blood pressure (CVP) ≤90 days. We also calculated the unadjusted hospital admission rates per patient per year (ppy) for the groups.

**Results:** We included data on 171,712 patients (HHHD n=4141, ICHHD n=167571). A larger proportion of HHHD patients were younger (HHHD=55.5, ICHHD=63.5 years), male (HHHD=65%, ICHHD=61%), and white race (HHHD=55%, ICHHD=47%). A greater proportion of HHHD patients achieved target albumin levels (HHHD=51%, ICHHD=37%), yet a slightly lower proportion of HHHD patients achieved MBD goals (HHHD=46%, ICHHD=49%). The proportion of patients with catheter exposure >90 days was relatively consistent between groups (HHHD=13%, ICHHD=15%). Patients treated with HHHD exhibited lower hospital admission rates (HHHD=1.07, ICHHD=1.55 admissions ppy).

**Conclusions:** Patients treated with HHHD more commonly achieved nutritional goals for albumin compared to those treated with ICHHD. HHHD patients may have unique challenges with catheter exposure and may make that many leading to lower MBD goal achievement compared to ICHHD. HHHD patients tended to have less hospital admissions compared to ICHHD, yet an adjusted analysis is needed to validate this observation in a population group with distinct demographics.

**Funding:** Commercial Support - Fresenius Medical Care North America

**SA-PO1076**

**Enhancement of Solute Clearance Using An Experimental Pulsatile Push Pull Dialysate Flow Mode for the Quanta SC+: A Novel Clinic-to-Home Hemodialysis System**

**Methods:** The pumping action of the prototype SC+ system was modified by altering software algorithms controlling the sequencing and timings of the valves and pumps associated with the flow balancing chambers that push and pull dialysate fluid to and from the dialyzer; no additional modifications to the hardware or consumables were required. Solute clearance performance was assessed in the prototype SC+ system across a range of molecular weights in two related series of laboratory bench studies. The first measured dialysate fluid moving across the dialyzer membrane using ultrasonic flowmeters to establish the validity of the approach; solute clearance was subsequently measured using fluorescently tagged dextran molecules as surrogates for uremic toxins. The second study used human blood to establish the validity of the approach; solute clearance was assessed in the prototype SC+ system across a range of molecular weights in two related series of laboratory bench studies. The first measured dialysate fluid moving across the dialyzer membrane using ultrasonic flowmeters to establish the validity of the approach; solute clearance was subsequently measured using fluorescently tagged dextran molecules as surrogates for uremic toxins. The second study used human blood to establish the validity of the approach; solute clearance was assessed in the prototype SC+ system across a range of molecular weights in two related series of laboratory bench studies.

**Results:** Initial testing with fluorescently-tagged dextran molecules (0.3 kDa, 4 kDa, 10 kDa and 20 kDa) established the validity of the experimental pulsatile push pull-pull mode in the prototype SC+ system to enhance clearance and demonstrated a 10 to 15% improvement above the current HD mode used in clinic today. Additional testing using human blood indicated a comparable performance to pre-dilution HDF.

**Conclusions:** The observed enhancement of solute transport is attributed to the disruption of the boundary layers at the fluid-membrane interface which, when used with blood, minimizes protein fouling and maintains the surface area available for mass transport. In contrast with current HDF technologies, this improvement in performance has been achieved without the introduction of any additional complexity to the device hardware or fluidic circuit consumable settings maintaining ease of use of the SC+ system.

**Funding:** Commercial Support - Quanta Dialysis Technologies

**SA-PO1079**

**A Study to Evaluate a New Hemodialysis Device in the Home**

**Methods:** A prospective multicenter, open-label, non-randomized, cross-over study was completed to evaluate Tablo in the home by subjects with end stage renal disease (ESRD) who are on stable dialysis regimens. The FDA-approved study required an In-Center arm with 32 treatments, a transition period of 8-16 treatments, and an In-Home arm with 32 treatments. Dialysis frequency was 4 times per week. The primary efficacy endpoint was a weekly standardized Kt/V of ≥ 2.1, and the primary safety endpoint was the mean number of adverse events from a pre-specified list. The secondary endpoint was ultrarfiltration (UF) rate within 10% of the prescribed UF goal.

**Results:** Thirty patients from 8 dialysis units in the US were enrolled, and 28 per-protocol patients completed 1742 treatments. Compliance to the protocol dialysis frequency in the per-protocol group was 97%. Preliminary analysis suggests the study met all safety and efficacy endpoints.

**Conclusions:** Patients in the study were representative of the overall dialysis population. Protocol compliance was high and preliminary data indicates study objectives were achieved.

**Funding:** Commercial Support - Outset Medical

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Baseline Clinical Data

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SA-PO1080

Validation of Revisions to the NxStage Dosing Calculator

Kristine Kubisik,1 Eric D. Weinhandl,1,2 Norma J. Otshuhn,1 Lorien S. Dalrymple,1 Michael A. Kraus,1 Franklin W. Maddox,1 Fresenius Medical Care North America, Waltham, MA; 2University of Minnesota, Minneapolis, MN.

Background: The NxStage Dosing Calculator (DC) is an online tool that can be used to identify hemodialysis prescriptions that achieve a specified standardized Kt/V on the NxStage System One (NSO) platform. The DC has recently been revised to align with formulae in Kidney Disease Outcomes Quality Initiative guidelines and to permit incorporation of residual renal function (RRF). We used home hemodialysis (HHD) patient data from a large dialysis organization to validate DC revisions.

Methods: We identified adult patients who initiated HHD with NxStage equipment in Fresenius Kidney Care (FKC) clinics between March 1, 2016, and December 1, 2018. Patients were followed from completion of HHD training to discontinuation of HHD with NxStage equipment at FKC. We collected patient-days with pre- and post-dialysis blood urea nitrogen (BUN) measurements and retained those with exact adherence to prescribed treatment frequency during the preceding 7 days. We derived model-predicted standardized (std) Kt/V from the HHD prescription, and observed std Kt/V from BUN measurements, before and after DC revisions.

Results: The cohort included 3427 patients and 23,408 patient-days with BUN measurements. Over 91% of patient-days were accompanied by 4 or 5 weekly treatments, and RRF was measured in 19%. Model-predicted and observed std Kt/V, given DC revisions, are displayed in the figure, with a smoothed trend in orange. DC revisions increased the proportion of variation in observed std Kt/V that was explained by model-predicted std Kt/V from 26% to 58%.

Conclusions: Revisions to the NxStage DC have improved concordance of predicted and observed std Kt/V in HHD patients, especially near guideline targets. RRF is influential on forecasted Kt/V, so continued reliance on RRF in HHD patients requires the inclusion of residual renal function (RRF). We used home hemodialysis (HHD) patient data from a large dialysis organization to validate DC revisions.

SA-PO1081

The Ambiguous Identity of Home Hemodialysis in Medicare Claims

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Background: Home hemodialysis (HHD) is performed in a home, which may be a private residence or a skilled nursing facility (SNF). Although the Centers for Medicare & Medicaid Services issued a condition code in 2005 for dialysis in a SNF, the code is rarely used. In Medicare claims, HHD is thus assumed to be performed by an unskilled caregiver. We analyzed Medicare expenditures among contemporary HHD patients, stratified by probable status of the HHD program as a SNF- or home-oriented provider.

Methods: Using 2016 Medicare Limited Data Sets, including 100% of institutional claims and 5% of physician/supplier claims, we tallied Medicare Parts A and B expenditures, excluding those for outpatient dialysis, for HHD patients. We used Medicare claims to evaluate how this inherent ambiguity to facilitate meaningful evaluation of outcomes on HHD.

Results: Total Medicare Parts A and B expenditures, excluding those for dialysis, were $52,678 and $191,242 per PY among HHD patients in facilities with <40% and ≥40% prior-year prevalence of SNF residency. This factor was associated with large relative rates in inpatient facility, skilled nursing facility, and ambulance transport expenditures, as shown in the table. Analysis of individual facilities with HHD patients and the highest values of prior-year prevalence of SNF residency routinely revealed providers that deliver on-site hemodialysis in the SNF setting.

Conclusions: HHD in Medicare claims clearly reflects two phenotypes. CMS must address this inherent ambiguity to facilitate meaningful evaluation of outcomes on HHD.

SA-PO1082

Surferace-Inside-Out Access Procedure for Effective and Quick Placement of Venous Catheters in Patients with Thoracic Central Venous Obstruction

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Background: Thoracic central venous obstruction (TCVO) associated with repeated insertion or long use of central venous catheters (CVCs) is common in hemodialysis populations. The Surferace System to Facilitate Access in Venous Occlusions (SAVE) Registry was designed to evaluate the performance of the Surferace, a novel inside-out procedure for patients with limited or diminishing upper body venous access or pathology impeding standard access methods. During this prospective, single-arm, multicenter, international registry, the Surferace System was integrated during routine clinical care to facilitate right-sided placement of CVCs in patients with TCVO.

Methods: Five sites enrolled 30 patients in the SAVE Registry. Enrollment occurred between February 2017 and September 2018. Patient demographics, medical history and type of TCVO based on Drolm et al (J Vasc Interv Radiol. 2018;29:454-460) were collected at enrollment. Twenty-nine of the 30 patients with TCVO required CVCs for hemodialysis and 1 for chronic apheresis. Surferace performance (success rates of CVC placement, procedural and fluoroscopy time), device-related adverse events, catheter malpositionings and postprocedural complications were documented during the procedure and upon hospital discharge.

Results: Baseline venography revealed 30 patients had Type 4 occlusions, 26.7% had Type 3, 16.7% had Type 2, and 26.7% had Type 1. Successful CVC placement was achieved in 29 patients (96.7%). Mean completion time was 24 ± 4.5 minutes, mean fluoroscopy time was 6.8 ± 4.5 minutes and mean contract volume use was 29.7 ± 22.2. The procedure was discontinued in 1 patient (3.3%) due to significant vascular anatomical tortuosity. There were no adverse events or complications.

Conclusions: The Surferace Inside-Out access procedure enables effective, safe and quick placement of right-sided venous catheters in patients with thoracic central venous obstructions.
SA-PO1083

Effect of Early Cannulation with Plastic Cannula on Patency of Arteriovenous Fistula for Hemodialysis

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Background: Plastic cannulas for hemodialysis have been used in Japan for many years; however, effect of early cannulation with plastic cannulas on arteriovenous fistula (AVF) patency is unknown. We studied if early cannulation with plastic cannulas would affect AVF patency.

Methods: ESRD patients who underwent primary AVF operations were divided into an early cannulation group with first cannulation time (FCT) within<10 days and a late cannulation group with FCT is ≥10 days. The Kaplan-Meier method and multivariable Cox regression models were used to investigate AVF patency.

Results: 122 patients were enrolled in the study (mean age, 72.5 yr; 64.8% male; 52% diabetes mellitus; 39% RCAVs), median FCT was 6 days. Kaplan-Meier analysis showed that there was no statistically significant between-group difference in primary or secondary patency rates. Early cannulation was not found significantly associated with primary patency or secondary patency after age, gender, the presence of diabetes mellitus, hypertension and being on hemodialysis were adjusted.

Conclusions: Early cannulation with plastic cannulas might not affect AVF patency, maybe we can cannulate AVFs earlier than 10 days after AVF creation to avoid the use of central venous catheters.

SA-PO1084

Assessment of Arteriovenous Fistula Maturation Using Central-Venous Oxygen Saturation and Estimated Upper-Body Blood Flow

Laura Rosales,1 Hanjie Zhang,1 Brenda K. Chan,1 Marilou Mateo,1 Seth Johnson,1,2 Stephan Thijssen,1 Peter Kotanko,1,2 Renal Research Institute, New York, NY; 1Icahn School of Medicine, New York, NY; 1Easy Water for Everyone, Yonkers, NY.

Background: Arterio-venous fistula (AVF) is the optimal vascular access in most hemodialysis (HD) patients. However, AVF maturation is difficult to assess. Central-venous oxygen saturation (ScvO₂) and upper-body blood flow (UBBF) increase during AVF maturation. We followed AVF maturation using ScvO₂ and estimated UBBF (eUBBF).

Methods: We studied 19 patients from an ongoing AVF quality improvement project. ScvO₂ and hematocrit were measured with Crit-Line (FMC, Waltham, MA) between minutes 5 and 20 into HD, and eUBBF was computed as recently described (Rosales, Blood Purif, 2019).

Results: Following AVF creation, ScvO₂ and eUBBF increased in 9 patients with unassisted AVF maturation and in 4 un-cannulated patients with good clinical AVF function (1 transplanted, 1 transferred, 2 awaiting cannulation) (Table 1). These indicators increased less in 5 patients requiring assisted AVF maturation and in one patient who succumbed to sudden cardiac death with a clinically matured AVF.

Conclusions: Our preliminary results indicate that ScvO₂ and eUBBF provide point-of-care bio-signals that report AVF maturation and hemodynamic adaptation to the AVF. Advantages of this method are low costs, operator-independence, and scalability.
Values represent median, 25th and 75th percentiles. CV, cardiovascular; ScvO2, central-venous oxygen saturation; eUBBF, estimated upper-body blood flow.

SA-PO1087
The Importance of Monitoring Blood Flow in the Maintenance of Vascular Access in Patients Under Hemodialysis
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Background: The usefulness of blood flow monitoring (QA) in arteriovenous fistula (AVF) of patients with End Stage Renal Disease (ESRD) under hemodialysis (HD) patients is a current controversy in the international literature. Although all of the clinical guidelines for vascular access include monitoring protocols to prevent thrombosis (VA), randomized clinical trials (RCTs) have failed to consistently demonstrate the benefits of QA-based surveillance protocols. We present our experience of evaluating the usefulness of QA measurement using Doppler (DU) ultrasound in patients under HD.

Methods: 168 patients from two HD centers were under follow up for 3 years. The classical QA tracking method was applied to all once a year and moretimes on clinical indications. The episodes of thrombosis in vascular access that occurred acutely (group 1) and the interventions episodes made on the basis of DU findings (group 2) were recorded.

Results: During the 3-year follow-up period, 24 interventions were required to restore the functioning of vascular access. Of these, 8 were made after an acute event (group 1) and 16 after a finding derived from a DU control (group 2). Of the 8 acute cases of AVF or graft thrombosis, 5 ended up with a central venous catheter. Of the 16 cases requiring intervention after an ultrasound finding 12 events maintained the type of vascular access they had and 4 ended up with a central venous catheter. Group 1 required hospitalization of more than one day in 3 cases, which did not occur in any of Group 2 incidents.

Conclusions: Periodic QA measurement using DU significantly helps maintain vascular access of patients, limiting their days of hospitalization and significantly contributing to their better quality of life.

SA-PO1086
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Background: Home hemodialysis (HHD) and peritoneal dialysis (PD) prevalence varies throughout the world. Home dialysis policies and clinician knowledge affect home dialysis prevalent nations worldwide. Questions explored patient reimbursement, telehealth, patient training, solo dialysis and patient contact.

Methods: A 13 item web-based questionnaire was distributed to home therapy program clinicians in the 30 highest home dialysis prevalent nations worldwide. Questions explored patient reimbursement, telehealth, patient training, solo dialysis, home and clinic visit frequency. IRB approved surveys were independently translated into 9 languages with translation validation by an external translation service.

Results: 395 respondents from 30 nations using 7 different languages responded. 64% were aligned with combined HHD and PD programs, 32% PD only and 7% HHD only. 29% of programs had less than 20 patients, 30% had 20 to 50 patients, 22% had 50 to 100 patients and 19% had greater than 100 patients. 31% of all programs reported patient costs reimbursement, with non-US programs much more likely to report reimbursement than US programs (US 11%, non-US programs 59%, χ² = 93.6, p < 0.0001). Telehealth use was low throughout the world (23% prevalence), contrasting with 83% of respondents agreeing telehealth would improve home dialysis care, 31% of all programs enabled flexible training out of work hours. 72% of US clinicians agreed that monthly clinic visits were needed in comparison to 44% of non-US clinicians (χ² = 83.7, p < 0.0001). 31% of respondents agreed that dialysis partners are always required for home dialysis.

Conclusions: Global variation in home therapy practices, knowledge and attitudes exist. Telehealth, cost reimbursement, training flexibility and acceptance of solo dialysis is low. Addressing these hurdles to home dialysis may increase home dialysis growth.
Where Should the Non-Tunneled Catheter Tip Be Placed for Hemodialysis? Fourth vs. Second Intercostal Space

Héctor R. Ibarra-Sifuentes,1 Jose L. Avila Velazquez,2 Raymundo Vera,2 Giovanna Y. Arteaga Muller,2 1Universidad Autonoma de Nuevo Leon, Monterrey, Mexico; 2Hospital Universitario, Monterrey, Mexico.

Background: Non-tunneled catheters (NTC) for hemodialysis are an indispensable vascular access and very common in patients in need of hemodialysis, especially urgently. The insertion method used for the placement of NTC can reduce serious complications.

Methods: Randomized clinical trial with adult patients at the University Hospital, Autonomous University of Nuevo Leon, Monterrey, Mexico, who required emergency hemodialysis by NTC. The NTC were inserted percutaneously with the ultrasound-guided modified Seldinger technique. Patients were randomized to NTC tip placement on the fourth intercostal space (4IS) and to the second intercostal space (2IS). The main outcome are to number of dysfunction, repositioning and relocation episodes due to NTC placement.

Results: The study included 115 patients who were placed on NTC for hemodialysis, with an average age of 51 years, 55% were female, the mean height was 163 cm, no difference between the groups. The incidence of catheter dysfunction and catheter relocation were not different. Catheter repositioning was presented in 50 and 16% for the 4IS insertion and 2IS groups, respectively (p <0.001).

Conclusions: The placement of the hemodialysis NTC tip on the 2IS decreases the incidence of repositioning, without affecting the incidence of dysfunction or repositioning when compared to 4IS. The search for new methods of catheter placement to reduce the potential complications of invasive treatments on renal replacement therapy is still pending.

Table 1. Primary outcome in classic and intervention group.

<table>
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<th>Classic Group (4IS)</th>
<th>Intervention Group (2IS)</th>
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<tr>
<td>Dysfunction (%)</td>
<td>44(42)</td>
<td>24(41)</td>
<td>0.39</td>
</tr>
<tr>
<td>Repositioning (%)</td>
<td>25(59)</td>
<td>8(18)</td>
<td>0.001</td>
</tr>
<tr>
<td>Relocation (%)</td>
<td>0(0%)</td>
<td>1(25%)</td>
<td>0.13</td>
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4IS, fourth intercostal space; 2IS, second intercostal space.

Ultrason-Guided Protocol Safely Eliminates Chest Radiography After Non-Tunneled Catheter Placement in Urgent Hemodialysis

Héctor R. Ibarra-Sifuentes,1 Jose L. Avila Velazquez,2 Raymundo Vera,2 Giovanna Y. Arteaga Muller,2 1Universidad Autonoma de Nuevo Leon, Monterrey, Mexico; 2Hospital Universitario, Monterrey, Mexico.

Background: Despite its morbidity and mortality, the Non-tunneled catheter (NTC) continues to be an indispensable vascular access when imminent need for Hemodialysis. The confirmation of the proper NTC placement and complications detection are a real concern to optimize patient safety.

Methods: Prospective, comparative study. Included patients aged >17 years with life-threatening complications (uremic syndrome, potassium >6.5 mmol/L, acidosis pH <7.2 with high anion gap and HCO3 <-15 mmol/L and pulmonary edema) all resistant to saline flush test and performed thorax evaluation for pleural sliding and pleural point with US and chest x-ray (CXR). Objective is to compare successful venous placement and immediate detection of complications derived from NTC placement with US and CXR.

Results: 113 patients were involved, 60% in the emergency room. Their mean age was 50 years, 62% were male. The main causes of NTHC placement were uremic syndrome (41%) and fluid overload (28%). The mean blood urea nitrogen was 111 mg/dL. The confirmation of the proper NTC placement and complications detection are a real concern to optimize patient safety.

Conclusions: The US is an effective tool for the assessment of adequate NTC placement and complications detection in patients with urgent need of hemodialysis when compared to CXR.
SA-PO1092

A Tragic Missed Opportunity: Leadless Cardiac Devices in Hemodialysis Patients
Sayee Sundar
Patients
Background: There is a frequent need for placement of cardiac implantable electronic devices (CIEDs) in hemodialysis patients. Placement of a CIED is associated with central vein stenosis, infections and access failure. Cardiac electrophysiology has advanced significantly with the availability of s-ICDs and Leadless pacemakers. The goal of this study is to assess the effectiveness of these devices in patients.
Methods: We conducted a retrospective study of adult ESRD patients who underwent leadless cardiac device placement between January 2014 - September 2018.
Results: Among patients who underwent leadless device placement, 14 patients were on renal replacement therapy (15.38%). Mortality among these patients after leadless device placement was 33.3%. There were no episodes of bacteremia requiring long term antibiotics or extended hospitalization post device placement. Patients with AVF required interventions due to stenosis of their peripheral veins, however the access remained patent until the end of the follow-up period.
Conclusions: A small minority of patients on dialysis underwent leadless device placement. Theses devices are associated with lesser incidence of catheter related bacteremia and sustained access patency in patients. Consideration should be given to the placement of such devices in patients on or close to needing renal replacement therapy.

Access characteristics in patients pre and post leadless device implantation

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<tr>
<td>Time of Device Placement</td>
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</tr>
<tr>
<td>Bacteremia prior to device placement</td>
<td>75% (38/51)</td>
<td>63% (25/40)</td>
<td>68% (26/38)</td>
</tr>
<tr>
<td>Incidence of Central Venous Stenosis</td>
<td>6.3% (14/225)</td>
<td>8.5% (25/295)</td>
<td>0</td>
</tr>
<tr>
<td>Need for intervention after device implantation</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bacteremia post leadless device placement</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Access patency post device implantation</td>
<td>56.3% (7)</td>
<td>55.33% (6)</td>
<td>55.33% (6)</td>
</tr>
<tr>
<td>Mortality</td>
<td>25% (3/12)</td>
<td>6.33% (2/32)</td>
<td>0</td>
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SA-PO1093

Reducing Early Catheter-Related Bloodstream Infection in Hemodialysis Patients
Timothy J. Koh, Benjamin Z. Khoo, Sanamatum Ningombam, See Cheng Yeo.
Tock Seng Hospital, Singapore, Singapore.

Background: Dialysis catheter-related blood stream infection (CRBSI) is a leading complication in hemodialysis (HD) patients, and is associated with increased risk of mortality, invasive procedures, extra hospitalization and/or increase in length of stay. Poor tunneled dialysis catheter (TDC) care by patient, inadequate skin preparation before TDC insertion and lack of prophylactic antibiotics during TDC insertion may contribute to early CRBSI. We examined the role of bundled interventions to reduce early CRBSI in HD patients with newly inserted TDC.
Methods: Between April to September 2017, we instituted a bundle of measures to reduce CRBSI in patients from two designated wards (intervention group); patients in other wards received usual care (control group). In the intervention group, daily chlorhexidine bath was administered for all patients prior to TDC insertion and nasal decolonization was performed for methicillin-resistant Staphylococcus Aureus carriers. In this group, prophylactic intravenous antibiotics was also administered at TDC insertion and topical antibiotics were applied to the exit site post-insertion. Patients were educated on TDC care and this was reinforced prior to discharge. Early CRBSI was defined as any new bacteremia occurring within 30 days of TDC insertion, and the rate of CRBSI was compared between the intervention and control groups.
Results: 308 TDC insertions or exchanges were performed during the study period (153 in intervention group and 155 in control group), of which there were 18 (5.8%) episodes of early CRBSI. Microbiological profile includes gram positive (8 episodes, 44.4%), gram negative (7 episodes, 38.9%), polymicrobial (2 episodes, 11.1%) and fungal (1 episode, 5.6%) organisms. In the intervention group, early CRBSI occurred in 5 (3.3%) TDC insertions while early CRBSI occurred in 13 (8.4%) TDC insertions in the control group, with a trend towards significance (p = 0.056). The interventions were well tolerated and cost effective, with the project resulted in significant healthcare cost savings.
Conclusions: The frequency of early CRBSI was successfully decreased, with a trend towards significance, using a comprehensive bundle of interventions. Further follow-up with regards to CRBSI frequency and analysis on the effectiveness of individual interventions would be helpful in assessing the utility of these measures.

SA-PO1094

Long-Term Outcomes of Catheter-Related Bloodstream Infections
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Background: Catheter-related bloodstream infections (CRBSIs) are common in patients receiving hemodialysis through a central venous catheter. In addition to antibiotics, treatment may include replacement of the catheter, exchange over a guide wire, or the catheter maybe left unchanged (salvage therapy). While these modalities are equally efficacious in the short run, the effect on long term infectious complications like endocarditis and epidural abscesses is not known. The purpose of our study was to determine the long-term complications of CRBSI and determine if catheter salvage or exchange is associated with an increased risk of long-term complications.
Methods: We retrospectively studied 100 randomly selected adult patients on hemodialysis admitted to a 1000 bed academic university hospital between May 1st, 2010 and April 30th, 2017 with CRBSI. Baseline demographics and clinical characteristics were stratified by line disposition, and cost effective, with the project resulted in significant healthcare cost savings. The mean age was 59.6 ± 15.7 years with 36% males and 64% females. Methicillin-resistant Staphylococcus aureus (MRSA) was the most common organism isolated (26%). 45% of catheters were replaced, 43% were exchanged, and 12% were salvaged. After excluding those who died and had catheter discontinued, 28% of the 75 patients developed long term complications. The long-term complications rates were 40% for catheter salvage, 32% for replacement and 21% for exchange (p=0.383). In univariate analysis there was no difference between groups. However, when adjusted for age, organism and ICU stay, patients with catheter exchange were less likely to develop long term complications compared to those with salvage therapy (adjusted OR: 0.14; 95%CI: 0.02-0.83). There was no statistically significant difference between the other groups.
Conclusions: Our results showed that there is a high incidence of long-term complications in patients admitted with CRBSI. The incidence was highest in those with catheter salvage. These results suggest the need for caution with catheter salvage and an adequately powered randomized controlled trial to determine the long-term safety of catheter salvage in patients with CRBSI.
SA-PO1095
Epidemiology and Clinical Outcomes of Staphylococcus aureus Bacteraemias in Haemodialysis Patients: 12-Year Single-Centre Experience
Jonathan W. Hurst,1,2 Moira Stanley,3 Jayakerrthi Rangaiah,1 David Makanjuola,1
1Renal unit, Epsom & St. Helier University Hospitals NHS Trust, Surrey, United Kingdom; 2Renal unit, Epsom & St. Helier University Hospitals NHS Trust, Surrey, United Kingdom; 3Renal Unit, Epsom & St. Helier University Hospitals NHS Trust, Surrey, United Kingdom.

Background: Patients on haemodialysis are at risk of access associated infections. The risk is greater in patients dialysed through lines, than those dialysing via arteriovenous fistulae (AVF) or grafts (AVG). Studies have shown that the most commonly implicated organism is Staphylococcus aureus (SA), which has a tendency to cause metastatic infections e.g. endocarditis, osteomyelitis. We decided to look at the incidence and clinical outcomes in haemodialysis (HD) patients with SA bacteraemia in patients at our centre over the last 12 years.

Methods: Data were collected from the hospital’s microbiology database of all the confirmed bacteraemia episodes in HD patients between 2007 and 2018. We looked at the demographics, type of dialysis access, and the outcomes following the bacteraemias.

Results: There were 261 bacteraemias in 1361 patients who had a cumulative total of 32,000 dialysis episodes over the 12 year period. Of the patients with bacteraemias, 164 (62.8%) were male. The median age was 67 years (range 18-96). The dialysis access at the time of the bacteraemia was as follows: AVG/AVG 57 (22%), dual access - AVG or graft + line - 50 (20%), dialysis line 147 (56%), not documented 7 (3%). The blood cultures grew methicillin-sensitive SA (MSSA) in 71% and methicillin-resistant SA in 29% of cases. 204 (77%) cases occurred in patients dialysing through lines. Details about complications were available in 199 patients and are shown in Table 1.

Conclusions: Our data show that the bacteraemias and complications were most common in patients dialysing with lines, and emphasise the importance of trying to achieve dialysis through AVFs or grafts as soon as is possible.

Table 1 – Complications following SA bacteraemias

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>NUMBER (%)</th>
<th>LINES</th>
<th>AVG/AVG</th>
<th>DUAL</th>
</tr>
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<tbody>
<tr>
<td>Death</td>
<td>7</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>13</td>
<td>9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>20</td>
<td>22</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>48</td>
<td>37 (74%)</td>
<td>11 (23%)</td>
<td></td>
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SA-PO1096
Reduction in Number of Hospital-Acquired Methicillin-Resistant Staphylococcus aureus Dialysis Catheter Related Bloodstream Infections: Role of Nasal Mupirocin and Chlorhexidine Body Wash
Streekanth Koduri, Chang Yin Chionh. Changi General Hospital, Singapore, Singapore.

Background: Central Venous Catheter-Related Bloodstream Infections (CRBSI) are an important cause of hospital acquired infection associated with morbidity, mortality and cost. Patients undergoing haemodialysis using a catheter are at significant risk for developing CRBSI, especially with Methicillin-resistant Staphylococcus aureus (MRSA), resulting in serious complications. In our 1000-bed regional hospital, the average CRBSI(MRSA) rate was 0.56 per 1,000 catheter days. A quality improvement project was initiated with an aim to reduce the rate by 50%.

Methods: Following the formation of a multidisciplinary team, the catheter insertion protocols and catheter hygiene protocols were harmonised throughout the hospital. A decolonization protocol with Mupirocin 2% nasal cream along with Chlorhexidine bodywash for 5days, was initiated prior to dialysis catheter insertion. Monthly data on prescription and delivery of nasal and skin decolonisation protocol was collected. The CRBSI (MRSA) rates were collected monthly by averaging the number of infections per 1000 catheter days.

Results: Analysis of the data from July 17 – November 2018 showed a significant improvement in the CRBSI rates, after the robust implementation of nasal and skin decolonization protocol (>95%).

Conclusions: The causes of CRBSI can be multifactorial and a multidisciplinary approach is required to reduce the infection rates. With nasal and skin decolonization prior to dialysis catheter insertion, the CRBSI rates, especially related to MRSA can be reduced significantly, as shown in our experience.

SA-PO1097
Use of Gentamicin-Citrate Lock Reduced Catheter-Related Bloodstream Infection Rates in Hemodialysis Patients: Results of a Natural Experiment
Wael F. Hussein,1,2 Fang Yang,1 Suni J. Sun,1 Graham E. Abra,1,2 Brigitte Schiller.1,2 Satellite Healthcare, San Jose, CA; 1Department of Medicine, Division of Nephrology, Stanford University School of Medicine, Palo Alto, CA.

Background: Use of central venous catheters (CVC) is a major risk factor for infections, a leading cause of morbidity and mortality in hemodialysis (HD) patients. Use of gentamicin 320 µg/mL in 4% sodium citrate lock (GCL) was previously shown to reduce the rate of CVC-related bloodstream infection (BSI). We report on the change of CVC-related BSI rates in four centers experiencing high BSI rates while using heparin catheter lock (period 1 [P1]) after switching to GCL (period 2 [P2]).

Methods: Retrospective observational study. Patient characteristics at time of switch to GCL were obtained from the provider’s EHR. CVC patient-months and reported events of CVC-related BSI were obtained from the NHISN database. The rate for pooled rates for P2/P1 was calculated and tested for significance.

Results: There were 684 and 896 CVC patient-months in P1 and P2 respectively. Mean patient age was 64 ± 14 years, and 48% were female. Monthly CVC-related BSI rates are shown in Figure 1. Pooled CVC-related BSI rates were 2.8 and 0.6 per 100 patient-months for P1 and P2 respectively, representing an 80% reduction in the rate of BSI (rate ratio 0.20, 95% Confidence interval 0.08 – 0.54, p = 0.0004).

Conclusions: These results are consistent with results from a previous trial, but in real-practice setting. Use of the gentamicin-citrate lock significantly reduces CVC-related BSI.

Figure 1
Methods: We retrospectively studied incident HD patients at the Hospital Civil de Guadalajara Fray Antonio Alcalde (HC) and the U.S. Renal Research Institute clinics (RRI) between 2014-2018. We compared CVC rates at HD initiation and conversion rates between months 1 and 6 between HC and RRI, respectively. At HD initiation CVC prevalence was 97% at HC and 69% at RRI, respectively. The CVC conversion rate between months 1 and 6 was 11% in HC, respectively (p=0.0004). Albumin was the only significant variable associated with continuous CVC status in the RRI group (OR 0.52, CI 0.95 0.37-0.44). An association was observed, although not significant between diabetes and the persistence of the catheter in HC patients (OR 0.57, CI 0.34-0.9).

Conclusions: CVC prevalence and conversion rates differ between RI and RRI. Higher CVC prevalence in HC patients at HD initiation is likely due to more frequent “crashing” into HD, less pre-dialysis care, and socioeconomic disparities, reflecting the realities of an urban public hospital providing HD to a largely uninsured population. The presence of diabetes in HC seems to contribute as a barrier to CVC conversion, perhaps due to the economic cost that it entails. The impact of CVC conversion rates on patient outcomes warrants future studies.

SA-PO1099

Outcomes of Upper Limb Arteriovenous Fistula After Insertion of Ipsilateral vs. Contralateral Tunnelled Vascular Catheters: A Single-Centre Experience

Jason Diep, Angela Makris, Imelda De Guzman, Jeffrey Wong, Ananthakrishnapuram N. Aravindan, Govind S. Narayanan. Liverpool Hospital, Greenfield Park, NSW, Australia.

Background: Observational data suggest that the use of central venous dialysis catheters is associated with reduced subsequent Arteriovenous Fistula (AVF) maturation and survival, but it’s unclear if catheters directly affect AVF function. Catheter related central vein stenosis could affect flow and maturation of a subsequent AVF on the same side. To explore this further we aim to compare the outcomes of AVF created ipsilateral or contralateral to previous Tunnelled Vascular Catheters (TVC).

Methods: We retrospectively examined our vascular access database and electronic medical records of all patients who started dialysis at all units linked to Sydney Southwest Local Health District. We identified 142 patients who started dialysis with a TVC and subsequently had their first AVF created between Jan 2013 and Dec 2017. For patients with multiple AVFs only the first was included. All fistulas were monitored as per local policy. Successful fistula use (cumulated with two needles for a 2 consecutive weeks) was analysed at 6 and 12 months after initial creation. We used Chi-square test and logistic regression to analyse outcomes.

Results: 40 AVFs (12 upper arm, 33 right arm) were created ipsilateral to previous TVC insertion side and 102 AVFs (31 upper arm, 5 right arm) were contralateral. Median age (68 years, range=29-84; 66 years, range=25-87; p=0.38), the proportion of males (77.5% and 68.6%, p=0.29), and prevalence of diabetes (60.0% and 63.7%, p=0.70) were similar between ipsilateral and contralateral groups respectively. At 6 months, 40.0% of ipsilateral AVFs were functioning compared to 59.6% of contralateral AVFs (OR=0.45; CI 0.21-0.99; p=0.05). After adjusting for other factors (age, sex, diabetes, and hypertension) using a backwards conditional regression, non-smokers (p=0.005) and contralateral AVF placement (p=0.021) were associated with a greater AVF function at follow-up.

Conclusions: Successful use of AVF was lower at 6 months in patients with AVF created ipsilateral to prior TVC insertion. Careful planning of prior TVC and future AVF locations should be guide management of long term vascular access.

SA-PO1100

The Diagnostic Value of Multi-Detector CT Venography for Catheter-Related Central Venous Stenosis in Hemodialysis Patients

Letian Yang,1 Yuliang Zhao,2 Tianlei Cui,1 Ping Fu,3 West China Hospital of Sichuan University, Chengdu, China; Division of Nephrology, West China Hospital, Sichuan University, Chengdu, China.

Background: Central venous stenosis (CVS) is a common complication in hemodialysis patients, especially those who are dialyzed through a catheter. The objective of our study was to assess the diagnostic value of Multi-detector CT venography (MDCTV) for catheter-related CVS compared with conventional digital subtraction angiography (DSA) in hemodialysis patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Incident Vascular Access Outcomes among the Study Cohorts

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<tr>
<td></td>
<td>Model 1 OR (95% CI)</td>
<td>Model 2 OR (95% CI)</td>
<td>Model 3 OR (95% CI)</td>
</tr>
<tr>
<td>AVF Fatal or Incident ESRD</td>
<td>586 (76.4%)</td>
<td>44,531 (63.5%)</td>
<td>327 (2.5%)</td>
</tr>
<tr>
<td>AVF Fatal or Incident ESRD</td>
<td>1,904 (347)</td>
<td>52,786 (17.8)</td>
<td>2.56 (95% CI)</td>
</tr>
<tr>
<td>CCI tertile, AVF vs AVG</td>
<td>250 (416.85)</td>
<td>54,801 (18.5)</td>
<td>1.89 (2.0, 2.7)</td>
</tr>
<tr>
<td>Any form of Vascular Access creates timely</td>
<td>110,584 (20.0)</td>
<td>3,640 (2.8)</td>
<td>2.98 (2.55, 3.51)</td>
</tr>
<tr>
<td>AVF used or planning transfer</td>
<td>1,762</td>
<td>10,269 (0.03)</td>
<td>2.02 (1.70, 2.41)</td>
</tr>
</tbody>
</table>

OR: Odds Ratio, CI: confidence interval

SA-PO1102
Patient Values Toward Vascular Access Across Differing Age Groups
Anamika Adwanye,1 Neill D. Duncan,1 Edwina A. Brown,2 1Hammersmith Hospital, London, United Kingdom; 2Imperial College London, London, United Kingdom; 3Renal and Transplant Centre, Imperial College London, London, United Kingdom.

Background: Current guidance strongly supports the arteriovenous fistula over a catheter in all patients regardless of age. However, an increasing proportion of the prevalent haemodialysis population is now made up of older and comorbid patients who may require a greater healthcare burden to achieve a fistula. It has been demonstrated in other areas of healthcare that this patient group have distinct healthcare values, defined as fixed general preferences regarding treatment goals, when compared to younger patients. The aim of values in vascular access preference has not been studied.

Methods: Structured interviews were conducted in a group of prevalent haemodialysis patients, all unaware of the purpose of the study. Questionnaires described a set of renal healthcare scenarios, with patients asked to make a trade-off decision for each. Priority scores for four treatment goals were determined by weighted analysis of the decisions. The treatment goals were: longevity, comfort, aesthetics and convenience.

Results: From 106 patients enrolled across 4 dialysis satellites, 104 patients (aged 16-94, 56% male) completed interviews for analysis. Questionnaires revealed the most important values in order of descending priority score (mean±se): convenience 3.7±0.8, comfort 2.6±0.7, aesthetics 1.2±0.7, and longevity 5.0±0.8. Compared to those under 55, older patients (over 70) unconsciously assigned higher priority scores to convenience (7.9 vs -1.3, p<0.001) and comfort (6.5 vs -2.9, p<0.001), and lower priority scores to aesthetics (-5.2 vs 4.6, p<0.001) and longevity (-9.2 vs -8.4, p<0.001). Access choices similarly predicted priorities: compared to those with a fistula, patients dialysing via catheter assigned higher priority scores to convenience (4.8 vs -0.3, p=0.007) and comfort (4.6 vs -4.2, p=0.001), and lower priority scores to aesthetics (-2.7 vs 3.7, p=0.001) and longevity (-6.7 vs -0.8, p<0.001). In a matched group analysis, the effect of age and access on healthcare priorities were independent.

Conclusions: Unconsciously assigned priorities show that amongst older patients, convenience and comfort are more important than longevity and aesthetics, and access choices appear to depend on similar values. Healthcare values should be understood when making access decisions with patients, particularly in older age groups.

SA-PO1104
The Impact of Comorbidity Index on the Association Between Vascular Access Type and Clinical Outcomes Among Elderly Patients Undergoing Hemodialysis
Jong Hyun Jhee,1 Seoung woo Lee.2 1Inha University College of Medicine, Incheon, Republic of Korea; 2Inha University Hospital, Incheon, Republic of Korea.

Background: The optimal type of vascular access for the elderly undergoing hemodialysis is controversial. As the patient group have distinct healthcare values, defined as fixed general preferences regarding treatment goals, when compared to younger patients. The aim of values in vascular access preference has not been studied.

Methods: Total of 23,110 patients with ≥65 years undergoing hemodialysis were recruited from the Korean end-stage renal disease registry data (2001-2018). Study subjects were stratified into tertile according to simplified Charlson comorbidity index (CCI) and compared the survival and hospitalization rate among the type of vascular access.

Results: Among all tertiles of CCCI, AVG use showed highest risk of mortality than AVF use. In the lowest to middle tertile, no difference was observed in survival rates between the use of AVF and AVG. However, in the highest tertile, AVG use showed higher risk of mortality than AVF use. When subjects were classified according to a combination of CCCI tertile and access type (AVF vs. AVG), patients with the highest CCCI with AVG showed a 1.75-fold increased risk of mortality than those with the lowest tertile with AVG. Hospitalization rates due to access malfunction were highest in patients with AVG in all tertiles. In the highest tertile, patients with AVG showed increased rates of hospitalization compared to those with AVF due to access malfunction. However, hospitalization rates due to access infection were highest in patients with AVG in all tertiles.

Conclusions: The use of AVG may be of benefit and switching to AVG should be considered in elderly hemodialysis patients with a high burden of comorbidity.
SA-PO1105

The Impact of Vascular Access Type on the Survival and Quality of Life in Incident Hemodialysis Patients: Comparisons Among Arteriovenous Fistula, Graft, and Temporary Catheters

Do Hyoung King,1 Chun Soo Lim,2 Hallym University Hangang Sacred Heart Hospital, Seoul, Republic of Korea; 2Seoul National University Boramae Medical Center, Seoul, Republic of Korea.

Background: Arteriovenous fistula (AVF) is the preferred vascular access for haemodialysis (HD); however, the association between vascular access and quality of life (QOL) is not well-known. We investigate the relationships between HD vascular access and all-cause mortality, health-related quality of life (HRQOL) and depression in a large prospective cohort.

Methods: A total of 1461 patients for whom HD was newly initiated were prospectively enrolled. The initial vascular access types were classified as AVF, arteriovenous graft (AVG) and central venous catheter (CVC). The primary outcome was all-cause mortality and the secondary outcomes were HRQOL, depression and all-cause hospitalisation. Kidney Disease Quality of Life Short Form 36 and Beck’s depression inventory scores were measured to assess HRQOL and depression, respectively.

Results: Of 1461 patients, 314 patients started HD via AVF, 76 via AVG, and 1071 via CVC. In the survival analysis, patients with AVF or AVG showed significantly better survival than those with CVC (p=0.015). The numbers of annual hospitalisation were not different among the groups. The AVF and AVG groups had a significantly higher Kidney Disease Quality of Life Short Form 36 score and a significantly lower Beck’s depression inventory score than the CVC group at 3 months and 12 months after the initiation of dialysis.

Conclusions: Patients with AVF or AVG have a better survival and HRQOL score and are less depressed than those with CVC. These suggest that the choice of vascular access in incident HD patients is important in terms of mortality and quality of life.

SA-PO1106

Hemodialysis Costs by Vascular Access Type and Outcomes in the Incident Year

Joanna Willetts,2 Sheetal Chaudhuri,2 Maria Radonova,2 Eric D. Weinhandl,2,3 John W. Larkin,2 Len A. Usyv,2 Terry L. Ketchersid,2 Franklin W. Maddux,1 Fresenius Medical Care, Waltham, MA; 2Fresenius Medical Care North America, Waltham, MA; 3University of Minnesota, Minneapolis, MN.

Background: We profiled Medicare expenditures over time among incident hemodialysis (HD) patients in an End Stage Renal Disease Seamless Care Organization (ESCO), stratified by vascular access type. The statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of the Centers for Medicare & Medicaid Services (CMS). The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Methods: We identified adult HD patients in a large dialysis organization (LDO) who: 1) were treated in an ESCO clinic, 2) had Medicare as payer, 3) had arteriovenous fistula/graft (AVF/AVG) implanted ≥90 days from first date of dialysis (FDD) or exclusively had a central venous catheter (CVC) throughout follow-up. We compared average costs of care per member per month (PMPM) in AVF/AVG versus CVC patients from 90 days to 6, 9, or 12 months after FDD. We stratified those with outcomes and censored their data in subsequent periods.

Results: Patients with an AVF/AVG implanted had lower average Medicare expenditures from 90 days from FDD to the 6, 9, and 12-month follow-up compared to those treated exclusively with a CVC (Figure 1; all p<0.05). Costs did not differ in any follow-up period among AVF/AVG versus CVC patients who died, received a transplant, or transferred out of the facility. However, survival was 6, 4, and 1 percentage points higher in AVF/AVG versus CVC patients at the 6, 9, and 12-month follow-up periods, respectively.

Conclusions: Compared to incident HD patients with exclusive CVC, those with an AVF/AVG placed within 90 days of initiation had a lower cost of care over the first year of HD. Costs in those with outcomes during a follow-up period were not distinct between AVF/AVG versus CVC groups.

Funding: Commercial Support - Fresenius Medical Care North America

SA-PO1107

Vascular Access Type Was Not Associated with Mortality and the Risk for Cardiovascular Death in Elderly Chinese Hemodialysis Patients

Yang Yu, Ping Fu. West China Hospital of Sichuan University, Chengdu, China.

Background: The objective of this study was to examine the impact of VA type on cardiovascular and all-cause mortality as well as the predictors for outcome in elderly Chinese patients.

Methods: In the retrospective study, patients who initiated HD aged a 70 years and received a primary VA creation were enrolled between January 2007 and October 2018. Clinical characteristics of VA, and outcomes were collected from the electronic medical record and the local Death Index. Kaplan-Meier analysis, and multivariate regression analysis were employed.

Results: A total of 358 elderly Chinese HD patients with median aged 74(72-78) years was analyzed. During the study period of 25.8 (12-43) months, 54 patients (15.1%) and 113 patients (15.1%) died of cardiovascular events and all-cause, respectively. The modality of VA type was not associated with mortality. Furthermore, CHF and DBP were the independent predictors for cardiovascular mortality (HR for CHF =3.462; HR for DBP per 1 mmHg elevated =1.033).

Conclusions: The modality of VA types showed insignificant effect on mortality in elderly Chinese population, while the presence of CHF and preoperative DBP might be used for the risk assessment of cardiovascular death.

SA-PO1107

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Hemodialysis Access in the Elderly and Survival

Jose E. Navarrete, Emory University, Atlanta, GA.

Background: To determine if achieving the goal of having an AV fistula impacts survival in elderly dialysis patients.

Methods: Incident hemodialysis patients age 70 or older admitted to Emory Dialysis program form 1/2011 to 12/2015 were followed until death, transplant, or censoring up to 12/31/18. Demographic, laboratory and hemodialysis data were obtained. Patients were categorized as C if they only dialyzed with a catheter, G if they were able to dialyze with a graft and F if they used a fistula for dialysis.

Results: 189 patients were included. 30%, 29% and 41% of patients used C, G or F respectively. Demographics and comorbidities were similar among groups but diabetes was more common (65%) in G users than C or F (40 and 56%). Use of C was associated with lower survival compared to G or F (Figure 1). Patients using C were more likely to be hospitalized than those using G (RR 1.8, CI 1.1-3.1, p=0.005) or F (RR 2.6, CI 1.5-4.5, p=0.01). Hospitalization risk was higher in patients with G compared to F (RR 1.4, CI 0.9-2.4, p=0.3) but the difference was not statistically significant. IV antibiotics use was more common in patients with C. 10.5%, 6.5% and 3.7% of patients used IV antibiotics in the catheter, graft and fistula groups respectively (p=0.05).

Conclusions: Elderly patients dialyzed with a catheter had lower survival than patients dialyzed with a graft or a fistula. There was no survival difference between patients using grafts or fistulas for dialysis. Patients using a dialysis catheter were significantly more likely to receive IV antibiotics and were hospitalized more often than patients using a fistula or a graft. There was no difference in hospitalization rate between G and F. These results underscore the importance of avoiding dialysis catheters as long term dialysis AV access and suggest that AV graft could be a reasonable dialysis access option in elderly patients.
SA-PO111

Evaluating Factors Predicting Outcomes of Secondary Patent of Arteriovenous Grafts for Hemodialysis

Ioannis E. Giammikouris,1 Stavros Spiliopoulos,2 Periklis P. Kyriazis,3 Luisa Scarpati,2 Giuseppe Bacchini.4 MedFil SA Private Hemodialysis Center, Athens, Greece; 2ATTIKO University Hospital, Athens, Greece; 4Beth Israel Deaconess Medical Center, Chicopee, MA; 4Università degli studi della Campania Luigi Vanvitelli, Naples, Italy; 5Nephrology, Hemodialysis and Peritoneal Dialysis Unit, Vascular Access Unit and Renal Transplantation, A. Manzoni Hospital, Lecco, Italy.

Background: Our objective was to analyze outcomes in terms of secondary survival (CSS) and secondary patency rate (SPR) of AVG and to determine prognostic factors for these outcomes.

Methods: It was a retrospective, single-center analysis. Incident HD patients that received implantation of an AVG for angiogenesis from January 2015 to December 2018 were included. Demographic factors, timing, type, and site of implanted AVG, as well as types of treatment of VA malfunction or failure, were recorded. Outcomes included CSS and SPR (%) at 12, 24, 36 and 48 months. Kaplan-Meier survival analysis was conducted; univariate and multivariate analyses were used to evaluate prognostic factors.

Results: Data from 223 patients were analyzed. Those involved 119 proximal (arm) AVG, 101 loop (forearm) AVG, and 1 leg AVG, of which 147 were ePTFE grafts, 39 acute cannulation AVGs, and 37 biological vascular conduits. CSS was 49±4 months and SPR was 63%, 52%, 43% in 12, 24, 36 and 48 months, respectively. Multivariate analysis demonstrated that secondary patency was not associated with age, gender, duration in HD, graft position, stent deployment or use of cutting balloon angioplasty. Patency was negatively affected by graft type (acute cannulation HR, 3.09, 95% CI 1.66–5.75, p=0.005, biological HR, 0.70, 0.39–1.24, p=0.218), presence and number of successfully treated thrombotic events, with differences, noted depending on the type of treatment selected (Fogarty thrombectomy HR, 3.63, 1.89–6.98, p=0.005, Treterota thrombolysis HR, 3.14, 1.53–6.43, p=0.002). A positive correlation was demonstrated between the incidence of new pre-emptive angioplasties and VA secondary patency (HR,0.90, 0.83–0.98, p=0.019). After 4.2±4.5 angioplasties per access, the association of CSS and stenosis proved to be weak (HR, 0.74, 0.32–1.70, p=0.474), a finding that requires further analysis.

Conclusions: Factors such as age, site or time on dialysis, traditionally thought to adversely affect access prognosis may not influence secondary outcomes of AVG. The use of new technology conduits, stenting or sophisticated endovascular catheters and declogging techniques may not contribute to prolonging access survival. Prompt stenosis recognition and pre-emptive correction could be a milestone in our continuous challenge for improving patency.

SA-PO1112

Comparing Outcomes of Forearm Loop and Arm Curved Configurations of Arteriovenous Grafts for Hemodialysis

Ioannis E. Giammikouris,1 Stavros Spiliopoulos,2 Periklis P. Kyriazis,3 Luisa Scarpati,2 Giuseppe Bacchini.4 MedFil SA Private Hemodialysis Center, Athens, Greece; 2ATTIKO University Hospital, Athens, Greece; 4Beth Israel Deaconess Medical Center, Chicopee, MA; 4Università degli studi della Campania Luigi Vanvitelli, Naples, Italy; 5Nephrology, Hemodialysis and Peritoneal Dialysis Unit, Vascular Access Unit and Renal Transplantation, A. Manzoni Hospital, Lecco, Italy.

Background: We conducted a comparative analysis of outcomes of newly placed proximal upper arm straight grafts (pAVG) and disal forearm loop grafts (dAVG).

Methods: Retrospective, single-center analysis. Incident dialysis patients with newly placed AVGs involving the brachial or radial artery, pAVG or dAVG, were studied from 2015 to 2018. Primary survival (PS), primary assisted survival (APS) and secondary survival (CSS) (months) and patency rates for both conduit configurations were studied from 2015 to 2018. Primary survival (PS), primary assisted survival (APS) and newly placed A VGs involving the brachial or radial artery, pA VG or dA VG, were proximal upper arm straight grafts (pA VG) and distal forearm loop grafts (dA VG).

Results: Data from 215 patients were analyzed. Those involved 115 proximal (arm) AVG, 101 loop (forearm) AVG, and 1 leg AVG, of which 147 were ePTFE grafts, 39 acute cannulation AVGs, and 37 biological vascular conduits. CSS was 49±4 months and SPR was 63%, 52%, 43% in 12, 24, 36 and 48 months, respectively. Multivariate analysis demonstrated that secondary patency was not associated with age, gender, duration in HD, graft position, stent deployment or use of cutting balloon angioplasty. Patency was negatively affected by graft type (acute cannulation HR, 3.09, 95% CI 1.66–5.75, p=0.005, biological HR, 0.70, 0.39–1.24, p=0.218), presence and number of successfully treated thrombotic events, with differences, noted depending on the type of treatment selected (Fogarty thrombectomy HR, 3.63, 1.89–6.98, p=0.005, Treterota thrombolysis HR, 3.14, 1.53–6.43, p=0.002). A positive correlation was demonstrated between the incidence of new pre-emptive angioplasties and VA secondary patency (HR,0.90, 0.83–0.98, p=0.019). After 4.2±4.5 angioplasties per access, the association of CSS and stenosis proved to be weak (HR, 0.74, 0.32–1.70, p=0.474), a finding that requires further analysis.

Conclusions: Factors such as age, site or time on dialysis, traditionally thought to adversely affect access prognosis may not influence secondary outcomes of AVG. The use of new technology conduits, stenting or sophisticated endovascular catheters and declogging techniques may not contribute to prolonging access survival. Prompt stenosis recognition and pre-emptive correction could be a milestone in our continuous challenge for improving patency.
Renal transplant in March 2013, Hepatitis C, history of Banff IA acute cell mediated rejection (OCR 2013), and was transplanted for 2 years. In March 2019. He also had nephrotic-range proteinuria, hypertension without any other symptoms. He underwent transplant kidney biopsy, which showed Congo red-negative fibrillar deposits in glomeruli. Immunofluorescence was consistent with FGN with other findings. He also had high Hepatitis C viral load. Immunofluorescence showed no monoclonal spike. FGN in this patient is presumed secondary to chronic Hepatitis C, thus was referred for Hepatitis C treatment and oncology referral for cancer screening.

SA-PO1117

BK Polyomavirus Nephropathy with Multiorgan Involvement: Whole-Genome Sequencing Data from a Killer Virus

Sanjeeet Roy,1 Carol J. Weida,2 Jeffrey S. Huo,3 Philip Roehrs,3 Piotr A. Miezckowski,4 Volker Nickerleit,1 The University of North Carolina at Chapel Hill, Chapel Hill, NC; 2Levine Children’s Hospital, Charlotte, NC; 3Atrium Health, Levine Children’s Hospital, Charlotte, NC; 4Pathology, Carolinas Pathology Group, Charlotte, NC.

Introduction: Post kidney transplantation “organ limited” BK-polyomavirus (BKPyV) nephropathy (BKN) is a known complication. BKPyV infections with multi-organ involvement and severe morbidity are rare. 6/10 reported cases occurred in patients with lymphoproliferative disorders, with AIDS (3/10) and post renal transplantation (1/10). Whether severe immunosuppression, specific BKPyV strains, and/or viral gene mutations promote systemic viral spread is unknown. Here we report the first case of fatal BKN with multi-organ involvement from which detailed deep virus genome sequencing data has been made available.

Case Description: Patient: 24-year old woman with sickle cell anemia, status post CD34+ selected, T-cell depleted allogeneic peripheral blood stem cell transplantation (March 2013). Clinical data: Multiple toxic episodes of GVHD. Since post day 174 progressive BKPyV viremia to very low CD4 T cell counts, and hepatic lymphoid infiltrates. Since day 159 progressive renal failure. Since day 631 respiratory distress; no hemorrhagic cystitis. Since day 651 pancreatitis. On day 696 patient death due to renal and respiratory failure. Autoimmune findings: Productive PyV infection of both kidneys (PVN class 3), pancreas, and lungs with diffuse alveolar haemorrhage. Severe depletion of bone marrow and lymphoid organs. Whole Genome Sequencing data (from kidney, lung and pancreas): No diagnostic genomic mutations; systemic infection by epidemic BKPyV strain B2. Viral mutations restricted to NCCR control domain with severe deletions, duplications and insertions in the “FQN” NCCR sequences (largely sparing the “O” and “S” sequences). BKPyV- NCCR mutations more abundant and profound than those reported in BKN. No genetic evidence of mutant BKPyV ‘metastatic’ spread from one organ site to another.

Discussion: This is the first report identifying the common B2 strain of BKPyV in a kidney transplant patient. BKPyV infection is a previously unsuspected cause of fatal multi-organ BKN with multi-organ involvement from which detailed deep virus genome sequencing data has been made available.
and iron stains with numerous intracytoplasmic targetoid inclusions, consistent with pathognomonic Michaelis-Gutmann bodies. Cultures were positive for E. coli. The patient was treated with 4 weeks of ceftriaxone with subsequent resolution of his groin swelling.

**Discussion:** While malakoplakia is a rare diagnosis, this should be considered in the differential of any immunosuppressed patient with a mass. Tissue diagnosis, to confirm with specific request for PAS and von Kossa staining allows for identification of the pathognomonic Michaelis-Gutmann bodies. Cultures identify a causative organism and allow for targeted treatment. Most commonly, E. coli is the underlying pathogen, but Klebsiella, Pseudomonas, Enterococcus, and Streptococcus have been identified. Finally, careful evaluation of the immunosuppressive regimen should be undertaken if malakoplakia is identified.

**SA-PO1119**

An Interesting Case of Anti-HLA-C Antibody-Mediated Acute Humoral Rejection and Fabry-Like Zebra Bodies in a Renal Transplant Recipient

Mohammad W. Abuzeineh, Ahmad J. Ziadeh, Preethi Yerram. Division of Nephrology, University of Missouri, Columbia, MO.

**Introduction:** Detection of Donor Specific antibodies (DSA) is essential in diagnosing Antibody-mediated renal allograft rejection (AMR). HLA-C antibodies testing is not part of routine DSA pre-transplant evaluation, but they have been reported to cause AMR. We present a case of AMR secondary to DSA against HLA-C, and incidental finding of ultrastructural zebra-bodies under electron microscopy (EM), raising suspicion for undiagnosed Fabry’s disease, eventually determined to be of uncertain significance.

**Case Description:** A 39-year old African American male with ESRD due to hypertensive nephropathy underwent 2A/2B/2DR mismatched cadaveric transplant in 2014. Post-transplant Creatinine (Cr) was 1.4-1.6 mg/dl. Four years later, Cr was found to be elevated at 2.16 mg/dl. Allograft biopsy showed early chronic transplant arteritis with focal fibrinoid necrosis (Fig 1), with weak and focal C4d deposits on IF.

The patient developed nephrotic range proteinuria and hematuria. Repeat biopsy showed capillaritis with specific request for PAS and von Kossa staining allows for identification of the ultrastructural zebra-patterned lipid inclusions in podocytes (Fig 1), suspicious for donor-glomerulopathy without evidence of acute cellular or humoral rejection. EM showed finding of ultrastructural zebra-bodies under electron microscopy (EM), raising suspicion of Fabry’s disease. Cultures identify a causative organism with specific request for PAS and von Kossa staining allows for identification of the ultrastructural zebra-patterned lipid inclusions in podocytes (Fig 1), suspicious for donor-glomerulopathy without evidence of acute cellular or humoral rejection. EM showed finding of ultrastructural zebra-bodies under electron microscopy (EM), raising suspicion of Fabry’s disease. In this case, the presence of Fabry’s disease was revealed by the incidental finding of ultrastructural zebra-bodies under electron microscopy (EM), raising suspicion of Fabry’s disease. The patient was treated with 4 weeks of ceftriaxone with subsequent resolution of his groin swelling.

**Discussion:** This case report emphasizes the role of HLA-C antibodies in causing AMR, and demonstrates the need for their recognition in the pre- and post-transplant period. In addition, the incidental presence of zebra-patterned lipid inclusions in podocytes in transplant renal biopsy doesn’t necessarily indicate Fabry’s disease.
SA-PO1122  
**Collagenodibrotic Glomerulopathy in a Renal Transplant Patient**  
Sarah Gilligan, Divya Raghavan, Monica P. Revelo Penafiel, Josephine Abraham. University of Utah, Salt Lake City, UT.

**Introduction:** Collagenodibrotic glomerulopathy is a rare disease that can occur in childhood in an autosomal recessive inheritance pattern or sporadically in adults. It is non-immune mediated and is characterized by deposits of type III collagen in the mesangial and subendothelial areas of the glomeruli. Per prior case series, the average age of onset is 40 years. The rate of progression is variable and it sometimes results in end-stage renal disease.

**Case Description:** The patient is a 66 year old male with ESRD due to biopsy proven ANCA-negative pauci-immune crescentic glomerulonephritis, coronary artery disease, atrial fibrillation, and hypertension who underwent living unrelated renal transplant via paired exchange in December of 2016. His anti-rejection regimen was tacrolimus, everolimus, and prednisone. His post-transplant creatinine nadir was 1.5 - 2.0 mg/dL but had slowly risen to 3.0 – 3.8 mg/dL in the months prior to evaluation. He had a negative DSA, low positive BK blood titers (peak of 244,000 copies/mL down to 838 copies/mL), and proteinuria of 500 – 1000 mg/g. His renal transplant biopsy demonstrated chronic changes with 30% intimal fibrosis and tubular atrophy and arteriolar hyalinization secondary to calcineurin inhibitor toxicity with no evidence of transplant rejection. The glomeruli exhibited focal accumulation of PAS positive material in the capillary lumina and in the mesangium. Immunofluorescence was negative. On electron microscopy, there were subendothelial and mesangial deposits of curvilinear collagen fibrils compatible with collagenodibrotic glomerulopathy. Unfortunately, additional tissue was not available for immunohistochemical staining. The patient’s native renal biopsy was reviewed with no evidence of similar deposits. The donor’s records were also reviewed showing systemic sclerosis and nephropathy. In consultation with infectious disease we started oral letermovir 480mg twice for 7 days then changed to daily dialysis until viral load became undetectable. Her viral load has downtrended to <2.1 log 10 IU/mL on letermovir after 2 weeks of treatment. Neutropenia has recovered, and her AKI has improved.

**Discussion:** Letermovir is currently being studied for treatment of CMV resistant to ganciclovir (ID NCT03728426, phase 2 investigation). Here we present a case of an individual with proven UL97 mutation-driven ganciclovir-resistant CMV who developed severe side effects precluding further use of ganciclovir and was started on Letermovir for treatment of CMV. CMV viral load improved to barely detectable levels on treatment with letermovir alone, without marrow suppressive or nephrotoxic side effects.

SA-PO1123  
**Allograft Murcymycosis Presenting as AKI**  
Aimen Liaqat, Praveen Kandula, Acedaloma M. Adeboye, Hameedza Khan. 1Saint Barnabas Medical Center, Livingston, NJ; 2Newark Beth Israel Medical Center, Newark, NJ.

**Introduction:** Murcymycosis is a life-threatening complication of kidney transplantation associated with a 50% mortality rate. About 25 cases of renal involvement have been reported in the literature.

**Case Description:** A 62-year-old asymptomatic diabetic male was seen in the clinic 6 weeks after an uncomplicated 0 antigen mismatch living donor kidney transplant from his sister. He received basiliximab induction and standard immunosuppression. Labs showed an acute rise in creatinine (0.8 mg/dL to 1.5 mg/dL). Transplant ultrasound revealed hydronephrosis and creatinine worsened despite stent placement. Allograft biopsy was negative for rejection. His graft function worsened and dialysis was started on day 5. A nuclear scan showed decreased uptake in upper and middle poles. Intra-operative allograft exploration, biopsy and angiogram on day 7 revealed good perfusion but fungal hyphae were seen. A pulmonary nodule was noted on Chest X-ray ordered for worsening respiratory status on day 7. Whole body imaging revealed 3 scattered, cavitary pulmonary nodules suggesting disseminated fungal disease. Emergent transplant nephrectomy was performed and a repeat wedge biopsy revealed hyphae in the glomerular, tubular and vascular segments suggestive of allograft mucormycosis. Immunosuppression was stopped and Amphotericin was initiated.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only  
Underline represents presenting author.  
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with APRT deficiency. Patient was started on allopurinol, fluid infusion and low purine diet. However, her symptoms were continued with gradual decrease and a suspicious pathogenic variant for the APRT sequence. Renal allograft function remained poor and progressed to primary nonfunction of the renal allograft.

Discussion: Although 2,8-DHA crystals, often misdiagnosed, resemble calcium oxalate crystals in being birefringent under cross-polarized light, crystals have a slightly yellow-brown coloration, and unlike oxalates, are argyrophilic with Jones silver stain. Timely diagnosis of 2,8-DHA nephropathy and aggressive management with xanthine dehydrogenase inhibitor and low purine diet may salvage the renal allograft.

SA-PO1126
West Nile Virus: A Peculiar Case of Fever and Encephalopathy in a Transplant Patient
Kurtis J. Swanson, Fahad Aziz, Sandesh Parajuli. UW Health, Madison, WI.

Introduction: West Nile Virus (WNV) is an uncommon viral encephalitis. Here we describe an unusual presentation of WNV encephalitis in a kidney transplant recipient.

Case Description: 65 year old woman with ESKD due to fibriillary glomerulonephritis, recurrent UTIs, T2DM and living related donor kidney transplant with basiliximab induction. CMV -/+, EBV -/+ , no PRA/DSA maintained on standard triple immunosuppression who presented with fever, dysuria. On presentation she was febrile, tachycardic, normotensive, and with normal mentation. She recently used to take multi-drug resistant E. Coli UTI, but had persistant symptoms, positive UA and started on empiric piperclerin-tazobactam. Urine culture grew the same E. Coli. Blood cultures remained negative. She was narrowed to ceftriaxone. Despite appropriate coverage, she remained febrile, weak, and developed a dense hypoactive delirium. She developed dysphagia prompting Neurology consultation and head imaging, which were unremarkable. Over days, her mental status did not improve and exam changed with new spasticity/hyperreflexia. A lumbar puncture was performed showing lymphocytosis and CSF WNV IgM positivity via ELISA testing with an index value of 9.75 (1.1 greater suggestive of WNV). With this diagnosis, her immunosuppression was reduced to azathioprine/prednisone along with 1 dose of IVIG. Over days, her delirium resolved. She had a prolonged course of rehabilitation. Her graft function remained stable throughout her illness.

Discussion: West Nile Virus is a rare disease associated with marked neurological sequelae including weakness often lasting months. Diagnosis is often challenging, as manifestations can be non-specific and involve multiple organ systems. A high index of suspicion and thorough neurologic evaluation are key to diagnosis. CSF IgM is a useful test, specific for neurovascuos WNV as IgM does not cross the blood brain barrier. Interpretation can be difficult as it usually takes 4-10 days to manifest. Interestingly, it can persist for 12 months i.e. may represent prior infection in some cases. Aside from insect repellent, no other preventative measures or directed therapies exist to quell this infection, which ultimately requires supportive care. West Nile Virus is a key differential in the transplant patient with encephalopathy and its recognition is vital to guiding prognosis and management.

SA-PO1127
Contrary to Expectation: Preserved Renal Function After Using PD-1 Inhibitor Cemiplimab-rwlc in a Kidney Transplant Recipient
Muhammad Leehroz, Svetonir N. Markovic, Aleksandra Kukla. Mayo Clinic, Rochester, MN.

Introduction: The use of the immune checkpoint inhibitors in transplant recipients with malignancy is associated with the risk of graft failure due to acute rejection. Here we present the first reported case of using Cemiplimab-rwlc (Libtayo), a recently approved programmed death receptor-1 (PD-1) blocking antibody for locally advanced and metastatic cutaneous squamous cell carcinoma (CSCC), in a kidney transplant recipient.

Case Description: 48 yo male with a history of ESRD secondary to ADPKD, J. Am Soc Nephrol 30: 2019, 1059 underwent pre-transplant for multi-drug resistant E. Coli UTI, with Cemiplimab (Libtayo). Prednisone was discontinued. He underwent excision of scalp lesion and right cortical mastoid metastatectomy while on the full dose of Sirolimus, with Cemiplimab (Libtayo). Prednisone was discontinued. He received 5/6 ABDR HLA mismatch living donor kidney transplant in May of 2016. He received Thymoglobulin induction and had class II DSAs (DR4 with MFI 1975). He received Tacrolimus, MMF and Prednisone. Protocol allograft biopsy was performed at 2 years post transplant and was negative for rejection. He received 16 units/ml (borderline) at 2 weeks and progressed to >40 units/ml at 4 weeks, following which he was started on Losartan and PLEX extended to 15 sessions. 3 months after the transplant, nephrotic range proteinuria persisted (10-12 g), however further escalation of immunosuppression was prevented by disseminated trichophyton infection and recurrent surgical site abscesses. Creatinine had increased to 2.4 mg/dl and a repeat biopsy showed diffuse collapsing glomerulopathy. C4d remained diffusely positive. Allograft function continued to decline and he returned to dialysis 8 months post-transplant.

Discussion: Literature reports a substantial risk of rejection in kidney transplant recipients who are treated with immunotherapy. However, as our case shows, PD-1 inhibitor Cemiplimab (Libtayo) can be used with preserving allograft function on a Sirolimus-based immunosuppression regimen. More data is needed in to guide clinicians and to appropriately counsel patients regarding the risks and benefits of immunotherapy medications.

SA-PO1128
Sampling Site Matters: A Falsely Elevated Tacrolimus Level After Stopping IV Infusion in a Patient with Central Venous Catheters
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Introduction: Tacrolimus levels abnormalities constitute a major concern to transplant nephrologists. Based on these values; decisions are made to adjust Tacrolimus doses to achieve adequate immunosuppression. The recognition of pitfalls with these laboratory tests becomes crucial to better interpret the accuracy of these results, specifically when dealing with critically ill patients using intravenous Tacrolimus where a large subset of these patients have central venous catheters that are used for infusions and blood sampling. We are reporting a case of falsely elevated Tacrolimus levels after discontinuation of the medication.

Case Description: A 52-year-old male with history of gastraparesis and kidney transplantation in 2011, presented with sever nausea, vomiting and inability to tolerate oral intake including his oral tacrolimus for one day prior to admission. On presentation, his Tacrolimus level was 3.1 ng/mL. Intravenous continuous infusion of Tacrolimus was initiated via a PICC line. Two days later, his symptoms have resolved and subsequently transitioned back to oral Tacrolimus. Next day Tacrolimus trough (drawn from the PICC line after multiple flushes) came back at 38.9 ng/mL, repeated level confirmed to be more than 30 ng/mL. Immediately, his oral tacrolimus was held. Interestingly, he did not exhibit any signs or symptoms of tacrolimus toxicity and his renal function remained stable at baseline. Rechecked daily troughs for the next 3 days were 23, 17 and 19 ng/mL, despite holding tacrolimus. Simultaneous samples were drawn from both PICC line and peripheral vein showed great discrepancy with troughs of 39.0 ng/mL and less than 3.0 ng/mL respectively. Historically, a similar misinterpretation occurred which led to prolonged hospital stay with potential compromise to his immunosuppression.

Discussion: Falsely elevated Tacrolimus levels in samples drawn from central venous catheters have been reported to last several days despite rinsing the catheter. Studies have shown evidence of reversible adsorption of the drug from the inner walls of different catheters. Raising awareness to this misleading phenomenon helps avoiding dangerous dose reductions of the immunosuppressive drug and unnecessarily prolonged hospital stay. Sampling for Tacrolimus level should always be drawn from peripheral veins.

SA-PO1129
Angiotensin II Type I Receptor (AT1R) Antibody-Associated Collapsing FSGS in a Renal Allograft
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Introduction: Post renal transplant de novo collapsing FSGS could be associated with AT1R antibody.

Case Description: A 66-year-old man with type 2 diabetes mellitus underwent pre-emptive renal transplant for CKD of unproven etiology. He was HLA high risk with low level donor-specific DPl antibodies and was induced with ATG and maintained on mycophenolate, tacrolimus and prednisone. Cytotoxic and flow cytometry cross matches were negative. Four weeks later he was noted to have proteinuria, which soon progressed to nephrotic range, while creatinine remained at baseline (1 mg/dl). Kidney biopsy was suggestive of acute humoral rejection with G1 glomerulitis, mild PTCitis and 60% C4d. HLA screen showed persistent low-level antibodies against DR52. Endothelial cell cross match was negative, indicating a non-HLA antibody mediated process. Treatment was initiated with pulse steroids, IVIG, plasmapheresis. AT1R antibody level was 14 units/ml (borderline) at 2 weeks and progressed to >40 units/ml at 4 weeks, following which he was started on Losartan and PLEX extended to 15 sessions. 3 months after the transplant, nephrotic range proteinuria persisted (10-12 g), however further escalation of immunosuppression was prevented by disseminated trichophyton infection and recurrent surgical site abscesses. Creatinine had increased to 2.4 mg/dl and a repeat biopsy showed diffuse collapsing glomerulopathy. C4d remained diffusely positive. Allograft function continued to decline and he returned to dialysis 8 months post-transplant.

Discussion: AT1R receptor is highly expressed on endothelial cells and podocytes and antibodies against it are known to cause acute humoral rejection. AT1R antibodies could potentially cause FSGS by enhancing the effects of AT II, which regulates matrix synthesis and cell proliferation. It also enhances the expression of transient receptor potential cation channel 6, which leads to FSGS in animal models. This report illustrates a case of AT1R antibody mediated humoral rejection with progression to an unusual clinical presentation (de novo collapsing FSGS), which was resistant to aggressive therapy.
SA-PO1130
A Unique Immunosuppression Strategy in a Patient with Atypical HUS Undergoing Kidney Transplant
Sohaib Zahid, Kristin Krupa, Kiumars Ranbar tabar, Kalathil K. Suresh Kumar, Sabilla M. Hussain, Allegheny Health Network (Nephrology, Allegheny Health Network, Pittsburgh, PA; AHN, Pittsburgh, PA; Allegheny General Hospital, Pittsburgh, PA).

Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is a rare disease with estimated incidence of 1-2 per 1,000,000 caused by uncontrolled activation of alternative complement pathway due to genetic mutations mainly in complement inhibitor factors. Herein, we present a patient with aHUS who underwent deceased donor kidney transplantation (DDKT) and successfully treated with a unique immunosuppressive strategy.

Case Description: A 2-year-old female had a complicated pregnancy at age 18 with pre-eclampsia requiring emergent cesarean section. Post-partum, she developed acute kidney injury, anemia, thrombocytopenia and elevated LDH with normal ADAMTS-13 levels. Kidney biopsy showed acute thrombotic microangiopathy (TMA). Genetic testing revealed heterozygous missense mutations in complement factor H and complement factor H-related gene 5. She was diagnosed with atypical HUS and initialed on eculizumab but without renal recovery and was maintained on hemodialysis. Five years later patient was called in for DDKT with KDPI of 14%. Her PRA was high at 76%. She received a dose of eculizumab pre-operatively followed induction with by Thymoglobulin and methyl prednisolone. We chose maintenance immunosuppression with belatacept instead of tacrolimus along with mycophenolate mofetil (MMF). Eculizumab was continued. Her creatinine improved to 0.9mg/dl. Two months post-transplant, she developed acute T-cell mediated rejection type 1b successfully treated with methyl prednisolone followed by maintenance steroid therapy and increased dose of MMF. Serum creatinine remains at 1 mg/dl at 1 year follow up.

Discussion: Immunosuppressant management in aHUS patients with high PRA undergoing kidney transplant is challenging. Calcineurin inhibitors and DDKT itself are potential triggers for opportunistic infection leading to TMA. Belatacept is a selective T-cell co-stimulation blocker which has not been reported to induce TMA. Our case demonstrates the safety and efficacy of Thymoglobulin induction followed by belatacept/MMF maintenance along with eculizumab in highly sensitized patient with aHUS.

SA-PO1131
Success of Intensive Immunosuppression to Prevent Post-Transplant Recurrence of C3 Glomerulonephritis in Children
Eloise Collin, Anne F. Maisin, Marie-Alice Macher, Theresa Kwon, Christine Boissier, Isabelle Vrillon, Veronique Fresneau-Bacchi, Georges Deschênes. CHU Toulouse, Toulouse, France; Pediatric Nephrology, APHP, Robert-Debre Hospital, Paris, France; Pediatrics, University Hospital of Nancy, Nancy, France; Immunology, APHP, HEGP, Paris, France.

Introduction: C3 glomerulonephritis (C3GN) is characterized by the dysregulation of complement alternative pathway and is frequently associated with autoantibodies stabilizing the C3 or C5 convertase. There is currently no specific treatment and the renal outcome is variable. Immunosuppression is not typically used for the prevention of C3GN recurrence post-transplantation.

Case Description: Two patients received a living donor transplant and one a deceased donor transplant. Bi-nephrectomy was performed 5 +/-2 months before transplantation. Steroids (60mg/m²/d) and MMF (1500mg/m²/d) were started at least 1 month prior to transplant. Eculizumab was started 14 days before transplant in the 2 patients with a living donor and the 3rd patient was on long-term treatment. One session of immunoadsorption was performed 8h prior the renal graft for all. They received an induction by thymoglobulin or Basiliximab followed by Tacrolimus [T0 : 8-10 mg/2], mycophenolate mofetil (MMF) [1.5-2 g/d for 3 months]. Both patients achieved serum creatinine of 1.2mg/dl at 3 months only showed C3 deposits in 1 patient without any inflammation. After a follow-up of 3, 6 and 15 months, none of the patients developed proteinuria or hematuria under Eculizumab. One patient developed a BK virus replication (4.8 log) at M4 that was managed by anti-viral treatment and dialysis. No recurrence was observed. Both patients achieved a stable renal function 1 year after the transplantation.

Discussion: Intensive immunosuppression pre and post-transplant may prevent post-transplant recurrence of C3GN.

SA-PO1132
De Noo N Cytomegalovirus-Triggered FSGS After Kidney Transplantation Associated with APOL1 Risk Allele
Malikia Gupta, AnujaJava, Washington University in St. Louis, St. Louis, MO.

Introduction: Recurrent and de novo glomerulonephritis (GN) account for 18% to 22% of death censored kidney allograft failures. We report a case of de novo cytomegalovirus (CMV)-associated FSGS after kidney transplantation from an African American (AA) donor.

Case Description: A 52-yr-old White female (WF) with ESRD secondary to HTN underwent a 4-antigen mismatched, CMV D+/R-, deceased donor renal transplant from a 47-year-old male African American donor. A year post-transplant, she presented with abdominal pain, diarrhea, and fever. Creatinine was 1.3 mg/dl, which worsened to 7.9 mg/dl over 5 days. Spot urine protein creatinine ratio (UPCr) was elevated. Infectious workup revealed CMV viremia (29,7460 IU/ml). Patient had discontinued valganciclovir (VC GV) 3 months after transplant. Allograft biopsy revealed podocyte effacement. Despite treatment for the CMV viremia (VC GV 900 mg po qd and discontinuation of MMF), Cr worsened and hemodialysis (HD) was initiated. VGC GV was switched to IV ganciclovir 3 x wk with HD leading to clearance of viremia. Creatinine improved and HD was discontinued in April 2019. UPCR improved to 7. Biopsy tissue sent for APOL1 risk variant genotyping revealed compound heterozygosity for G1/G2.

Discussion: Approximately 13% of AA carry two APOL1 risk variants. Increased risk of graft loss following high CMV DNA load and CMV transplantation is associated with these alleles. However a second hit is required. Mechanisms for CMV-induced podocytopathy via injury to permeability barrier have been postulated. Our case exemplifies CMV as a second hit causing podocytopathy in a recipient with heterozygosity for APOL1 in an AA donor. Studies to better understand the mechanisms and predisposing factors for APOL1-associated kidney diseases are critical since recipients from donors with the risk alleles may warrant tailored management. Of note, the mate kidney was transplanted in a 48-yr-old WF who recently completed the 9-month CMV prophylaxis. Questions arise: 1) Should the duration of viral prophylaxis be extended in the second patient, 2) Should increased frequency of viremia screening be considered and, 3) Should aggressive antiviral strategies be considered at first identification of viremia?

SA-PO1133
Donor Derived Cell-Free DNA Positivity: Does It Always Denote Allograft Rejection?
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Introduction: Donor derived cell free DNA (dd-cfDNA) is a novel serum biomarker now available to predict acute rejection in renal allografts. Presence of dd-cfDNA > 1% suggests allograft injury; caused by acute rejection. We describe a rare form of post-transplant lymphoproiferative disorder (PTLD) presenting as positive dd-cfDNA.

Case Description: A 64 yo white male who underwent living related kidney transplant 3 years earlier with baseline serum creatinine(Cr) around 1.5 mg/dl presented with worsening allograft function. Serum Cr was 9mg/dl with 4.5 grams/day proteinuria. Elevated dd-cfDNA level at 2.5% prompted a renal allograft biopsy. Light microscopy showed mild mesangial matrix expansion, Immunofluorescence showed >3 deposition of lambda light chain in a linear pattern along glomerular and tubular basement membrane suggestive of lambda light chain deposition disease(LCDD)-refer to figure 1. A subsequent bone marrow biopsy was consistent with lambda light chain restricted plasma cell dyscrasia. Patient was started on chemotherapy with cyclophosphamide, bortezomib, and dexamethasone along with plasmapheresis. Within a month, his renal allograft function improved with Cr of 1.6 mg/dl. After 6 months, he underwent autologous stem cell transplant(SCT)and currently remains in remission on Ixazomib. Bone marrow biopsy and kidney biopsy have been normal. Cr remains at 1.3-1.5mg/dl one year post SCT. Repeat dd-cfDNA levels remained <1%.

Discussion: This is the first reported case of lambda restricted LCDD, a rare form of PTLD in renal allograft presenting as positive dd-cfDNA. Elevated dd-cfDNA in our patient likely reflects allograft injury resulting from parenchymal infiltration with neoplastic cells along with light chain deposition. Our case highlights the need to include unusual causes of allograft injury in the differential diagnosis in patients presenting with renal allograft dysfunction and elevated dd-cfDNA. Allograft biopsy remains the gold standard in reaching a definite diagnosis.

SA-PO1134
Non-T Cell Depleting Induction Therapy Predisposes to Early Human Adenovirus Infection as Compared with T-Cell Depleting Therapy: Case Report and Review of Literature
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Introduction: Human Adenovirus (HAdV) infections are increasingly recognized in post kidney transplant patients. We report a unique case of early post op HAdV infection presenting with a space occupying lesion in the allograft, evolving to bladder masses. We reviewed the literature to assess the effect of non-T cell depleting agents on frequency of early and late HAdV infections.

Case Description: A 38-year-old male, with end stage kidney disease (ESKD) due to IgA nephropathy underwent deceased donor renal transplant (DDRT). He received induction with Basiliximab. Post op course was uneventful. On post op day 8 he was admitted with fever (39.2 deg. C) and diarhhea of 2 days duration. Upon review of systems he had mild cough with mucoid sputum. On exam, he was tachycardiac with no allograft tenderness. Rest of the physical exam was unremarkable. Cellexct was held. The BioFire Film Array was positive for adenovirus. There was no viremia. He was lymphopenic and mild lymphocytopenia. Creatinine improved and HD was discontinued in April 2019. UPCR improved to 7. Biopsy tissue sent for APOL1 risk variant genotyping revealed compound heterozygosity for G1/G2.

Discussion: Approximately 13% of AA carry two APOL1 risk variants. Increased risk of graft loss following high CMV DNA load and CMV transplantation is associated with these alleles. However a second hit is required. Mechanisms for CMV-induced podocytopathy via injury to permeability barrier have been postulated. Our case exemplifies CMV as a second hit causing podocytopathy in a recipient with heterozygosity for APOL1 in an AA donor. Studies to better understand the mechanisms and predisposing factors for APOL1-associated kidney diseases are critical since recipients from donors with the risk alleles may warrant tailored management. Of note, the mate kidney was transplanted in a 48-yr-old WF who recently completed the 9-month CMV prophylaxis. Questions arise: 1) Should the duration of viral prophylaxis be extended in the second patient, 2) Should increased frequency of viremia screening be considered and, 3) Should aggressive antiviral strategies be considered at first identification of viremia?
serum creatinine rose from 0.9 to 1.2 mg/dL. Colonicoscopy biopsy showed microscopically colitis and also showed a space occupying lesion in the upper pole of the kidney and a mass in the bladder. Fever resolved on hospital day 8 without additional interventions. Cystoscopy revealed multiple masses in the bladder and in the ureter. Bladder biopsy was consistent with cystitis cystica glandularis.

Discussion: Non T-cell depleting agents prevent further T cell mediated immune responses while allowing other cell surface protein receptors such as CD48, CD80, and CTLA4, to be available for adenosiviral entry. This causes the host to be vulnerable to viral entry in the early post-transplant period. Adenovirus integrates into the DNA, promotes cell division and bacterial proliferation. Literature review supports that early HADV infections occur predominantly in patients who received non T-cell depleting induction therapy (Table 1). Therefore, a high index of suspicion for HADV infection should be maintained in febrile patients who receive non T-cell depleting induction therapy.

Table 1: Induction Therapy and Pattern of HADV infection.

<table>
<thead>
<tr>
<th>Early Induction Therapy</th>
<th>Delayed Induction Therapy</th>
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</thead>
<tbody>
<tr>
<td>Basiliximab/Tacrolimus</td>
<td>TPE/IVIg</td>
</tr>
<tr>
<td>TPE</td>
<td>TPE/IVIg</td>
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</table>

P value = 0.00039.

Result is significant at P <0.05.

SA-PO1135

Simultaneous Acute Rejection and Recurrent Focal Segmental Glomerulosclerosis: A Match Made in Renal Transplantation

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Introduction: Simultaneous recurrent focal segmental glomerulosclerosis (FSGS) and acute rejection is extremely rare in kidney transplant recipients. In resistant FSGS cases failing conventional immunosuppression, addition of repository corticosteroid injection (Acthar Gel®) may lead to proteinuria resolution.

Case Description: A 34-year-old man underwent deceased donor kidney transplantation for ESRD related to possible FSGS. Other medical history included hypertension and obesity. He had immediate allograft function with basiliximab induction. Maintenance regimen included tacrolimus, mycophenolate and prednisone. Eleven weeks after transplantation, he had sudden onset of nephrotic-range proteinuria (urine protein-creatinine ratio of 11.3 g/g from baseline of 0.5 g/g), generalized edema and acute kidney injury (serum creatinine 1.4 mg/dL from baseline 1.6 mg/dL). Kidney transplant biopsy was performed expecting histologic evidence of recurrent FSGS. Surprisingly, biopsy showed Banff II-B acute cellular rejection and segmental podocyte injury. He was treated for rejection and recurrent FSGS with anti-thymocyte globulin, solnemedrol, plasmapheresis (TPE) and IVG. Following TPE and immunosuppression intensification, his proteinuria improved briskly to 0.37 g/g with parallel decline in creatinine to baseline. Despite ongoing TPE and IVG, his proteinuria recurred (8-10 g/g) with worsening creatinine. Repeat kidney biopsy showed complete resolution of rejection, but with 25% residual foot process effacement. With failure of two doses of rituximab and 40 TPE sessions to improve his proteinuria, he started corticosteroid injections twice weekly. After 3 months of corticosterin, TPE was stopped, and corticosterin tapered off over another 3 months. He is now in complete remission of proteinuria with stable kidney function.

Discussion: Pre-transplant FSGS patients should be closely monitored in the post-transplant period for FSGS recurrence. Simultaneous presence of two of these diagnoses underscores the importance of performing kidney biopsy in those with proteinuria and acute kidney injury post-transplantation. Recurrent FSGS treatment in allografts resistant to conventional treatments may remit with corticosterin. Concurrent acute vasculitis rejection and recurrent FSGS is rare. In the era of significant organ shortage, all options should be tried to save the allograft.

SA-PO1136

Letermovir Therapy for Resistant Cytomegalovirus in a Kidney Transplant Recipient: Case Report

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Introduction: Cytomegalovirus (CMV) infection is a leading cause of morbidity in kidney transplant recipients. Resistant CMV strains and medication toxicities complicate treatment. We describe a case of multi-resistant CMV suppressed with letemlovir after treatment with second line agents.

Case Description: A 63 year old female with history of living donor kidney transplant (CMV donor + / recipient -) presented with severe diarrhea and leukopenia a month after receiving valganciclovir prophylaxis. CMV viral load was 544,002 copies/mL and she was given 3 weeks of treatment with 2 months of prophylaxis using valganciclovir. Low level of viremia followed discontinuation of prophylaxis. After the viral load exceeded 30,000 copies/mL treatment was resumed without successful viral suppression. Genotyping revealed resistance to valganciclovir, foscarnet, and cidofovir. She was initiated on foscarnet and high dose ganciclovir. Upon therapy discontinuation, viral load increased again and oral letemrovir 480 mg daily was started. Since introducing letemovir she maintained CMV suppression for 3 months. For treatment course please see figure 1.

Discussion: Resistance to agents for the treatment of CMV is increasing. Valganciclovir alternatives have significant toxicities and necessitate parenteral administration. Letermovir is a novel agent that inhibits the cleavage of CMV DNA concatemers by targeting the pUL56 subunit of the terminase enzyme complex. Letermovir is not myelosuppressive, it is available in an oral formulation, and does not require dose adjustments for renal function. Recently letemovir was approved for CMV prophylaxis in allogeneic hematopoietic stem cell transplant recipients, but use in solid organ transplant is being investigated. Letermovir for salvage therapy has been reported but widespread use has not been adopted due to the low barrier to resistance. Our unconventional approach using combination foscarnet and ganciclovir treatment then switching to letemovir presents a possible niche for agent’s use to sustain suppression of a multidrug resistant CMV.

SA-PO1137

Fanconi Syndrome from Adenovirus Treatment in a Renal Transplant Patient: A Rare Complication from Novel Therapy with Brincidofovir

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Introduction: Brincidofovir is an oral pro-drug of cidofovir currently in Phase III clinical trials. In comparison to cidofovir, it displays lower nephrotoxic potential. We present a case of Fanconi syndrome within a week of therapy of brincidofovir for a patient with Adenovirus infection. This rare side effect has not been reported in the literature.

Case Description: We present a 62 year old woman with chronic kidney disease due to diabetes mellitus-2 and hypertension, who received a deceased donor kidney transplant. Induction therapy included alemtuzumab, solumedrol, and mycophenolate mofetil. Her baseline serum creatinine post-transplantation was 0.7 mg/dL. Two months later her renal function deteriorated to 2.4 mg/dL. A renal biopsy was performed which showed no evidence of acute cellular or antibody mediated rejection. However, BK virus as well as Adenovirus was found in both blood and urine. Immunosuppression medications were minimized; IVIG therapy for severe BK viremia and brincidofovir for Adenovirus viremia was initiated due to worsening viremia (656,000 copies/mL). She was readmitted to the hospital five days later due to acute graft dysfunction and a repeat biopsy revealed cellular IIA rejection. She completed the first course of brincidofovir but was readmitted for worsening renal function and brincidofovir was restarted due to reemergence of Adenovirus. Due to sepsis requiring ICU management, immunosuppression medications were stopped. On follow-up in the hospital, the patient was found to have glycogenuria, phosphaturia, hypouricemia and hypouricemia consistent with Fanconi syndrome. Aggressive electrolyte repletion was started and Brincidofovir stopped as this was determined to be most likely cause. Electrolyte imbalances gradually improved after stopping brincidofovir.

Discussion: Brincidofovir was utilized as therapy for Adenovirus infection due to its availability in an oral formulation, and does not require dose adjustments for renal function. Despite ongoing TPE and IVIg, his proteinuria recurred (8-10 g/g) with worsening creatinine. Repeat kidney biopsy showed complete resolution of rejection, but with 25% residual foot process effacement. With failure of two doses of rituximab and 40 TPE sessions to improve his proteinuria, he started corticosteroid injections twice weekly. After 3 months of corticosterin, TPE was stopped, and corticosterin tapered off over another 3 months. He is now in complete remission of proteinuria with stable kidney function.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
were suggestive of MIDD. He was treated with steroids, and creatinine improved to 0.80mg/dL, though no improvement in pancreatic-function, leading to the resumption of insulin.

Discussion: The pancreas-kidney Donor was a 25-year-old white-healthy male with KDPI-20. Given the donor’s age, donor-derived MIDD would be unlikely. The recipient SPP, UIPEP, and free-light-chain ratio were unremarkable. There was no pathological evidence of MIDD in his gastrointestinal and spleen biopsies. Whether the deposits are donor or recipient derived is unclear. We plan to closely monitor with yearly free light chains, and bone-marrow biopsy. Recurrence of MIDD is almost universal in kidney-allografts even without detectable paraprotein. The etiology for graft-failure remains elusive, though MIDD as a contributor is a theoretical possibility. Our case shows the importance of early transplant biopsy with the performance of IF and EM for all patients with suspected glomerular pathology.

SA-PO1139
De Novo Transthyretin Amyloidosis After Domino Liver Transplant Causing Kidney Graft Failure: A Case Report
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Introduction: Domino Liver Transplant (DLT) refers to a sequential transplant (Tx) where a recipient receives a liver from a donor who has usually Familial Amyloid Polyneuropathy (FAP), DLT increases the chance of getting a liver but poses the risk of the recipient manifesting amyloidosis years later. The current case describes a patient who received a kidney Tx 13 years after a DLT and developed de novo systemic amyloidosis with neuropathy.

Case Description: Male 69 y.o., diagnosed with Hepatitis C and Hepatocellular Carcinoma, underwent a DLT transplant with a liver from a FAP donor. After 13 years of Tx he developed ESRD due to Cyclosporine toxicity and recurrent pyelonephritis. One year later he underwent a deceased donor kidney Tx under Basiliximab, Mycophenolate and Tacrolimus immunosuppression. Three years later, he presented progressive lower limbs paresis and weakness (electronuromyography confirmed polynuropathy); anasarca, dyspepsia and bilateral pleural effusion (echocardiography showed new diastolic dysfunction and myocardial hypertrophy) and progressive symptomatic hypotension episodes. Because of non-proteinuric subacute kidney graft failure dysfunctions and dyspepsia he was hospitalized and initiated hemodialysis. Kidney graft biopsy demonstrated acute tubular necrosis (ATN), light glomerulitis, C4d and Congo Red negative, and no signs of Tacrolimus toxicity. On the other hand, sural nerve biopsy stained Congo Red positive and confirmed Amyloid Neuropathy. Graft failure was attributed to ischemic injury, due to arterial hypotension secondary to autonomic neuropathy. Other features as neurogenic anasarca, dyspnea and bilateral pleural effusion (echocardiography showed new diastolic dysfunction and myocardial hypertrophy) and progressive symptomatic hypotension episodes. Because of non-proteinuric subacute kidney graft failure dysfunctions and dyspepsia he was hospitalized and initiated hemodialysis. Kidney graft biopsy demonstrated acute tubular necrosis (ATN), light glomerulitis, C4d and Congo Red negative, and no signs of Tacrolimus toxicity. On the other hand, sural nerve biopsy stained Congo Red positive and confirmed Amyloid Neuropathy. Graft failure was attributed to ischemic injury, due to arterial hypotension secondary to autonomic neuropathy. Other features as neurogenic anasarca, dyspnea and bilateral pleural effusion (echocardiography showed new diastolic dysfunction and myocardial hypertrophy) and progressive symptomatic hypotension episodes. Because of non-proteinuric subacute kidney graft failure dysfunctions and dyspepsia he was hospitalized and initiated hemodialysis. Kidney graft biopsy demonstrated acute tubular necrosis (ATN), light glomerulitis, C4d and Congo Red negative, and no signs of Tacrolimus toxicity. On the other hand, sural nerve biopsy stained Congo Red positive and confirmed Amyloid Neuropathy. Graft failure was attributed to ischemic injury, due to arterial hypotension secondary to autonomic neuropathy. Other features as neurogenic anasarca, dyspnea and bilateral pleural effusion (echocardiography showed new diastolic dysfunction and myocardial hypertrophy) and progressive symptomatic hypotension episodes. Because of non-proteinuric subacute kidney graft failure dysfunctions and dyspepsia he was hospitalized and initiated hemodialysis. Kidney graft biopsy demonstrated acute tubular necrosis (ATN), light glomerulitis, C4d and Congo Red negative, and no signs of Tacrolimus toxicity. On the other hand, sural nerve biopsy stained Congo Red positive and confirmed Amyloid Neuropathy. Graft failure was attributed to ischemic injury, due to arterial hypotension secondary to autonomic neuropathy. Other features as neurogenic anasarca, dyspnea and bilateral pleural effusion (echocardiography showed new diastolic dysfunction and myocardial hypertrophy) and progressive symptomatic hypotension episodes. Because of non-proteinuric subacute kidney graft failure dysfunctions and dyspepsia he was hospitalized and initiated hemodialysis. Kidney graft biopsy demonstrated acute tubular necrosis (ATN), light glomerulitis, C4d and Congo Red negative, and no signs of Tacrolimus toxicity. On the other hand, sural nerve biopsy stained Congo Red positive and confirmed Amyloid Neuropathy. Graft failure was attributed to ischemic injury, due to arterial hypotension secondary to autonomic neuropathy. Other features as neurogenic anasarca, dyspnea and bilateral pleural effusion (echocardiography showed new diastolic dysfunction and myocardial hypertrophy) and progressive symptomatic hypotension episodes. Because of non-proteinuric subacute kidney graft failure dysfunctions and dyspepsia he was hospitalized and initiated hemodialysis. Kidney graft biopsy demonstrated acute tubular necrosis (ATN), light glomerulitis, C4d and Congo Red negative, and no signs of Tacrolimus toxicity. On the other hand, sural nerve biopsy stained Congo Red positive and confirmed Amyloid Neuropathy.

Discussion: This case illustrates the occurrence of Transthyretin Amyloidosis with severe manifestations in a recipient of DLT. We point out the differential diagnosis of MIDD in his gastrointestinal and spleen biopsies. Whether the deposits are donor or recipient derived is unclear. We plan to closely monitor with yearly free light chains, and bone-marrow biopsy. Recurrence of MIDD is almost universal in kidney-allografts even without detectable paraprotein. The etiology for graft-failure remains elusive, though MIDD as a contributor is a theoretical possibility. Our case shows the importance of early transplant biopsy with the performance of IF and EM for all patients with suspected glomerular pathology.

SA-PO1140
De Novo Minimal Change Disease Immediately After Renal Transplantation
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Introduction: De novo minimal change disease (MCD) is quite a rare cause of post-transplant nephrotic syndrome (NS). Only a few cases have been reported, partially due to the stringent criteria for this diagnosis. We report a challenging case of de novo MCD while the patient was on induction therapy immediately after transplantation.

Case Description: A 49-year-old male with end-stage kidney disease due to nephroclerosis received ABO-compatible living kidney transplantation from his 47-year-old wife with four mismatches in HLA typing. Induction therapy included steroids, mycophenolate mofetil tacrolimus and basiliximab. At post-transplantation day 4, serum creatinine increased to 8.05 mg/dL with massive proteinuria (11.6 g/d). Although the flow cytometric crossmatch test for HLA came back negative, the patient received steroid pulses, plasma exchange and rituximab for possible recurrent focal segmental glomerulosclerosis (FSGS). Kidney function and proteinuria were improved soon after those treatments. Post-transplantation day 8 showed no specific glomerular light microscopy; however, foot process effacement of podocytes was noted under the electron microscopy. De novo MCD was diagnosed. The patient has been achieved complete remission for one year since the transplant.

Discussion: De novo MCD after kidney transplantation is quite rare, but seems to have favorable prognosis. Nephrotic-range proteinuria usually develops immediately or shortly after transplantation, even when the patient is on induction therapy. Due to indistinguishable clinical course as well as similar histology of FSGS and MCD, it is possible that patients labeled as FSGS who respond readily to steroids or plasmapheresis may have MCD rather than FSGS. Therefore, the diagnosis of de novo MCD should be always considered even when induction therapy is given, especially if minimal light microscopic findings are detected.

SA-PO1141
Not a Classic Chickenpox Infection: Retinal Necrosis in a Renal Transplant Patient
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Introduction: Viruses are common opportunistic infection among kidney transplant patients. Varicella-zoster virus (VZV) is often reactivated at 6 to 12 months after transplant as Herpes Zoster (HZ). Primary VZV infection is less common and is more severe. We present the case of a kidney transplant recipient with a severe complication of primary VZV infection.

Case Description: A 42-year-old-woman with hypothyroidism, post-transplant diabetes mellitus, end stage kidney disease post kidney transplant (2006) on Tacrolimus 2mg in the morning and 1.5 mg in the evening, mycophenolic acid 360 mg thrice daily, levothyroxine and insulin regimen was admitted to our institution after ophthalmology evaluation. Four weeks prior to admission she was hospitalized at another institution due to primary VZV infection, reported relative with HZ and no prior VZV vaccination, she was treated with intravenous (IV) acyclovir and discharged home with oral (PO) acyclovir after no new skin lesions occurred. Two weeks after initial onset she developed a rash at the dorsum of the hands and left eye blurry vision. She was evaluated by ophthalmology and was admitted with left acute retinal necrosis due to HZV. Evaluation was significant for no fever, no visible vesicular skin lesions but impaired left pupillary reflex and left facial nerve palsy. Laboratory results showed leukocytosis, creatinine level on baseline, 1.8 mg/dL, and hyperglycemia. She was started on acyclovir 1 gram IV every 8 hours, IV hydration and mycophenolic acid was discontinued. She received intravitreal ganciclovir every 48 hours for two weeks. After the second dose of ganciclovir she noticed improvement of blurry vision and resolution of symptoms after first week of treatment. She was discharged home with PO acyclovir 800 mg every 4 hours and decreased mycophenolic acid dose to 180 mg twice daily.

Discussion: Our patient developed a rare complication of primary VZV infection, acute retinal necrosis, 13 years after kidney transplant. Recent studies show incidence of VZV after kidney transplant is less than 1%. This case emphasizes the importance of VZV vaccination in the pre-transplant period and vaccination of close contacts. Early and prompt intervention is needed in those patients with visual complications since they are at risk of vision loss.

SA-PO1142
Utility of Donor-Derived Cell-Free DNA for Detecting Allograft Rejection with PD-L1 Checkpoint Inhibitor Use
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Introduction: Donor derived cell free DNA (dd-cfDNA) is a useful biomarker that originates from allograft cells undergoing injury. Levels <1% have strongly correlated with absence of active rejection. We describe a case where serial dd-cfDNA monitoring allowed the use of immune checkpoint inhibitor therapy in a renal transplant recipient.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Case Description: A 72 year old man with ESRD from ADPKD underwent living unrelated kidney transplant in Dec 2010. His immunosuppression regimen included tacrolimus 2mg bid, mycophenolate 500mg bid and prednisone 5mg daily. In July 2017, he was diagnosed with metastatic squamous cell cancer. He underwent radiation therapy followed by chemotherapy with Cetuximab. However, in the setting of disease progression, PD-L1 inhibitor was considered. A baseline dd-cfDNA was 0.23%. PD-L1 inhibitor, Pembrolizumab, was initiated in Nov 2017 with serial dd-cfDNA monitoring (weekly x 8 weeks, followed by monthly). Despite serum creatinine fluctuations (Fig 1), the relative change in dd-cfDNA of <65% and overall <1% (Fig 2) reassured of a low likelihood of active rejection, allowing the continuation of therapy. Pembrolizumab was used for about 1 year; however, subsequent imaging was concerning for local disease progression and Pembrolizumab was discontinued in Nov 2018. Thereafter, his dd-cfDNA returned to baseline with excellent allograft function, suggesting that the initial elevation may have been from tumor death.

Discussion: Dd-cfDNA is a helpful noninvasive marker for diagnosing graft rejection with checkpoint inhibitor use. Future investigations into sequencing the dd-cfDNA will help determine whether it is of tumor vs allograft origin.

Fig 1

SA-POI144
A Unique Case of Persistent Hypoxia in a Post-Kidney Transplant Patient due to Occlusion from Hemodialysis Reliable Outflow Graft Causing Right to Left Shunt

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Introduction: The Hemodialysis Reliable Outflow (HeRO) vascular access graft is a method of vascular access able to bypass a central venous occlusion. Cavannus within the superior vena cava (SVC) can lead to occlusion and syndromes such as SVC syndrome, subclavian steal and esophageal varices. We report a unique case of a chronically occluded HeRO graft in a renal transplant patient causing SVC occlusion leading to right to left shunting and hypoxia.

Case Description: A 56 year-old woman presented with worsening shortness of breath and documented hypoxia. She also had left arm weakness without swelling. She had a history of ESRD with HeRO graft which connected her left brachial artery to the left internal jugular vein and emptied into the IVC. It had not been used for 10 years since her first kidney transplant. The graft had occluded. A TTE with bubble study revealed bubbles in the left heart when injected in the left arm after Valsalva concerning for right to left shunt. Her HeRO graft was obstructing the SVC, left brachiocephalic vein (BCV), and left subclavian vein and she was found to have a persistent vein of Marshall with Cardinal vein extending from the mid portion of the BCV to the left superior pulmonary vein. The proximal section of the HeRO graft was removed and endarterectomy with patch angioplasty were performed on the BCV and SVC and the cardinal vein was ligated. After surgery her hypoxia had resolved.

Discussion: This is a case of a complication of long-term unused vascular access in a renal transplant recipient. Vascular occlusion is a common complication of indwelling catheters but can produce atypical symptoms. We have not been able to find any similar case studies of central occlusion induced hypoxia. This was a result of a shunt from abnormal vasculature that worsened with progressive obstruction of the left brachiocephalic vein. Removal of the offending catheter and ligation of the shunt cured the patient of her presenting symptoms. Detailed coordination between cardiology, vascular surgery, cardiothoracic surgery, and renal teams was vital for diagnosis and management.

SA-POI145
Angiotensin II Type 1 Receptor Antibody (AT1-R Ab) Mediated Rejection in HLA-Incompatible Kidney Transplant Recipient

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Introduction: Donor-specific antibodies (DSAs) create an immunologic barrier to transplantation. The IgG degrading enzyme derived from Streptococcus pyogenes (IdeS), an endopeptidase, cleaves human IgG into Fab(′)2 and Fc fragments inhibiting complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity. We report unique case of non-HLA antibody mediated rejection in IdeS recipient

Case Description: A 40 years old male with history of ESRD due to IgA nephropathy who received IdeS as part of a phase 2 IRB approved trial in preparation for positive flow crossmatch deceased donor kidney transplant. Immediately post IdeS his crossmatch became negative. Patient also received IV alemtuzumab and rituximab for induction as part of the study protocol. One-week post-transplant, HLA-DSA rose to the cytotoxicity positive level and he was empirically treated for antibody mediated rejection with 11 sessions of plasmapheresis and intravenous immunoglobulin (IVlg). His HLA-DSA became flow negative. Maintenance immunosuppression included prednisone 5 mg daily, tacrolimus 2 mg bid, mycophenolate 500mg bid and losartan 50 mg daily. Six months later, laboratory data revealed an increase in serum Cr from 1.0 to 1.4 mg/dL and HLA-DSA remained flow negative. Further histocompatibility testing showed increase in pre-transplant level of AT1-R Ab from 14 units/ml to >40 units/ml (positive=17 units/ml). Kidney pathology detected chronic active antibody mediated rejection. Patient was immediately started on IV solumedrol and losartan 50 mg daily, he also finished 5 sessions of plasmapheresis and IVlg. One week later, serum Cr trended down to 1.0 mg/dL and AT1-R Ab level dramatically improved to 10 units/ml.

Discussion: Although reduction of HLA-DSA with therapies such IdeS has allowed successful transplantation in highly sensitized patients, screening and surveillance for non-HLA antibodies such as AT1-R antibodies may be required in this high risk population to prevent antibody mediated rejection.
SA-PO1146
AT,R and ETAR Antibodies, Proteinuria, and Renal Dysfunction in Pediatric Kidney Transplantation
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Background: Activating autoantibodies to Angiotensin II Type 1 Receptor (AT,R) and Endothelin type A receptor (ETAR) are non-HLA antibodies which have been associated with poor kidney allograft outcomes. However, the association of these antibodies with proteinuria and renal dysfunction is unknown. We aimed to determine the association of AT,R and ETAR antibodies (Ab) with proteinuria and renal allograft function in pediatric kidney recipients (KTRs).

Methods: 65 pediatric KTRs were monitored for 2 years after transplantation. ETAR-Ab and AT,R-Ab (ELISA) were measured at 6 months (m), 12m, and 24m post-transplant and during episodes of rejection. Based on a receiver operating curve analysis, > 10 and ≥1.030, alkaline PH (≥8.5) and gross hematuria (r), proteinuria was defined as ≥1+ (30-100 mg/dl) on urinalysis. Samples were excluded for factors that may result in false positives including high specific gravity ≥1.030, alkaline PH (≥8.5) and gross hematuria (r).

Results: AT,R-Ab and ETAR-Ab were positive in 38 (58%) and 24 (37%) of patients during the first 24m post-transplant respectively. Proteinuria was present in 84 of 323 urinalysis samples (26%) with 44 patients (68%) positive during the first 24m post-transplant. We found that patients with both AT,R -Ab and proteinuria had greater declines in kidney function than patients with either (p=0.004, Figure 1a). This relationship was also observed in patients with ETAR-Ab and proteinuria (p=0.018, Figure 1b).

Conclusions: Pediatric KTRs with AT,R-Ab, ETAR-Ab, and proteinuria have greater declines in kidney function in the first 24m post-transplantation. This association highlights the potential detrimental effects of non-HLA antibodies on the renal allograft in the pediatric population.

SA-PO1147
Impact of Persistent and Transient Donor-Specific Antibodies Within First Year After Kidney Transplantation
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Background: The importance of Donor Specific Antibody (DSA) surveillance within 1st year (yr) post kidney transplant remains unclear. We studied the impact of DSA pattern during the 1st yr post-tx on clinical outcomes.

Methods: 931 patients (pts) from 2013-17 were enrolled (HLA Compatible, Flow, unmatched negative). Pts were grouped into Transient DSA (T-DSA, n=66; 1 positive test, Class I/II), Persistent DSA (P-DSA, n=115; >1 positive test, Class I/II), and No DSA (N-DSA, n=750) within 1yr post-tx. DSA testing was done at 1.6.9.12 mos. Biopsies (protocol &12 mos, & indication) were included. Surrogate marker for this study included incidences of TCGR and ABMR. Outcomes measured were pt survival, graft survival and composite of pt loss, graft loss and gFR <20ml/min at last follow-up.

Results: During the 1st yr, DSA was detected in 19% of pts (7% T-DSA vs 12% P-DSA). There were no differences in baseline or tx characteristics, other than increased sensitization (cPRA-20%) in P-DSA pts (67% vs 47%, p<0.001). P-DSA pts developed DSA earlier for Class I (75%136 vs 121±132 days, p=0.03) and II (63±184 vs 192±185 days, p<0.001), when compared to T-DSA pts. at a yr, N-DSA detection was far less in N-DSA pts (Class I/II 4.8%) than in T-DSA (Class I/II 53%/62%, p<0.001) or P-DSA (Class I/II 64%/69%, p<0.001) pts. P-DSA pts experienced more clinical TCGR (14 vs 8%, p<0.04), ABMR (12 vs 0.8%, p<0.001), & less normal biopsies (4 vs 11%, p<0.02) than N-DSA pts, and more ABMR than T-DSA pts (12 vs 0%, p<0.003). There were no differences in sub-clinical TCGR/inflammation, tacrolimus levels, renal function, pt survival, or death censored graft survival among all groups. However, lower composite outcome was noted with T & P-DSA pts (Figure 1).

Conclusions: Persistent and Transient DSA within 1yr had similar outcomes and lower composite outcome when compared to No DSA pts. Thus, detection of DSA within 1yr, whether Persistent or Transient, is detrimental to renal allograft.

SA-PO1148
Impact of Treatment of Borderline Rejection on Subsequent T Cell-Mediated Rejection in Kidney Transplant Recipients
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Background: The optimal management of borderline rejection (BR) seen in the early post-transplant period is unclear. Studies have shown that BR is associated with higher Subclinical or Clinical T-Cell Mediated Rejection (TCMR) within 1yr post-transplant. However, the role of steroids in attenuating this risk is unclear. We performed this study to evaluate the impact of treating BR with steroids on subsequent development of TCMR.

Methods: Adult kidney transplant recipients (N=183) with Subclinical or Clinical BR in the first 3 months post-transplant based on Banff 2005 criteria were divided into two groups: (i) No treatment group (N=143), and (ii) Steroid treatment group (N=40). We excluded prior TCMR, Antibody mediated rejection (AMR) and BK virus nephritis. All the patients with BR had their maintenance immunosuppression (MIS) optimized. All patients were to be treated with thymoglobulin (97%) or basiliximab (3%) and a rapid steroid taper over 5 days per protocol. Standard MIS was with tacrolimus and mycophenolate mofetil. Recipient, donor and transplant variables were similar between the groups. The subsequent development of subclinical and clinical TCMR over the course of the first year was followed.

Results: Refer to Results Table

Conclusions: Treatment of BR in early post-transplant period with steroids was not associated with lower rates of TCMR at 1-year post transplant. However, steroid dose varied in our study from 1 to 3 doses of methylprednisolone. Further studies with uniform dosing of steroids are required to establish definite treatment strategies for BR.
mTORi. 12 patients were found to have borderline rejection on protocol biopsies (7 on mTORi, 5 on MPAs). 42 patients did not have any inflammation on biopsies. 57 patients remained on belatacept, and 8 were converted to tacrolimus. Patients who had biopsy-proven rejection or borderline changes had significantly higher %CD8+CD28- T cells, and those who had rejection with low %CD8+CD28- were found to have high CD2hi CD28hi in CD8(-CD38-) T-cells. Belatacept patients receiving everolimus had more stable TIGIT expression on regulatory T cells.

Conclusions: This trial of combining belatacept with mTORi shows that it is possible to reduce the rate of acute rejection in belatacept-based regimens. The synergy between the two drugs may be related to mTORi’s inhibitory effect on memory CD8+CD28-CD38- cells that are refractory to costimulatory blockade. Pretransplant immunotyping to identify those with low percentage CD8+CD28- & CD2hi CD28hi in CD8(-CD38-) may reduce the risk of rejection on belatacept.

SA-PO1150
Use of Antithymocyte Globulins (ATG) to Treat Rejection in Kidney Transplantation

Background: ATG is used to treat steroid-resistant T-cellular mediated rejection, vascular rejection and mixed rejection in kidney transplant recipients. Most of the studies which examined the efficacy and the safety of ATG did not include patients on modern immunosuppression regimes. In addition, they did not examine in detail the side effects of this potent treatment.

Methods: We studied the long-term efficacy and side effects of ATG in renal transplant recipients, who were treated with ATG between 2011-2018. We analysed the demographics, the types and rates of infection and cancer, the readmissions, the graft and patient survival.

Results: 87 (56 males) patients were treated with ATG in the study period. The mean age was 45 ± 13.5 years. The follow-up was 50.4 ± 36.0 months. The ATG was effective in treating rejection in 57 patients (66%). However, 49 patients (56%) developed viral and infections after ATG use with 20 (23%) patients developing severe infections (including 3 fungal infections and 1 mycobacterium infection). 40 patients (46%) were readmitted at least once for complications related to ATG. 5 (6%) patients developed severe infections after ATG. The graft and patient survival with ATG was associated with increased risk of viral infections (p=0.027). This remained significant in logistic regression (p=0.033).

Conclusions: ATG is an effective treatment for rejection in kidney transplantation. However, it seems that it is associated with an increased risk of viral infections. In our cohort, older patients treated with ATG were at higher risk of death. This association will be investigated further.

SA-PO1151
Preformed Donor-Specific Antibodies in Complement-Dependent Cytotoxic Cross Match Negative Living Unrelated Male-to-Female Spousal Kidney Transplantations Are Associated with an Increased Risk of Acute Antibody-Mediated Rejection

Background: Shortage of deceased donor kidneys has led to increased numbers of living unrelated kidney, in particular spousal, donors. Female recipients of a spousal kidney have an increased risk for pre-immunization and acute antibody-mediated rejection (ABMR). The aim of this study is to assess the incidence of ABMR and preformed donor-specific antibodies (pDSA) in living unrelated donors (LURD) and to identify risk factors for acute ABMR.

Methods: We identified all 349 ABO compatible, CDC-match negative, LURD transplants performed at our transplant center between 1997 and 2015. All for-cause biopsies were classified according to the Banff 2017 classification. All patients with ABMR were retrospectively tested for the presence of pDSA with multiplex and single antigen tests (Luminex). Risk factors for immunization were extracted from personal demographics, the types and rates of infection and cancer, the readmissions, the graft and patient survival.

Results: The overall incidence of biopsy-proven acute rejection in the first 6 months was 20% (TCMR: 85%; ABMR: 15%); median time to onset of ABMR was 8 days (range 5-75 days). Outcome was poor in ABMR as compared with patients with TCMR or those without graft loss (p=0.04). In preformed donors, 62% of the recipients developed pDSA. Eight patients with ABMR were female (73%) and six of these (75%) were recipients of a spousal kidney. Of these spousal pairs had given birth to a child of their kidney donor and 5 received blood transfusions prior to transplantation. Retrospectively 80% of spousal recipients with ABMR had pDSA in the multiplex or single antigen test.

Conclusions: Female spousal kidney recipients have a relatively high risk of ABMR. Traditional methods for detecting pDSA are not sensitive enough to rule out pDSA. Multiplex and single antigen should be included in the standard work-up of potential female spousal kidney transplant recipients to prevent ABMR and guide the option of (over- or cross-over) donation.

SA-PO1152
Clinical Significance of Pretransplant Donor-Specific HLA Antibodies in Kidney Transplant Recipients of Hispanic Population

Results: We identified 60 patients with pretransplant DSA and paired them based on donor type, induction therapy and maintenance immunosuppression to 60 KT recipients that did not have pretransplant DSA. The incidence of AR was higher in the pretransplant DSA group (35.5% vs. 15.2%, p=0.011) and the median time between KT and AR episodes was shorter in the pretransplant DSA group [12.8 (8.3-23.6) vs 32.1 (25.9-40.6) months, (p=0.0001)]. After 37.4 (range 29.2-52.5) months of follow up, eGFR was similar between groups [65.0 ± 22.0 vs 69.8 ± 21.4 ml/min/1.73m² (p=0.19)] and there was no difference in graft survival (87.7% vs 96.7%; p=0.240) between groups with and without pretransplant DSA, respectively.

Conclusions: Although there is a higher incidence of rejection, KT recipients with pretransplant DSA had similar eGFR and graft survival. Therefore, this group of high immunological risk could still be considered candidates for KT. One limitation of this study is the small sample size and short follow-up time. However, we propose that induction therapy with lymphocyte depleting agents and powerful maintenance immunosuppression, combined with follow-up strategies as protocol biopsies with early follow-up, subclinical rejection or could provide similar graft survival in KT recipients with and without pretransplant DSA.

SA-PO1153
Absence of Histologic Improvement Despite Reduction of Donor-Specific Antibodies with IVIG Treatment of Kidney Transplant Recipients

Results: While there was no significant difference in baseline eGFR between groups, there was a significant decrease in eGFR in the control group at 18 months (Figure 1), and 23% of the control group had graft loss, compared to 0% in the treatment group. Ten recipients in the IVIG cohort met the definition of “respondor.” There were no significant differences in graft function between responders and non-responders at start of IVIG or at 18 months post-treatment (Table 1). There was no change in pre- and post-IVIG histologic Banff scores in both respondents and non-responders (Figure 2a and 2b).

Conclusions: IVIG therapy is associated with DSA reduction and stabilization of renal allograft function in some patients. However, despite significant reduction in DSA,
there was no change in histologic parameters after IVIG therapy. Prospective randomized controlled trials with longer-term follow-up are needed to evaluate the beneficial impact of IVIG.

SA-PO1154
Quantitative Assessment of Active and Chronic Lesions in Renal Allograft Biopsies to Improve Reproducibility, Clinical Correlations, and Outcome Prediction
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Background: Banff classification system is based on recognition and scoring of descriptive lesions allowing for pathogenetic classification of rejection. Although expert pathologists readily recognize these lesions, the routine semi-quantitative Banff scoring can be poorly reproducible. Specific immunohistochemical (IHC) stains and new imaging techniques can allow for more precise quantification of tubulitis, interstitial fibrosis (IF), and microvascular involvement (MVI) (Delsante, TL2018).

Methods: Tubulitis: we included 12 transplant biopsies of CMR, borderline and no rejection from Parma Hospital (Italy). Analysis of whole slide images of CD3-PAS IHC stained sections allowed for continuous scoring of tubulitis, and results were correlated with urinary CXCL9 levels (a biomarker of cell-mediated rejection). IF: Measuring second harmonic generation (SHG) signal on FFPE unstained kidney section, we assessed collagen deposition in 57 kidney transplant biopsies (Johns Hopkins Hospital-JHU). MV1 was quantified in 75 biopsies from JIH using a dual IHC stain (CD3-endothelium and CD45-leaveoocytes); quantitative scores of peritubular capillaritis and glomerulitis were correlated with donor specific antibodies (DSA) levels and graft outcome

Results: Tubulitis quantitative scores showed significant correlation with urinary CXCL9 levels in patients with histological diagnosis of CMR, borderline lesions or no significant tubular involvement: mean CD3+ cell per tubule (r2 0.75), tubulitis ratio (r2 0.66) and CD3+ cells is most inlamed tubule (r2 0.70). Measurement of interstitial collagen deposition using SHG outperformed standard Banff score in predicting graft failure having screening 3.37 times per 2SD unit increase of SHG density, 95% CI: (1.06-14.16). The use of CD3-CD45 dual stain increased interobserver reproducibility of Banff ptc score and significantly correlated with serum DSA levels and risk of graft loss. In the same cohort, glomerulitis scores showed no correlation with DSA/allograft outcome. Continuous Banff lesions (ptc, t and ci/ct) quantitative measurements can increase clinical correlation compared to semi-quantitative scoring. Quantitative methods are being studied in larger cohorts to confirm clinical and prognostic significance.

SA-PO1155
Significance of Revised Diagnosis for Chronic Active T Cell-Mediated Rejection in 2017 Banff Criteria: Surveillance of 1-Year Screening Biopsy
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Background: Banff classification revised in Banff 2017 consensus may be useful for prognostication and may help detect unfavorable prognosis cases in kidney transplant patients who underwent 1-year SB.

Conclusions: The chronic active TCMR diagnosis revised in Banff 2017 consensus may be useful for prognostication and may help detect unfavorable prognosis cases in kidney transplant patients who underwent 1-year SB.

SA-PO1156
Treatment of C3 Glomerulopathy in Kidney Transplant Recipients: A Meta-Analysis
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Background: C3 glomerulopathy (C3G), a rare glomerular disease mediated by alternative complement pathway dysregulation, is associated with a high rate of recurrence and graft loss after kidney transplantation (KTx). We aimed to assess the efficacy of different treatments for C3G recurrence after KTx.

Methods: Databases (MEDLINE, EMBASE, and Cochrane Database) were searched from inception through 05/03/2019. Studies that reported outcomes of adult KTx recipients with C3G were included. Effect estimates from individual studies were extracted and combined using random-effects. Protocol for this meta-analysis was registered with PROSPERO (no. CRD42019125718).

Results: Twelve studies (7 cohort studies and 5 case series) consisting of 122 KTx patients with C3G (73 C3GN and 49 DDD) were included. The pooled estimated rates of allograft loss among KTx patients with C3G were 33% (95% CI: 12%-57%) after eculizumab, 42% (95% CI: 2%-89%) after therapeutic plasma exchange (TPE), and 81% (95% CI: 50%-100%) after rituximab. subgroup analysis based on type of C3G was performed. Pooled estimated rates of allograft loss in C3GN KTx patients were 22% (95%CI: 5%-46%) after eculizumab, 56% (95% CI: 6%-100%) after TPE, and 70% (95% CI: 24%-100%) after rituximab. Data on allograft loss in DDD KTx patients after different treatment modalities were limited (1 cohort and 1 case series, 4,6% (67%) after eculizumab, 1PE (case series, 0.2% (0%) at 6 months and rituximab (1 cohort, 3/ 100% allograft loss). Among 66 patients (38 C3GN, 28 DDD) who received no treatment (likely due to stable allograft function at presentation and/or clinical judgment of physicians), pooled estimated rates of allograft loss were 32% (95% CI: 7%-64%) and 53% (95% CI: 89%-77%) for C3GN and DDD, respectively. Among treated C3G patients, data on sMAC were limited to patients treated with eculizumab: 80% patients with elevated sMAC before eculizumab responded to treatment. In addition, all patients who responded to eculizumab had normal sMAC level after post-eculizumab.

Conclusions: Our study suggests that KTX patients with C3G treated with eculizumab had the lowest incidence of allograft loss (33%) when compared to those treated with TPE or rituximab. Among those who received no treatment for C3G due to stable allograft function, there is an incidence of allograft loss of 33% in C3GN and 53% in DDD.
The results of classification and genetic analysis
SA-PO1161

Outcomes of Different Induction Therapies in ABO-Incompatible Renal Transplant Recipients in the Tacrolimus Era
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Background: ABO-incompatible renal transplantation is emerging as a safe and potentially acceptable routine procedure; however, outcomes of different induction therapies in ABO-incompatible renal transplant recipients (RTRs) remain insufficiently explored in the tacrolimus era.

Methods: Using data from organ procurement and transplantation network, all ABO-incompatible RTRs maintained on tacrolimus between 2000 and 2017 were retrospectively reviewed. Data including age, sex, gender, ethnicity, functional status, diabetes, body mass index, cold ischemia time, number of previous transplants, panel reactive antibodies, donor type, donor age, HLA-mismatches, number of acute rejection episodes, induction therapies, maintenance immunosuppression, recipients and graft survival were collected (Table 1). Based on induction therapies administered, RTRs were divided into two groups: anti-thymocyte globulin (ATG) or interleukin-2 receptor antagonist (IL-2RA). Inverse probability weights were used to adjust confounders among different groups using propensity score analysis. Cox hazard regression analysis for adjusted data (IL-2RA). Inverse probability weights were used to adjust confounders among different groups using propensity score analysis. Cox hazard regression analysis for adjusted data

Results: Out of 14,414 RTRs, 8844 received IL2-RA while 5570 received ATG for induction. There were no significant differences between the IL2-RA and ATG groups in terms of early post-operative acute rejection episodes, induction therapies, maintenance immunosuppression, recipients and graft survival were collected (Table 1). Based on induction therapies administered, RTRs were divided into two groups: anti-thymocyte globulin (ATG) or interleukin-2 receptor antagonist (IL-2RA). Inverse probability weights were used to adjust confounders among different groups using propensity score analysis. Cox hazard regression analysis for adjusted data

Conclusions: In the tacrolimus era, ATG as compared to IL2-RA induction therapy does not have a favourable graft or survival outcomes in ABO-incompatible RTRs.

SA-PO1162

Comparison of Clinical Outcomes Between High Anti-A/B Antibody Titer vs. Low Titer in ABO-Compatible Kidney Transplantation
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Background: ABO incompatible(ABOi) kidney transplantation(KTP) reduces the waiting time of deceased donor KTP and extends the pool of living donor KTP. In recent data, ABO incompatible(KTP) is known to have no significant difference in long term outcome as compared to ABO compatible. However, high A/B antibody titer is still a challenge to overcome in ABO compatible. This study, high anti A/B antibody and low titer Ab were compared in ABOi KTP

Methods: We retrospectively evaluated 95 cases of ABOi KTP recipients from 2009 to 2018 in Bong Seng Memorial Hospital, BUSAN, South KOREA. High-titer isoahemagglutinin patients were defined by IgG anti A/B titres ≥1:256. There were 28 patients with high titer and 67 patients with low titer group. Primary outcome was patient survival and graft survival. The secondary outcome was bleeding tendency, biopsy proven rejection, plasmapheresis number, cost of induction.

Results: There was no statistical difference in the baseline characteristics between high and low titer group. Patient survival rate in the high titer group was not statistically significant compared to the low titer group. There was no significant difference in graft survival rate(Figure 1). There were no differences in complications such as bleeding tendency and number of blood transfusions. However, the anti-A/B antibody titer(49 ± 37 vs. 502 ± 384)(p=0.00) and the number of plasmapheresis(3.8 ± 1.7 vs. 7.2 ± 2.5)(p=0.00) were significantly lower in the low titer group. There was no difference in complications such as pyramids, amnesia, and myocardial infarction after transplantation. There were no significant differences in infection and rejection

Conclusions: High A/B antibody titer ABOi KTP showed no inferiority in clinical outcome compared to low titer. The authors suggested that the high Anti A/B antibody titer lower the medical alert thresholds from concomitance to high risk.

SA-PO1163

Reuse of Immunoadsorption Columns in ABO-Incompatible(ABOi) Kidney Transplantation: A Single-Center Experience
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Background: ABO-incompatible (ABOi) Kidney Transplantation has results comparable to ABO compatible transplantation. This is because patients are desensitized at the pre-transplant stage using apheresis & Rituximab therapy with tacrolimus (ITAC) based immunosuppression. In some patients, baseline titers are very high and repeated plasma exchange sessions also fail to bring titer to the desired level. Immunoadsorption (IA) technique is very effective in reducing titers in such cases. But, IA therapy is quite expensive, hence we have tried to reuse the filter to see the effectiveness.

Methods: 190 ABOi transplants have been performed at our center since 2012. Patients received Rituximab and triple immunosuppression. Baseline IgG & IgM were tested with gel method and it ranged from 1: 2 to 1: 1024. The antigen-specific IA technique was used in 64 patients. Two types of IA filters were used Glycosorb – glycosorb & Adsopak. IA columns were reused after regeneration. No. of column reuse, adverse events, and Anti A/B antibody titers were assessed. Glycosorb filter was processed by rising with 1000ml saline and sterilized with Ethylene trioxide(ETO). Adsopak column was reused by different regeneration technique using saline wash, acidic solution followed by buffer and alkaline solution and regeneration solution(sodium azide).The column was placed at 2° to 8°C. Antibody titers were estimated in the blood taken 10 minutes before the end of the procedure from the line immediately after the Column. Negative or low amount of treated indicated effective antibody removal at the end of treatment desirous of the results. Columns were used maximally for 3 times.

Results: 64 ABOi patients underwent antigen-specific IA1 and could be transplanted. In 4 patients, the titers did not come to target levels and these had to subject to therapeutic plasma exchange to achieve the target levels. Incidence of hypotension, fever with rigors & failure to bring down the titer was significantly higher in adsopak filter as compared to Glycorex filter. Column reuse resulted in a cost saving of 5000 to 10,000 USD per patient.

Conclusions: Although IA technique is very effective, it is expensive and the cost of treatment increases considerably. Reuse sessions were tolerated well and titer could be reduced to target levels.

SA-PO1164

Kinetic Characteristics and Validation of a Patient-Based Model for Therapeutic Plasma Exchange in Transplant Patients
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Background: Therapeutic plasma exchange (TPE) has become an important tool in kidney transplantation. The American Society of Apheresis gives TPE a category 1 indication for antibody mediated rejection (AMR). Understanding the kinetics of macromolecule removal is fundamental for rational prescription, optimization, and recognizing limitations of the TPE.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We evaluated 12 patients with biopsy confirmed AMR, who had indication for TPE. Each patient received 5 treatments every other day with 1.5 plasma exchanges, and all treatments where replaced with 5% albumin solution. Considering that Luminex is not a quantitative assay, we measured immunoglobulins (IgG, IgA, IgM) by immunoturbidimetry, and LDL cholesterol before and after each treatment. By knowing the initial value of macromolecules, their intravascular distribution, and the reduction ratio, we calculated the intravascular refill between treatments. Refill was independent of time, and constant for each patient through all treatments. We also identified three refill patterns. With this information we developed a predictive model for macromolecule kinetics during TPE, and conducted an internal validation of the model.

Results: We evaluated distribution prediction of the model and we obtained good correlation: IgG (r=0.94, 95%CI=0.91-0.96, R²=0.88, P <0.001), IgA (r=0.89, 95%CI=0.84-0.92, R²=0.8, P <0.0001), IgM (r =0.89, 95%CI=0.85-0.93, R²=0.80 P <0.0001), LDL (r =0.94, 95% CI= (0.92-0.96), R²=0.89 P <0.0001). The Bland Altman plots to evaluate agreement: IgG (Bias=0.3, SD of Bias 23.45, 95% Limits of agreement (-45–46)), IgA (Bias= -8.4, SD of Bias 13.95, 95% Limits of agreement (-35 to 19)), IgM (Bias= -0.13, SD of Bias 29.4, 95% Limits of agreement (-58 to 58)), and LDL (Bias= -17, SD of Bias 31.47, 95% Limits of agreement (-78 to 44)).

Conclusions: The model predicted accurately the distribution of macromolecules after multiple treatments. The correlation and agreement was especially good for IgG, and IgA. Although the correlation was good for LDL, concordance was not, this can be explained by the intravascular distribution and the short half-life of this molecule. The model was programmed in an app format for IOS to make it practical. A validation cohort is being conducted.

SA-PO1165
Outcomes and Complications Following ABO-Incompatible Kidney Transplantation Performed After Desensitization by Antigen-Unspecific Immunoadsorption Devices

Background: Due to the current organ shortage, ABO incompatible (ABOi) transplantations have been increasingly performed in recent years. The results seem comparable to those of compatible transplantations, but there have also been reports of increased side effects possibly due to the desensitization therapy.

Methods: To address an increase in severe infectious complications, we compared the outcomes of 48 ABOi transplant recipients to outcomes of 96 matched ABO compatible (ABOc) controls transplanted at Heidelberg University Hospital from 2005 to 2018. In addition, we conducted a subanalysis of high-titer (≥1:256) recipients compared to low-titer (<1:256) recipients.

Results: Over a follow-up period of 8 years, ABOi transplant recipients had comparable graft and patient survival as well as graft function compared to ABOc patients. T cell-mediated and antibody-mediated rejections were not different between groups. In ABOi transplant recipients, urosepsis (23% vs. 9%; p=0.019) and pneumonia with opportunistic pathogens (8% vs. 1%, p=0.025) appeared more frequently. As a consequence, a significantly higher number of deaths from infection have been observed after ABOi transplantations (6% vs. 0%, p=0.010). High-titer recipients (isoagglutinin titer of ≥1:256) showed a higher incidence of BK virus replication and postoperative bleeding complications.

Conclusions: ABOi kidney transplant recipients may be safely transplanted, even when they have a high anti-A/B antibody titer before surgery. However, particular attention has to be paid to severe infectious complications. Especially pneumonia causes an increased frequency of deaths from infections in ABOi kidney transplant recipients during early follow-up.
SA-PO1166

Recipient ABO Blood Group May Be Associated with Increased Mortality Risk Among Patients with Kidney Transplants

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Background: Blood groups A and B have been associated with increased risks of cardiovascular disease, infection and cancers. To date, the effect of recipient ABO blood group on patient survival has not been studied in ABO-matched solid organ transplantation.

Methods: All Australian and New Zealand transplant recipients who received ABO-compatible primary kidney transplant between 1995-2016 were analysed using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. The exposure was recipients’ ABO blood group, with the primary analysis being O /-non-O and secondary analysis Individual blood groups. Outcome was patient survival. Recipient age, gender, ethnicity, body mass index, smoking status, comorbidities, primary kidney disease; donor type, age and gender; and transplant era were included in the multivariable model as confounders.

Results: Of 15,523 kidney transplant recipients, blood group O was not associated with patient survival (hazard ratio (HR) 0.97, 95% confidence interval (CI) 0.91-1.05) compared to non-blood group O recipients. Blood group A was associated with reduced patient survival compared to non-blood group A recipients (HR 1.10, 95% CI 1.02-1.18).

Conclusions: This analysis suggests that blood group A recipients may have had reduced patient survival compared to non-A recipients. Further research is required to confirm these findings and determine the source of this difference. It biological or unmeasured confounders.

SA-PO1167

Mythbusters: Is Your ABO Titer Method Safe for Patients?

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Background: As transplantation of group A2 kidneys to group B patients becomes increasingly common, so does the practice of sending titors to reference labs, some of whom may not be performing their titors in a way that promises optimum patient safety and outcomes. ABO titer cutoff for transplant eligibility differs widely between institutions, largely due to differences in titration methods. Our study sought to refute the notion that a DTT-treated titer read at immediate spin (IS) is an accurate assessment of IgG titer and to suggest widespread adoption of more appropriate, traditional titer testing methods.

Methods: A method comparison study was performed by testing Anti-A titters of 10 group B kidney transplant candidates at immediate spin (IS), traditional tube method (tube-AHG), DTT-treated IS (IS DTT), and DTT-treated tube method (AHG DTT). Dilution controls were performed for each patient.

Results: All IS and 9 of 10 AHG titters were reduced by DTT treatment. The amount of reduction varied, as shown in Table 1, suggesting that the proportion of ABO titter which is IgM vs. IgG varies individually. The highest AHG tube titter (256) was reduced down to an IS DTT titter of only 4. In this instance a patient with a high titter Anti-A would have been given an A2 transplant at many institutions which use IS DTT titters.

Conclusions: Traditional titer methods which measure IgM and IgG provide a more comprehensive and clinically valuable view than DTT-treated titters. The practice of performing IS DTT-treated titters and reporting as IgG titter is misleading, with possibly harmful implications for patients. Titer performance must be standardized to prioritize confounders.

Table 1

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SA-PO1168

Graft Survival and Patient Outcomes in ABO-Incompatible Kidney Transplant with Baseline High and Low Isoagglutinin Titers Compared with ABO-Compatible Transplant

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Background: ABO incompatible kidney transplantation (ABOKT) helps to increase donor pool. No study till date has compared outcomes in high & low baseline isohemagglutinin titters to that in compatible transplants (ABOKT). This study attempts to evaluate correlation of baseline anti-A & anti- B isoagglutinin titers on graft survival and patient outcome in ABOKT as compared to ABOKT.

Methods: This was a retro-prospective observational study evaluating 954 renal transplant recipients. Of these, 873 patients underwent ABOKT. Of 81 patients who underwent an ABOKT, 67 belonged to low titer group (baseline IgG ≤1:64) and 14 belonged to high titer group (baseline IgG≥1:128). Patients were followed up for 1 year. Graft survival, rejection episodes, patient survival & infections were assessed.

Results: Mean age of patients who underwent ABOKT, ABO-high titer group was 40.47±12.38, 37.99±16.21 & 40.37±12.4 years respectively. Mean donor age was 45.08±10.26, 49.11±14.24 & 45.91±10.15 years respectively. Majority of donors were females-68.8%-78.6% & 78.1% respectively. Chronic glomerulonephritis was most common cause of ESRD. HLA mismatches were lower in the ABOKT group. Death censored graft survival was lower in high titer group (92.3%) compared to ABOKT group (98.5%), p≤0.231. Graft survival in low titer group (98.6%) was comparable to ABOC group (97.8%) (p≤0.326). Presence of DSA was higher in patients with baseline high titer group. The rejection was lower in ABOKT groups (6.5%) when compared to ABOC high (21.4%) & low titer groups (13.4%) respectively (p≤0.063 and 0.033). Antibody mediated rejections were significantly fewer in ABOKT group(1.8%) vs high titer(21.4%) & low titer group(11.9%) (p≤0.003 and p≤0.001). Patient survival was better in ABOKT group (97.9%) compared to high (92.9%) and low titer (94.0%) groups. Most deaths were attributed to infections. Low titer group fared better than high titer group in having lesser infection episodes, though difference was insignificant(p=0.532).

Conclusions: High baseline isoagglutinin titters are associated with poor graft survival in ABOI grafts compared to ABOC grafts, even though the difference was not significant. High baseline antibody titters are associated with significantly greater number of rejections & infections.

SA-PO1169

Association Between Post-Transplant Donor-Specific Antibodies and Recipient Outcomes in Simultaneous Liver-Kidney Transplant Recipients

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Background: There is a dearth of published data regarding the presence of post-transplant Donor Specific Antibodies (DSA), especially C1q binding DSA (C1q-DASA), and patient and kidney allograft outcomes in simultaneous liver-kidney transplant (SLKT) recipients.

Methods: We investigated 85 consecutive patients who underwent SLKT between 2009-2015 in our center. Associations between presence of post-transplant DSA [persistent and/or newly developed (de novo)] and C1q-DASA, and all-cause mortality and the composite outcome (mortality, allograft kidney loss, and antibody-mediated rejection) were examined using unadjusted and age and sex-adjusted Cox proportional hazards regression models.

Results: The mean age at transplantation was 56 years. Sixty and 26% of the patients were male and African-American, respectively. Twelve patients (14%) had post-transplant DSA and 7.8% had C1q-DASA. The presence of post-transplant DSA was significantly associated with increased risk of mortality (unadjusted model: Hazard Ratio (HR)=2.72, 95%Confidence Interval (CI): 1.06-6.98 and adjusted model: HR=3.20, 95%CI: 1.11-9.22) and the composite outcome (unadjusted model: HR=3.18, 95%CI: 1.31-7.68 and adjusted model: HR=3.93, 95%CI: 1.39-11.10) compared to the DSA negative group (Figure). There was no significant association between the presence of C1q-DASA and outcomes (adjusted model: HR=1.67, 95%CI: 0.43-6.45 for mortality, and HR=2.61, 95%CI: 0.70-9.75 for the composite outcome).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Conclusions: The presence of post-transplant DSA was significantly associated with increased risk of all-cause mortality and composite outcome including kidney allograft loss and ABMR. The presence of post-transplant DSA should not be ignored in routine patient care after SLKT even though pre-transplant sensitized status is usually neglected at the time of SLKT.

SA-PO1170

Renal Microvascular Autoregulation in an Ischemia-Reperfusion-Induced Model of Acute Kidney Injury
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Background: Autoregulation alters renal vascular resistance (RVR) to keep glomerular filtration rate (GFR) stable during arterial pressure fluctuations. Ischemia-reperfusion (IR)-induced acute kidney injury exhibits increased RVR and decreased GFR. Our previous study revealed that autoregulation was impaired in IR, but improved with acute treatment of ROS-scavenger and NADPH-oxidase-inhibitor. Therefore, we hypothesize that chronic antioxidant treatment (Tempol) preserves autoregulation by reducing oxidative stress and inflammation in IR rats.

Methods: Rats underwent 60 minute bilateral renal arterial occlusion, with or without Tempol (2mM, drinking water; 7 days), or sham surgery. Afferent arteriole (AA) autoregulatory behavior was assessed in blood-perfused juxtamedullary nephrons. Glomerular function was assessed by plasma creatinine, GFR using FITC-sinistrin, and proteinuria/albuminuria.

Results: SBP was normal across groups: 126-145mmHg (P>0.05) over 7 days. Plasma creatinine increased with IR (1.68 ± 0.09 vs. 0.96 ± 0.04mg/dL in sham), P<0.05, but remained normal in IR+Tempol rats (1.05 ± 0.12mg/dL). Shams (n=3) exhibited pressure-dependent vasoconstriction. Control AA diameter averaged 12.2 ± 0.9um and decreased 32.3% from 65 to 170mmHg. In contrast, IR rats (n=2) lost autoregulatory capacity. AA diameter passively increased by 25% over 65-170mmHg, whereas IR+Tempol rats (n=2) maintained pressure-dependent vasoconstriction. GFR for shams remained constant (0.9-1.3mL/min/100g), while Tempol improved GFR to 0.5 compared to IR+Tempol rats (n=2) maintained pressure-dependent vasoconstriction. GFR for shams remained constant (0.9-1.3mL/min/100g), while Tempol improved GFR to 0.5 compared to IR+Tempol rats (n=2) maintained pressure-dependent vasoconstriction. GFR for shams remained constant (0.9-1.3mL/min/100g), while Tempol improved GFR to 0.5 compared to IR+Tempol rats (n=2) maintained pressure-dependent vasoconstriction. GFR for shams remained constant (0.9-1.3mL/min/100g), while Tempol improved GFR to 0.5 compared to IR+Tempol rats (n=2) maintained pressure-dependent vasoconstriction. GFR for sham conditions treated with HG suggested increased glucose uptake. Canagliflozin reduced the glucose uptake in both NG and HG treated tissue sections (P<0.0001 for HG and P<0.01 for NG groups). Likewise, 100 µm canagliflozin significantly reduced lactate after both glucose conditions. High glucose increased sucrase and KIM1 were also reduced by canagliflozin.

Conclusions: Above results support the hypothesis that SGLT2 inhibitors, by blocking glucose uptake, can revert the metabolic changes induced by hyperglycemia and protect against tissue injury.

SA-PO1171

Endothelin-1 Promotes Renal Iron Deposition in Murine Models of Iron Overload
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Background: Diabetes is associated with high rates of renal tubular glycosuria, reabsorbing high kidney glycolytic activity and higher production of kidney injury markers. Canagliflozin is an SGLT2 inhibitor, used for type 2 diabetes and considered to have beneficial effects on the progression of diabetic kidney disease. This study tested the effects of Canagliflozin on renal metabolism in mouse kidney slices.

Methods: Kidneys were harvested from C57Bl/6 WT mice, sliced to 0.15 µm thick sections and incubated in media containing 7.2 mM glucose (NG) or 25 mM glucose (HG), without or with canagliflozin (1, 10 and 100 µM). Conditioned media was collected after 24h of incubation and metabolites were measured using YSI bioanalyzer and gas chromatography-mass spectroscopy. Additionally, kidney injury marker KIM1 was measured by ELISA. Kidney tissues were frozen, sectioned to 10 µm sections using cryostat for mass spectrometry imaging (MSI) to identity spatial changes in glucose.

Results: In conditioned media, significant reduction in glucose (p=0.0001), and succinate and significant lactate (p=0.001) increase was noted in, HG compared to NG. MSI depicted increase in glucose in tissue sections treated with HG suggested increased glucose uptake. Canagliflozin reduced the glucose uptake in both NG and HG treated tissue sections (p<0.0001 for HG and p<0.01 for NG groups). Likewise, 100 µm canagliflozin significantly reduced lactate under both glucose conditions. High glucose induced sucrase and KIM1 were also reduced by canagliflozin.

Conclusions: These data suggest ET-1 contributes to renal iron overload.

SA-PO1172

The SGLT Inhibitor Canagliflozin Reverts Hyperglycemia-Induced Metabolic Changes in Mouse Kidney Sections
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Background: Dent Disease type 1 (DD1) is an X-linked disorder characterized by the development of fluid filled cysts, is the fourth leading cause of renal failure in the US and is mainly caused by mutations in the genes PKD1 or PKD2 encoding the proteins Polycystin1 (PC1) and Polycystin2 (PC2) respectively. Localization of PC1 and PC2 to the cell surface is important for their function in cells, with a positive correlation between reduced surface protein levels to disease severity. The objective of this project was to quantify surface localization of a number of missense variant PC1 proteins, and combination of variants.

Methods: The single PC1 variants (p.Arg3272Cys, p.Met3346Leu, and p.Thr3720Met) were created by site directed mutagenesis and introduced into the full length PC1 tagged construct. In addition, variant combinations were similarly generated (p Thr3720Met+p.Arg3272Cys, p.Met3346Leu+p.Thr3720Met, and p.Arg3272Cys+p.Met3346Leu). The expression of these constructs in the three A549 fibroblasts, epithelial cells from the kidneys were transfected with constructs containing these single and combination variants. Immunofluorescence staining of the transfected cells was used to visualize the surface localized proteins.

Results: The intensity of the immunofluorescence signal, as determined by flow cytometry, indicated the amount of protein properly localizing to the cell membrane. The single variants were found to have reduced surface localization compared to wild type, with the surface localization further lowered as the number of significant variants increased.

Conclusions: Therefore an in cis combination of missense variants can significantly reduce PC1 surface localization, showing that a combination of hypomorphic alleles can result in a fully inactivating allele.

SA-PO1174

Electrogenic Transport Function of Low Temperature Rescued CLC-5: R345W Mutation and Towards Dent Disease Novel Therapies
Meihui Zhang. Mayo Clinic, Rochester, MN.

Background: Dent Disease type 1 (DD1) is an X-linked disorder characterized by low molecular weight proteinuria, hypercalciuria, nephrocalcinosis, and kidney stones. DD1 has no effective therapy or treatment, although it is known to be caused by mutations in the CLCN5 gene encoding CLC-5, a voltage-gated chloride channel. This study tested the hypothesis that lowering the incubation temperature from 37 to 27°C would rescue the electrophysiology of CLC-5 harboring the R345W mutation.

Methods: CLC-5 single amino acid substitutions (R345W mutation) were generated using site-directed mutagenesis, and their effect on whole cell chloride currents were measured.

Results: The R345W mutation decreased whole cell chloride currents by 50% compared to controls (p<0.05). This effect was rescued by lowering the incubation temperature from 37 to 27°C, resulting in a 30% increase in current density. The effect of the R345W mutation was also rescued by the addition of the chloride channel activator furosemide, indicating that the reduced current density was due to reduced channel function.

Conclusions: These findings suggest that lowering the incubation temperature from 37 to 27°C may be a novel therapeutic strategy for DD1 patients.
Methods: Thus, we used whole cell patch-clamp electrophysiology to measure transport functions of transiently transfected renal proximal tubule cells (LLC-PK1 expressing wild type (WT) or R345W mutated CIC-5 incubated at 37 or 27°C.

Results: Cells expressing WT exhibited strongly outward rectifying current at positive holding voltages whereas R345W expressing cells incubated at 37°C demonstrated reduced current. Intriguingly, R345W expressing cells incubated at 27°C demonstrated significantly increased transport function compared to R345W expressing cells incubated at 37°C. We have also successfully established LLC-PK1 cell lines that stably express eGFP/HA double-tagged WT and mutant CIC-5. Using Western blot analysis, we documented that CIC-5 expression levels were sufficient to use these cells to screen candidate chaperones.

Conclusions: These results establish a rationale and the tools to explore the effect of pharmacological chaperones to facilitate proper protein folding and maturation of DDI mutations, including R345W. Results could suggest new therapies for some populations of DDI patients who currently have no specific therapy available.

SA-POI175
Recessive Mutations in TNL1 Are a Potential Novel Cause of Nephrotic Syndrome in Humans
Roxyana Fouladi. Harvard University, Cambridge, MA.

Background: Nephrotic syndrome (NS) is characterized by a significant loss of protein in the urine causing hypoalbuminemia and edema. NS is categorized into steroid sensitive (SSNS) and steroid resistant nephrotic syndrome (SRNS). SRNS is steroid resistant nephrotic syndrome is the second most common cause of chronic kidney disease in the first three decades of life. Mutations in over 59 genes provide a monogenic cause in up to 20% of NS cases (JASN 26:1279, 2015). This implies that novel genetic and mechanistic causes of NS may explain some of the currently undiagnosed ~70% of cases. The mechanisms of steroid action in SSNS are still unknown and treatment options for SRNS are limited.

Methods:
To identify additional monogenic causes of NS we performed whole exome sequencing in >2,000 individuals with NS. We identified a homologous TNL1 mutation in B3328-21 (c.5964_5966del, I1989del). We screened an additional cohort of 605 patients with NS with a Fluidigm Access ArrayTM for TNL1 mutations and identified a compound heterozygous mutation in patient A3788-21 with SSNS (c.235A>G, M97 and c.3491G>C, S1164T).

Results: TNL1 encodes a protein that binds to and activates integrins, coupling them to the actin cytoskeleton (FEBS Letters; 392:2108, 2010). Podocyte specific Tnl1 knock out mice have been described to develop an altered podocyte cytoskeleton structure, proteinuria, focal segmental glomerulosclerosis, and die at the age of 10 weeks likely due to renal failure (JCTF 124:1098, 2014).

Conclusions: In conclusion, we have identified mutations of TNL1 as a potential novel cause of nephrotic syndrome.

SA-POI176
Plasma Fibroblast Growth Factor 23 (FGF23) and Protein Alpha-1-Microglobulin/Bikunin Precursor (AMBP) as Predictors of Cardiovascular Disease (CVD) Endpoints in The Boston Kidney Biopsy Cohort (BKBC)
Debbie Adam. Harvard University, Cambridge, MA.

Background: Chronic Kidney Disease (CKD) is a risk factor for the development of Cardiovascular Disease (CVD). Research into nontraditional risk factors could help to provide more information as to why this complex relationship exists. Specifically, fibroblast growth factor 23 (FGF23) and protein c1-microglobulin/bikunin precursor (AMBP) have both shown promise as renal failure biomarkers in CVD-related clinical trials. From this knowledge, we hypothesized that elevated levels of plasma FGF23 and AMBP in CKD patients would demonstrate an accelerated time to CVD endpoint.

Methods:
The population of interest were patients enrolled for a native kidney biopsy between 2006 and 2018 at Massachusetts General Hospital (MGH) and Brigham and Women’s Hospital (BWH). Biological specimens were collected on all consented patients over the age of 18. Plasma FGF23 and protein AMBP were measured using multiplex immunoassay (inter-assay CV <10% for blind replicate samples). Univariate and multivariate regression models were generated to assess if plasma FGF23 and AMBP were predictors of CVD outcomes in CKD patients.

Results:
Patients with the highest levels of plasma FGF23 had a 3.16 fold risk of reaching the composite CVD endpoint relative to patients with lower levels of plasma FGF23 (HR=3.16 (1.08-9.95), p<0.05). Patients with mid-levels of plasma protein AMBP had a .312 risk of reaching the CVD endpoint compared to patients with lower levels of plasma protein AMBP (HR=3.12 (1.22-7.98), p<0.05).

Conclusions:
It can be inferred from our findings that plasma FGF23 can be used to predict cardiovascular outcomes in CKD patients, while the same cannot be said categorically for plasma protein AMBP.

SA-POI177
IL-6 Mediated Activation of the Mineralocorticoid Receptor via Rac1
Oishi Paul. Emory University, Atlanta, GA.

Background: Hypertension (HTN) is characterized by excessive sodium (Na+) reabsorption and increased cytokine production, including interleukin 6 (IL-6). Aldosterone (Aldo) is the primary ligand for the mineralocorticoid receptor (MR) and studies suggest MR inhibition lowers HTN. However, aldosterone levels are not always increased in HTN, suggesting alternate MR activation. Data from our laboratory have shown that IL-6 can activate the MR in vitro, and that Rac1 inhibition reduces mineralocorticoid response element (MRE) transcription. We hypothesize that IL-6 activates the MR via Rac1 in the late distal convoluted tubule (DCT), increasing activity of epithelial sodium channel (ENaC), a primary Na+ transporter in the late DCT (DCT2).

Methods: Using a voltohmmeter, we measured transresistive resistance and voltage to calculate current in our cell culture model for DCT2 (mDCT5 cells). Cells were transfected with Rac1 expression vectors and treated (IL-6 (100ng/mL)).

Results: While IL-6 increased ENaC activity, Rac1 knockdown inhibited IL-6 induced ENaC (-1.16-fold change/baseline) activity. Since we observed that IL-6 induces nuclear MR translocation, we investigated whether Rac1 affects IL-6 mediated MR translocation. We cotransfected MR-eGFP tagged constructs and Rac1 expression vectors into mDCT5 cells. Cells were treated with IL-6 and visualized with confocal microscopy. Following IL-6 treatment, MR nuclear translocation was observed; however, with Rac1 knockdown, decreased MR translocation was observed.

Conclusions: We are the first to demonstrate cytokine-mediated ENaC activation in the DCT2. Additionally, these data suggest that Rac1 is crucial for IL-6 mediated ENaC activation and MR translocation, providing an alternate mechanism for increased ENaC Na+ transport during HTN.

SA-POI178
Inhibition of Lymphangiogenesis Exacerbates Cisplatin Nephrotoxicity
Elisa Farrell. The University of Alabama at Birmingham, Birmingham, AL.

Background: The lymphatic system is a complex network of channels responsible for lipid transport, fluid homeostasis, and immune response. The creation of new lymphatic vessels, or lymphangiogenesis, occurs primarily in development, though studies show that vascular endothelial growth factor C or D (VEGF-C or -D) stimulate de novo lymphangiogenesis in disease through their receptor, VEGFR-3. We have previously shown this process to occur following acute kidney injury (AKI). However, no previous studies have evaluated whether lymphangiogenesis is beneficial or harmful in AKI.

Methods: This study utilized MAZ51 [10 mg/kg bodyweight in DMSO intraperitoneally (i.p.)]; a VEGFR-3 kinase inhibitor, to block lymphangiogenesis in a model of cisplatin nephrotoxicity (20 mg/kg bodyweight in saline i.p.). Mice were harvested 3 days post-cisplatin injection. Biomarkers of renal function, injury, inflammation, and lymphangiogenesis were measured.

Results: We report that inhibition of lymphangiogenesis exacerbates cisplatin nephrotoxicity. MAZ51 treated mice experienced significantly worsened kidney function, measured by elevated serum creatinine (1.1 ± 0.3 vs. 0.3 ± 0.05 mg/dL), decreased glomerular filtration rate (11.9 ± 3.9 vs. 80.6 ± 20.6 µL/min), and increased serum cytokin C. MAZ51 mice also experienced significantly increased expression of intrarenal KIM-1, compared with cisplatin alone treated mice. We also observed a significant rise in intrarenal inflammatory markers (Csf1, Ccl2, Tnfa) and heme oxygenase-1 (Hmox1), as well as increased cell death, compared with cisplatin alone controls.

Conclusions: Taken together, our study describes a novel role for lymphangiogenesis as an adaptive response following cisplatin AKI and may be a promising target for therapeutic intervention.

SA-POI179
Role of Histone Deacetylase-1 in Interstitial Fibrosis
Kathryn Aldaz. The University of Alabama at Birmingham, Birmingham, AL.

Background: Acute kidney injury can lead to chronic kidney disease through myofibroblast secretion of extracellular matrix (ECM) leading to interstitial fibrosis and a loss of kidney function. We reported that following ischemia-reperfusion-injury (IRI), the transcriptional regulator, histone deacetylase-1 (HDAC1) is increased in the kidney. Inhibition of HDAC1 reduced IRI-mediated interstitial fibrosis. We hypothesized that fibroblast HDAC1 was profibrotic and developed an inducible HDAC1 fibroblast knockout (KO) mouse.

Methods: Fibroblast HDAC1-1 was deleted in adulthood, and the male mice underwent sham or bilateral IRI (2-weeks of reperfusion) surgeries.

Results: Plasma creatinine was significantly elevated in control IRI mice (0.20 ± 0.02 mg/dl) compared to sham (0.12 ± 0.001) or KO mice (sham = 0.13 ± 0.009, IRI = 0.14 ± 0.02, PGenotype = 0.2, PSurgery = 0.02, Pinteraction = 0.03) suggesting that the KOs had better kidney function. Interstitial sirius red staining, α-smooth muscle actin (cssma), and fibrotenin expression was increased in the control IRI mice compared to shams or KO mice. Normal Rat Kidney (NRK52E) fibroblasts transduced with human HDAC1 or empty vectors. Injury was simulated by treatment of cells with TGF-β1, a master regulator of myofibroblast activation. Overexpression of HDAC1 did not significantly affect myofibroblast markers (cssma, fibrotenin). TGF-β1 treatment led to myofibroblast activation, regardless of HDAC1 level. Interestingly, HDAC1 was found to suppress p53 expression, a master regulator of the cell cycle.

Conclusions: Together, our data suggest that fibroblast HDAC1 is profibrotic, but it may be through regulation of myofibroblast cell cycle, rather than direct effects on ECM secretion.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Cystatin C Utilization for Kidney Assessment in Acute Care

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Background: Serum cystatin C (CysC) is a kidney biomarker used most extensively for staging chronic kidney disease. Recently the potential role for CysC in acute care has been recognized; however, settings where it is clearly useful remain to be defined. Our objectives were to retrospectively evaluate trends and patterns of inpatient use of CysC in a tertiary hospital where the test was readily available.

Methods: This was a single-center, observational study of adults hospitalized at Mayo Clinic with a CysC result between 2011–2018. CysC testing was available in house, with a turnaround time of ≤3 hours, and per provider discretion within 1 exacerbation. During 2 years of the 7-year study period, a vancomycin IQ project using CysC was conducted in 3 ICUs. Analyses of CysC ordering trends over time used Poisson regression. Descriptive statistics characterized the context for use.

Results: Over 7 years, 8168 CysC levels were obtained, during 4890 inpatient admissions, for 4337 patients. We found a 28-fold increase in CysC use over time (2011-0.74 tests per 1000 patient-days, 2018: 21 tests per 1000 patient-days; P=0.02; Figure). Nephrology was consulted in 40% of cases. The majority (72%) of patients underwent CysC testing during 1 of 3 scenarios: 1) AKI, 2) expected alterations in muscle mass, and 3) vancomycin dosing in the ICU QI project. Non-GFR determinants of CysC were identified with 47% of tests, most frequently corticosteroid use.

Conclusions: In this cohort of inpatients with ready access to CysC testing, CysC utilization significantly increased over the last 7 years. Themes for use included renal-dosing of drugs, AKI monitoring, and to assess GFR in patients with altered muscle mass. Non-GFR determinants frequently occurred, exposing opportunities for misinterpretation. Additional studies are warranted to define the optimal role for CysC in the inpatient setting.

Cystatin C Tests Per 1000 Patient-Days

Tests Per 1000 Patient-Days

Results

- Over 7 years.
- D0, D1, D2, D3, D4, D5, D6, D7.
- No-Cystatin C (NC) = 10.
- Cystatin C (C) = 20.
- Cystatin C (C) = 30.
- Cystatin C (C) = 40.
- Cystatin C (C) = 50.
- Cystatin C (C) = 60.
- Cystatin C (C) = 70.
- Cystatin C (C) = 80.
- Cystatin C (C) = 90.
- Cystatin C (C) = 100.
- Cystatin C (C) = 110.
- Cystatin C (C) = 120.
- Cystatin C (C) = 130.
- Cystatin C (C) = 140.
- Cystatin C (C) = 150.
- Cystatin C (C) = 160.
- Cystatin C (C) = 170.
- Cystatin C (C) = 180.
- Cystatin C (C) = 190.
- Cystatin C (C) = 200.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Kidney and Patient Outcomes After AKI in a Dialysis Centre in Sokolov from January 2017 to July 2018
Erika Štekelová, FM, Věkla Hladeře, Czechia.

Background: The incidence of acute kidney injury (AKI) is increasing. Epidemiological studies can not reliably clarify this phenomenon. Since January 2017 to July 2018 were treated 66 patients with hemodialysis due to AKI in dialysis centre in Sokolov. Our local objective was to show the clinical function and mortality. We also want to present our usual procedures for the treatment of AKI.

Methods: We evaluated dates of group of acutely dialysed patient on our dialysis centre by retrospective analysis. Our attention was focused on mortality and irreversible decline in kidney function of patients overall and in relation to age, gender and pre-existing chronic kidney disease (CKD).

Results: Patients with acute kidney injury had a maintenance phase that typically lasted between 7 and 21 days. The duration was dependent upon the length and severity of the initial ischemic episode; whether or not recurrent ischemia occurred or exposure to nephrotoxins was ongoing. An irreversible decline in kidney function after recovery was more likely in patients over age 65 years, in male sex and those with pre-existing chronic kidney disease and with heart failure. AKI during hospitalization is associated with high in-hospital mortality. In our patient group this mortality was up to 48%.

Conclusions: From our short-term follow-up of a relatively small group of patients have been produced conclusions similar to those from multicentre reputable studies. Patients who develop AKI should be evaluated because of the risk of new onset or worsening of pre-existing CKD.

Observational Analysis of Patients with Liver Cirrhosis Receiving Continuous Renal Replacement Therapy: A Single-Center Experience in Korea
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Background: To date, there was few data about liver cirrhosis (LC) patients undergoing continuous renal replacement therapy (CRRT) despite of a high mortality rate.

Methods: A total of 155 LC patients who initiated CRRT in intensive care unit (ICU) were enrolled and finally analyzed 142 patients retrospectively excluding 13 patients with liver transplantation from January 2013 to December 2018.

Results: The enrolled patients were admitted to the ICU for the following reasons: infection (25.4%), other LC-related complications (23.2%), gastrointestinal (GI) bleeding (16.2%), acute kidney injury (AKI) (9.2%), cardiovascular events (5.6%) and others (20.4%). The most common cause of starting CRRT was AKI with shock (76.1%) mostly associated with GI bleeding (31.7%) and sepsis (26.1%). In-hospital mortality was 67.6% and the most common cause of death was other LC-related complications (36.5%). Compared with survivor group, use of vasopressor(%) and SOFA, APACHE II, MELD were significantly higher in non-survivor group (91.8±7.5 vs. 88.6±7.2, p=0.000; 73.5±7.3 vs. 64.6±6.1, p=0.000; 33.6±7.98 vs. 29.8±7.14, p=0.006; 33.1±5.3 vs. 30.6±5.13, p=0.015) whereas fhr urine output before CRRT is lower in non-survivor group (91.7±12.3±6.3 vs. 214.7±8±23±91, p=0.004).

In laboratory values, white blood cell count and prothrombin time INR were significantly different between survivor and non-survivor group. The use of vasopressor(%) and albumin (OR 0.435, 95% CI 0.231-0.818, p=0.001) were associated with mortality.

Conclusions: In-hospital mortality of cirrhotic patients received CRRT was much higher than that of all patients received CRRT, which was previously reported as 53.7%. SOFA score, fhr urine output before CRRT and albumin were associated with mortality.

New Oral Anticoagulants and the Risk of Post-Contrast AKI After Computed Tomography with Intravenous Contrast Medium
Seemin Cho, Dong Iwan Yun, Yong Chul Kim, Haejung Lee, Dong Ki Kim, Kwon Wook Joo, Yon Su Kim, Seung Seok Han. Seoul National University Hospital, Seoul, Republic of Korea.

Background: Post-contrast acute kidney injury (PC-AKI) is a great concern in relation to worse renal outcome. However, the relationship between the use of new oral anticoagulants (NOACs) and the risk of PC-AKI remains unresolved.

Methods: A total of 2,158 patients who received prophylactic hydration with normal saline and N-acetylcysteine before and after computed tomography with intravenous contrast medium were reviewed. Among them, NOAC and warfarin were used in 34 and 65 patients, respectively. The risk of PC-AKI was compared between patients with and without these agents. Additionally, a propensity score matching was performed in a 1:4 block for variables such as age, sex, weight, contrast volume, blood pressure, comorbidities, and baseline serum creatinine. PC-AKI was defined as an increase in serum creatinine by ≥0.3 mg/dl or ≥1.5 times above baseline within 96 hours. The risk of end-stage renal disease or all-cause mortality was also evaluated.

Results: The events of PC-AKI occurred in 141 patients (6.5%). The risk of PC-AKI in the NOAC group was not higher than in the warfarin or non-agent group: odds ratios were 0.72–2.96 and 2.0–6.6–5.61, respectively. The risks of end-stage renal disease and mortality after contrast media use did not differ between the groups. These trends remained consistent irrespective of multivariable adjustment. When a propensity score matching was applied, the NOAC group had a similar risk of PC-AKI to the non-use group with an odds ratio of 1.2 (0.32–4.11).

Conclusions: The use of NOAC does not increase the risk of PC-AKI in patients who undergo computed tomography with contrast medium.

Comparison of Renal Function and Clinical Variables Between Patients With Sepsis And Cardiac Insufficiency
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Background: Heart failure (HF) is associated with large number of comorbidities that contribute to unfavorable outcomes, including acute renal failure (ARF). Sepsis is the leading cause of ARF in the critically ill patient.

Methods: We analyzed the medical records of 77 critically ill patients hospitalized at the Intensive Care Unit (ICU) of Hospital Israelita Albert Einstein. Patients hospitalized with decompensated HF and patients with a diagnosis of sepsis were compared. We collected demographic data, blood count parameters, renal function, liver enzymes, blood pressure and need for blood transfusion between HF and sepsis groups. KDIGO classification for acute renal injury. We performed t-test of student and chi-square to perform comparisons.

Results: Respiratory infection was the main cause of sepsis followed by gastrointestinal and bloodstream infections. KDIGO 2 was the most commonly found in all patients. Main finding was lower ejection fraction is associated with blood pressure and need for blood transfusion. Red Cell Distribution Width was higher in patients with decompensated HF when compared to septic patients (16.1 ± 2.1, 14.7 ± 1.8, P = 0.02). Mean corpuscular刊
Incidence of AKI in Intensive Care Units in Brazil: a Cohort Study

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Background: The Nephrocheck (NC) is an emerging marker in the diagnosis of kidney damage, especially in ill critical patients. Chronic kidney disease (CKD) could be a confounding factor in its clinical use. The aim of our study is to assess NC performance in the prediction of acute kidney disease (AKI) or the need of continuous renal replacement therapy (CRRT) in CKD patients.

Methods: We followed a group of 692 patients hospitalized in intensive care between 6/2017 and 9/2018. Demographic parameters, comorbidities, BMI, SOFA score, NC: Procalcitonin, lactate and serum Creatinine (S-Cr) levels were collected. Mide to severe CKD was defined by an eGFR of 15 and 60 ml / min, while AKI was defined by an increase of S-Cr ≥ 0.3 mg / dl in 48 hours, or by an increase of 50% of basal S-Cr or diuresis ≤ 0.5 ml / kg in 6 hours. All continuous parametric variables were presented as mean and standard deviation, while continuous nonparametric variable were reported as median with interquartile range (IQR). All categorical variables were reported as percentage. T Student, Kruskal Wallis, and Pearson’s chi-square tests were used to compare continuous and categorical variables, as appropriate. Finally, we evaluated the AKI predictors and the predictor of CRRT need by logistic regression. All tests were performed with the SPSS version 20 package.

Results: 14% of patients had an eGFR <60 ml / min. CKD Patients presented a higher prevalence of AKI (61% vs 23% < p < 0.001) and higher need of CRRT (14.4% vs 2.6% < p < 0.001), if compared to patients with eGFR ≥60 ml / min. Moreover, in CKD patients NC value showed a good ability to predict CRRT needs (OR1.05 p = 0.018) but it failed to predict AKI development (OR 1.03 p = 0.31).

Conclusions: By our preliminary results, the levels of NC in mild to severe CKD patients seem able to predict the need for CRRT.

Funding: Private Foundation Support

Age as a Protective Factor from Mortality due to AKI

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Background: We aimed to study if clinical features can be used to evaluate prognosis in AKI.

Methods: This is a retrospective, observational study. Inclusion Criteria: Adult Pts, SCR increase >20%, Cohort: 2746 hospitalized patients (Mean age: 63; SD: 14; Sex: 71%males). Studied parameters: Age (using subgroups of <65s≤65, ≤65s≤65 85s<85), SCR (basal-with previous measurement- and initial-at the diagnosis of AKI-), acute chronic health status (Individual Severity Index -ISI and Karnofsky-KPS), treatment type (IHD,CRRT or both) and in-hospital mortality.

Results: We performed a multivariate logistic regression analysis of mortality risk due to AKI including age, sex, initial and basal SCR, standardised ISI and KPS prognostic indexes and type of AKI treatment received. AKI in the elderly (≥65yo) was more functional (49%(vs34%) and required less RRT (25%(vs29%). Mean ISI was higher and mean KPS was lower in ≥65; however, we stratified them and found the elderly were less likely to die when treated with high KPS (ISI≥5 vs ≤5:19%, KPS≥70% vs<70%:23%) We found RRT, high ISI and low KPS to be the predictors of mortality. Mortality was lower in elderly patients (overall mortality rate: 473pts<17%; 65: 257pts - 9%; ≥65: 216pts<8%). Age’s association with mortality was inverse (OR=0.98, 95%CI=0.96- 0.98; being ≥65 and the association with lower mortality had a greater magnitude Table 1) the association with being ≥65yo remained similar, but the ≥85 group mortality association was not statistically significant.

Conclusions: Age is inversely associated with mortality due to AKI in our sample, this association being statistically significant when evaluated on its own, and also when comparing rates between <65yo and ≥65yo. Age is not an adverse prognostic factor of in-hospital mortality due to AKI. The association between being ≥65yo and mortality suggests age is a protective factor from mortality due to AKI.

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PUB014
Dual Plasma Molecular Adsorption System Combined with Plasma Exchange and CVVH Improve Acute Liver Failure and Acute Renal Failure After Cardiopulmonary Bypass
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Background: Cardiovascular surgery patients use hypothermia cardiopulmonary bypass, may cause important organ ischemic injury, for example postoperative acute renal failure and acute liver failure, dual plasma molecular adsorption system (DPMAS) combined with plasma exchange, continuous CVVH can effectively improve liver function and renal function.

Methods: December 2018 - February 2019, Department of Cardiology, the First Affiliated Hospital of Xi’an Jiaotong University, underwent extracorporeal circulation, combined with plasma exchange, continuous CVVH can effectively improve liver function and renal function.

Results: One of the 3 patients underwent 3 times of PE+DPMAS, one case performed 2 times of PE+DPMAS, and one case performed PE+BS330. Total bilirubin: preoperative 16.26±6.91umol/L, first post 0h 72.23±31.95umol/L, first After 24h 91.1±11.0umol/L, after the second treatment 0h 55.35±8.41umol/L, after the third treatment 192±8.63umol/L; creatinine: before operation 65±15.13umol/L, the first before 251±49.1umol/L, after the first treatment 0h 202±165.463umol/L, after the first treatment 24h 182.67±112.5umol/L, after the second treatment 0h 188±151.32umol/L, after the second time 98±107.5±63.35umol/L.

Conclusions: 24h after treatment compared with before treatment: total bilirubin decreased 24%, direct bilirubin decreased 33%, indirect bilirubin decreased 40%, AST decreased 89%, ALT decreased 66%, as DPMAS treatment mode can directly and effectively remove various kinds of patients Toxic substances, toxins, significantly shorten the course of disease.

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PUB015
Anuric AKI with Rapid Recovery Secondary to Vancomycin and Aminoglycoside Nephrotoxicity
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Introduction: The increasing use of higher vancomycin doses has been associated with an increased incidence of vancomycin induced AKI, although the precise mechanisms remain unclear. We report a rare case of anuric AKI secondary to concomitant use of high doses of vancomycin and an aminoglycoside, which resolved completely after discontinuing these antibiotics and serial dialysis sessions using highflux membranes.

Case Description: A 22 year old woman with cystic fibrosis-associated bronchiectasis developed fever, dyspnea and a productive cough, consistent with a cystic fibrosis exacerbation. Her baseline kidney function was normal (serum creatinine 0.8 mg/dl). She was started on empiric antibiotics, including vancomycin 1 gm IV TID and tobramycin 180 mg IV daily. One week later she presented to the emergency department with a 5-day history of lower extremity edema, anorexia, profound nausea, and anuria (80 ml daily). She was afebrile, and her vital signs were stable. Pertinent labs included: serum creatinine of 12.6 mg/dl, random vancomycin level 200 mcg/ml, random tobramycin level 18 mcg/ml. Urinalysis revealed muddy-brown granular casts suggestive of ATN. Renal ultrasound was unremarkable. She was suspected as having anuric AKI due to vancomycin and gentamicin toxicity. The antibiotics were stopped, and she underwent 7 sessions of intermittent hemodialysis using high-flux membranes over the ensuing 2 weeks, with serum vancomycin and tobramycin reduced into the therapeutic range. Her urine output improved dramatically, and her renal function returned to normal.

Discussion: Vancomycin and aminoglycoside interactions are on the rise, coinciding with the increase in recommended therapeutic vancomycin trough levels. The rapid rise in serum creatinine levels reflects both the AKI itself, as well as the competition of vancomycin and creatinine secretion by the same organic cation transporter in the proximal tubule. Synergistic use of vancomycin with an aminoglycoside may lead to worsening nephrotoxicity and can be mitigated by monitoring their plasma levels and subsequent withdrawal as necessary. Temporary hemodialysis using high flux membranes may hasten renal recovery by rapidly lowering the serum antibiotic levels.

PUB016
Relationship Between the Presence of Infectious Disease and Clinical Outcomes of Patients with Cardiorenal Syndrome Type 1
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Background: Cardiorenal Syndrome type 1 (CRS-1) can be triggered by an infection. The pathophysiological basis is vascular congestion, which is why it has been treated with diuretics and hemodynamic strategies. However, different strategies of diuretics, but in the presence of infection, where the inflammatory, neurohormonal and hemodynamic effects can compromise the efficacy of the diuretics and potentially worsen clinical evolution. Here we compare the clinical evolution during the hospitalization of CRS-1 patients with and without infection.

Methods: This is a retrospective cohort study conducted in the Hospital Civil of Guadalajara “Fray Antonio Alcalde”, from January 2015 to September 2019. Patients hospitalized in CRS-1 patients, we showed the clinical evolution and treatment strategies analyzed according to the presence or absence of infection. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Results: We identified 63 patients classified as having CRS-1, 28 (44.4%) were classified as having an infectious disease, the mean age in the group of infection was 62 years (±14.6) and 58 (±12.4) in no infection group. There were no statistically significant differences between the clinical outcomes of both groups, we found that in the infection group, the median length of hospital stay was 8 days and 7 days in the no infection group (p=0.065). Three patients (10.7%) of the group with infection received renal replacement therapy and 1 (2.9%) of the group without infection (p=0.315). In the group with infection 2 patients died (7.1%), while none in the uninfected group (p=0.194). sCr values trend to diminish in a similar manner through the both groups. Serum sodium trend to increase thought the hospitalization but there was no significant difference between groups. During hospitalization we found that all patients received furosemide at least the first 3 days of hospital stay, in addition the strategy of diuretics chosen for the treatment was similar between groups.

Conclusions: Here we show that the clinical evolution of patients with CRS-1 is similar in the presence or absence of infection. We anticipate that this study may be a reason to expand knowledge in patients with CRS-1 and the presence of infection.
**PUB017**

**Before Crystalluria: High-Dose Amoxicillin Infusion Leads to Intracellu-
lar Amoxicillin-Induced Nephrotic Osmosis**


**Background:** Amoxicillin (AMX) is one of the most commonly prescribed antibiotics. Its renal toxicity is poorly described. The presence of urinary AMX crystals during acute kidney injury (AKI) has been proposed as a mechanism of intra-tubular precipitation. To date, deposition of AMX crystals within the kidney has not been reported.

**Methods:** We describe two cases of AMX-associated AKI and analysis of their renal biopsies using Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). We then injected escalating doses of AMX (200-3000mg/kg/day intraperitoneally) for 2 days into rats and for up to 9 days in mice. Crystallization, renal function and histology of rodents were analyzed at sacrifice.

**Results:** Two patients of 58 and 68 years old were hospitalized for bacterial meningitis and developed ARF following high-dose AMX injection. They received 12/day and 25/g day intravenously respectively. Optical microscopy analysis of their renal biopsies revealed in both cases severe tubulopathy with unexplained osmotic nephrosis (ON) lesions (Fig 1A). In one case, the FTIR analysis combined with the SEM showed an intracelluar-tubular AMX deposit (Fig. 1B and C). Crystalluria was not observed in these two cases. Experimentally, injection of high dose AMX in rodents resulted in ARF with acute tubular necrosis and conspicuous ON lesions. No intrapericellular AMX crystals or crystalluria were observed.

**Conclusions:** Our study suggests that in both humans and rodents, high dose AMX infusion leads to a yet unsuspected tubular toxicity. Renal lesions are featured by tubular ON surrounding intracellular-tubular deposits of AMX.

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**PUB018**

**Granulomatous Interstitial Nephritis (GIN) in a Patient with B-Cell Lymphoma**

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**Introduction:** GIN is a rare disease, seen in less than 1% of renal biopsies. The commonest causes are infections, drug reactions, and sarcoidosis. We present a case of GIN in an elderly patient who presented with acute kidney injury (AKI) in the setting of recurrent B-cell lymphoma (BCL).

**Case Description:** A 67-year old Caucasian gentleman with history of large BCL in complete remission (2009), admitted with a relapse in November 2018, with weight loss, high grade fever of unknown cause and non-oliguric AKI requiring hemodialysis (HD). Physical examination showed no pertinent findings. Past Medical history included hypertension, with no prior history of kidney disease, liver disease or diabetes. Imaging showed bilateral enlarged kidneys (14 cm each). PET scan showed increased activity in both kidneys, liver and cervical lymph nodes, consistent with relapse of BCL. No mediastinal or abdominal/pelvic lymphadenopathy were noted. MRI of brain and bones, marrow biopsy were unremarkable. Patient received multiple courses of antipyretics, antibiotics (Zosyn, Vancomycin) and 3 rounds of salvage chemotherapy with R-GCP followed by DHAC, with no significant improvement in renal function.

**Discussion:** Labs revealed anemia (Hb 10.4) and elevated serum creatinine (Cr) 5.8 mg/dl. (Baseline Cr 1.0-1.1). No other electrolyte or liver function tests abnormalities were noted. Urine exam showed 2 protein, > 5 RBC and 0.9 g proteinuria, with no RBC casts or abnormal WBCs. Autoimmune profile, complement levels and infectious profile, were all unremarkable. Serum ACE level was 26 U/l (ref 8-53). Percutaneous renal biopsy revealed diffusin GAIN with CD3 positive (+) T cells and macrophages, no CD 20 + B cells, providing evidence against lymphomatous infiltration. Special stains for fungi and AFB were negative. The patient was subsequently started on prednisone 60 mg/day and received HD for 2 months. Kidney function subsequently improved, HD was stopped, and prednisone was tapered off after 8 weeks of use. Following month, patient underwent autologous stem cell transplant with most recent Cr 1.6 mg/dl and no proteinuria. GIN in this case was related to antibiotics used for fever of unknown origin. Although uncommon, GIN should be considered in the differential diagnosis of AKI in the setting of lymphoma with renal enlargement. Timely diagnosis and optimal management ensure a good outcome.

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**PUB019**

**Multiple Myeloma with the Onset of Ankylosis and Arthralgia and Subsequent Hypercalcemia and Acute Renal Injury: A Case Report**

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**Introduction:** Ankylosis and arthralgia have rarely been reported as initial manifestations in multiple myeloma (MM).

**Case Description:** Here we reported a male patient with the onset of ankylosis and arthralgia, who had been seeing rheumatologists for one month without any conclusive diagnosis until admission due to hypercalcemia and acute renal injury. MM was confirmed by bone marrow aspirate. Renal impairment due to cast nephropathy and nephrocalcinosis was confirmed by renal biopsy. He reported improvement of ankylosis and arthralgia in both knees after plasma exchange and hemodialysis and was then referred to Hematology Division, where he received three courses of dexamethasone and bortezomib chemotherapy. Renal function did not recover completely.

**Discussion:** Ankylosis and arthralgia are rare in MM and the mechanisms are not clear. Further immunological blotting might help to elucidate the pathogenesis.

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**PUB020**

**Clinical Profile and Outcome of Dialysis-Requiring AKI Among Elderly Patients in St. Luke’s Medical Center-Quezon City from January 2014 to January 2019**

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**Background:** The incidence rate of AKI is highest in the elderly. It is related to an increased rate of mortality, morbidity, and hospitalization, with the elderly population at high risk of developing dialysis-requiring AKI. It has been established that the temporal incidence of dialysis-requiring AKI and mortality has not yet been recently characterized, hence this study aims to determine the clinical profile and outcome of dialysis-requiring AKI among this population.

**Methods:** This is a descriptive, non-observational, retrospective, case series study. It includes elderly patients 65 years old and above, admitted at the center from January 2014 to January 2019 who were diagnosed to have dialysis-requiring AKI and underwent hemodialysis.

**Results:** Among the 193 eligible patients, mean age was 77.08 ± 8.31, 55.44% males and 44.56% females. Most common co-morbidities identified were hypertension and diabetes. The most common encountered complication during hemodialysis was hypotension. The 30-day mortality rate is 61.66% and average length of hospital stay was 18 days. The average days from the day of hospitalization to initiation of hemodialysis was an 3 days. There is a significant change from baseline creatinine levels and eGFR to its measurements upon renal recovery.

**Conclusions:** Diagnosis of dialysis-requiring AKI in the elderly is associated with a poor outcome. It is related to an increased in-hospital stay. The most common complication observed during hemodialysis is still hypotension. Renal recovery can be expected when eGFR returns to baseline levels. There is a significant change from baseline creatinine levels and eGFR to its measurements upon renal recovery.
Complications Associated with CRRT in a Community Hospital

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Background: Continuous renal replacement therapy (CRRT) is used for the treatment of critically ill patients with acute kidney injury, who are unable to tolerate intermittent hemodialysis due to hemodynamic instability. Complications of CRRT are the result of vascular access, bleeding, and electrolyte imbalances. In February 2016, CRRT became available in our community hospital in Chesterfield, Missouri. We investigated our initial complications associated with CRRT in our hospital and compared to complication rates reported in the literature.

Methods: We conducted a retrospective study of adult patients initiated on CRRT at St. Luke’s Hospital in Chesterfield between February 2016 and May 2018. The data were collected via Cerner Powerchart EMR.

Results: Among 52 qualified patients, there were a total of 162 dialysis sessions. Complications as number per dialysis session were as follows: 0/162 infections, 69/162 electrolyte imbalances, 3/162 arrhythmias, 7/162 bleeding, and 13/162 access problems. Out of the 69 electrolyte imbalances, 46 sessions had hypophosphatemia and 5 sessions had hypokalemia.

Conclusions: In a community hospital setting, within our first two years of implementing CRRT, we saw expected electrolyte imbalances in our patients (hypophosphatemia and hypokalemia); however, our incidence was less than in the literature. Infection, arrhythmias, and access related complications were also comparable to or lower than those in the literature. We attribute this to a common EMR order set, limited CRRT utilization to our medical and surgical ICUs, and initiation of CRRT limited to nephrology.

AKI due to Anticoagulant Related Nephropathy (ARN) and Thin Basement Membrane Disease (TBMD): Old Entities with a New Twist

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Introduction: ARN is a significant but under recognized complication of anticoagulation that is also associated with increased renal morbidity and all-cause mortality. It is defined as AKI without any other obvious etiology in the setting of INR>3, in patients on warfarin. TBMD is a relatively common cause of micro and less often macroscopic hematuria in adults.

Case Description: 66 year old male with hypertension, rheumatic heart disease with mechanical aortic and mitral valve replacement in 1995, on chronic warfarin therapy was admitted with AKI with serum creatinine 4.1mg/dl, (baseline 1.3 mg/dl a month ago), anemia and brown colored urine for a week. His INR on admission was 2.8. All other pertinent history was negative. Physical exam and renal ultrasound were unremarkable. Urinalysis showed dysmorph red blood cells. Work up including ANA, anti-GBM, HIV, Hepatitis panel, ANCA, Complements, SREP, UPEP were negative. His warfarin was held and he was started on heparin infusion for renal biopsy. Renal biopsy showed acute tubular injury with recent and remote intratubular hemorrhages mostly in distal tubule. The intratubular granules stained positive for Gomori’s stain, all consistent with ARN.

Electron microscopy showed TBMD. With limited data on alternative anticoagulation options for mechanical heart valves, warfarin was restated at lower therapeutic goal, with subsequent improvement of renal function.

Discussion: ARN is known to most likely develop within 6-8 weeks of initiation of therapy, in the background of over anticoagulation. TBMD was most likely an additional risk factor that made our patient vulnerable to ARN. Although our patient was within therapeutic INR goal for his disease, it was higher than 3 few times in past. The dilemma is that although he had lived with these conditions, what triggered him to have an event now? We postulate that there may be a plausible third trigger that unmasked his underlying pathology. The other unsolved puzzle is management of patients who need warfarin and traditionally warrant higher INR goal. Our case is therefore unique with respect to timelines of presentation, and ARN diagnosis with no clear evidence of over anticoagulation for his clinical condition.
**PUB024**
Effects of 5-HT3A Antimetabolite Drugs on Cisplatin-Induced Nephrotoxicity
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**Background:** Cisplatin is an important component of chemotherapy for patients with lung, head, and neck, and cervical cancer that induces cellular apoptosis by forming intranuclear DNA crosslinks that prevent DNA transcription. While desirable for malignant cells, cisplatin cytotoxicity in renal cortex leads to AKI. Tubular epithelial cell exposure to cisplatin is determined by its transport via organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1). MATE1 is inhibited by 5-hydroxytryptamine-3 receptor antagonists (5-HT3 RA) commonly used as antiemetics in oncology. Our data indicates that ondansetron use in mice results in greater GFR loss relative to other 5-HT3 RA. We sought to examine the association of 5-HT3 RA use in patients receiving cisplatin with AKI.

**Methods:** In retrospective chart review, we identified 7,094 patients who received cisplatin, of which 3,997 (56.3%) were treated with a 5-HT3 RA that included either granisetron, ondansetron or palonosetron. Fisher’s exact test was used for testing associations between categorical variables. Multivariable associations with AKI were analyzed using logistic regression.

**Results:** Ondansetron accounted for 27% of overall 5-HT3 RA use. AKI was observed in 1,737 or 24.5% of patients receiving cisplatin. 5-HT3 RA use was independently associated with lower risk of AKI (OR 0.38; 95% CI, 0.23-0.65, p< 0.001). Other significant multivariable associations with AKI are found in Table.

**Conclusions:** Protective effect of 5-HT3 RA use in humans, contrary to our animal model, is likely accounted for by lesser inhibition of MATE1 by the most commonly used palonosetron. Increased risk of cisplatin-induced tubular toxicity in this scenario is likely further offset by the lower risk of pre-renal AKI from vomiting and anorexia, incited by cisplatin. Effects of the individual 5-HT3 RA on renal outcomes are the subject of active investigation.

**OR (95% CI) p = value**

| Age | 0.81 (1.01-1.22) | <0.01 |
| Methylprednisolone | 1.46 (1.76-1.86) | <0.01 |
| Black race | 3.92 (1.90-7.98) | <0.01 |
| White race | 2.71 (1.43-5.14) | <0.01 |
| 5HT3 RA use | 0.38 (0.23-0.65) | <0.01 |

**PUB026**
Incidence of Contrast-Induced Nephropathy in Intermediate- to Very High-Risk Groups from a Single Center
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**Background:** Contrast induced nephropathy (CIN) is defined as an elevation of serum creatinine (Scr) of more than 25% or a≥0.5 mg/dl from baseline within 48-72 hours in the absence of alternate causes of acute kidney injury. Incidence of CIN in patients has been heterogeneously reported to be as low as 2% and as high as 50% depending upon the setting and population under scrutiny. It is an area of active clinical research and much controversy. There is no placebo controlled randomized controlled trials that establishes causation in CIN. Recently many studies have mushroomed that suggested that the risk of CIN is perhaps overestimated. Considering the international debate and the local scenario, we conducted this study to estimate the incidence of CIN in our center.

**Methods:** This prospective study was conducted between January and December 2018. It was approved by the ethical review committee and informed consent was taken from all patients. The patients in nephrology service with contrast media exposure and having Crcl between 20ml/min/2 and 60ml/min/2 were included in the study. As per CIN risk scoring system, only patients with intermediate to very high risk scores for CIN were included. Baseline creatinine was measured and post exposure RFIs were recorded at 24, 48 and 72 hours.

**Results:** Age: The patients ranged between 24 and 75 years (Mean 57 years) and 66% were of them were males. 80% of the patients underwent coronary angiography and 20% received contrast for computerized tomographic scans. Patients were equally distributed in the categories of intermediate, high and very high risk for CIN. 80% were hydrated per protocol prior to contrast exposure. Mean Scr of the cohort at baseline and after 72 hours were 2.12mg/dl and 2.10mg/dl respectively. Only 1 patient out of 30 patients, from the very high risk group, developed CIN.

**Conclusions:** The incidence of CIN in our small but high risk cohort was 3.3%. Among subgroup of the coronary artery disease patients that underwent angiography, majority benefited from life-saving interventions that were initially withheld for the overfear of CIN. National level studies should document the local incidence so that informed decisions could be formulated tilting the risk benefit ratio of contrast exposure maximally in favor of the patients.

**PUB027**
Can a Patient Develop Rapidly Progressive End-Stage Pyelonephritis? Diana Mahbod, Dallas Renal Group, Garland, TX.

**Introduction:** Certain diagnoses can be inferred based on a kidney biopsy specimen alone. Pyelonephritis is one of these diagnoses, with a neutrophil-rich interstitial infiltrate, neutrophilic rimming of tubules with tubulointerstitial infiltrates, and neutrophilic casts. These findings are in contrast to acute interstitial nephritis which would demonstrate lymphocyte-rich inflammation. While AIN can progress rapidly and lead to dialysis-dependence, often improving with high dose steroids, acute pyelonephritis has not been described to lead to sudden onset renal failure with long-term dialysis dependence.

**Case Description:** A 57 year old male with history of chronic lymphoedema presented with a creatinine of 22 from baseline 0.8 several years prior. There was no evidence for UTI or obstruction. Urine studies revealed trace blood, moderate LE, 11 WBC and 2 RBC per HPF, with spot urine P/Cr of 4.5 grams/gram. Serologies and renal ultrasound were unrevealing except for large kidneys. Hemodialysis was initiated the day after admission for uremia and kidney biopsy revealed findings consistent with acute pyelonephritis. EM findings of patchy foot-process effacement suggested a possible unsampled focal segmental glomerulosclerosis. The patient remained dialysis-dependent despite a course of high-dose steroids, and rebiopsy was recommended but refused by the patient.

**Discussion:** Clinical context is crucial for interpretation of a pathology specimen but certain conditions such as acute pyelonephritis demonstrate pathognomonic findings. In this case, the biopsy findings were unexpected, especially the progression to presumed end-stage renal disease. When faced with diagnostic dilemmas, the clinician must consider whether alternative treatments exist to reverse the kidney damage, and alternative diagnoses must also be considered, with possible benefit to repeat kidney biopsy.
### PUB028

**Atg5 Overexpression in Proangiogenic Cells Significantly Improves Cell-Mediated AKI Protection**

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**Background:** Acute Kidney Injury (AKI) significantly worsens the prognosis of hospitalized patients. Cell-based strategies have been established as reliable option for improving AKI outcomes in experimental AKI. Our studies performed in recent years utilized Proangiogenic Cells (PACs). Autophagy (AP) is commonly regarded as process of endogenous self-defense. The AP cascade, which may be stimulated by either substrate deprivation or certain exogenous / endogenous stressors, involves the activation of numerous proteins, the so-called Autophagy-related proteins (Atg proteins). Among these, Atg5 has been suggested to play a key role in augmenting AP. The current study evaluated whether selective Atg5 activation in syngeneic murine PACs may result in improved cell-mediated AKI protection.

**Methods:** Cultured murine PACs were selectively transfected for Atg5. Successful transfection was verified by detecting red fluorescing cells. AKI was induced in male C57/Bl6N mice (8-12 weeks) by bilateral renal ischemia (IRI - 40 minutes). Transfected cells were i.v. injected post-ischemia. Mice were analyzed 48 hours and 6 weeks later.

**Results:** IRI induced significant kidney excretory dysfunction as reflected by higher serum creatinine levels (48 hours and 6 weeks). Cell administration (either native or after transfection) did not improve AKI outcomes at 48 hours. At 6 weeks, injection of native cells resulted in lower serum creatinine, this effect was even more pronounced if transfected cells were applied.

**Conclusions:** Together, our data show that selective Atg5 overexpression in murine PACs substantially augments cell-mediated AKI protection in the long-term. Thus, a new strategy for improving AKI protective effects of PACs has been identified.

### PUB029

**Validation of Transcutaneous Fluorescence for Monitoring Gut Permeability**

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**Background:** At the gastrointestinal mucosa billions of microbes are in close contact with the host immune system. The maintenance of this barrier is vital for health and its compromise has been implicated in a variety of acute and chronic illnesses, including sepsis and chronic kidney disease. We have previously used transcutaneous fluorescence to measure the glomerular filtration rate using a fluorescent, inert i.v.-injected marker. We hypothesized that the transcutaneous fluorescence method can be adapted to measure intestinal permeability following oral gavage of a suitable marker.

**Methods:** Intestinal permeability was studied in the context of sepsis caused by the cecal ligation and puncture (CLP) surgical procedure. We compared 40 kDa FITC-Dextran and FITC-Ficoll as fluorescent markers. They were administered by oral gavage 3 hours prior to CLP to enable loading of the intestines. A transcutaneous fluorometer was attached to the skin (covering the spine) of each mouse, enabling the appearance of the fluorophore in the circulation to be detected. The stability of the fluorophores was evaluated in the blood and urine using ultrafiltration.

**Results:** Using the FITC-Dextran, post-mortem examination revealed significant fluorescence in the bladder despite the 40 kDa size of the parent molecule. After ultrafiltration of the urine, the fluorescence was able to pass through a 10 kDa filter indicating degradation, probably in the GI tract. In contrast, fluorescence from the injected FITC-Ficoll was not found in the urine. Following CLP, an increase in transcutaneous fluorescence was detected at ~3 hours that was absent in the sham.

**Conclusions:** This technique is a viable new approach for the measurement of intestinal permeability that avoids the need for blood collection. FITC-Dextran is degraded and can be filtered by the kidney. Using FITC-Ficoll should prevent underestimation of gut permeability due to glomerular filtration of fluorophore. Consistent with hemorrhagic ascites, we measured systemic dysfunction, intestinal permeability was detected ~3 hours after the induction of sepsis. We propose that gut permeability should be added to conventional multi-organ failure scores.

**Funding:** NIDDK Support

### PUB030

**Biomarker-Based Differentiation of Hemodynamic and Intrinsic AKI Agrees with Clinical Adjudication by Nephrologists**

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**Background:** We aimed to determine if clinical adjudication by nephrologists agrees with the biomarker-based differentiation of AKI by urine biomarkers.

**Methods:** We abstracted and created graphical trends of longitudinal variables from 430 deceased donors charts. AKI was defined as a 0.3 mg/dL or 50% increase from the lowest recorded creatinine value. Three nephrologists independently reviewed AKI cases to adjudicate into hemodynamic, intrinsic or mixed subtypes; final diagnosis was determined by majority adjudication. If all three nephrologists disagreed, the phenotype was designated as mixed. We measured urine biomarkers at organ procurement and evaluated differences among AKI subtypes. Our secondary analysis assessed the association between subtypes and recipient delayed graft function (DGF) and 1-year eGFR.

**Results:** Of 430 donors, 68% had AKI; 36% were adjudicated as hemodynamic, 29% intrinsic, and 35% mixed. Stages 2 and 3 AKI, central venous pressure (CVP), and ventilator oxygen requirement were significantly higher in intrinsic AKI. There were no differences in vasopressor use or fluid balance. Biomarkers were significantly different in intrinsic AKI compared to other subtypes (Figure). In secondary analysis, intrinsic AKI was independently associated with higher odds of DGF [OR (95%CI); 2.52 (1.30, 4.88)] and lower 1-year eGFR [B coefficient (95% CI); -8 [-14.2, -3)] as compared to hemodynamic AKI after adjusting for donor and recipient characteristics. Results were similar when comparing intrinsic AKI to the mixed subtype.

**Conclusions:** Clinically adjudicated hemodynamic and intrinsic AKI were shown to be biologically different by urine biomarkers and were associated with different recipient outcomes.

**Funding:** Private Foundation Support

### Distribution of Urine Biomarkers Among AKI Subtypes

#### PUB031

**Kidneys Progressing from AKI to CKD Gradually Lose Their Inherent Potential to Recover**

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**Background:** It is increasingly clear that AKI can result in the development of CKD in humans. Murine renal unilateral ischemia-reperfusion injury (without contralateral nephrectomy; UIRI) models this AKI-CKD progression in the injured kidney (Le Clef et al, Plos One 2016). In mice, we and others demonstrated that contralateral nephrectomy (Nx), when performed shortly after UIRI (i.e. 3 days), is able to nearly completely attenuate the progression to CKD. Although non-translatable, Nx can be considered an experimental therapeutic intervention that incites inherent physiological repair/recovery

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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mechanisms in the nephron. Here, we investigate in rats to what extent contralateral Nx is able to attenuate renal injury in the setting of progressive renal damage when performed well beyond the acute injury phase, i.e. increased Nx delay time after UIRI.

Methods: AKI was induced in male Wister rats by left UIRI (60 min, 35°C body temp) after which contralateral Nx was performed 3, 10 or 20 days later. Renal function was assessed by serum/urine creatinine and transcutaneous GFR measurement 24 h and 72 h after Nx and weekly thereafter. In controls no Nx was performed until 24 h before euthanization at week 11 to allow renal function assessment at that time. Rats were euthanized 11 weeks after Nx. Renal histology was evaluated by light microscopy.

Results: When no Nx was performed, renal function of the injured kidney decreased 44% compared to sham at week 11. Nx at day 3 induced full functional recovery from week 5 after Nx on, whereas Nx at day 10 and 20 led to a persistent 20% loss of renal function from week 1 after Nx on (p<0.05). Nx at day 3 was able to attenuate renal atrophy and tubulointerstitial expansion. Nx at day 10 and 20 were less efficient and led to 1.6 (p<0.05) and 2.6 (p<0.05) fold increase of tubulointerstitial area compared to sham. There was no difference in renal function outcome between Nx at day 10 and 20.

Conclusions: Early contralateral Nx after UIRI rescues renal function and morphology, whereas delayed Nx does not allow full recovery of the injured kidney. These results imply that an early contralateral kidney loses its intrinsic (contralateral) recovery potential once and that an early intervention is more efficient in averting CKD outcome. The contribution of compensatory hypertrophy versus epithelial repair needs to be investigated.

PUB032
Role of Endothelial KLF4 in Determining the Severity of Cisplatin-Induced AKI in Mice
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Background: Cisplatin is a common cause of AKI in humans. The role played by the Kruppel-like Transcription factor-4 (KLF4) in the pathogenesis of cisplatin-induced AKI is not well known. This study had two objectives: i) to develop a novel model of cisplatin-induced AKI in mice and ii) to use this model to determine whether KLF4, expressed in endothelial cells (EC KLF4), contributes to determining the severity of this form of renal failure.

Methods: Cisplatin-induced AKI was induced by giving 3 daily doses of cisplatin (15mg/kg) (or its vehicle) to mice by intraperitoneal injection. Blood samples were obtained on Day 0 (immediately before the first dose of cisplatin/vehicle), and again on Days 4, 8 and 12.

Results: In wild type (WT) mice, the creatinines on Day 0 were comparable in the vehicle- and cisplatin-treated mice (0.099±0.005 and 0.112±0.004mg/dl respectively). On Day 4, the creatinines in vehicle- and cisplatin-treated mice were no different from those on Day 0. However, on Day 8, the creatinine in the cisplatin-treated group increased to 0.414±0.127mg/dl, and was higher than the creatinine in the vehicle-treated mice (0.122±0.007mg/dl) (p<0.001). On Day 12, the creatinine in the cisplatin-treated mice fell to 0.201±0.005mg/dl (p<0.01 vs day 8), and was comparable to the creatinine in the vehicle-treated mice (0.112±0.01mg/dl). We next compared the effects of cisplatin-induced injury in EC KLF4 KO mice and their Cre controls. The creatinines in the vehicle- and cisplatin-treated Cre and KO mice on Day 0 were comparable. On Day 4, all the KO mice (but none of the Cre mice) died after blood samples were obtained. The creatinine in cisplatin-treated KO mice on Day 4 was considerably higher (1.061±0.01mg/dl) than in the vehicle-treated KO mice (0.110±0.007mg/dl) (p<0.001). In the Cre mice, the creatinines in the vehicle- and cisplatin-treated mice on Day 4 were comparable to each other and to the creatinines on Day 0.

Conclusions: We have developed a model of cisplatin-induced AKI which is characterized by a developmental phase followed by a recovery phase. This pattern is similar to that observed in humans with AKI. We also show that EC KLF4 plays a major role in protecting endothelial cells from injury, and in reducing the severity of renal failure caused by cisplatin.

Funding: Private Foundation Support

PUB033
Interaction of Properdin and Macrophages in Renal Ischemia-Reperfusion Injury and Its Related Models
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Background: Properdin, the only positive regulator of complement alternative pathway, may also act as a pattern-recognition molecule. Macrophages play critical roles in the kidney. Here, we investigate in rats to what extent contralateral Nx is performed, renal function of the injured kidney decreased 44% compared to sham at week 11. Nx at day 3 induced full functional recovery from week 5 after Nx on, whereas Nx at day 10 and 20 led to a persistent 20% loss of renal function from week 1 after Nx on (p<0.05). Nx at day 3 was able to attenuate renal atrophy and tubulointerstitial expansion. Nx at day 10 and 20 were less efficient and led to 1.6 (p<0.05) and 2.6 (p<0.05) fold increase of tubulointerstitial area compared to sham. There was no difference in renal function outcome between Nx at day 10 and 20.

Conclusions: Early contralateral Nx after UIRI rescues renal function and morphology, whereas delayed Nx does not allow full recovery of the injured kidney. These results imply that an early contralateral kidney loses its intrinsic (contralateral) recovery potential once and that an early intervention is more efficient in averting CKD outcome. The contribution of compensatory hypertrophy versus epithelial repair needs to be investigated.

Funding: Private Foundation Support

PUB034
Escherichia coli-Associated Hemolytic Uremic Syndrome (HUS) Treated with Eculizumab
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Introduction: Eculizumab, a terminal complement inhibitor, is enjoying use in a number of complement-disregulatory diseases. A major use of eculizumab is treatment of atypical hemolytic-uremic syndrome (STAHUS). Since Shiga toxin-associated HUS (STAHUS) are driven by toxic complement dysregulation, it stands to reason that eculizumab might provide therapeutic benefit in STAHUS.

Case Description: A 41-year old white male presented with a 2-day history of abdominal pain and frankly blood diarrhea. The only antecedent event of note was consumption of sushi. Initial exam showed normal vital signs and bilateral lower abdominal tenderness without signs of peritonitis. He received empiric antibiotics (ciprofloxacin and metronidazole) along with supportive care. Over 24 h he developed hypotensive encephalopathy, severe azotemia with oliguria, and a sharp drop in hemoglobin and platelet count. After 96 h his stool culture disclosed E. coli O157:H7, thus prompting the diagnosis of E. coli O157:H7-associated hemorrhagic enterocolitis with probable neurologically significant HUS. He underwent one session of plasma exchange followed by a single 900-900mg dose of eculizumab. Continuous hemodialysis was ultimately initiated for oliguric AKI. After almost 3 weeks in hospital he enjoyed a near-total recovery and was discharged to a rehabilitation facility prior to return home. The chronology of key clinical events and laboratory parameters is shown in the figure.

Discussion: We demonstrate here the favorable clinical course of Shiga toxin–associated hemolytic–uremic syndrome (STAHUS) following a single dose of the terminal complement inhibitor eculizumab in an otherwise healthy adult patient. Successful cases like this add to the base of evidence that eculizumab is useful in treating multiple diseases driven by complement system dysregulation.
understanding in the pathophysiology of rhabdomyolysis at the muscular level induced by activation of neurohumoral response, tubular damage induced by renal vasoconstriction, described in multiple review papers, involves fluid sequestration and subsequent

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Muscle-Renal Syndrome

Introduction: Pathophysiology of non-traumatic rhabdomyolysis caused by viral infection has been poorly understood. We present a case of Adenovirus infection causing severe rhabdomyolysis and ARF that required dialysis for 2 weeks before complete clinical recovery.

Case Description: 29-year-old African American female with hypertension presented with flu like symptoms and decreased urine output. She had body aches, sore throat, loss of appetite, fevers/chills, and bilateral lower extremity weakness for four days. She had hives, rash, and bilateral lower extremity weakness for one day. She subsequently developed severe acute kidney dysfunction exhibited as elevated BUN and creatinine level at day 2 after cisplatin injection. Mice with pretreatment of CHP showed markedly attenuated cisplatin-induced acute kidney injury. Additionally, pretreatment of CHP improved the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) that are the enzymes to defense against oxidative stress. Comparable findings were observed in the expression of p53, Bax, caspase-3, and c-Jun which is associated with apoptosis, especially intrinsic apoptotic pathway. In cultured hTECs, which is a human kidney epithelial cells, CHP showed a protective effect against oxidative stress that induced by H2O2. Additionally, live cell frequency was increased with CHP dose dependent manner. This study demonstrated that CHP may protect against cisplatin-induced cell apoptosis and AKI through suppression of p53 and up-regulation of antioxidant defense.

Conclusions: Together, this study demonstrated that CHP may protect cisplatin-induced AKI through inhibiting apoptosis. Considering the effects of CHP, it can be applied to the AKI protection.

PUB038

Isoliquiritigenin Attenuates Lipopolysaccharide-Induced AKI Through Suppression of the HMGB1 Pathway Against Ferritinophagy

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Background: Septic acute kidney injury (AKI) mainly results in life-threatening renal dysfunction involving renal tubular injury to bring heavy burden to patients in intensive care unit (ICU). However, there is still a lack of therapy to prevent septic AKI effectively and inexpensively.

Methods: To observe the role and novel mechanism of isoliquiritigenin (ISL) which isolated from the roots of licorice in septic AKI, we used LPS to induce renal tubular injury and then observed the expression of HMGB1 and HMGB1-related pathways. In this study, we sought to investigate whether and how cyclo(His-Pro) prevents cisplatin-induced AKI in mice.

Results: Cyclo(His-Pro) (CHP) is an endogenous cyclic dipeptide that exerts cellular protective effects against anti-oxidative damages. However, the role and mechanisms for CHP in preventing cisplatin-induced nephrotoxicity remains largely unknown. In this study, we sought to investigate whether and how cyclo(His-Pro) prevents cisplatin-induced acute kidney injury (AKI) mouse model.

Methods: In this study, a single intraperitoneal injection of cisplatin (10 mg/kg) was employed to induce AKI in C57BL/6 mice. To determine the role of CHP on cisplatin-induced AKI, the mice were pretreated with CHP or vehicle by gavage at a dosage of 5 mg/kg or 10 mg/kg 1 h before cisplatin injection. To explore the cell protective effect of CHP, in vitro study was also performed with primary cultured human tubular epithelial cells (hTECs). ROS assay was tested to measure antioxidant effect of CHP.

Results: The mice developed severe acute kidney dysfunction exhibited as elevated BUN and creatinine level at day 2 after cisplatin injection. Mice with pretreatment of CHP showed markedly attenuated cisplatin-induced acute kidney injury. Additionally, pretreatment of CHP improved the activity of superoxide dismutase (SOD) and glutathione peroxidase (GPx) that are the enzymes to defense against oxidative stress. Comparable findings were observed in the expression of p53, Bax, caspase-3, and c-Jun which is associated with apoptosis, especially intrinsic apoptotic pathway. In cultured hTECs, which is a human kidney epithelial cells, CHP showed a protective effect against oxidative stress that induced by H2O2. Additionally, live cell frequency was increased with CHP dose dependent manner. This study demonstrated that CHP may protect against cisplatin-induced cell apoptosis and AKI through suppression of p53 and up-regulation of antioxidant defense.

Conclusions: Together, this study demonstrated that CHP may protect cisplatin-induced AKI through inhibiting apoptosis. Considering the effects of CHP, it can be applied to the AKI protection.
Cysteinyl-tRNA Synthetase Alleviates Renal Ischemia Reperfusion Injury Through Its Anti-Pyroptosis Role in Tubular Epithelial Cells

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Background: Acute kidney injury (AKI) is a common yet poorly treated entity, characterized by high mortality and significant risk of developing chronic kidney diseases. The pathophysiological mechanism of AKI remains underinvestigated.

Methods: To further elucidate the mechanism of AKI, we performed a detailed molecular characterization of ischemia reperfusion injury(IRI) model both in vitro and in vivo.

Results: The data comprising label free proteomics analysis in renal tubular epithelial cells, histological studies of renal tissue from IRI rat model, and molecular characterization of targeted gene activity provided a comprehensive profile of injury and repair responses in kidney due to IRI. Label free proteomics analysis and renal histological studies highlighted cysteiny-l- tRNA synthetase (CysRS) was associated with renal tubal atrophy following IRI. CysRS was shown to alleviate IRI both in vitro and in vivo through its suppression of NLRP3 inflammasome assembly, thus reducing the renal tubal epithelium damage mediated by caspase-1 dependent cellular pyroptosis.

Conclusions: Our current study identified CysRS could alleviate renal IRI damage through its anti-pyroptosis role in tubular epithelium. The findings might provide valuable evidence for investigating pathological mechanisms and novel therapeutic targets for AKI. Feng Yunlin, Li Yi should be addressed as corresponding authors and these two authors contributed equally to this study.

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Role of Necroptosis in Contrast-Induced Nephropathy in a Rat Model of CKD and Its Modification by Tolvaptan

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Background: Risk of contrast-induced nephropathy (CIN) is high in patients with chronic kidney disease (CKD). However, there is no specific preventive measures for CIN in CKD. In this study, we examine role of necroptosis in the mechanism of CIN in CKD and its possible modification by tolvaptan and saline infusion.

Methods: Using male SD rats, CIN was induced by subnephrectomy (5/6 nephrectomy, SNx), and CIN was induced by administration of indomethacin (10mg/kg), L-NAME (10mg/kg) and contrast medium (1600 mg/kg). First, rats were divided into sham (n=6), SNx (n=17), and SNx+CIN (n=17). Forty eight hours after induction of CIN, serum creatinine (sCr), blood urea nitrogen (BUN), urinary albumin creatinine ratio (ACR) were measured and protein expressions in the kidneys were examined by western blot. Next, we assessed the effect of necrostatin-1 (Nec-1, 1.65 mg/kg), a necroptosis inhibitor, injected just before and 24 hours after induction of CIN on renal function. Finally, we examined the effect of Tol (10 mg/kg) combined with saline infusion on CIN in CKD, we compared SNx (n=7), SNx+CIN (n=11) and SNx+CIN+Tol (n=8).

Results: SNx+CIN increased in sCr, BUN and log ACR compared with other groups, and also increased in caspase 3, cleaved caspase 3, caspase 8, RIP1, RIP3 (Fig.1), suggesting that renal damage in CIN was associated with activation of apoptosis/necroptosis signals. sCr (0.69 vs 0.56 mg/dl, P<0.01), BUN (37.2 vs 28.6 mg/dl, P<0.01) and log ACR (5.9 vs 4.5, P<0.01) were lower in Nec-1-treated SNx+CIN than in vehicle-treated SNx+CIN. Tol partially improved BUN and ACR and suppressed elevation of RIP1 and RIP3 levels in SNx+CIN (Fig.2).

Conclusions: Necroptosis contributes to CIN in CKD and its detrimental effect may be suppressed by tolvaptan.

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Uncovering a Functional Loop Between Renal Tubular Epithelial Cells and Double Negative T Cells

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Background: Renal epithelia is a major tissue in kidney. Renal epithelial cells play an important role in inducing defensive mechanism and fully participate in renal innate immune responses. On the other hand, CD4-CD8- double-negative (DN) T cells, a rare population in periphery are preferentially localized into renal epithelial tissues and spontaneously proliferate in the steady state and protect against AKI. However, the functional relationship between renal epithelial cells and kidney DN T cells are unknown. We hypothesize that renal epithelial and kidney DN T cells regulate each other homeostasis and function.

Methods: To test this hypothesis, we used B6 wild type and MHC knockout mice, T cell functional assays and in-vitro co-culture system. Renal tubular epithelial cells and lymphocytes from both kidney and lymph node were isolated, cultured and analyzed by flow cytometry.

Results: Our data demonstrate that renal tubular epithelial cells (RTE) induce significant expansion of DN T cells in cultures. Addition of DN T cells with RTE significantly increased the frequency (DN, 1.2 ± 0.6 vs RTE+DN; 13.8 ± 3.5, p<0.0001) and absolute cell number (DN, 0.2 ± 0.1x10⁶ vs RTE+DN; 2.9 ± 0.9x10⁶, p<0.0001) of DN T cells in co-culture. The increased DN T cell number is due to increased activation and proliferation of DN T cells. Further, the activation and proliferation is TCR-independent. The increased DN T cell number is due to increased activation and proliferation of DN T cells. In-vitro experiments show that IL-7, a product of epithelial cells, significantly increases DN T cell proliferation (DN; 30.1% ± 10.5 vs DN+IL-7; 36.3 ± 2.5, p<0.0001). In addition, the IL-7 dependent expansion of DN T cells is limited to PD-1+ DN T cell subsets. Transwell experiments show that cell-mediated interaction is necessary for enhanced DN T cell proliferation in co-culture. Reciprocally, DN T cells also increased the survival of kidney epithelial cells in co-culture. However, the underline mechanism are unknown and investigated further.

Conclusions: These findings demonstrate a previously unknown mechanism and functional relationship between RTE and DN T cells, and its role in maintaining each other homeostasis and function. Ongoing studies are evaluating these responses during AKI and repair.

Funding: NIDDK Support

PUB044

The Effect of Nintedanib on Renal Interstitial Fibrosis

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Background: Pericyte is known as the main source of myofibroblast in renal interstitial fibrosis. However, the mechanism of mediating pericyte-myofibroblast transitions is unclear. In this study, we examined the effect of nintedanib, a triple kinase inhibitor of platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptors (FGFR) and vascular endothelial growth factor receptor (VEGFR) on renal fibrosis to identify the main factor inducing pericyte changes.

Methods: Surgically created unilateral ureteral obstruction (UUO) mouse model was used to generate progressive renal fibrosis. 3 groups were assigned; control group (sham operation), UUO 10 days and UUO 14 days. Nintedanib was given by gavage after ureteral ligation. Pericyte was confirmed by PDGFR-beta and NG2 double stain.

Results: In UUO (D10) group, decrease of pericyte and vascular density, and increase of interstitial fibrosis were observed. These findings were more noticeable in the UUO (D14) group. Compared with the UUO (D10) group, interstitial fibrosis was attenuated in the nintedanib treated UUO (D10) group, and pericyte was increased. In the nintedanib treated UUO (D14) group, the fibrosis progressed more than nintedanib treated UUO (D10) group. But they showed ameliorated interstitial fibrosis and increased number of pericytes compared to the UUO (D14) group.

Conclusions: Nintedanib treatment resulted in attenuation of renal interstitial fibrosis in UUO mouse model. And nintedanib decreased pericyte-myofibroblast transition. This is thought to be due to VEGFR inhibition.

PUB045

Paradigm Shift: Sepsis-Induced AKI Not due to Hypotension

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Introduction: The patient is a 65 y/o man with a history of CKD 4 (eGFR 20-25 ml/ min), diabetes, chronic stable heart failure without recent exacerbation and hypertension. He was diagnosed with sepsis-associated acute renal failure (AKI) but in the absence of hypotension related etiology as to suggest acute tubular necrosis. We subsequently hypothesize that sepsis-induced AKI may be the sequelae of an adaptive to maladaptive inflammatory response rather than a purely hemodynamic phenomena.

Case Description: On presentation he was lethargic, hypothermic at 35.1 deg C, heart rate up to 107, eGFR 18 ml/min, peripheral leucocytosis 25 K/cmm, however his blood pressure (BP) was stable. The mean arterial blood pressure was significantly higher than 75 mmHg (94.65 mmHg) throughout hospital course and he did not require vasopressors or have shock. He was diagnosed with sepsis from ascending urinary tract infection due to Enterobacter Cloacae, which the source and was initially treated with Cefepime which was later changed to Levofoxacin in response to sensitivity report. Blood cultures, serology for HSV 1/2 PCR were negative. The patient however sustained AKI and given his comorbidities and previous CKD, he sustained inexorable decline in renal function and ended up needing to start dialysis due to uremic symptoms, with a new clinical designation as end-stage renal disease.

Discussion: We wish to point out that practicing clinicians are increasingly recognizing a concept we call “sepsis-induced AKI”. It has been known that sepsis, major surgery, heart failure and hypovolemic shock are all associated with AKI & traditionally was taught to be due to ischemia on the basis of macro hemodynamic changes. However we document that AKI can occur in the absence of global hypoperfusion. In a paper published by Hermando Gomez et al. published in Shock. 2014 Jan; 41(1): 3-11 they attempted to put forward a theory for AKI in the absence of shock (or hypotension) involving DAMPs/PAMPs, abnormal signaling and oxidative stress response. Circulating factors from burn patients with sepsis-induced AKI can induce tubular and glomerular alterations in septic patients which do not have AKI. Crit Care. 2008; 41(1): 2-11 they attempted to put forward a theory for AKI in the absence of shock (or hypotension) involving DAMPs/PAMPs, abnormal signaling and oxidative stress response. Circulating factors from burn patients with sepsis-induced AKI can induce tubular and glomerular alterations in septic patients which do not have AKI. We hypothesize that sepsis-induced AKI may be the sequelae of an adaptive to maladaptive inflammatory response rather than a purely hemodynamic phenomena.
Results: In vehicle-treated mice, the only significant differences observed were a decrease in cell proliferation in cisplatin-treated WT vs. KO mice to AKI. In response to cisplatin, plasma CySS and GSH decreased, while both Cyx and CySS increased in the kidney in both genotypes. Cis had no effect on the kidney levels of any of the forms of GSH, but in the liver, all 3 forms (GSH, GSSG and CySSG) were decreased in Cis WT and KO compared to controls. MCP-1, a prominent cytokine in AKI, was upregulated in the liver of both genotypes. No significant differences were found in TGR5 or GATase activity with either treatment or genotype. IHC for 4-HNE showed no differences between genotypes for vehicle-treated kidneys, while Cis resulted in an increase in 4-HNE staining within the cortex and juxtamedullary (J/M) region of both genotypes, more marked in the C57 KO kidneys, especially in the J/M regions.

Conclusions: We conclude that loss of NHERF1 does not lead to changes in kidney GSH metabolism but does so in liver. Cis results in more pronounced expression of the 4-HNE adducts in the KO vs WT mice kidneys. Therefore, the increased susceptibility of KO mice to Cis n nephototoxicity may be related to increased sensitivity to Cis itself.

Funding: Veterans Affairs Support

PB0407
Suppression of Nrf2 Activity by HIF-1α Promotes Fibrosis After AKI
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Background: Acute kidney injury (AKI) is a rapid reduction in renal function due to damage to tubular epithelia and can occur after ischemia/reperfusion injury (IRI). Ischemic injury results in both impaired oxygen and nutrient delivery to the kidney. Kidney tubular epithelial cells are particularly vulnerable to ischemic injury. To offer protection, cellular mechanisms have evolved to mitigate the damage of IRI while attempting to restore cellular homeostasis. Specifically, two notable cellular pathways are activated including nuclear factor erythroid 2 like 2 (Nrf2) and hypoxia inducible factor 1α (HIF-1α).

Methods: C57BL/6 mice were subjected to IRI. Ischemia times were titrated to induce mild to severe injury and kidneys were harvested at various acute and chronic time points post-reperfusion. To simulate mild and severe injury conditions in vitro, proximal tubal HK-2 cells were exposed to either nutrient replete or nutrient deficient conditions, respectively, in the presence of HIF activation with cobalt chloride (CoCl3).

Results: The protective Nrf2 activity is activated by mild ischemia but is suppressed by severe ischemia in vivo. Mimicking these results, HIF-1α activation in nutrient replete conditions in vitro enhances Nrf2 nuclear localization and activity, while HIF-1α activation in nutrient deficient conditions suppressed Nrf2 activity. Localization and activity of Nrf2 were restored upon siRNA-mediated knockdown of HIF-1α. These effects were not due to direct interaction between HIF-1α and Nrf2, since these proteins did not co-immunoprecipitate in vitro.

Conclusions: Our data confirm that severe AKI leads to a maladaptive reduction in Nrf2 activity and ultimately to renal fibrosis. This may be due to Nrf2 inhibition by HIF-1α under severe ischemic conditions. We propose that the capacity to recover from an ischemic insult can be attributed to regulation of the Nrf2 pathway by HIF-1α.

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PB0408
Metabolic Alterations in a Mouse Model of Cisplatin-Induced AKI
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Background: Cisplatin-induced acute kidney injury (AKI) occurs in 1/3 of cisplatin-treated patients. Cisplatin-AKI is diagnosed by elevated serum creatinine (SCr), but nephrototoxicity develops before measurable changes to SCr. Novel diagnostic/predictive markers of AKI may explain why only certain cisplatin-treated patients get AKI. Cisplatin-induced AKI is more susceptible to cisplatin-AKI than C57BL/6. These two strains were used to model the interindividual variability of cisplatin nephrototoxicity. We aim to: 1) Measure metabolic differences between FVB/N and C57BL/6 mice using metabolomics; 2) Test whether AKI is a model for interindividual variability of cisplatin nephrotoxicity. We aim to: 3) Mimicking these results, HIF-1α activation in nutrient replete conditions in vitro enhances Nrf2 nuclear localization and activity, while HIF-1α activation in nutrient deficient conditions suppressed Nrf2 activity. Localization and activity of Nrf2 were restored upon siRNA-mediated knockdown of HIF-1α. These effects were not due to direct interaction between HIF-1α and Nrf2, since these proteins did not co-immunoprecipitate in vitro.

Conclusions: Our data confirm that severe AKI leads to a maladaptive reduction in Nrf2 activity and ultimately to renal fibrosis. This may be due to Nrf2 inhibition by HIF-1α under severe ischemic conditions. We propose that the capacity to recover from an ischemic insult can be attributed to regulation of the Nrf2 pathway by HIF-1α.

Funding: NIDDK Support, Other NIH Support - NIH P30 DK079307; NIH T32 DK061296, Private Foundation Support

PB050
Anemia and Kidney Function Decline Among the Middle-Aged and Elderly in China: Results from the China Health and Retirement Longitudinal Study (CHARLS)
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Background: Chronic kidney disease (CKD) is a public health burden worldwide. Anemia is common among patients with CKD and closely associated with kidney function progression. However, less is known regarding the longitudinal association between anemia and kidney function decline among the middle-aged and elderly population in China. The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative longitudinal study starting from 2011. Participants without creatinine and demographic data in 2011 and 2015 were excluded. Anemia was defined according to WHO standards and rapid decline in kidney function was defined as a >16.9% (Quartile 3) decline in estimated Glomerular Filtration Rate (eGFR) calculated using the CKD-EPI equation during two visits. Multivariate logistic regression model was used to investigate their association.

Results: Altogether 7210 eligible participants were included in the final analysis, with a mean age of 58.6 ± 8.8 years. Rapid decline in kidney function occurred among 1802 (25.0%) participants. Those with rapid decline were more likely to be male, older, and to have lower eGFRs, anemia and hypertension. Anemia was significantly associated with rapid kidney function decline after adjusting for potential confounding factors (OR=1.64, 95% CI=1.32-2.04). The model using the continuous variable of hemoglobin (per 10 g/L) confirmed a positive association (OR=1.40, 95% CI=1.14-1.70).

Conclusions: Anemia is an important risk factor for the progression of CKD among the middle-aged and the elderly in China. Effective interventions targeting anemia could help reduce the risk of kidney failure.

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PB049
In Vitro Models of AKI Reveal Cell Type-Specific Cytokine Responses
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Background: The nature and severity of the renal injury determine the progression from AKI to CKD. Renal tubular epithelial fibroblasts is the final common pathway in end-stage renal disease and is characterized by abnormal deposition of extracellular matrix (ECM) produced by myofibroblasts. The role of TGFβ and MCP-1 in renal fibrosis is well known but there is also evidence for a role of different cytokines such as IL-18 and IL-15. However there is no significant data about these mediators in acute kidney injury. We reproduced three different in vitro model of AKI (septic, ischemia-reperfusion and toxicity drug related) with the aim to observe the response of these mediators to an acute insult that potentially could be considered as markers of AKI.

Methods: Primary human proximal tubular cells phenotypically expressing GGTase were cultured in collagen, plasma and cellular fibroenecin and harvested the supernatant of culture medium. We reproduced an in vitro model of AKI with Na3N for ischaemia reperfusion, gentamicin as toxic drug and LPS (Lipopolysaccharides) as septic model. The treatment lasted for 18 hours followed by RNA extraction and PCR. Collagen and plasma-cellular fibroenectin samples were tested for IL-18, IL-15, TGFβ and MCP-1. We also analysed the NAG secreted by tubular cells in cell culture medium and we compare NAG with NAGL.

Results: Significantly higher NAG activity was detected in Na3N, LPS and gentamicin models of AKI compared to control (p=0.0014, 0.0125 and 0.0028). NAGL results were below the level of detection. Results from the LPS model tended to be extremely variable with no obvious pattern despite relatively consistent NAG results. There was no significant change in TGFβ expression in any of the models. Gentamicin and Na3N induced distinctly different cytokine responses. Gentamicin induced MCP1 and IL15 while reducing IL18 expression. Na3N tended to increase MCP1 but to a lesser degree and did not alter the IL15/IL18 ratio. Unexpectedly untreated cell on cellular fibroenectin without treatment altered MCP1 expression.

Conclusions: Our pilot data indicates that the cytokine responses of renal epithelial cells to AKI varies significantly depending on the nature and not the severity of the injury. The relative expression of key opposing mediators such as IL15 and IL18 may influence the nature of the renal recovery.
**Association of anemia with rapid decline in kidney function in CHARLS, 2011-2015**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
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<tr>
<td>Age</td>
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<td>Sex</td>
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<td>Anemia</td>
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*Adjusted for age, gender, residence, education, medical insurance, personal consumption expenditures, cardiovascular disease, hypertension, hyperuricemia, high sensitivity C-reactive protein, body mass index, central obesity, smoking, drinking, and baseline eGFR.

**Background:** CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; OR, odds ratio.

**Results:**

**PUB051**

**Cumulative Intravenous Iron in Incident Hemodialysis Patients and Spikes of Serine Alamine Aminotransferase**

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**Background:** Use of intravenous iron (IV Fe) is vital in the management of anemia in hemodialysis (HD) patients. In the general population, elevated alanine aminotransferase (ALT) is associated with increased serum iron parameters, possibly exhibiting evidence of liver injury. We aimed to determine the association of cumulative IV Fe and other known liver risks with spikes in monthly ALT levels in incident HD patients.

**Methods:** This retrospective quality study examined incident HD patients over 14 years. Baseline demographic and clinical characteristics included age, dialysis vintage, sex, race, ethnicity, weight, cumulative IV iron given, statin use, viral hepatitis status, diabetes mellitus, laboratory results (albumin, ferritin and TSat%) and recent hospitalization. Analysis included general estimation equations for assessment of spikes in monthly ALT (defined as >56 U/L, the upper end of normal of the lab) as the dependent outcome.

**Results:** The cohort included 585 incident HD patients: mean age at ESRD=57.2±16.1 years; 40.2% female; 27.1% non-Hispanic White and 30.9% Black; 48.5% DM; and 12.5% Hep C antibody positive. 155 (26.5%) patients experienced at least one spike of ALT. General estimation equations suggested that cumulative IV Fe by age was inversely associated with spike in ALT. However, the interaction term of Ferritin*cumulative IV Fe was positively associated with spikes of ALT; we found other factors associated with spikes in ALT (see Table 1 for significant factors). Other factors analyzed but not associated with a spike in ALT included: vintage, serum albumin, gender, race, ethnicity, DM and recent hospitalization.

**Conclusions:** Cumulative IV Fe by itself was not positively associated with spikes in ALT, whereas serum Ferritin was strongly associated. Since IV Fe is often withheld from patients with high Ferritin levels, we included the interaction term of Ferritin with IV Fe in the analysis; we found this combined factor was positively associated with ALT spikes. In the full analysis, other factors positively associated with ALT spikes included: younger age, lower body weight, higher TSat%, on statin therapy, and positive Hepatitis C status.

**Funding:** Clinical Revenue Support

**PUB052**

**Comparative Study Between Darbeopetin vs. Metoxi Polietien Glycoprotein Beta (CERA), in the Treatment of Anemia in Patients with Chronic Hemodialysis: Randomized Clinical Trial**

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**Background:** At present, we have different etiopathogenesis stimulating agents (ESA) for the treatment of anemia in chronic hemodialysis. In the last ten years, new ESA have been improved as Darbeopetin (DA) and methoxy polyethylene glycol epoetin beta (CERA), these ESA have better pharmacologic efficacy and less frequency of administration. We did a randomized clinical trial between DA and CERA in the treatment of anemia in hemodialysis.

**Methods:** 160 adults patients in chronic hemodialysis with anemia (Hb 8 g/dl, Hto 24%) were included, patients with malnutrition, cancer, multiorganic failure and older than 75 years were excluded. Patients were randomized in two groups, DA (n=80) received 40 mg every 5 days, subcutaneous route and CERA group (n=80) received 75 mcg, every 10 days, subcutaneous route. The medications were taken in a double blind way. Hb and Hto were taken at the beginning of the study and monthly during 4 months. Ferrum was taken at the beginning and at the end of the study. ANOVA was used for the comparison of values the Hb and Hto in the different measures. P values less 0.05 were considered significant.

**Results:** The basal values of Hb and Hto in the DA group were: 9±1 g/dl and 27±2%, in the M group were: 8.9±1 g/dl and 20±1% (p > 0.05), at the end of study in the DA group Hb 12±1 g/dl and Hto 36±2% in the M group Hb 11.9±1 g/dl and Hto 35±1% (p > 0.05). Ferritin and transferrin saturation were similar in both groups at the beginning and at the end of the study (p > 0.05).

**Conclusions:** Darbeyopetin and Mircaera had the same efficacy in the treatment of anemia in chronic hemodialysis, there were not differences. Both options are useful for the treatment in patients in hemodialysis.

**Funding:** Government Support - Non-U.S.

**PUB053**

**Novel Probe to Detect Autophagy Flux in Proximal Tubular Cells**

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**Background:** Autophagy is a pathway to degrade or recycle damaged organelle and macromolecules. In autophagy, autophagosome including part of cytosol and waste fuses with lysosome and the content is degraded by hydrolitic enzymes. As autophagosome forms, microtubule-associated protein light chain 3 (LC3-3-5) is conjugated with phosphatidylethanolamine to become LC3-II. Many of present methods to measure autophagy utilize LC3 as a marker, such as GFP-LC3 or western blotting (WB) to detect the conversion of LC3-I to -II. The existing methods have several limitations, such as the static evaluation of autophagy instead of flux evaluation or their reliability. In this study, we applied a novel probe, GFP-LC3-REP-LC3-MG to measure autophagy flux developed by Kanzuka, Morishita and his colleagues to proximal tubular cell line, HK2. Endogenous ATG4 cleaves the probe into equimolar GFP-LC3 and REP-LC3-MG. While GFP-LC3 is degraded as autophagy proceeds, REP-LC3-MG stays intact and serves as internal control. Thus, the ratio of GFP-LC3 to REP-LC3-MG reflects the activity of autophagy flux. We used this probe with the probe to evaluate autophagy flux in hypoxia or hypoxia inducible factor (HIF) stabilizer, enadostad.

**Methods:** We transfected HK2 cells with pMRX-GFP-LC3-REP-LC3-MG, using lipojecterine 3000 (Thermo Fisher Scientific, USA). After selecting the cells with puromycin, single cell cloning was performed to pick up colonies without homologous recombination. Autophagy flux was evaluated using flow cytometry (BD biosciences, USA), and 1-GFP/REP was calculated. We exposed the cells to amino acid deprivation, a response inducer, for 4 hours and compared the results of the probe with expression of LC3 WB. We also measured the autophagy flux in HK2 cells in 1% O2 for 0-48 hours and HIF stabilizer, 10 mM enadostad for 0-48 hours.

**Results:** With amino acid deprivation, autophagy flux was increased compared to normal medium, which was comparable to the result of WB. Under 1% hypoxia, autophagy was also increased over time, reaching almost 100% by 48 hours. Enadostad increased autophagy more slowly.

**Conclusions:** We established HK2 cells stably transfected with autophagy probe for flux evaluation. After validating the cells using amino acid deprivation, we evaluated the autophagy flux in hypoxia and HIF stabilizer and found that it was increased in both settings.

**Funding:** Government Support - Non-U.S.

**PUB054**

**Inhibition of Angiotensin-Converting Enzyme 2 by Fibrolast Growth Factor 23 Through FGFR1**

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**Background:** Fibrolast growth factor 23 (FGF-23) is a protein which is responsible for phosphate and vitamin D metabolism in humans. Renin angiotensin-aldosterone system (RAAS) activation leads to phosphate retention and FGF-23 elevation in chronic kidney disease. This study was designed to investigate the unclear influence and mechanism of FGF-23 on angiotensin-converting enzyme 2 (ACE-2) of RAAS.

**Methods:** Rat renal tubular epithelial cells (NRK-52E) were treated with 0, 10, 25 and 100 ng/mL FGF-23 for 24h, respectively. Then renal epithelial cells were treated with 100 ng/mL of FGF-23 for 6, 12 and 24h, respectively. ACE-2 expression was detected by RT-PCR and western blotting. Angiotensin 2 (Ang-2) in cell supernatant was detected by enzyme linked immunosorbent assay (ELISA). Immunofluorescence was used to detect the localization and expression of ACE-2. FGF receptor 1 (FGFR1) was inhibited using FGFR1 inhibitor (PD173074).

**Results:** 100 ng/mL FGF-23 significantly inhibited mRNA and protein levels of ACE-2 in renal epithelial cells compared with 0, 10, and 25 ng/mL FGF-23 groups respectively. FGF-23 inhibited ACE-2 expression in a time-dependent manner, which was most significant at 24h. 100 ng/mL FGF-23 increased Ang-2 expression in the supernatant of renal epithelial cells compared with the control group by ELISA. Moreover, immunofluorescence found that the granular fluorescence of ACE-2 expressed mainly in the cell membrane and cytoplasm, and the fluorescence intensity of ACE-2 decreased after the treatment of 100 ng/mL FGF-23 compared with the control group. Treatment of FGFR1 inhibitor PD173074 (25nmol/mL) blocked the inhibiting effect of FGF-23 on ACE-2 in renal epithelial cells.

**Conclusions:** FGF-23 can inhibit the expression of ACE-2 through FGFR1 in renal tubular epithelial cells. The cross-talk between FGF-23 and RAAS is complex and needs future studies to investigate.

**Funding:** Government Support - Non-U.S.
High-Dose Denosumab for the Management of Immobilization-Related Hypercalcemia in a Patient on Maintenance Hemodialysis: A Case Report

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Introduction: Immobilization-related hypercalcemia arises due to a higher rate of osteoblastic bone formation compared to osteoclastic bone resorption. Renal impairment increases the risk of immobilization-related hypercalcemia. There is limited evidence about the safety and efficacy of denosumab in the management of immobilization-related hypercalcemia in hemodialysis (HD) patients.

Case Description: We report a case of successful treatment of immobilization-related hypercalcemia with denosumab 120 mg. A 55-year-old woman admitted to the ICU with suspected catheter-related bacteremia that led to septic shock. After 13 days of admission, the patient’s corrected serum calcium rose to 3.39 mmol/l from a baseline of 2.52 mmol/l despite calcium carbonate and alfacalcidol discontinuation. Cinacalcet 60 mg once daily for 10 days, subcutaneous Cinacalcet 250 mcg/dose for 6 days, a single dose of intravenous Zoledronic acid 4 mg, and a single dose of subcutaneous denosumab 60 mg were sequentially administered without response. Thus, subcutaneous denosumab 120 mg was administered and resulted in a gradual decline of the corrected calcium level from 4.18 mmol/l to 2.45 mmol/l over 3 weeks. Corrected calcium level was maintained below 2.8 mmol/l for 2 months later without notable adverse reactions. The patient’s serum phosphorus level and PTH were within the normal ranges during the whole admission period.

Discussion: The management of immobilization-related hypercalcemia in ESRD patients include withholding calcium and vitamin D, HD using a low-calcium dialysate. There is limited evidence about the safety and efficacy of denosumab in the management of immobilization-related hypercalcemia in hemodialysis (HD) patients.

Results: Among 264 patients (male: 65%, diabetes: 42%), mean age was 65±12 years and the median dialysis vintage was 79 (39–144) months. Serum P tertiles (T1-T3) were <4.5, 4.5–5.5, and <5.5 mg/dl. The low (T1) serum P group exhibited significantly (P<0.05) lower normalized protein nitrogen appearance (nPNA), intact parathyroid hormone (iPTH), lean tissue index, BCMi (9.2±1.8, 8.9±1.8, and 7.2±2.0 kg/m2), intracellular water and significantly higher OH/ECW (9.2±10.0, 8.9±9.8, and 6.4±8.9, P<0.05) than other groups; BMD and coronary artery calcification score (CACS) did not differ. Serum Mg tertiles were <2.3, 2.4–2.5, and <2.5 mg/dl. Compared with other groups, the low (T1) serum Mg group showed lower nPNA and iPTH (P<0.05), but no significant differences in body composition parameters, BMD, or CACS. BCMi was significantly (P<0.05) associated with age (β=-0.30), presence of diabetes (β=-0.16), serum albumin (β=0.13), serum P (β=0.12), femoral BMD (β=0.23) [or radius BMD (β=0.41)], but not serum Mg or lumbar spine BMD. OH/ECW was significantly (P<0.05) associated with the presence of diabetes (β=0.21), serum P (β=0.13), and femoral BMD (β=-0.19) but not age, serum albumin, Mg, or radius or lumbar spine BMD.

Conclusions: In MHD patients, associations among serum P levels (but not serum Mg levels), body composition parameters (BCM, OH/ECW) and BMD were observed; serum P<4.5 mg/dl may indicate worse body composition and lower BMD.

Funding: Private Foundation Support

IPR052
Hip Fracture and CKD: Eighteen Years of a Temporary Perspective in a Spanish Hospital

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Background: Hip fracture (HF) is a frequent cause of morbidity and mortality in the elderly, who have a high incidence of chronic kidney disease (CKD). The recent concept of “uremic osteoporosis” shows that uremic toxins favor the loss of bone mass, increasing the rate of HF. However, CKD is not included in HF risk prediction tools, as FRAX. We study the characteristics of patients with CKD and HF, in order to determine if the impairment of renal function influences it prognosis to establish a risk profile of HF in CKD and to design intervention protocols. We compared patients with advanced CKD (GFR <20 ml / min) with the rest of patients with CKD (GFR >60 ml / min).

Methods: We have performed an observational, descriptive and transversal study of the characteristics of hospitalized patients with HF and ECR, from January 2000 to December 2018. The quantitative variables are expressed as median and interquartile range and qualitative ones are expressed as percentages. The comparisons were made with T of Student and Chi2, with a level of significance of p <0.05.

Results: In this period, 291 patients with CKD, were hospitalized for HF, 105 male (36.1%) and 186 female (63.9%). The rest of the variables are expressed in the following tables.

Conclusions: - CKD worsens the prognosis of HF: it makes surgical treatment difficult and increases the time of hospitalization and risk of death. - The increase in markers of bone mineral disease in advanced CKD favors the development of uremic osteoporosis, which is possibly responsible for this unfavorable profile of HF. - Patients with advanced CKD, heart failure and elevation of markers of the bone mineral disease, suffer a high risk of poor FC prognosis, needing special vigilance.

Associations of Body Composition, Bone Mineral Density, Serum Phosphate, and Magnesium Levels in Hemodialysis Patients

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Background: Sarcopenia, osteoporosis, hyperphosphatemia, and hypomagnesemia are reportedly associated with mortality in hemodialysis patients. This study aimed to assess the associations of body composition, bone mineral density (BMD), serum phosphate (P) and magnesium (Mg) levels in maintenance hemodialysis (MHD) patients.

Methods: Pre-dialysis laboratory data, post-dialysis body composition parameters by the Body Composition Monitor (Fresenius), and radius, lumbar spine, and femoral bone mineral density (BMD) using dual energy X-ray absorptiometry were assessed in MHD patients. Body composition, BMD, and clinical data were compared based on serum P and Mg levels. Multiple regression analyses for body mass index (BCM): fat-free mass without extracellular water, and overhydration/extracellular water (OH/ECW) were performed, respectively.

Results: In 1087 patients (male: 65%, diabetes: 42%), mean age was 65±12 years and the median dialysis vintage was 79 (39–144) months. Serum P tertiles (T1-T3) were <4.5, 4.5–5.5, and <5.5 mg/dl. The low (T1) serum P group exhibited significantly (P<0.05) lower normalized protein nitrogen appearance (nPNA), intact parathyroid hormone (iPTH), lean tissue index, BCMi (9.2±1.8, 8.9±1.8, and 7.2±2.0 kg/m2), intracellular water and significantly higher OH/ECW (9.2±10.0, 8.9±9.8, and 6.4±8.9, P<0.05) than other groups; BMD and coronary artery calcification score (CACS) did not differ. Serum Mg tertiles were <2.3, 2.4–2.5, and <2.5 mg/dl. Compared with other groups, the low (T1) serum Mg group showed lower nPNA and iPTH (P<0.05), but no significant differences in body composition parameters, BMD, or CACS. BCMi was significantly (P<0.05) associated with age (β=-0.30), presence of diabetes (β=-0.16), serum albumin (β=0.13), serum P (β=0.12), femoral BMD (β=0.23) [or radius BMD (β=0.41)], but not serum Mg or lumbar spine BMD. OH/ECW was significantly (P<0.05) associated with the presence of diabetes (β=0.21), serum P (β=0.13), and femoral BMD (β=-0.19) but not age, serum albumin, Mg, or radius or lumbar spine BMD.

Conclusions: In MHD patients, associations among serum P levels (but not serum Mg levels), body composition parameters (BCM, OH/ECW) and BMD were observed; serum P<4.5 mg/dl may indicate worse body composition and lower BMD.

Funding: Private Foundation Support
Thyroid Function Changes in Dialysis Patients with Severe Secondary-Hyperparathyroidism
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Background: Common complication of advanced Chronic Kidney Disease is secondary-hyperparathyroidism, which is associated with increased cardiovascular morbidity and mortality. While kidney-failure causes a wide array of thyroid abnormalities, little is known about whether uncontrolled hyperparathyroidism in dialysis patients is associated with thyroid-dysfunction and if this association has a relation to dialysis vintage and adverse cardiovascular outcomes.

Methods: Parathyroid hormone (PTH) levels were dichotomized into groups of <600 (controls: n=36) and ≥600 (study group: n=62). Serum levels of PTH, thyroid function tests were obtained and statistically analyzed during two different times within a month-period. Using chart review, cardiovascular events, defined as coronary artery disease, heart-failure, and/or sudden cardiac death, that occurred over the past 5 years were retrieved from the electronic medical records. In addition, dialysis vintage defined as short [<5 years] and long defined as [≥ 5 years] was obtained. A Spearman’s Rho correlation, Mann Whitney U test, and Fisher’s Exact test were performed to determine the relationships between PTH, TSH, and FT4.

Results: There was no relationship between the thyroid and PTH levels as was TSH by PTH group was non-significant (p=0.98), as was the FT4 by PTH group (p=0.98). Controls arm had a higher % of shorter vintage (68.6%) compared to the study-group (51.7%), which was non-significant (p=0.134). Conversely, those in the study arm had a higher proportion of those in longer vintage arm (48.3%) than the control arm (31.4%) (Fig 1). A higher proportion of those with CVD (83.3%) were found in the control arm (83.3%) than those in the PTH study group (74.0%); p=0.41, which was non-significant.

Conclusions: No correlation was found between the severity of 2HPT and development of thyroid dysfunction and no statistically significant difference between two groups in CV outcomes. However, dialysis vintage was longer in study vs. control arm.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Background: CKD is associated with insulin resistance which plays an important role in the pathogenesis of cardiovascular disease. In other hand, hyperphosphatemia that appeared in metabolic-bone disease, also associated with cardiovascular morbidity and mortality. The association between these two cardiovascular risk factors in CKD has not been determined yet.

Methods: This study was an observational analytic study with cross-sectional design, involving non-diabetic, predialysis CKD patients stage 3-5 from a tertiary referral hospital outpatient center in Surabaya. Insulin resistance is described by using Homeostatic Model Assessment - Insulin Resistance (HOMA-IR). Analysis of relationship between phosphate levels and HOMA-IR is done by Spearman correlation test. P value is significant if <0.05.

Results: There were 40 patients. Mean of HOMA-IR levels in patients in stage 3A was 1.34 (±SD 0.16), stage 3B 1.84 (±SD 0.58), stage 4.30 (±SD 1.23), and stage 5.189 (±SD 1.14), and from overall results were 2.13 (±SD 1.15). Mean of phosphate level in CKD stage 3A was 3.45 (±SD 0.53), stage 3B 3.70 (±SD 0.77), stage 4.42 (±SD 1.57), and stage 5.499 (±SD 0.44), and from overall results were 4.51 (±SD 1.08). There was no correlation between HOMA-IR and phosphate level in CKD.

Conclusions: There was no correlation between phosphate levels and HOMA-IR in CKD stage 3-5 non-diabetic predialysis patients

An Unexpected and Atypical Evolution Under Etelcalcetide

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Introduction: CINACalcet increases the sensitivity of the calcium membrane receptor (CaSR) to extracellular ionized Ca leading to decreased secretion of PTH. Etelcalcetide can activate the CaSR even under calcium free conditions indicating its additional function as direct CaSR agonist. Etelcalcetide have a higher biological efficacy (decrease of PTH) than Cinacalcet.

Case Description: A 60 years-old man, with obesity, diabetes-2, hypertension, ischemic cardiopathy, and polycystic disease, is treated for ESRD with chronic hemodialysis since October 2011. Hyperparathyroidism (shPT) has been treated by subtotal parathyroidectomy in April 2016. Recurrence of shPT occurred in 2018. Parathyroid MIBI scan (11/2018) identified an ectopic adenoma in the antero-lateral side of the medio-lobar region of the left thyroid lobe. Treatment with Etelcalcetide, along with the use of calcium enriched dialysis fluid (1.75 mmol/L) has been started in January 2018. Etelcalcetide is administered at the end of dialysis sessions, with a gradual increase in dosage. PTH remained very high for 13 months, followed by a collapse in February 2019 and a moderate rebound in April 2019 (Table). Alkaline Phosphatase, Bone Alkaline Phosphatase, Vit-D, Magnesium and Albumin are normal in April 2019.

Discussion: Similarly to Cinacalcet, Etelcalcetide is expected to cause rapid and dose-dependent decrease of PTH. Here, the response is very delayed with almost no detectable effect of Etelcalcetide on PTH. This state resembles to acquired pseudo-hypoparathyroidism despite the absence of hypocalcemia and PTH deficiency. In conclusion, this case suggests that Etelcalcetide can cause hypocalcemia not only by depressing PTH secretion but also might alter signaling pathways downstream to PTH receptor.

Etelcalcetide treatment demonstrates findings suggestive of medullary nephrocalcinosis on the right [Figure]. Patient had no history of nephrolithiasis in the past. Laboratory data did not demonstrate hypercalcemia, hypocalcemia, metabolic acidosis or hyperparathyroidism. Vitamin D level was low-normal. Urine stone risk profile revealed normal 24-hour excretion of calcium (127 mg), phosphorus (310 mg) and oxalate (28 mg) but hypocalciuria was noted with a very clear urinary [320-1240 mg/day] with high sodium excretion of 329 mmol/day [-90 for hyperparthensives]. Medication history did not reveal any drugs implicated in hypocalciuria. She was treated with citrate supplementation and advised to restrict dietary sodium and increase consumption of fruits and vegetables.

Discussion: Hypocalciuria, a well-known risk factor for nephrolithiasis and less commonly nephrocalcinosis is considered to be a systemic disorder. However, our case in addition to previously published small observational studies suggests that other local factors may play a role in the development of unilateral nephrocalcinosis. It is also not clear whether isolated hypocalciuria itself resulted in nephrocalcinosis or there was transient hypercalciuria in the past in our patient. It is of note that Once nephrocalcinosis is detected radiographically, it is unlikely to be reversed.

Unilateral Nephrocalcinosis and Isolated Hypocitraturia: A Curious Combination or Mere Coincidence?

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Introduction: Nephrocalcinosis is characterized by the deposition of calcium oxalate or phosphate in the kidney. A variety of inherited and acquired diseases have been implicated in the development of this condition. There have been reports of unilateral nephrocalcinosis, though unilateral cases have been reported. Herein, we present a unique case of unilateral nephrocalcinosis in a patient with hypocalciuria but with no associated hypercalcemia or hyperparathyroidism.

Case Description: A 56-year-old Hispanic woman with a history of hypertension was seen for a routine check-up. She presented with the chief complaint of left kidney disease. Serum creatinine was ~1.3 mg/dL, which was relatively stable compared to 4 months prior. A renal sonogram was obtained, which

Calcium Regulatory and Bone Turnover Biomarker Levels Do Not Indicate Presence of Osteoporosis and Osteopenia in ESRD

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Background: Concomitant BMD disorders like osteoporosis and osteopenia are often observed in ESRD patients. The criteria for diagnosis of a BMD disorder is through the evaluation of BMD by dual x-ray absorptiometry (DXA). This study aims to profile six biomarkers related to calcium regulation, bone turnover, and osteoblastic/osteoclastic activity in ESRD patients to determine if plasma levels of any markers were predictive of concomitant diagnosis of osteoporosis/osteopenia.

Methods: Plasma levels of osteopontin (OPN), bone morphogenic protein 7 (BMP-7), C-terminal collagen telopeptide 1 (CTX-I), IL-6, metalloproteinase (MPO) and 25-hydroxyvitamin D2 and D3 (25(OH)D) were measured via commercially available enzyme linked immunosorbent assays in ESRD patients (n=92) and 50 normal healthy control samples. The ESRD cohort was further stratified into two groups: those with additional diagnosis of osteoporosis or osteopenia (n=23) and those without a BMD disorder diagnosis (n=69). The biomarker levels in these groups were compared to each other and to the normal population via Dun’s multiple comparisons test. Diagnosis of a BMD disorder was based upon T score reports of those who underwent a DXA bone scan. T scores between -1.5 and -2.5 indicated osteopenia, while a T score less than -2.5 indicated osteoporosis.

Results: In ESRD patients (n=92), OPN, IL-6, and MPO were significantly elevated compared to normal plasma samples (p<0.001; p=0.0146, p=0.0001). CTX-I was significantly decreased in ESRD patients compared to normal plasma samples (p<0.001). There were no statistically significant difference in 25(OH)D levels or BMP-7 levels between the ESRD cohort and normal plasma samples (p>0.05). For all biomarkers evaluated, there was no statistically significant difference between ESRD patients with osteopenia/osteoporosis versus ESRD patients who did not have concomitant BMD disorder (p>0.05).

Conclusions: Overall, there were significant differences in biomarkers related to bone turnover and osteoblastic/osteoclastic activity in ESRD patients compared to the normal population. These findings support the hypothesis that bone metabolism is significantly affected in patients with ESRD.

Reducing Pill Burden of Phosphate Binders Has the Potential to Improve Patient Adherence

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Background: Pill burden and medication intolerance are important factors that influence phosphate binder adherence for managing hyperphosphatemia. The number and size of pills are key factors contributing to pill burden. We compared the pill burden of currently approved phosphate binders with lanthanum dioxycarbonate (RenaZorb), second-generation, lanthanum-based drug in development to evaluate its potential for improving patient adherence.

Methods: A literature analysis of phosphate-binding medications were examined to assess the impact of pill size and pill number on non-adherence in hemodialysis patients. We also compared their equivalent doses relative to the phosphorus binding capacity of 1 g calcium carbonate (PHED) in table 1.
Results: Amongst approved phosphate binders lanthanum carbonate and sucroferric oxytate have lower pill burden than other phosphate binders but higher discontinuation rates than some due to patient intolerance. Phase 1 data for lanthanum dioxycarbonate, suggest comparable urinary excretion of phosphate to published data for lanthanum carbonate.

Conclusions: Lanthanum dioxycarbonate has the potential to significantly improve patient compliance by offering a lower-in-class pill burden and smaller sized tablets to achieve similar therapeutic benefit as other phosphate binders. Reference: 1 Finn WM, DenupCiocca CJ, Joy MS et al. Double-Blind Dose-Ranging Study of Lanthanum Dioxidecarbonate. Renal Failure Shows High Phosphorus Binding Capacity. Kidney Week 2013, Atlanta, GA, Nov 5-10

Funding: Commercial Support - Unicycive Therapeutics Inc., Private Foundation Support

Dosages of selected phosphate binders required to reach a phosphorous binder equivalent dose (PBED). Table is modified from St. Peter

<table>
<thead>
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<th>Phosphate binder</th>
<th>Tablet strength (mg)</th>
<th>Tablet size (mm)</th>
<th>Dose of binder needed to reach a PBED of 9g/day</th>
<th>Approximate number of tablets to reach PBED of 9 g in 1 day</th>
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<tbody>
<tr>
<td>Calcium carbonate</td>
<td>648</td>
<td>13</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Calcium acetate</td>
<td>647</td>
<td>13</td>
<td>6</td>
<td>9</td>
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<tr>
<td>Lanthanum Carbonate</td>
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<td>Neverslate carbonate</td>
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<td>19-21</td>
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<td>500</td>
<td>11</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

* In US dialysis patients, PBED averages around 6 g/day. This means that patients require 6 g/day of calcium carbonate to control their serum phosphorous. Tablets are sold by weight of lanthanum and not of lanthanum carbonate.

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PUB065

High Fructose Diet-Induced Hypertension and Renal Damages Are Exacerbated in Dahl Salt-Sensitive Rats via Renal Renin-Angiotensin System

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Background: High-fructose diet (HFr) was reported to induce metabolic syndrome, salt-sensitive hypertension and multiple organ damages. However, it has been unknown whether the HFr-induced hypertension and renal damages exaggerate in subjects with salt sensitivity. Thus, we tested impacts of HFr on blood pressure, renal damages and expression of renal renin-angiotensin system(RAS) components in Dahl salt-sensitive (DS) and salt-resistant (DR) rats in a normal-salt intake condition.

Methods: Six-week old, male DS rats and DR rats were fed a control diet or a HFr (60% fructose) with a normal-salt content (1.25%) for 12 weeks. Systolic blood pressure (SBP) and urinary albumin excretion were measured every 2 weeks. After 12 weeks, plasma biochemical parameters and renal histology were examined. Furthermore, we tested effects of enalapril (10mg/kg/day) and candesartan (1mg/kg/day) in DS rats fed the HFr diet.

Results: Compared with the control diet, HFr significantly elevated SBP in DS rats (166±5 vs 115±2 mmHg) but not in DR rats (95±4 vs 90±2 mmHg). HFr induced albuminuria in both DS and DR rats (DS: 16.5±2.0 vs 3.9±0.4 mg/day; DR: 10.5±1.8 vs 5.0±0.7 mg/day). HFr significantly increased plasma triglyceride, uric acid and urea nitrogen in both DS and DR rats. However, HFr significantly increased creatinine clearance in DS rats but not changed in DR rats. HFr-induced glomerulosclerosis, podocyte injury and tubulointerstitial fibrosis exaggerated in DS rats compared with DR rats. HFr significantly increased the renal expression of renin, (pro)renin receptor (P) RR, angiotensin converting enzyme (ACE), angiotensin II type 1 receptor (AT1-R) in DS rats. In contrast to DS rats, HFr significantly decreased the renin and AT1-R expressions without changing the (P)RR or ACE expression in DR rats. Both enalapril and candesartan attenuated the HFr-induced hypertension, albuminuria, and renal damages in DS rats.

Conclusions: Even in the normal-salt intake condition, HFr-induced hypertension and renal damages are exacerbated in DS rats compared with DR rats via renal RA system. HFr may have a higher risk to develop hypertension and renal damages in subjects with salt sensitivity, and RAS inhibitors are effective against the HFr-induced renal damages.

Funding: Government Support - Non-U.S.

PUB066

Cordyceps militaris Preserves Nephrin Expression on Podocyte Under TGF-β1 and Hyperglycemia Stimulation

Chia-Chun Wu.1,2 Chi-enwei Hsiung.3 Ting-Feng Wu.4 Chi Mei Medical Center, Tainan, Taiwan; 1Pharmacy, Chia Nan University of Pharmacy and Science, Tainan, Taiwan; 2Southern Taiwan University of Science and Technology, Tainan, Taiwan; 3Phytomed Bio-Tech co., Ltd., Tainan, Taiwan.

Background: Cordyceps militaris (CM) is a kind of fungus used as herbal medicine for multiple purposes. The study aims to know the effect of CM on nephrin expression under the TGF-β1 and hyperglycemic stimulation.

Methods: Experiment 1: Cultured podocytes were divided into four groups treated with Group 1 Control, Group 2 TGF-β1 10ng/ml, Group 3 CM100mg/ml and Group 4 both CM and TGF-β1. Experiment 2: Podocytes were cultured in different mediums: Group 1 normal, Group 2 High glucose (HG, 30mM), Group 3 CM100umg/ml in normal medium, Group 4 CM100mg/ml in HG medium. Protein was extracted on day 6 for nephrin analysis.

Results: The nephrin expression was significantly lower in the TGF-β1 group and higher in the CM group than it was in the control group. When podocytes were treated with CM and TGF-β1 simultaneously, the CM could restore the nephrin expression as compared to TGF-β1 group (Figure 1A). Hyperglycemia suppressed the nephrin expression and CM significantly attenuated this effect (Figure 1B).

Conclusions: CM might not only enhance the nephrin expression of podocytes but also attenuate the nephrin suppression from TGF-β1 and hyperglycemia.

Funding: Commercial Support - Phytomed Bio-Tech co., Ltd Taiwan.

Nephrin expression on Day 6 after stimulation of (A) TGF-β1 and (B) hyperglycemia

PUB067

Irisin-Regulated mir-29 Expression in db/db Mice

Weibo Zhao.1 Dan Luo, Honchun Lin, Hui Peng. The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China.

Background: In mice, it has been demonstrated that irisin plays a key role in metabolic regulation, energy expenditure. Both animal and in vitro studies have suggested that irisin exerts anti-inflammatory effects modulating the production of cytokines as IL-6, IL-1β and TNF-α. Inflammation and its consequent fibrosis are two main features of diabetic nephropathy. mir-29b is a novel therapeutic agent capable of inducing progressive renal inflammation and fibrosis. However, the function of irisin and mir-29b for regulation for diabetic nephropathy remain unexplored.

Methods: Male db/db mice and their normal littersmates (db/m) at the age of week 12 were purchased from Laboratory Animal Services Centre, the Nanjing University of China. Groups of four mice were used, groups of db/m or db/db mice were treated with/without irisin, mir-29a-3p, mir-29a-1-5p mir-29c-1-5p, and mir-29c-5p were no significant change(P>0.05), the group of db/db mice were treated with irisin had higher level of mir-29b, lower body weight and blood sugar Compared with db/db mice without irisin treatment.

Conclusions: The irisin may regulate mir-29b level, and improved metabolic regulation, energy expenditure, and inflammation state.
MicroRNA Profile as a Therapeutic Target for Diabetic Nephropathy
Ittiza Hasan, Thomas Idorn, Otfi Mosenzon, Richard E. Pratley, Soren Rasmussen, Benjamin Wolthers, Michael Nauck. Friedrich Alexander University, Erlangen, Germany; Novo Nordisk A/S, Soborg, Denmark; AdventHealth Translational Research Institute for Metabolism and Diabetes, Orlando, FL; Novo Nordisk A/S, Copenhagen, Denmark; Diabetes Center Bochum-Hattingen, St Josef Hospital (Ruhr-UniBochum), Bochum, Germany; Hadassah Hebrew University Hospital, Jerusalem, Israel.

Background: Diabetic nephropathy is a leading cause of chronic kidney disease in diabetic patients requiring renal replacement therapy. Chronic low-grade systemic inflammation coupled with impaired microvascular function, podocyte apoptosis, epithelial to mesenchmal transformation and fibrosis are the critical hallmarks for the pathogenesis of Diabetic Nephropathy. MicroRNAs (miRNAs) regulate the function of various downstream molecular pathways involved in Diabetic nephropathy pathophysiology.

Methods: This review focuses on the recent developments and identification of therapeutic potential of various miRNAs on the prevention and treatment of Diabetic Nephropathy. An in-depth systematic review of full-text original articles published in English in a period between 2008 and 2019 and indexed in PubMed, Ovid Medline or Embase was conducted.

Results: Stimulation of miRNAs that are commonly downregulated and inhibition of miRNAs that are upregulated or modulation of an intermediary target for miRNAs were found to be renoprotective and reduce albuminuria, decrease mesangial cell proliferation, decrease epithelial to mesenchymal transition, reduce podocyte foot process effacement and apoptosis & inhibit glomerular or tubulointerstitial fibrosis.

Conclusions: Therapeutic agents targeting the miRNAs have the potential in the prevention of diabetic nephropathy as well as early treatment and prevention of progression.

Renal Function Decline in Type 2 Diabetes: Post Hoc Analysis of LEADER
Johannes F. Mann, Thomas Idorn, Otfi Mosenzon, Richard E. Pratley, Soren Rasmussen, Benjamin Wolthers, Michael Nauck. Friedrich Alexander University, Erlangen, Germany; Novo Nordisk A/S, Soborg, Denmark; AdventHealth Translational Research Institute for Metabolism and Diabetes, Orlando, FL; Novo Nordisk A/S, Copenhagen, Denmark; Diabetes Center Bochum-Hattingen, St Josef Hospital (Ruhr-UniBochum), Bochum, Germany; Hadassah Hebrew University Hospital, Jerusalem, Israel.

Background: Diabetic kidney disease (DKD) is a frequent complication in type 2 diabetes (T2D). Identifying patients at risk of fast DKD progression is key for early care. This LEADER post-hoc analysis describes patients with varying renal function decline.

Methods: LEADER (NCT01179048) was a randomized double-blind cardiovascular (CV) outcomes trial of liraglutide (0.1 mg/d) vs placebo, both added to standard care, in 9340 patients with T2D and high CV risk (median follow-up 3.8 years). Renal function (average decline in estimated glomerular filtration rate [eGFR] from month 6 to month 24 or later) was classified from patient-specific slopes estimated via linear regression. Disregarding treatment arms, patients were categorized according to annual eGFR decline (mL/min/1.73m2/year): ≤5% (77% of patients), >5 to 10% (17%), >10 to ≤15% (4%) or >15% (2%) and differences in baseline characteristics were investigated using 2-sided trend tests (Jonckheere-Terpstra for continuous, Cochran-Armitage for binary and Goodman and Kruskal’s Gamma for ordinal parameters).

Results: Overall mean (standard deviation) eGFR decline was 2.2 (5.7) mL/min/1.73m2/year. Largest average eGFR decline was associated with longer T2D duration (P=0.02), higher baseline A1C (P<0.001), urinary albumin-to-creatinine ratio (UACR; P=0.0001), systolic (P<0.0001) and diastolic blood pressure (BP; P=0.01), total cholesterol (P=0.02), being a current smoker (P=0.04) and insulin use (P<0.01). Patients with the largest eGFR decline tended to have higher eGFR at baseline (P<0.0001).

Conclusions: This post-hoc analysis confirmed the importance of glycemic levels, systolic BP levels and smoking status for the risk of fast annual eGFR decline (>5/mL/min/1.73m2). Fast annual eGFR decline was associated with baseline high eGFR.

Funding: Commercial Support - Novo Nordisk

Table. Renal decline according to baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>&lt;5 to ≤10%</th>
<th>&gt;10 to ≤15%</th>
<th>&gt;15%</th>
<th>Age, years</th>
<th>&lt;50</th>
<th>≥50</th>
<th>Age, years</th>
<th>&lt;50</th>
<th>≥50</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65</td>
<td>64.4±7.2</td>
<td>62.6±6.0</td>
<td>68.6±6.0</td>
<td>0.001</td>
<td></td>
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<tr>
<td>HbA1c, % (n, %)</td>
<td>59.3±6.4</td>
<td>65.4±4.7</td>
<td>65.1±5.7</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>32.5±6.1</td>
<td>31.0±6.1</td>
<td>31.5±6.3</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Duration, years</td>
<td>10.9±1.3</td>
<td>12.0±1.3</td>
<td>10.8±1.9</td>
<td>0.001</td>
<td></td>
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<tr>
<td>A1C, %</td>
<td>8.6±0.4</td>
<td>8.6±0.6</td>
<td>8.9±0.7</td>
<td>0.001</td>
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<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>78.0±20.9</td>
<td>75.5±22.7</td>
<td>74.6±20.1</td>
<td>0.001</td>
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<tr>
<td>UACR, mg/g</td>
<td>16.6±603</td>
<td>15.0±600</td>
<td>45.2±600</td>
<td>0.001</td>
<td></td>
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<tr>
<td>SBP, mmHg</td>
<td>137.7±17.4</td>
<td>138.0±17.7</td>
<td>137.8±17.9</td>
<td>0.001</td>
<td></td>
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<tr>
<td>DBP, mmHg</td>
<td>7.6±0.4</td>
<td>7.5±0.4</td>
<td>7.8±0.4</td>
<td>0.001</td>
<td></td>
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<tr>
<td>Smoking status, n (%)</td>
<td>68.7±10.2</td>
<td>102.1±14.2</td>
<td>42.3±13.5</td>
<td>0.001</td>
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<tr>
<td>LDL cholesterol, mg/dL</td>
<td>89.9±38.0</td>
<td>89.3±38.9</td>
<td>94.7±38.6</td>
<td>0.001</td>
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<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>249.0±139</td>
<td>254.9±178</td>
<td>273.4±178</td>
<td>0.001</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Insulin treatment, n (%)</td>
<td>26.7±33.2</td>
<td>62.7±46.0</td>
<td>41.2±46.0</td>
<td>0.001</td>
<td></td>
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</tbody>
</table>

Results: All patients had type 2 diabetes with the mean duration of 9.8 ± 8.8 years. Diabetic retinopathy was observed in 9 patients. At the time of renal biopsy, the mean values of age, serum creatinine level, eGFR, urinary protein level, Hba1c level, and systolic blood pressure were 55.0 ± 7.2 years, 1.4 ± 0.6 mg/dL, 47.7 ± 2.3 mg/dL/1.73 m², 5.2 ± 0.4 g/dL, 6.9 ± 1.8%, and 148 ± 22.7 mmHg, respectively. Renal biopsy findings included diffuse lesions in 11 patients, exudative lesions in 11 patients, nodular lesions in 9 patients, and mesangiolysis in 7 patients. According to the previous report, we divided patients into four groups (grades 1 to 4), those with the J-score 0-5 (grade 1), 6-10 (grade 2), 11-15 (grade 3), and 16-19 (grade 4), respectively. The detailed numbers of the patients in each group were as follows: one in grade 1, five in grade 3, and seven in grade 4. Renal events were found to be zero (0%) in grade 1, two (40%) in grade 3, and five (71%) in grade 4.

Conclusions: In our single-center study, we observed the trend of worsening renal prognosis as the grade of the J-score increased. This finding suggests the potential of the scoring system for prognostic prediction of DN.

Individual Effects of Liraglutide on Cardiorenal Risk Markers: Results from the LEADER Trial
Frederik Persson, Emilie Hein Zobel, Tine Hansen, Soren Rasmussen, Bernt Johan Von Scholten, Benjamin Wolthers, Peter Rossing, Steno Diabetes Center Copenhagen, Gentofte, Denmark; Steno Diabetes Center Gentofte, Gentofte, Denmark; Steno Diabetes Center Copenhagen, Gentofte, Denmark; Novo Nordisk A/S, Soborg, Denmark; University of Copenhagen, Copenhagen, Denmark.

Background: Liraglutide has pleiotropic effects improving cardiorenal risk markers and beneficial effects on cardiovascular (CV) outcome. This post-hoc analysis investigated cross-dependency in the individual treatment response to liraglutide in 6 cardiorenal risk markers.

Methods: LEADER (NCT01179048) randomized patients (n=3940) to liraglutide or placebo (n=1915) in addition to standard of care. We interrogated 6 markers at baseline and after 1 year of therapy: glycated hemoglobin (A1C), body weight, systolic blood pressure (SBP), urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR) and low-density lipoprotein (LDL) cholesterol. In the liraglutide group, ‘good responders’ in a specific marker were defined as those with a change from baseline greater than 5%.
Methods: This retrospective study was conducted with 201 outpatient patients with hemodialysis at our Blood Purification Therapy Center and our other related hemodialysis facilities (57 diabetic nephropathy and 144 others). Logistic regression analysis was conducted with outcome- measured as CVD death. Hemoglobin levels and blood pressure values before and after dialysis were summed up at 3, 6, and 12 months. A curve was obtained by changes in blood pressure per month and the area under the blood pressure curve (AUC) was calculated.

Results: Diabetic nephropathy was the highest mortality risk among underlying disease groups. A comparison with other underlying diseases revealed that significant differences were observed in the older age group (p<0.001) and a shorter history of hemodialysis (p<0.001) in patients with diabetic nephropathy. There was no significant difference in anemia control between two groups. Poor blood pressure control and higher dose of erythropoietin were found in patients with diabetic nephropathy. The multivariate analysis of risk factors for mortality in patients with diabetic nephropathy showed that smoking (odds ratio:OR) 4.71 [95%CI: 1.97–11.26, p<0.001], history of ischemic heart disease (OR: 2.56 [95%CI: 0.93–6.85, p=0.061], age (OR: 1.07 [95%CI: 1.03–1.13, p=0.002], and a history of dialysis therapy (OR: 0.78 [95%CI: 0.69–0.87, p<0.001]) were risk factors.

Conclusions: Introduction to hemodialysis for patients with diabetic nephropathy, given CVD mortality risk, is important to prevent the development of CVD shortly after hemodialysis. Furthermore, higher smoking rates with higher CVD mortality risk associated with smoking among patients with diabetic nephropathy suggested that smoking cessation is important for patients with diabetic nephropathy to improve their prognosis.

PUB074
Pentoxifylline in Diabetic Kidney Disease: The VA Pentoxifylline in End-Stage Renal Disease (VAPR) Trial

David J. Leechey,1,2 Kimberly Carlson,3 Donnica Reden,3 Linda Polzin,3 Christina E. Clise,4 Tamara Paine,1 Douglas E. Lammie,5 Rajiv Agarwals,3 James S. Kaufman,1 Robert Anderson,5 Grant D. Huang,4 Nicholas Emanuell.1

1Hines VA Hospital, Hines, IL; 2Loyola University Medical Center, Maywood, IL; 3Cooperative Studies Program Coordinating Center, Hines, IL; 4VA CSP CRPPC, Albuquerque, NM; 5Rochester VA Medical Center, Indianapolis, IN; 6VA New York Harbor Healthcare System, New York, NY; 7Omaha VA Hospital, Omaha, NE; 8Cooperative Studies Program Central Office, Washington, DC.

Background: Diabetic kidney disease (DKD) is the most frequent cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the U.S. The recent CREDENTIAL trial demonstrated that the sodium-glucose cotransporter 2 (SGLT2) inhibitor canagliflozin reduced ESRD and cardiovascular events in DKD patients with an estimated glomerular filtration rate (eGFR) of 30 to <90 mL/min/1.73m2 and a urinary albumin to creatinine ratio (UACR) of >300 to <3000 mg/g. This trial excluded patients with eGFR <30 or ≤50% of baseline.

Methods: VA PTXRX is a randomized, controlled multicenter Veterans Affairs (VA) Cooperative Study to test the hypothesis that PTX, when added to usual care, leads to a reduction in the incidence of ESRD and death in type 2 diabetic patients with DKD who were found on usual care plus placebo. Secondary endpoints will be: (1) 7 year survival of life (2) time until doubling of serum creatinine, (3) hospitalization for congestive heart failure, (4) a three-point MACE (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), (5) peripheral vascular disease, (6) percentage of participants with a 50% reduction in UACR from baseline to year 7, (7) rate of change in eGFR from baseline to year 7. The primary endpoint will be defined as 25% of the placebo group at six years with a risk reduction of 19% for PTX compared with the placebo group. The study aims to randomize 2510 participants to either PTX or placebo. Inclusion criteria are based on risk of ESRD from the KDIGO “heat map”; participants are assigned to risk strata based on estimated glomerular filtration rate (eGFR) and albumin to creatinine ratio (ACR). The sample size must be in the following categories: eGFR 15 to <30, eGFR 30 to <45 and UACR >30 mg/g; eGFR 45 to <60 and UACR >100 mg/g.

Results: N/A

Conclusions: If PTX is found to reduce the incidence of ESRD and/or death, this will provide another effective treatment for DKD which could extend to patient groups not currently candidates for SGLT2 inhibitors.

Funding: Veterans Affairs Support

PUB075
Effect on Major Renal Outcome of Continuous Metformin Use in Patients with Type 2 Diabetes and Advanced Kidney Disease: A Retrospective, Propensity Score-Matched, Common Data Model-Based Cohort Study

Young Eun Kim, Jong Chool Jeong, Ho Jun Chih, Ki Young Na, Dong-Wan Chae, Sejoong Kim. Seoul National University Bundang Hospital, Seongnam-si, GyeongGgi-Do, Republic of Korea.

Background: Metformin is an effective, inexpensive and widely used drug for type 2 diabetes (T2DM) patients. However, use of metformin is contraindicated in patients with advanced CKD owing to risk of lactic acidosis. Although several studies have revealed metformin-associated lactic acidosis has rare incidence rate, study for metformin effectiveness in those patients is hard to conduct because of established contraindication. This study aimed to generate a safe, evidence-based strategy to prevent the development in a T2DM patients with CKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Methods: We performed a retrospective, propensity score matched, observational cohort study by using The Observational Medical Outcomes Partnership common data model version 5. We used medical data of 1.82 million patients in a tertiary hospital in Korea from 2003 to 2017. Study participants were identified by drugs, diagnosis codes and laboratory test values in combination with event time. More than six months ongoing of metformin treatment after each index time of EPI-CKD eGFR ≤ 60 ml/min/1.73m² were considered as treatment group. Never use of metformin after three months since index time was considered as comparative group. Composite renal outcome was defined as receiving renal replacement therapy, having EPI-CKD creatinine-based eGFR ≤ 15 ml/min/1.73m² or in-hospital death. An adaptive propensity score-based matching (PSM), Cox proportional hazards model was used to analyze hazard ratio for the renal outcome.

Results: An 894 of metformin using patients and a 236 of non-metformin using patients were identified. After 1:1 PSM, we matched each of 154 patients in both groups. Mean age was 57.2 ± 5.4 years, respectively. Baseline age, sex distribution, EPI-CKD eGFR, HbA1c level and spot urine albumin-to-creatinine ratio were not significantly different between groups. Continuous metformin use was associated lower outcome risk (HR=0.29, 95% CI [0.10-0.81]; p=0.008).

Conclusions: Continuous use of metformin was associated with lower incident rate of composite renal endpoints in T2DM patients with reduced renal function equivalent to advanced CKD. This longitudinal real-world study may support benefit of metformin in T2DM patients having reduced renal function for major renal outcome.

Results from a Large Australian Linked Cohort Study (EXTEND45) Patterns of Hospitalisation in Individuals with and Without Diabetes: Results from a Large Australian Linked Cohort Study (EXTEND45) of Human Services) and for participants of the population-based 45 and Up Study (n = 267,153). MBS and PBS data was linked by the Sax Institute and all other data sources by the Centre for Health Record Linkage. Individuals with diabetes were identified using pre-specified criteria. All hospitalisations between January 2006 and June 2014 were identified and the proportion and mean LOS of hospitalisations calculated.

Results: Amongst 151,760 individuals with linked pathology data, 24,400 met the criteria for diabetes. Of these, 17,293 (70.9%) received glucose-lowering pharmacotherapy at any time during the study period. The annual mean number of overnight hospitalisations per individual was 0.33 for those without diabetes, 0.62 for those with diabetes but not receiving pharmacotherapy and 0.66 for those with diabetes and receiving pharmacotherapy. The diabetes cohorts had a higher proportion of hospitalisations due to CVD (7.6-8.9%) and ESRD (0.8%) than individuals without diabetes (6.0% and 0.3%, respectively). Mean LOS for admitted hospitalisations related to vascular and reparative care with and without diabetes and not receiving pharmacotherapy, and for those without diabetes was 6.13 (SD 8.12), 6.02 (SD 6.80) and 5.41 (SD 5.68) days, respectively. The corresponding mean LOS for ESRD-related hospitalisations was 15.4 (SD 18.0), 13.0 (SD 19.4) and 14.5 days (SD 17.6) days respectively. Limitations include sampling biases in the opt-in design of the 45 and Up Study.

Conclusions: Differences in the patterns of hospitalisation between individuals with and without diabetes were observed. Factors driving this warrant further investigation.

Analysis of 416 Non-Dialysis Inpatients with Diabetic Kidney Disease: A Retrospective Cohort Study Yannan Zhang, Le X. Peng, MeiFang Liu, XuSheng Liu, Le Zhang, Guangzhou University of Traditional Chinese Medicine, Guangzhou, China; The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China. Background: Diabetic kidney disease (DKD) has become one of the major causes of end-stage renal disease worldwide. In China, there is an obviously increasing trend of incidence. Our study aims to explore the survival of hospitalized patients with DKD through a single-center retrospective analysis.

Methods: Patients in hospital during 2011/01/01 to 2016/12/31 diagnosed with DKD but without commencing renal replacement therapy (RRT) at the time of diagnosis were included, excluding patients whose interval between the time of diagnosis and the time of receiving RRT less than 3 months or only with baseline follow-up data. Taking death or receiving RRT as a composite endpoint, survival time was compared after dividing patients into different groups according to whether angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) was or was not used, whether hemeturia occurred or not. Cox regression was used to analyze the influence of ACEIs, ARBs and hemeturia on the prognosis of DKD.

Results: 416 patients were enrolled, of which 155 received RRT, 31 died, 76 survived and 54 were lost to follow-up. The median survival time for the whole with composite endpoint was 27.53 months. The median survival time of patients in 3 or 4 stage chronic kidney disease (CKD) was 33.03 months while it’s 11.47 months in 5 stage CKD (P < 0.001). The median survival time of patients using ACEIs of ARBs was longer than that without using. The median survival time were 39.60 (43.70, 32.30) months and 17.60 (21.15, 12.05) months while those with hemeturia was 20.30 months (P = 0.002), and it’s risk of composite endpoint was higher compared with patients without hemeturia after adjusting for gender, age, BMI, duration of diabetes, history of hypertension and use of diuretics (HR = 1.603, 95% CI 1.040-2.115; P = 0.020).

Conclusions: The use of ACEIs or ARBs is considerably beneficial to the prognosis of DKD. Hemeturia is not conducive to the survival of patients with DKD, which needs further researches.

Patterns of Hospitalisation in Individuals with and Without Diabetes: Results from a Large Australian Linked Cohort Study (EXTEND45) Patterns of Hospitalisation in Individuals with and Without Diabetes: Results from a Large Australian Linked Cohort Study (EXTEND45) of Human Services) and for participants of the population-based 45 and Up Study (n = 267,153). MBS and PBS data was linked by the Sax Institute and all other data sources by the Centre for Health Record Linkage. Individuals with diabetes were identified using pre-specified criteria. All hospitalisations between January 2006 and June 2014 were identified and the proportion and mean LOS of hospitalisations calculated.

Results: Amongst 151,760 individuals with linked pathology data, 24,400 met the criteria for diabetes. Of these, 17,293 (70.9%) received glucose-lowering pharmacotherapy at any time during the study period. The annual mean number of overnight hospitalisations per individual was 0.33 for those without diabetes, 0.62 for those with diabetes but not receiving pharmacotherapy and 0.66 for those with diabetes and receiving pharmacotherapy. The diabetes cohorts had a higher proportion of hospitalisations due to CVD (7.6-8.9%) and ESRD (0.8%) than individuals without diabetes (6.0% and 0.3%, respectively). Mean LOS for admitted hospitalisations related to vascular and reparative care with and without diabetes and not receiving pharmacotherapy, and for those without diabetes was 6.13 (SD 8.12), 6.02 (SD 6.80) and 5.41 (SD 5.68) days, respectively. The corresponding mean LOS for ESRD-related hospitalisations was 15.4 (SD 18.0), 13.0 (SD 19.4) and 14.5 days (SD 17.6) days respectively. Limitations include sampling biases in the opt-in design of the 45 and Up Study.

Conclusions: Differences in the patterns of hospitalisation between individuals with and without diabetes were observed. Factors driving this warrant further investigation.

Conclusion: This is a prospective, longitudinal real-world study done from December 2014 to December 2016 in Department of Nephrology, Gandhi hospital, Hyderabad in 100 patients of type 2 Diabetes mellitus patients presenting with symptoms and signs of renal disease. These results will provide data on the patterns of hospitalisation in individuals with and without diabetes and comparing the hospitalisation rates and length of stay between the two groups.

Conclusions: This is a prospective, longitudinal real-world study done from December 2014 to December 2016 in Department of Nephrology, Gandhi hospital, Hyderabad in 100 patients of type 2 Diabetes mellitus patients presenting with symptoms and signs of renal disease. These results will provide data on the patterns of hospitalisation in individuals with and without diabetes and comparing the hospitalisation rates and length of stay between the two groups.
Conclusions: (1) Low serum BMP 7 and high TGF beta 1 levels may be used as screening tests for diabetic nephropathy and non-diabetic renal disease, instead of subjecting the patients to an invasive procedure like renal biopsy. (2) Low serum BMP 7 and high TGF beta 1 levels have a strong correlation with increasing severity of histopathological class of diabetic nephropathy.

PUB080

How Important Is Glucose Nephrotoxicity in Type 2 Diabetes Mellitus-Associated Cardiovascular Risk?

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Background: Diabetes mellitus is frequently associated with different macro and microvascular lesions, widely accepted as responsible for the high cardiovascular morbidity and mortality associated with this pathology. It is also accepted that diabetic nephropathy is part of this spectrum of vascular involvement. Recently several multicenter clinical trials have digged into this association between diabetes and cardiovascular disease. The first one, EMPAREG, showed that the inhibition of SGLT2 in the proximal tubule reduced the cardiovascular mortality, mortality from any cause, hospitalization due to chronic heart failure (CHF) and the progression of the renal lesion, but had little or no effect on non- lethal AMI or non- lethal stroke. The studies on SGLT2 that followed, CANVAS and DECLARE, have shown apparently discordant effects, with significant effects in some cardiovascular outcomes, but not in others. Although various explanations have been proposed, none justifies the heterogeneity between the studies. So, discussion about the existence or not of a class effect persists.

Methods: In this study, we perform a meta-regression of the three studies comparing the prevalence of any single or composite variable in the control group against the reduction in the risk obtained with every SGLT2. And we compared the results with those of the HOPE study.

Results: Meta-regression shows that SGLT2 blockade reduces in a risk-dependent manner cardiovascular mortality, hospitalization due to CHF and the progression of nephropathy, but not the risk of stroke or AMI. The results are exactly as expected according to the HOPE study if the primary mechanism of cardiovascular protection in diabetes mellitus type 2 treated with SGLT2 is the reduction in kidney damage.

Conclusions: We discuss the evidences of this interaction between ISGLT2 and renal tubular damage of different etiologies, the mediating role of the inflammammasome activated by the renal tubular lesion on vascular and cardiac damage and propose an explanation for the absence of effects at the central nervous system level.

Funding: Government Support - Non-U.S.

PUB081

Lipoprotein(a) and Decline in Renal Function, Incidence of Cardiovascular Disease, and Mortality in Individuals with Type 2 Diabetes and Microalbuminuria

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Background: Lipoprotein(a) (Lp(a)) has emerged as an independent risk marker for cardiovascular disease (CVD) in both general populations and populations with existing CVD. We investigated associations between Lp(a) concentrations and decline in renal function, incidence of CVD and all-cause mortality in individuals with type 2 diabetes, microalbuminuria and no history or symptoms of coronary artery disease.

Methods: A prospective cohort of 198 individuals with type 2 diabetes and microalbuminuria (moderately increased urinary albumin excretion rate (UAER) 30-300 mg/24h) was followed for 8-years. All-cause mortality and CVD (fetal and non-fatal) events were tracked from national registries. Yearly p-creatinine was measured after baseline in 76% of the participants. The renal endpoint was defined as eGFR-decline of >30% from baseline. Cox regression analyses were performed on Lp(a) concentrations at baseline and in the last two years (April 2017 to March 2019). Results: The mean follow-up time was 6.6 ± 1.8 years. A total of 15 death events and 44 CVD events were recorded. The Cox regression model with Lp(a) as predictor was adjusted for baseline eGFR, age, sex, systolic blood pressure, LDL-cholesterol, smoking, HbA1c, creatinine and urine albumin.

Conclusions: Our study found no association between baseline Lp(a) concentration and renal outcomes. This is in contrast to previous studies reporting a link between Lp(a) and renal disease.

Funding: Veterans Administration Informatics and Computing Infrastructure (VINCI) and a grant from ASTRAGAL Sas. Propensity matching for age, followup time and prior vascular disease was used to adjust groups. Results were compared by means, tests frequencies, odds ratio and p values (p<0.001).

Results: Of 57,985 patients with type 2 diabetes and microalbuminuria, 1,317 with dementia diagnosis (Dx) had treatment (Dx/TRT) and 475 had none (Dx_No/TRT), compared to controls (Ctrl/TRT, N=44,434, Ctrl_No/TRT, N=13,551). Followup was shorter with DX (Ctrl vs Dx: 5.5 vs 4.4 years). Baseline age and creatinine were similar (59.3 vs 66.2 yrs; creatinine 1.03 vs 1.03 mg/dl). TRT provided significant reduction in all-cause mortality in both groups, (Odds Dx 0.61, 95% CI 0.49-0.75 vs Odds Ctrl 0.85, 95% CI 0.84-0.87). TRT reduced the progression of CVD (Dx 0.63, 95% CI 0.51-0.79 vs Odds Ctrl 0.89, 95% CI 0.88-0.91). TRT reduced CVD (Dx 0.67, 95% CI 0.41-0.79 vs Odds Ctrl 0.98, 95% CI 0.98-0.95). The effect on new MI was significant in Control only (Odds 7.6, 95% CI 0.67-0.85). TRT reduced new diagnosis of retinopathy and nephropathy was not significant. Prior cardiovascular disease was more common with dementia (% difference Dx/Ctrl), e.g. CAD (117), CHF (92), CV A (496), HTN (67), MI (140), EP (247).

Conclusions: TRT is associated with significant reductions in progression of early CVD[AG1], all-cause mortality and new cardiovascular diagnoses in patients with dementia even while dementia is associated with increased prior cardiovascular disease.

Funding: Veterans Affairs Support

PUB084

Worsening of Dental Caries Is Associated with Arteriosclerosis Among Patients on Hemodialysis

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Background: Patients on hemodialysis (HD) must undergo HD therapy three times weekly and might be unable to visit a dentist. Dentists may hesitate to provide routine oral care to patients with HD, as they are medicated with anticoagulants and are thus particularly susceptible to bacterial infections; they might also experience drug reactions. Patients on HD possibly have worse oral status than healthy people; this might predispose such patients to systemic complications.

Methods: The dental caries and periodontitis statuses of 80 patients on HD and 76 healthy individuals (controls) were compared using the decayed, missing or filled teeth

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Expansion of Monocytic Myeloid-Derived Suppressor Cells in Patients Under Hemodialysis May Lead to Cardiovascular Disease and Death

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Background: The specific mechanism of cardiovascular vasculopathy in the context of end stage renal disease was not clear. In the present study, we investigated the clinical impact of myeloid-derived suppressor cell on hemodialysis patients and the mechanism.

Methods: Myeloid-derived suppressor cell was tested among hemodialysis patients under hemodialysis and analyzed with correlation with overall survival and cardiovascular disease was determined by survival analysis.

Results: Hemodialysis patients presented with a significantly higher level of monocytes myeloid-derived suppressor cells compared with healthy controls. Monocytes myeloid-derived suppressor cell positively correlated to circulation monocyte counts and share the same surface marker with monocytes. T cell proliferations were significantly abrogated by the addition of hemodialysis related M-MDSCs in a dose-dependent manner which confirmed that monocytes myeloid-derived suppressor cell, instead of monocyte, contributed to cardiovascular diseases. Besides, monocytes myeloid-derived suppressor cell presented higher level of CXCR4 and VLA-4 compared with monocytes, which indicated their enhanced capability to be recruited to atherosclerotic lesions. The expression of arginase I and activity of arginase also significantly raised in hemodialysis related monocytic myeloid-derived suppressor cells which indicated that they accelerated atherosclerosis by exhausting local L-arginine.

Conclusions: Above all, monocytic myeloid-derived suppressor cells was elevated in hemodialysis patients and an independent prognostic factor for overall survival and cardiovascular diseases. They might contribute atherosclerosis by enhanced recruitment to vascular lesions and exhausting local L-arginine.

Uremic Toxicity in Non-Pathological Profiles

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Background: High protein intake is associated with increased levels of albumin-bound uremic solutes in hemodialysis (HD) patients (p). We analyze the patterns of the prototypic uremic toxins Indoxyl Sulfate (IS) and β2microglobulin (β2M) relationship with protein metabolism and inflammation.

Methods: Study of 60 chronic HD p. 60±12 yrs (meansSD) years. 32 M/28 F. 34 standard HD / 26 postdilutional hemodiafiltration (HDF). 54 presidial diuresis <500 ml/24 h. Dialyzer: 54 polypropylene, 4 cellulose. HD time 244±25 min. QB 357±66 ml/min. Qp 500-800 ml/min. Pre/postHD serum IS total by HPLC. Pre/post (in HDF p) serum β2M by nephelometry. IS total by Solute Solver. Midweek sessions.

Results: β2M by nephelometry and IS total by Solute Solver. The mean total IS was 18,9±1.9 mg/L (p<0.006) and β2M was higher in the low vs high albumin group: 40.9±15.4 mg/L vs 29.4±(24.7±34.2) mg/L (p<0.002). IS higher in the high vs low dp β2M p group: 22.8 (18.7-26.7) vs 14.4 (10.6-18.8) mg/L (p<0.001). IS relationship with dp β2M was: 0.6 g/kg/day=12.9 mg/L, 0.6-0.79=16.2 mg/L, 0.8-0.99=17.7 mg/L, 1-1.19=23.4 mg/L, >1.2=21.7 mg/L.

Conclusions: IS concentrations had direct correlation to β2M determined by protein intake. β2M had inverse correlation to albumin level and direct correlation with CRP. Catabolic p showed both IS and β2M highest levels.

Funding: Government Support - Non-U.S.

Publish-Only

Ultrafiltration Volume During Hemodialysis and Its Correlation with Central Pressure Parameters

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Background: Determination of the ultrafiltration volume during hemodialysis (HD) is crucial for ESRD patients. It is challenging during HD to maintain a balance between excess fluid removal and hypoperfusion. Noninvasive central pressure measurement was utilized to identify the independent variables related to the ultrafiltration volume (UFV).

Methods: A cross-sectional study was performed to monitor the central blood pressure, using Mobil-O-Graph device, with peripheral brachial cuff for 10 hemodialysis sessions among 10 patients. The Central BP, Cardiac output (CO), Peripheral vascular resistance (PVR), Pulse Wave velocity (PWV), and Augmentation index (AII) were continuously monitored during the whole hemodialysis sessions. Age, gender, BMI and cardiovascular risk were recorded from the medical files. The total and hourly ultrafiltration volume were calculated from the patients Pre, Post dialysis weight and the dialysis machines. Significant univariate correlations were selected to generate a multivariate linear regression equation to test all the independent variables.

Results: The mean age for the patients was 55 years (SD 8.6), BMI 27.7 kg/m² (SD 4.7). Five of the patients were males. Mean number of CV risks were 2 in each patient, not counting ESRD. We recorded 136 measurements of central pressure, CO, PWV, PVR and AII over 10 Hemodialysis sessions. Mean CO was 5 l (SD 0.9), mean AII 28 (SD12), mean PWV 9m/s (SD 2), mean PVR 1858 dyn.s/cm² (SD 379), mean central pulse pressure 45mmHg (SD 16), mean central MAP 110mmHg (SD 12). The total and the hourly ultrafiltration volumes were recorded from the patients pre, post dialysis weight and the mean total UFV was 1891ml (SD 972) and the mean hourly UFV was 658ml (SD286). The total and the hourly UFV were significantly correlated with age, gender, BMI, CV risk, CO, PWV, TVR, PVR, and central pulse pressure. However, the AII and Central MAP were not significantly correlated. The UFV was determined by the age, gender, BMI, CV risk, CO, PWV, PVR, and central pulse pressure in a multivariate regression with an R² of 0.8.

Conclusions: Demographic factors, CV risk and central pressure measurement, including pulse wave velocity, Central pulse pressure, cardiac output and peripheral vascular resistance were independent variables that determined the ultrafiltration volume during dialysis with an accuracy of 80%.
Results from the First Use of High Flux Dialysis in Algeria
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Background: Traditional low-flux dialysis is the only treatment currently available in Algeria, while high-flux dialysis can improve renal disease patient’s health related quality of life. Water treatment remain one of the major obstacles to prevent this method from developing in our country. The aim of the study was to compare for the first time the effect of permeability of LF versus HF dialysis membranes on metabolic abnormalities control, Inflammation and body composition by bioimpedance spectroscopy.

Methods: Six prevalent patients on regular hemodialysis were enrolled in a prospective study, from M’sila hospital in Algeria, Chronic LF polysulphone membranes were used, all patients were switched to HF Polyethersulfone during one year. Predialysis samples were taken from the arteriovenous fistula while Postdialysis samples were taken from the arterial blood tubing after the dialyzer blood flow rate had been reduced to 80ml/ min. Standard biochemical parameters, Albunmiema, Creatinine, C-reactive protein, Vitamin B12 and intact parathyroid hormone concentration were analyzed with standard laboratory techniques, β2micoglobuline (β2M) by Chemiluminescence. The dialysis time and schedule, blood and dialysate flows, and the anticoagulation protocol were kept constant during the period after. Bacteriology water and Endotoxin assay were performed each three months.

Results: We observed a significant decrease of pre-dialysis levels of β2M 44.2±7.5,47±1mg/l, 25,49±2.1mg/ml respectively (p = 0.0002) and significant increase in Vitamin B12 between pre-HF and post HF dialysis (p= 0.001). However, we noticed no significant differences of the other parameters (Albumin, CRP,PTH), Hemoglobin mean levels remained stable with reduced erythropoietin doses. An increase in Lean tissue index and decrease in Fat occurred 6 months after the beginning of the trial (p=0,564 and 0,113). On the other hand, we should state that the removal of small toxins was similar with HF and LF.

Conclusions: HF dialysis membranes seems to be more efficient in terms of metabolic abnormalities control for chronic hemodialysis patients than low-flux membranes. Reduction of β2M and improvement of nutritional parameters are encouraging us to use HF in our setting. Our greatest pleasure was when HF proved its tolerance without evidence of major adverse side effects. HF dialysis is feasible in our context with limited resources, so we look forward to spread it in all of Algeria hospitals.

Funding: Government Support - Non-U.S.

Enhancing Volume Management in Hemodialysis Through Integration of Point-of-Care Ultrasonography
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Introduction: Volume overload is associated with increased morbidity and mortality in patients with end-stage renal disease (ESRD). In routine practice, physical examination is commonly used to estimate volume status and guide ultrafiltration (UF) in hemodialysis (HD) patients. Herein, we describe a case in which point of care ultrasonography (POCUS) uncovered volume overload in an apparently euvolemic patient and changed the management strategy.

Case Description: A 68-year-old woman with a history of ESRD on maintenance HD presented with severe dyspnea. On physical examination, blood pressure was 260/110 mmHg, lungs were clear to auscultation, and there was no pedal edema. The last HD treatment was 2 days prior and the patient was at her estimated dry weight at the end of therapy. Nitroglycerin infusion resulted in improvement in BP and complete resolution of dyspnea over the next few hours. Since there was an unexplained significant discrepancy between her presentation and physical exam, POCUS was performed to more objectively assess volume status. Despite her apparent clinical euvolemia, focused sonography of the inferior vena cava, lung, and the heart revealed presence of significant fluid excess implying the need for aggressive UF. We were able to perform POCUS-guided UF to achieve an impressive 6.8% reduction in weight within 3 hours with no adverse event. Sonographic findings (Figure) and BP showed progressive improvement throughout the UF session.

Discussion: This case highlights the capability of POCUS to enhance patient care in ESRD, not only through uncovering of concealed hypervolemia, but also by guiding the UF process. In addition, limited cardiac POCUS can provide insights into patient’s cardiac tolerance as transient changes in ventricular function and regional wall motion abnormalities are known to occur during HD. Future longitudinal studies need to explore whether these salutary effects translate into improved outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
**PUB092**

**Blood Pressure Elevation Just Before Cerebral Hemorrhage in Patients Undergoing Hemodialysis**

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**Background:** Pre-symptomatic blood pressure elevation is known to be associated with cerebral hemorrhage; however, only a few studies have reported this association.

**Methods:** This study included patients undergoing hemodialysis who were treated for cerebral hemorrhage at our hospital between 2008 and 2016 (case group) and patients treated at Nagasaki Renal Center between 2011 and 2012 (control group). Data regarding participants’ backgrounds were obtained from medical records and 3 consecutive dialysis charts just before the onset of cerebral hemorrhage (case group) and participants’ birthdays (control group).

**Results:** The case group included 99 patients (mean age 65 years, median dialysis vintage 87 months, 67% men), and the control group included 339 patients (mean age 67 years, median dialysis vintage 56 months, 57% men). Compared with the control group, the case group showed a significant increase in systolic blood pressure (approximately 6 mmHg) during the last among 3 dialysis sessions (P<0.02). After adjusting for age, sex, dialysis vintage, history of diabetes and cerebrovascular disease, serum hemoglobin, calcium, and phosphate levels, antiplatelet drug use, and fluid removal rate, logistic regression analysis showed that blood pressure elevation over baseline levels was significantly associated with cerebral hemorrhage (odds ratio 1.02 per/mmHg, P<0.001). Multiple regression analysis showed that in the case group, blood pressure elevation was significantly associated with a history of diabetes (P=0.03) and lower serum calcium levels (P=0.01) but not with weight gain between dialysis sessions.

**Conclusions:** Blood pressure elevation over baseline levels, which may reflect failure of vascular system autoregulation, was associated with cerebral hemorrhage. The tendency of blood pressure elevation may depend on a patient’s background.

**Funding:** Government Support - Non-U.S.

**PUB093**

**Percutaneous Left Atrial Appendage Closure: A Safe Alternative to Anticoagulation for Patients with Non-Valvular Atrial Fibrillation and ESRD on Hemodialysis**

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**Background:** The prevalence of non-valvular atrial fibrillation (NVAF) in patients with end-stage renal disease (ESRD) on hemodialysis is 13 to 27%. There is little evidence on the effectiveness and safety of vitamin K antagonists (VKAs) in them since their potential benefit have shown conflicting results. Moreover, direct oral anticoagulants are not recommended by current cardiology guidelines in patients on hemodialysis. Percutaneous left atrial appendage occlusion (LAOO) has demonstrated to be an alternative therapeutic option to anticoagulation for stroke prevention in NVAF. However, the evidence of its use in patients on hemodialysis is scarce. The aim of this study is to present our single-center experience of LAAO in ESRD patients on hemodialysis.

**Methods:** Retrospective chart review of clinical records, demographics, LAAO procedure and derives, complications, post-procedure therapy and outcomes of patients with ESRD on hemodialysis and NVAF who underwent a percutaneous LAAO in our center between January 2017 and January 2019.

**Results:** Eight patients (six males) with ESRD on hemodialysis underwent a percutaneous LAAO in our center. The mean age was 67.5 years (range 56–81; SD±7.2). All patients had permanent NVAF. The mean dialysis duration was 8.49 years (range 0.83–14.8; SD±6.2). The mean CHADS2-VASc and HAS-BLED scores were high [4.75 (SD±1.16) and 4.62 (SD±0.91), respectively]. All patients had history of a major hemorrhagic event (BARC Score ≥3). Contraindications for anticoagulation were gastrointestinal hemorrhage (n=3), repeated bleeding from the dialysis vascular access (n=3), intracranial hemorrhage (n=1) and massive epistaxis (n=1). All devices (5 Amplatzer-Amulet, 2 Watchmann and 1 LAmbre) were implanted successfully. Post-procedural antithrombotic regimen was based on antiplatelet therapy during 3.1±1.24 months. No deaths, cardioembolic events, device thrombosis or peri-device leaks, major adverse effects according to VARC criteria, or major bleeding were reported during a mean follow-up of 14.24 months (SD±9.44).

**Conclusions:** Percutaneous LAAO could be a safe and an effective alternative to anticoagulation in patients with NVAF and CKD in hemodialysis. Further studies will be necessary to confirm this hypothesis.
The NLRP3 Inflammasome Plays an Important Role in IL-1β Secretion in Hemodialysis Patients

Denise Maga,1 Livia D. Alvarenga,2 Ludmila F. Cardozo,1 Roberta Salarolli,2 Bruna Paiva,1 Jessyca S. Brito,1 Drielly V. Reis,1 Julie ann Nemperio.1,2

Background: Inflammomas have been elucidated as an important inflammatory agent in several diseases, including chronic kidney disease (CKD). These molecules are multimetric protein complexes that act as activators of the inflammatory process and can also be induced by other inflammatory mediators considered agonist, for example, the Nucleic Factor-kB (NF-kB). The most studied inflammasome is NLR pyrin-domain-containing protein 3 (NLRP3) that cleaves pro-interleukin 1β (IL-1β) to IL-1β mature, which is involved with activation of acute phase response proteins in the liver such as C-reactive protein, leading to systemic inflammation. Therefore, the aim of the present study was to evaluate the possible involvement between gene expression of NLRP3 and IL-1β in hemodialysis (HD) patients.

Methods: Eleven HD patients [63.6% female, 50.9 ± 17.9 years, (49.0 – 213.0) months on HD] were included in this study. Blood samples were drawn after 12h fasting, and the peripheral blood mononuclear cells (PBMC) were isolated. Quantitative Real-Time PCR analysis was performed using 7500 Real-Time PCR System (Applied Biosystems) to evaluate the mRNA expression encoding NLRP3, IL-1β and NF-kB. High sensitive C-reactive protein (hs-CRP) plasma levels were analyzed using Beckman® kit by automatic biochemical analyzer.

Results: NLRP3 mRNA expression was 0.83 ± 0.35, IL-1β was 2.1 ± 1.6 and NF-kB was 0.91 ± 0.32. The plasma levels of CRP were 4.3 (2.5 – 10.7) mg/dL. There was a positive correlation between the expression of the inflammatory factor NLRP3 and IL-1β (r = 0.73, p-value = 0.02) and between NLRP3 and hs-CRP (r = 0.75, p-value = 0.03).

Conclusions: The NLRP3 gene expression may lead to increased IL-1β gene expression and increased plasma hs-CRP levels. Then, the inflammasome-IL-1β axis should be explored in CKD patients and therefore, as the NLRP3 inflammasome has been shown to be an important inflammatory marker, it may be a new target for alternative therapies in CKD patients on HD.

Funding: Government Support - Non-U.S.
platform will offer a novel tool dialysis facilities can use to design and implement quality improvement projects around all steps of transplantation. Transplant centers can also make use of the IT platform to inform quality improvement projects around waitlist criteria and waitlist management. Nephrology practices can make use of the IT platform to actualize population-health level tracking the transplant education, referral, evaluation and listing of prevalent patients with advanced chronic kidney disease (CKD) and/or end-stage renal disease (ESRD).

**Case Description:** Technical Requirements: 1. Active on the federally certified Health IT product list 2. Linked to a patient record with unique patient identifier (UPI) 3. Facilitates instant and bi-directional communication capabilities among the patients, payers, providers, and other Health IT systems: a. Videos/Pictures/Files/Medical Imaging b. Recorded audio and video calls c. Text messaging d. Customizable Notifications e. Delivered/Read receipts f. Acknowledgment emojis g. Patient record data fields

**Discussion:** This proposal includes organ transplant with metrics and IT infrastructure/ platform to support the communication and coordination of the patients and providers in the network. The OmniLife platform provides the infrastructure supporting all technical requirements above, including an upcoming interface with BlueButton 2.0. OmniLife leverages existing IT systems to accelerate implementation throughout the provider network. Aim 1: implement the IT platform among an ESRD care provider network. Aim 2: reduce the cost of care for the patient population through better coordination of patients among providers.

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**PUB100**

**Vascular Access Transition and Hemodialysis Adequacy in Hemodialysis Patients**

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**Background:** Fistulas are regarded as the best choice for vascular access in hemodialysis (HD) patients because they are associated with improve survival, and less infectious complications specially in incident patients. However, in Mexico, more than 90% of patients who start on HD with a non-tunneled central venous catheter (CVC), and the transition to a permanent vascular access is delayed for months or years. The Instituto Mexicano del Seguro Social (IMSS) is the largest health institution in Mexico who provide HD service. Due to the high incidence of end stage renal disease, this institute subrogate HD treatments from private ambulatory units, and the patients selected for this service are receiving HD sessions usually for two to three years. Our objective was to test if the change from non-tunneled CVC to fistulas or tunneled CVC were associated with better adequacy in chronic HD patients.

**Methods:** During March 2018 to April 2019 as part of a continuous improvement program, we changed all non-tunneled catheters to fistulas or tunneled catheters. We measured urea reduction ratio (URR), standard KT/V as well as hemoglobin and erythropoetin dose, serum calcium and phosphates before and after the vascular access change.

**Results:** A total of 50 (32.1%) patients changed their vascular access. The median time elapsed before the vascular replacement was 18 months (QR 6.7-32.6). 22 (44%) were male and 28 (56%) female. The median age was 49.4 years (QR 29.3-62.7). There were no differences between URR, KT/V, hemoglobin levels, erythropoetin dose or phosphate before and after the vascular change, however, there was a lower serum calcium after the change.

**Conclusions:** Change of vascular access to a fistula is not associated with better adequacy in terms of urea, anemia or calcium and phosphates.

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**PUB101**

Use of XGBoost Machine Learning Model to Forecast the Changes in Dry Weights of Hemodialysis Patients

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**Background:** Making a clinical estimation of dry weights in the hemodialysis (HD) patients is a routine among renal physicians. The objective of this study was to develop a machine learning app to estimate dry weight of HD patients alongside the conventional clinical methods.

**Methods:** This was a prospective cohort study carried out from Jul to Dec 2018, at a tertiary care hospital in Pakistan. All the consenting patients (by non-probability convenience sampling) who had received HD for at least 3 months were included. A total of 78 patients were enrolled. An MBBS qualified physician administered a proforma to the patients at the start of a one-month observational period recording predictors like age, sex, income, HD related variables etc. Dry weight as an outcome was estimated clinically by the in-charge renal consultant at the start and end of this observational period. We used R statistical software version 3.5.2 for the analysis.

**Results:** The study population included 53% (42/78) males and a median age of 58 years. We divided the data into training and testing sets and built four models from the training set; Linear regression (R2=0.24, RMSE=9.71), Gradient Boost (R2=0.24, RMSE=1.72), Random forest (R2=0.31, RMSE=1.58) and Xgboost (R2=0.39, RMSE=1.52). The best performing model Xgboost which was able to explain about 39% variance in the dependent variable. A mobile app was later developed which takes in the predictors from last month and can estimate dry weight change expected in a given patient. There are plans to increase the sample size thus improving the accuracy of the model and to perform a cost-benefit analysis in terms of work-hours saved per week down the line.

**Conclusions:** We were able to develop a predictive model using Xgboost machine learning algorithm which could estimate a change in dry weight in a given HD patient one month from the start of the enrollment. This model was then implemented in the form of a mobile app which can be used by clinicians around the world to get a better estimate of dry weight changes in their HD patients. Future plans are to increase the sample size to further improve the accuracy.
**PUB102**

Malnourished CKD Patients: Screening Malnutrition Using a Short Nutritional Assessment Questionnaire and Body Mass Index

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**Background:** Malnutrition is prevalent among hemodialysis patients. Its diagnosis and treatment is important because of its adverse consequences. However, an ideal and comprehensive nutritional assessment tool is time-consuming and expensive. A valid, quick and easy screening tool is therefore essential to its recognition and subsequent management. Short Nutritional Assessment Questionnaire is a 3 item screening tool developed by statistical analysis of 26 questions to determine 3 questions most predictive of nutrition status - unintentional weight loss, decreased appetite and use of supplemental drinks or tube feeding. It is >75% sensitive and 83.5% specific. Patients with SNAQ score ≥ 2 points are considered malnourished.

**Methods:** This cross-sectional correlational study determined malnutrition prevalence among hemodialysis patients at University of Santo Tomas Hospital using SNAQ and body mass index and their association. Nutritional status of 94 patients was evaluated by completion of SNAQ and BMI measurements.

**Results:** Subjects consisted of 50 women and 44 men, with mean age of 58 years. Based on SNAQ scores, 10% were moderately malnourished and 14% were severely malnourished. Based on Asia-Pacific BMI Classification, 11.7% was underweight and 47% was overweight-obese. Using Spearman R, there is a statistically significant moderate negative correlation between SNAQ scores and BMI (inverse relationship). This supports that SNAQ can be used to predict malnutrition but since the correlation is only moderate at best, it cannot be used to exclude the diagnosis.

**Conclusions:** Undernutrition among hemodialysis patients is not as prevalent as expected however, increasing prevalence of overweight/obesity is an emerging concern. SNAQ can be used to aid in recognition of malnutrition and as such, its use among hemodialysis patients should be encouraged.

**PUB103**

Centre-Level Factors Independently Affect Survival in Hemodialysis Patients: Findings from a Multicentre Cohort in India

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**Background:** Mortality of patients on dialysis in India is higher than that reported from western countries. Clinical and socioeconomic factors play an important role in determining survival of these patients, as do differences between dialysis centres. We examined differences in survival across dialysis centres in a large Indian dialysis network, accounting for patients’ characteristics.

**Methods:** We analyse data from 12,640 patients who received dialysis at 129 centres managed by NephroPlus, India’s largest dialysis provider between January 2014 and December 2017. The outcome is the time since the patient comes to the dialysis centre until death or end of follow-up. We use a mixed effects Cox proportional hazard model to examine the differences in mortality between dialysis centres, after accounting for the patient characteristics.

**Results:** Of the 12,640 patients, 3060 (24%) died during the follow-up period (median of 342 days). 4090 (32%) patients were lost to follow up. The 129 dialysis centres were distributed across cities in urban (33%), semi-urban (26%) and rural (41%) areas of India. 64% were setup under PPP programs (Public Private Partnership). About 54% were visited by a nephrologist at least once a week. The overall unadjusted mortality rate was 21.3 per 100 patient years. The individual-level variables that were associated with the outcome were age, having temporary dialysis catheter, history of heart attack or heart failure and lower income and less education. There was substantial variation in mortality between dialysis centres after accounting for the individual-level variables – with centre effects ranging between less than half to over 2.26 times the average risk, and an estimated variance of 0.18. Dialysis centres with high patient volume performed better than low-volume centres. Also, dialysis centres in the rural areas fared worse than the ones in urban areas.

**Conclusions:** There exist differences in survival between dialysis centres that are not explained by patients’ individual characteristics. Of the various centre-level characteristics that we explored, patient volume was found to be associated with patient survival. Future research should explore other possible explanations for observed variation in patient survival across dialysis centres – differences in care practices and other patient characteristics.

**PUB104**

It Is Not Just Care: Haemodialysis Patients Free from HCV Infection in Qatar - A Multidisciplinary Approach

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**Background:** Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV). Chronic hepatitis C develops in most people infected with HCV and can cause serious complications, such as end-stage liver disease. Although no vaccine is available to protect against hepatitis C, interventions can prevent HCV transmission. HCV infection can be treated with antiviral drugs and, in most cases, successfully cured, reducing the risk of morbidity/mortality and theoretically risk for transmission. Qatar National Plan for HCV control by 2020 was launched in December 2014, elaborated by a group of stakeholders from the Qatar ministry of Public Health and Hamad Medical Corporation. Then Approved and adopted by the Qatar Government (MOHP). In 2017, WHO accepted to support the development and implementation of national multispectral policies and strategies for hepatitis C prevention and control in Qatar, based on local epidemiological context of HCV. The prevalence of HCV in Haemodialysis patients in Qatar is 8.4%.

**Methods:** Non-Interventional, single-Center cohort study, including retrospective collection of real world data on 64 Haemodialysis patients infected with HCV, 33 of them completed the 12 weeks treatment and 12 weeks follow up period. Using of Omnitsavir, Pariaprevir, and Ritonavir (Viekirax) has been accepted as a treatment option in this group of patients.

**Results:** From 64 HCV positive Patients we initiate the treatment for 33 patients for 12 weeks and 100% of them cured, during the treatment biochemical values was within normal limits.

**Conclusions:** The outcome of first phase treatment of Hepatitis C in patients on HD is highly effective, it was 100 %. Successful HCV antiviral treatment will decrease the risk for infection transmission within dialysis units, and reduce the occurrence of complications occurring after kidney transplantation.

**PUB105**

Evaluation of a Mobile Digital Health Intervention (patientMpower) to Capture Patient-Reported Data and Symptoms and Optimise Fluid Management in Hemodialysis

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**Background:** Digital health tools to capture relevant patient-reported health data are available for many chronic conditions but few are available for haemodialysis patients. patientMpower is a mobile digital health intervention which connects wirelessly to measurement devices [e.g. blood pressure (BP) meter, digital weighing scales] enabling patients to have real-time access to relevant health data and encourage greater participation in managing their condition.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Methods: We designed a prospective, pilot-scale, open-label, randomised, 2 x 28-day crossover, sham-controlled protocol to evaluate PatientMPower in optimising fluid management (NCT03403491). After a 2-week run-in, ambulatory haemodialysis patients were randomly allocated to PatientMPower app-assisted scales+BP meter, or to a sham version of the app [sham intervention] for 27 [± 1] days. Sham intervention was over to the alternative intervention for 28 days with no washout. (See Figure.) The planned sample was 50 patients. There was no change to patients’ usual care. Patients were asked to record weight, BP, symptoms, fluid intake & medicines adherence daily during the mPmp period. mPmp calculated and displayed weight gain relative to individualised target (dry) weight to each patient. mPmp delivered tailored feedback messages (dependent on actual weight gain) to optimise fluid intake between dialysis sessions. Sham intervention did not enable patients to record any data and did not provide feedback.

Results: Primary endpoint was patient engagement (usage metrics & patient questionnaire). Secondary endpoints were comparisons of Pmp vs. sham on clinical-observed interdialytic weight gain (IDWG), ultrafiltration volumes and BP. Patient-recorded and clinical-observed IDWG and BP were also compared.

Conclusions: This design allows evaluation of engagement with a mobile digital approach to feedback relevant information to haemodialysis patients. It can provide data on the impact of active self-monitoring on hemodialysis parameters.

Funding: Commercial Support - patientMPower Ltd, Government Support - Non-U.S.

PUB106
Association of Religious Affiliation with Hospitalization Rates in the Dialysis Population
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Background: People reporting spirituality tend to have better physical and mental health, especially for lower income, clinically ill patients. (Koeing, 2015. Adv. Mind BODY Med). We investigated if belonging to a spiritual congregation is associated with improvements in hospitalization in hemodialysis (HD) patients from a large dialysis organization (LDO) in the United States.

Methods: We used data from adult HD patients who had a comprehensive social work assessment completed in 2017. We analysed responses to the questions: “Is spirituality an important part of a patient’s life” and “If yes, are they a member of a spiritual community?” Information on congregation number and adherents per county was obtained from the 2010 US Religion Census. A Poisson regression analysis was utilized for comparisons of stress among patients and caregivers (p = 0.071), at which time the lowest Functional Capacity in the patient (p = 0.010) is also observed. Patients tend to be more physically limited (p = 0.013) with an increase in the large physical domain (p = 0.005) and increase social aspects over time (p = 0.080). As for caregivers, they tend to increase vitality (p = 0.093), as well as to increase levels of emotional social support (p = 0.087) together with a decrease in physical stress symptoms (p = 0.051).

Results: As for caregivers, presented the death perspective as unknown (27.90 ± 5.49), followed by the concept of post-death reward (27.48 ± 7.87) and death as a natural phenomenon (22.38 ± 4.05). It is observed that the belief about death as a natural phenomenon is less frequent among patients (21.00) when compared to caregivers. There was no impact of the psychological variables of patients and caregivers at the beginning of follow-up on mortality.

Conclusions: Caregiver overload is remarkable. Because it is a disease with high mortality, it is fundamental to approach beliefs about death in patients and family caregivers.

PUB107
Mental Health and Perspectives on Death in Patients with CKD and Their Family Caregivers: A Prospective Study
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Background: The treatment of chronic kidney disease (CKD) generates overload in the health of patients and caregivers. Objective: To assess the physical and mental health and perspectives about the death of patients and their family caregivers.

Methods: Prospective cohort study in a four-year follow-up. Evaluation by questionnaires (Socio-economic, Short Form-36, ILSSY (Inventory of Lipp Stress Symptoms), HADS (Hospital Anxiety and Depression Scale), SSFS (Social Support Perception Scale), Fatigue Pictogram and Brief Perspective on Death Scales). Analysis performed in SPSS 17.0.

Results: As the initial time 21 patients and 21 caregivers participated, in the second evaluation 14 patients and 21 caregivers. Patients had a mean age of 57.28 years (± 16.29). The caregivers had a mean age of 53.89 years (± 15.61). Over time, levels of anxiety and depression tend to decline in patients (P = 0.028) and caregivers (P = 0.017). In patients the stress level tended to decline (P = 0.082) including the psychological symptoms of stress (P = 0.001). It should be emphasized that initially there is a difference in the evaluation of psychological symptoms of stress among patients and caregivers (P = 0.071), at which time the lowest Functional Capacity in the patient (p = 0.010) is also observed. Patients tend to be more physically limited (p = 0.013) with an increase in the large physical domain (p = 0.005) and increase social aspects over time (p = 0.080). As for caregivers, they tend to increase vitality (p = 0.093), as well as to increase levels of emotional social support (p = 0.087) together with a decrease in physical stress symptoms (p = 0.051).

Regarding beliefs about death, most interviewees presented the death perspective as unknown (27.90 ± 5.49), followed by the concept of post-death reward (27.48 ± 7.87) and death as a natural phenomenon (22.38 ± 4.05). It is observed that the belief about death as a natural phenomenon is less frequent among patients (21.00) when compared to caregivers. There was no impact of the psychological variables of patients and caregivers at the beginning of follow-up on mortality.

Conclusions: Caregiver overload is remarkable. Because it is a disease with high mortality, it is fundamental to approach beliefs about death in patients and family caregivers.
Demographics, body composition, and history of cardiovascular diseases were assessed as covariates. The cut-off of the MoCA score of the diagnosis of cognitive impairment was 22 points. The European Working Group on Sarcopenia in Older People (EWGOP) diagnostic criteria were applied to diagnose sarcopenia. The muscle mass was measured using Bioimpedance analysis and muscle strength was measured using handgrip strength.

Methods: Of the patients included, 55 (women 36.4%) were diagnosed with sarcopenia (46.6%). The incidence of sarcopenia was higher in older patients (67.0 vs 70.0, p=0.046), but there was no difference in other variables. There was significant difference in the cognitive impairment ratio according to the presence or absence of sarcopenia (31 (56.3%) vs 14% (p=0.04). The Odd ratio (95% confidence interval) of cognitive impairment was calculated sarcopenia status. Compared to non-sarcopenic, sarcopenic hemodialysis patients had the ORs of 1.09 (95% CI of 1.05-1.15, p=0.030) for cognitive impairment.

Conclusions: Sarcopenia was significantly associated with cognitive impairment in hemodialysis patients. Cognitive impairment reduces the quality of life of hemodialysis patients. Therefore, it is important to prevent sarcopenia, which can cause cognitive impairment in hemodialysis patients.

PUB110
Prevalence and Risk Factors of Anemia in 1161 Patients on Maintenance Hemodialysis
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Background: Management of anemia is a remarkable issue in hemodialysis. Studies on prevalence and risk factors of anemia, especially the dialysis related factors in patients undergoing hemodialysis are limited.

Methods: A multi-center cohort study enrolled 1161 patients on maintenance hemodialysis from ten medical centers in South Guangdong, China from July 2016 to September 2016 for research on prevalence and risk factors of anemia.

Results: There were 1161 patients enrolled in the cross-sectional study, among whom 215 patients presented with anemia (Hb<130g/L), with the rate of 21.3%; 520 patients with hemoglobin concentration of 100-120g/L, with the rate of 45.1%. Comparing to the normal hemoglobin group (NHB group, 1104feb:<130g/L), patients in anemia group presented with shorter duration of dialysis (26.10±23.33months vs. 35.16±6.87 months in NHB group, p=0.003), less use of arteriovenous fistulas as dialysis access, less use of low molecular heparin for anticoagulation, fewer times of hemofiltration therapy, with the rates of 78%, 82%, 39.2% and 9.2% (vs. 89.2%, 91.6%, 57.3%, 16.6% in NHB group, p<0.001, 0.003, 0.010, 0.200, respectively. And they showed lower serum creatinine (1.69±2.288.5mg/dL vs. 0.96±0.17mg/dL in NHB group, p<0.001), albumin (35.39±4.89g/L vs. 38.62±3.69g/L in NHB group, p=0.001), triglyceride (1.30±0.68mmol/L vs. 1.79±1.72mmol/L in NHB group, p<0.001), calcium level (2.10±0.26mmol/L vs. 2.19±0.29mmol/L in NHB group, p<0.001). Adjusting Logistic regression analysis indicated that the frequency of dialysis atwice weekly (OR=1.721, 95%C I 1.201-2.466, p=0.003), use of unfractionated heparin for anticoagulation (OR=1.822, 95% CI 1.104-3.006, p=0.019) and hyperalbuninemia (OR=2.112, 95% CI 1.463-3.049, p=0.001) were independent risk factors of anemia in hemodialysis patients.

Conclusions: 21.5% patients on hemodialysis in South Guangdong presented with anemia (Hb<90g/L). 45.1% patients presented with hemoglobin concentration of 100-120g/L. The risk factors of anemia contained dialysis access, less use of low molecular heparin for anticoagulation, fewer times of hemofiltration therapy, with the rates of 78%, 82%, 39.2% and 9.2% (vs. 89.2%, 91.6%, 57.3%, 16.6% in NHB group, p<0.001, 0.003, 0.010, 0.200, respectively. And they showed lower serum creatinine (1.69±2.288.5mg/dL vs. 0.96±0.17mg/dL in NHB group, p<0.001), albumin (35.39±4.89g/L vs. 38.62±3.69g/L in NHB group, p=0.001), triglyceride (1.30±0.68mmol/L vs. 1.79±1.72mmol/L in NHB group, p<0.001), calcium level (2.10±0.26mmol/L vs. 2.19±0.29mmol/L in NHB group, p<0.001). Adjusting Logistic regression analysis indicated that the frequency of dialysis atwice weekly (OR=1.721, 95%C I 1.201-2.466, p=0.003), use of unfractionated heparin for anticoagulation (OR=1.822, 95% CI 1.104-3.006, p=0.019) and hyperalbuninemia (OR=2.112, 95% CI 1.463-3.049, p=0.001) were independent risk factors of anemia in hemodialysis patients.

PUB111
Behavior of High-Sensitivity Cardiac Troponin I Levels in Asymptomatic Hemodialysis Patients
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Background: Troponin levels are markers of myocardial injury. The interpretation of high-sensitivity troponin I levels in the context of hemodialysis (HD) patients is not clear, and there is no reported evidence of its behavior during HD treatment.

Methods: Prospective cohort of 33 prevalent asymptomatic HD patients. Venous blood samples were taken to measure the Troponin I levels, during 5 different time periods, at the start of the next HD session (T4). The Troponin I levels are expressed in normal range (16 ng/L), 80% with history of CVD. TnI levels were: T0: 7.4 ng/L (1.3-62.4), T1: 7.1 ng/L (1.2-64.1), T2: 7.2 ng/L (1.6-69.3), T3: 5.9 ng/L (1.6-59.5), and T4: 6.7 ng/L (1.3-63.2). Women had significantly lower TnI levels than men (p=0.03) in all sample times. Eighteen patients had history of CVD and 72.2% systemic arterial hypertension, dialysis vintage was 25.6 months, median with minimum and maximum. Non-parametric statistics were used.

Results: The mean age of the population was 41.5 years, 60.6% were female, 36.3% had diabetes, 72.2% systemic arterial hypertension, dialysis vintage was 25.6 months, median with minimum and maximum. Non-parametric statistics were used.

Conclusions: The measurements of hsTnI levels during the HD remained stable with slight decrease in the different time tests, which suggest that the troponin I is not dialyzable due to its molecular weight. Troponin I levels were higher than the general population (16 ng/ml) in 15% of the cases. Patients with a history of CVD had higher levels of hsTnI in all measurements. The analysis of Echocardiographic changes and their relation to changes in troponin is still pending in order to have a better correlation of the biomarker with the dynamics of the heart.

PUB112
More Frequent In-Center Dialysis Associated with Decreased Hospitalization Length of Stay

Background: According to the United States Renal Data System (USRDS) as of 2017, ESRD patients on average are admitted to the hospital nearly twice a year and about 35% ESRD discharged have a readmission within 30 days. Approximately 33% total Medicare expenditures for dialysis patients are from hospitalizations, representing a significant financial burden. In 2014, Nxstage Dialysis Center in St. Louis, MO started doing more frequent in-center hemodialysis. We investigated the effect more frequent in-center hemodialysis on our patient’s hospital days per year.

Methods: We conducted a retrospective study of adult patients undergoing more frequent hemodialysis at Nxstage Dialysis Center in St. Louis, MO between July 2014-March 2015. The data was collected via Charity EMR.

Results: Between July 2014 and May 2015, a total of 14 patients were treated with more frequent hemodialysis. Of the 14 patients, 11 patients were hospitalized. In 2016, the hospital readmission rate was 16%. [Figure 1]

Conclusions: We found our patient population with more frequent in-center hemodialysis had clearly lower hospital days per patient year and readmission rates when compared with the national average as reported by USRDS. In 2016, our average hospital day per patient year was 6.64 days compared to 11.3 days. The 30-day readmission rate for hemodialysis patients in 2016 was 37% versus our more frequent in-center rate of 16%. One limitation of our study was our small sample size. However, more frequent in-center hemodialysis was associated with a decreased length of stay and readmission rates.

Figure 1.
He was hospitalized on October 3, 2018 because of hematemesis. He received transfusion of one unit of platelets which were leukocyte-reduced and irradiated; he was intubated and underwent bronchoscopy but required no red blood cell transfusions. Over the next two months, he was hospitalized twice for endocarditis and once for a dental procedure but he received no transfusions. Routine testing on April 2, 2019 revealed the presence of HBsAg, HBeAb and HBeAg but no HBeAb. Ten days later, the HBeAg result was negative; HBeAb and HBeAg were positive; HBsAb and HBsAg were negative; his HBV viral load was 1149 IU/ml. Three weeks later, his antigen and antibody results were unchanged; HBV viral load decreased to 211 IU/ml.

Discussion: This case points out the difficulty in identifying new HBV infection in patients with HIV infection and CKD. In this case, the source of exposure is unclear. The only documented opportunity for exposure occurred during a hospital admission six months prior to detectable HBsAg serologies. The only documented transfusion was platelets which are not common carriers of viral infections. It also points out the difficulty in identifying the true virilologic status of such patients. Our patient has had HBsAg for almost 15 years so should not be susceptible to new infection yet serologies indicate a change in his antigen status and the presence of viral DNA in his blood. The role of his HIV infection is unclear as it is its influence on his hepatits serologies.

**PUB114**

**Prevalence of Metabolic and Cardiometabolic Syndrome in Patients on Hemodialysis Program**

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**Background:** The prevalence of metabolic syndrome (MS) and cardiometabolic syndrome (CMS) in hemodialysis (HD) patients is not well studied. The aim of this study was establish the prevalence of those syndromes in patients on hemodialysis program.

**Methods:** Cross-sectional study done in the HD unit. The MS was defined by ATP3 and harmonization criteria. To determine CMS, we included hyperuricemia and high LDL-c. We used descriptive statistic, absolute and relatives frequencies.

**Results:** Sixty seven patients were evaluated with mean age 40.16±16.12 years. Thirty-six were women (54%). Mean of dry weight was 56.1±9.66 kg; BMI 22.16±3.2 kg/m²; mean of systolic blood pressure 134.24±21.93 mmHg and diastolic of 76.04±15.24 mmHg. Cholesterol 139.39±31.9 mg/dL; triglycerides 139.69±74.14 mg/dL; LDL-c 70.02±28.11 mg/dL; HDL-c 41.34±3.2 mg/dL; albumin 3.95±0.6 g/dL; and uric acid (UA) of 6.98±2.15 mg/dL. Nine patients (13%) had underweight; 73% (49) normal weight and 13% (9) overweight and obesity (Figure 1A). With ATP3 criteria, we identified MS in 36% (24) of patients and with harmonization criteria 40.4% (27) (Figure 1B); CMS was identified in 54% (36) patients (Figure 1C).

**Conclusions:** The prevalence of MS and CMS in HD patients was common; however, the diagnostic criteria for those syndromes should be validated in patients with ESRD. HD by itself, increases the risk of death 20-fold higher than general population, the presence of MS concurrent with ESRD could be increasing substantially the risk for cardiovascular diseases.

**PUB115**

**Database Construction for Hemodialysis Patients in Sichuan Province**

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**Background:** The incidence of hemodialysis(HD) is escalating dramatically in recent years, which brings about great challenge and also opportunities for Sichuan Quality Control Center of Renal Disease. In order to acquire general information, patient distribution, medical staff, medical equipments and the principle clinical indexes of HD patients, basing on previous experience in software designing, we initiated a provincial renal database, providing free HD software for the whole province.

**Methods:** The provincial database was a web-based database, which was set up with free connections to the HD software. In order to help dialysis center in Sichuan. We provided a free software (Jiangsu Huibang Information Technology Co., Ltd.), which could pack the data and upload to the provincial database. We also provide a connection protocol for other HD software that was already installed in HD facilities. The provincial database did not open manually input function in order to reduce the tasks for HD staff. The database was set up in May 2018. The free HD software was open for application from May 2018. Survey and visit interview was carried out to help setting up the database.

**Results:** There were 171 HD centers (around 1/2 of HD centers in Sichuan Province) completing the installation of free HD software by April 2019, among which, 77 HD centers began to upload data to provincial database. There were 11583 HD patients in the database, accounting for about 1/3 of the HD patients in the whole province. The mean age was 55 years for the reported patients with a female proportion of 41.46%. The proportion of HD patients within treatment target for hemoglobin, serum calcium level, serum phosphorus level and serum albumin was 37%, 52% and 58% and 84% in year 2018.

**Conclusions:** A new strategy for setting up a provincial database from providing software in dialysis centers is an efficient way, which is not only good for dialysis quality control, but also is important for registry based studies.

**Funding:** Government Support - Non-U.S.
A New Approach to Assess Patient-Reported Outcomes of Patients with ESKD in an International Randomized Clinical Trial
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Background: The CONVINCE trial is an outcome-based RCT comparing high-dose hemofiltration (HDF) versus conventional high-flux hemodialysis (HD) in nine European countries. Primary objective is the comparison of all-cause mortality, one of the secondary objectives is the comparison of the experienced health status of patients. The aim of the CONVINCE Consortium was to develop a toolbox to assess the patient health status with a particular focus on constructs related to pathophysiological changes following implementation of the two dialysis modalities, which is applied in the CONVINCE trial.

Methods: We applied a state-of-the-art approach to develop the conceptual framework for the toolbox. Health aspects and constructs relevant for ESKD patients were identified in due consideration of international initiatives such as the SONG Initiative and ICHOM, a thorough literature review and interviews/focus groups with patients and experts. Psychometrically advanced instruments in combination with new measurement approaches were incorporated in the toolbox and applied in the CONVINCE trial.

Results: Out of 11 identified health domains and 41 ESKD-specific symptoms and health beliefs, 16 health domains and 13 symptoms were described in the toolbox according to the conceptual model of the CONVINCE trial. The compilation of the PRO assessments balanced comprehensiveness, respondent burden, and goal of measurement. Items to assess the proximal outcome recovery time and treatment-related fatigue were developed using state-of-the-art methods. Generic outcomes, e.g., physical function, depression and fatigue are measured by use of the psychometrically advanced tools of the PROMIS® initiative. Data collection started in Nov 2018 aiming to include 1,800 patients, which should be followed up for 24 months including approx. 16 measurement points. First results of the baseline assessment will be presented.

Conclusions: The application of the toolbox using psychometrically advanced tools, instead of an off-the-shelf PRO measure, facilitates the assessment according to a specific research objective. Thus, the impact of ESKD and treatment on patients can be accurately evaluated.

Funding: Government Support - Non-U.S.

Incident Dialysis Patients in a Country with High Prevalence of CKD
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Background: In our country with a population around 10,000,000 inhabitants, by the end of 2018, 13,000 patients(pts) were treated with dialysis, 2007 of which incident pts. The majority started hemodialysis(HD), only 8.7% peritoneal dialysis(PD). Our aim was to compare characteristics and outcomes of both modalities in a single-center serving a population of around 450,000 inhabitants.

Methods: A retrospective cohort study with 652 incident pts on renal replacement therapy admitted in our ICU (January 2013 and December 2017) in a single-center with follow-up until December 2018. Charlson Comorbidity Index(CCI) was calculated and pts divided into modality. Kaplan-Meier survival curves were estimated for subgroups defined by age (<65 vs >65) and a Cox proportional hazards regression used to estimate relative mortality risk, adjusting for CCI.

Results: 556(85.2%) started HD and 96(14.8%) PD. On HD 61.2%(n=340) were male vs 68.9%(n=67) on PD; median(QR) age 73(64-81) vs 57(51-70), 27% vs 26% were <65 and 30.6% vs 55.2% <80. In addition, 48.9%(n=272)vs37.5%(n=56) diabetes. The median(QR) CCI was 8(6-10) vs 3.3(3-6)(p=0.001). Younger pts had 1-year survival rate of 89.1% on HD vs95.2% on PD; 3-year 77.9% vs 88.6% and 5-year 76.2% vs74.9%. In older pts 1-year 70.5% vs86.2%; 3-year 47.1% vs74.3% and 5-year 34.6% vs74.3%. A Kaplan-Meier analysis showed a better survival for PD(74.8%) in older pts while no difference was found in younger pts (p=0.096). In a multivariable analysis, we found that pts being educated about dialysis was predictor of choosing PD(p=0.001). A multivariate analysis showed that CCI(OR 4.16, CI 95% 1.96-8.82; p=0.001) and HD(OR 2.87, CI 95% 1.55-5.6; p=0.006) were independent predictors of mortality in older pts, while in younger pts the modality had no influence but CCI was an independent predictor of mortality(OR 5.19, CI 95% 2.51-10.72; p=0.006).

Conclusions: A higher percentage of PD incident pts compared to the national average was found, and in pts eligible for both modalities, previous education about dialysis was a predictor of choosing PD. Our cohort shows better survival for PD compared to HD in older pts and that higher CCI is associated with worst outcomes regardless of age.
and symptoms that are evident, this causes that the intervention is only palliative. The objective was to establish a hierarchy of primary cognitive deterioration (PCD) in patients with chronic kidney disease on dialysis therapy.

Methods: A multicenter (3 IPS), cross-sectional study was conducted. The patients were given the Montreal Cognitive Assessment (MoCA) questionnaire with prior informed consent and the most paraclinical data (Hemoglobin, Sodium, BUN, Serum Creatinine) Kt/V. Date of the first dialysis were recorded. Base disease and comorbidities. To establish a possible structure of dependence between the FAD and the Factors enunciated, the correlation coefficient was calculated, for which a generalized multivariate linear model (GML-M) was used. This was constructed using the own values of each Factor, through the technique of adding Factors.

Results: A total of 62 patients on dialysis were evaluated. 58.5% were men. The overall average age was 53 ± 16 years (women: 47 ± 16 years | men: 58 ± 15 years). The time on dialysis was 7.5 ± 5 years (women: 7 ± 5 years | men: 8 ± 5 years). Associated comorbidities were Hypertension (68%), Diabetes Mellitus (32%), Urinary Tract Infections (3%). Only two patients (3.5%) obtained not to classify them with primary cognitive impairment. A correlation of mixed effect between Age and Time on dialysis, however the value of R² is moderately weak (31.2%) although the significance value indicates that these are very significant (p-value <0.05), these results indicate the need to include the dose values in the model of dialysis as well as laboratory parameters, as well as co-morbidities and other relevant clinical data.

Conclusions: According to the Coef. Determination and Correlation is determined by the ratio of serum creatinine, phosphorous and total cholesterol, being a multivalued model dependent on the inverse interaction with the patient’s age.

PUB122

Allergic Reactions Associated with Bicarbonate Bath During Hemodialysis
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Introduction: Allergic reactions during hemodialysis (HD) treatment have been well explained in the past. Most common causative factors implicated are secondary to dialyzers with synthetic or cellulose membranes. Other agents like latex, intravenous iron supplements, heparin and formaldehyde have also been reported. We report a case of end stage renal disease (ESRD) patient on HD with severe allergic reaction secondary to bicarbonate bath.

Case Description: We report a case of a 49-year-old gentleman with ESRD on HD secondary to diabetes and Hypertension, on HD for the last 5 years. Patient has been complaining of allergic reactions including rash and hives within half an hour to one hour after initiation of hemodialysis. His HD session was terminated earlier on few occasions in the setting of hypotension, contributed by anaphylactic reaction, in addition to hemodynamic changes. He was thoroughly investigated for any possible cause of allergic reaction and extreme caution was used in terms of changing the dialyzer types, latex exposure and any commonly implicated solution or medication, with no success. He was prescribed anti-allergic medications and emollients with limited response. Allergic reactions usually subsided soon after HD session. After close observation and exclusion of any possible causative factor, he was found to be allergic to standard powdered bicarbonate cartridge by Gambro. He was switched to liquid bicarbonate solution and his allergic reaction completely resolved on following HD sessions.

Discussion: Allergic reactions due to variety of substances has been reported during HD sessions. As per literature review, the allergic reactions secondary to bicarbonate bath have not been reported in the past. Nephrologists and dialysis center staff should be vigilant to identify this rare cause of anaphylactic reaction.

PUB123

Impact of Cinacalcet on Secondary Hyperparathyroidism (SHPTH)
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Background: SHPTH is caused by reduced phosphate (P) excretion and hydroxylation of vitamin D (vitD) leading to decreased calcium (Ca) levels and stimulation of parathyroid hormone (PTH) secretion. Clinical findings include decreased bone mineralization and increased rates fractures, cardiovascular disease and mortality. SHPTH is treated with P binders, vitD analogues (analogues) and calcimimetics (CM) like cinacalcet which suppresses PTH secretion via the calcium-sensing receptor. CM were added to the prospective payment system in January 2018; analogue use increased while CM use decreased.

Methods: Our QAPI program monitors levels of Ca, P and PTH with a goal of maintaining: >86% of patients with Ca 8.5-10.2 mg/dL, 57% with P 3.5-5.5 mg/dL and >90% with PTH 100-750 pg/mL. Here, we evaluate the cost and effectiveness of CM using an intention-to-treat approach.

Results: Results from the 4th quarter of 2017 (baseline) were compared to the 3rd quarter of 2018 and the 1st quarter of 2019 for 996 patients present at all three time points. Ca was decreased and significant change; there were statistically significant increases in P and PTH. (See figure).

Conclusions: CMs have not improved management of SHPTH in our real world analysis. Based on our average cinacalcet cost of $17.32 per treatment and the apparent lack of benefit, our analysis argues against use of cinacalcet for treatment of SHPTH.

Funding: Clinical Revenue Support

PUB124

Atypical Dialyzer Membrane Reaction: A Mask Behind the Curtain
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Introduction: Prior to the advent of the polysulfone dialyzer membrane, dialyzer reaction was common with cellulose dialyzers and easily identified. In this report, we present a case of atypical dialyzer reaction manifesting as only difficulty in achieving ultraltration without eliciting the other classical dialyzer reaction symptoms. Our case is unique in the atypical pattern and feature of presentation of this dialyzer.

Case Description: A 56 yr old male with history of HTN, DM, and slowly progressive chronic kidney disease with nephrotic range proteinuria initiated on hemodialysis (HD) for acute renal failure with oliguria in setting of left foot cellulitis. Clinical examination reveals fluid overload with bilateral lung crepitations and 3 + bilateral pedal edema. His dialysis orders were Polysulfone high flux dialyzer F180 dialyzer. He had gradual increasing duration of HD from 2.5 hrs to 4 hrs on the third session with increasing blood.

Pre-Hemodialysis blood pressure (BP) was 140/160s systolic range. His BP meds were typically held pre-HD with last dose over 12 hrs pre HD. Patient repeatedly had

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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drops in his systolic BP to the 80s with symptoms of fatigue and dizziness requiring IVF boluses during the session. His post dialysis weight continued to be higher than his pre-dialysis weight. Daily HD and increasing adjustment of blood flow as well low temp bath did not yield any changes. Dialyzer change on his 3rd session to F250 also did not make any difference. He did not describe any rash or fever with negative cultures and absence eosinophilia. Echocardiogram was normal. A suspected dialyzer reaction was elicited and dialyzer switched from the F series to the cellulose triacetate high flux. Patient on his 4th HD treatment and first with Ex 170 was able to tolerated HD well with no drop in BP and target UF of 2.3 L obtained successfully. Subsequent dialyses were uneventful despite transition to the Ex 210 dialyzer use. Outcome Patient’s symptoms resolved after changing from the polysulfone series to a different one, a cellulose-based dialyzer membrane.

Discussion: In this patient, the atypical pattern of presentation neither fit the classic type A or Type B reaction. Episodic dialyzer reaction is rare at initiation in the absence of cardiac disease or pericardial tamponade. This case is atypical due to absence of these other causes of hypotension and resolution of the clinical symptoms with change of dialyzer membrane.

PUB125
Factors Associated with Achievement of a High Convective Volume Target on Post-Dilution Online Hemodiafiltration (HDF)
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Background: A higher convective volume (23 liters, 3x/week) has been associated with a lower risk of death in post-dilution online HDF. We aimed to identify factors associated with achieving a high weekly volume of convection.

Methods: Retrospective analysis of all HDF patients at 13 dialysis units in Brazil in 2018. A convective volume of 69 L/week was considered the lowest adequate HDF dose. Results: A total of 286 patients (67% men, 39% diabetes, 62±16 years-old, 33% with tunneled catheter, 43% on more frequent HDF [14±4x/week, 29% on daily HDF] and 63% incident on HDF) underwent to 28,078 HDF sessions in the period. Weekly HDF time was 71±73 min (56.7±72 min) and blood flow 347±45 mL/min. Weekly convective volume was 65±16 L/week. The median (IQR 69.0±87.6) L/week, with 75.7% reaching the target of 69 L/week. In the logistic regression model, having the target of 69 L/week as the dependent variable, female gender (P=0.001), age (P=0.035), hemoglobin >12 g/dL (P<0.001) and use of catheter (P<0.001) were associated with the risk of not achieving the minimum dose, whereas blood flow <350 mL/min (P=0.001), weekly HDF time <12 hours/week (P=0.001) were independent factors positively associated with a high convective volume.

Conclusions: A high convective volume can be achieved by most of the unsellected patients on HDF. The weekly HDF time is a modifiable variable that can be used to achieve the appropriate weekly convective volume.

PUB126
A Prospective Study on the Association Between Ultrafiltration Rate and Mortality in Hemodialysis Patients: The Effect Modification by Muscle Mass
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Background: The association between ultrafiltration rate (UFR) and mortality may be affected by muscle mass or volume status in maintenance hemodialysis (MHD) patients. However, there are no prospective data about those association in patients receiving MHD.

Methods: This was a prospective observational study on the patients (a 18 years old) who have been on MHD for at least three months and gave informed consent. A portable whole body bioimpedance spectroscopy device (BCM) was used for bioimpedance analysis measurement at baseline. Primary outcome was all-cause mortality.

Results: Among 169 patients, mean (SD) age was 62 ± 12 years and male were 59%. Mean (SD) UFR was 12.8 (11.1) mL/h/kg. Median (interquartile range, IQR) overhydration by volume by BCM was 2.4 (1.4, 3.9) L. Median (IQR) lean tissue index (LTI) (calculated as lean tissue mass/height²) was 12.4 (10.4, 14.6) kg/m². The median follow-up duration was 1.4 years. In an adjusted Cox regression analysis, greater mortality was associated with higher UFR. This association remained consistent even after adjusting for overhydration status. However, the association between UFR and mortality was modified by LTI (Pinteraction=0.03); the association was only significant in patients with LTI of less than 12 kg/m².

Conclusions: Higher UFR was associated with increased all-cause mortality regardless of volume status in MHD patients. However, muscle mass may modify the association with higher UFR and increased mortality.

Funding: Government Support - Non-U.S.

PUB127
Hospitalisation and Mortality in Hemodialysis Patients in India: A Single-Center Prospective Study
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Background: In India over 2 lakh new cases develop end stage kidney failure every year but only 10-20% are able to continue long term dialysis. USRDS 2014 hemodialysis (HD) data shows that average number of hospitalization was 1.7/patient/yr & duration of stay was 10.9 days. There is paucity of data on hospitalization & mortality in HD population from India. We prospectively studied the hospitalization & mortality in HD patients at our center.

Methods: All patients who came to our center for HD from Nov 2016 to May 2019 were the subjects of this study. Patients who had HD for less than a month or were on immunosuppressives or having underlying malignancy were excluded. Details of all the hospitalizations/mortality were recorded & their relation with age, sex, underlying DM & CAD was studied. Analysis was done using SPSS 23.

Results: 395 patients came to our multi-specialty center for HD during the study period. Of these, 70 patients had HD for less than a month and were excluded; remaining 325 formed the study group. There were 201 males. Mean age of the study group was 56±14.98 years (range 18-84) & mean duration of follow up was 11.6±5.96 mo (range 1-31). Of these 325 patients, 40 received renal transplant, 46 died & 80 left for other centers after a mean follow up of 6.3±5.96 mo, 11.46±5.90 mo & 9.98±5.14 mo respectively. 198 (60.9%) of these 325 patients had 348 hospitalizations (mean 1.07±1.32 hospitalization/patient). Total days of hospitalization were 1736 days (mean 8.77±10.03). The underlying reason for hospitalization was Infections (33%), Cardiopulmonary (31%), Vascular access related (19%), CNS complications (7%), & other causes were 10%. Hospitalization was significantly higher in those with advanced (age≥60 years) (p=0.044). Presence of diabetes, gender & CAD status didn’t show any significant association. 46 patients died after a mean follow up of 11.46±5.90 months. Mean age of this group was 61.45±13.29 years. Causes of death were sepsis (50%), CV events including SCD (39.1%), CVA in 6.5 % & miscellaneous causes in 4.34%. Mortality was significantly higher in those with advanced age(p=0.026) DM(p=0.026) & CAD (p=0.043).

Conclusions: Our follow up study of 11.46 months shows, hospitalization rate of 1.07/patient with duration of hospitalization 8.77 days. Infections were the leading cause of hospitalization & death. Advanced age, DM & CAD were associated with bad outcome.

PUB128
Risk Factors for Mortality in the Short- and Long-Term in Patients with Chronic Renal Disease After Renal Replacement Therapy
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Background: Chronic Kidney Disease in Stage V (CKDS) and its need for Renal Replacement Therapy (RRT) has increased markedly in recent decades by the rise of chronic diseases and the opening of services to marginalized populations, generating relevant costs in health systems, the effect should be evaluated objectively to improve their efficiency. Objective: Evaluate the survival of patients with CKDS in RRT from a population favored with a new financing system (SIS) in a General Hospital of MINSA, Lima-Peru, identifying the variables associated with poor prognosis.

Methods: Were studied patients benefiting from the SIS with ERCS incidents to the Emergency of the Hospital Cayetano Heredia (HCH) who entered TRR between September 2014 to December 2017 in whom survival was evaluated and analyzed factors associated with mortality. The evaluation was finalized in July 2018.

Results: 374 patients with CKDS for RRT were studied, 169 were admitted for emergency and 205 on an outpatient basis. The variables found in this population were: age greater than 45 years (p = 0.000), female sex (p = 0.002) and admission to the program for emergency (p = 0.000).

Conclusions: Age (~ 45 years), female sex and admission to the program for emergency were the conditions associated with higher mortality in patients benefiting from SIS to receive RRT.
Prevalence of Obesity and Overweight in a Peripheral Dialysis Center and Its Association with Comorbidity Evaluated Through the Charlson Index

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Background: The obesity is accompanied by many comorbidities, it could be deduced that obese patients on hemodialysis (HD) follow the same pattern and therefore would be more prone to present cardiovascular complications. However, this hypothesis has not been proven yet. In fact, several studies have observed an inverse relationship between the Body Mass Index (BMI) and mortality, phenomenon called “paradoxical obesity. Objectives: To evaluate prevalence of obesity / overweight in a HD center and the body composition of HD patients by bioimpedance spectroscopy (BCM, Fresenius Medical Care), obtaining the fat tissue index (FTI) and the lean tissue index (LTI). Study the presence of different pathologies using the Charlson Comorbidity Index (CCI) and evaluate the relationship between the different diseases that make it up with obesity / overweight.

Methods: Cross-sectional descriptive study in January 2017 that included 73 patients. The BMI according to the WHO (World Health Organization) was analyzed and grouped the patients according to the FTI in tertiles: FTI < 13.00; FTI = 13.01-19.00; FTI>19.01. All the pathologies that make up the CCI, renal diagnosis, laboratory values and clinical parameters of HD were recorded.

Results: The prevalence of obesity was 28.77% and overweight was 32.88%. When comparing the BMI according to the WHO (World Health Organization) was analyzed and grouped the patients according to the FTI in tertiles: FTI < 13.00; FTI = 13.01-19.00; FTI>19.01. All the pathologies that make up the CCI, renal diagnosis, laboratory values and clinical parameters of HD were recorded.

Results: The prevalence of obesity was 28.77% and overweight was 32.88%. When studying the BMI with the different pathologies that make up the CCI, it turned out that the overweight patients presented a significantly higher percentage of diabetes with organic damage (P = 0.047). On the other hand, when relating the FTI with pathologies of the CCI, it was found that the percentage of patients with Congestive Heart Failure (CHF) was significantly higher as the tertile of the FTI was higher (P = 0.020). When finding these percentage differences by pathology, an ROC curve analysis was performed. This analysis revealed the FTI as a predictor of Congestive Heart Failure (AUC = 0.689, P = 0.028, CI 95% = 0.527-0.852), not being a predictor of this comorbidity the BMI (AUC = 0.645, P = 0.093, CI 95% = 0.455-0.806).

Conclusions: Over 60% of patients in the analyzed cohort were overweight or obese. Only diabetes with organic damage was associated with overweight, while Congestive Heart Failure with a higher FTI. Our results suggest that FTI determined by BCM can help predict better comorbidities than BMI, especially CHF.

Verification of Nutrition Maintaining Effects by Using Anti-Thrombotic PMMA Membrane (VENUS STUDY)

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Background: Nutritional status and QOL are the most important indicators for the prognosis of dialysis patients, and the dialysis prescription which enables to maintain the nutritional status and improve QOL should be needed. Polymethylmethacrylate (PMMA) is a synthetic dialysis membrane with protein adsorpive property and was reported that it had beneficial effects on nutritional status and QOL of dialysis patients. In VENOUS study the beneficial effects of newly introduced anti-thrombotic PMMA (NF membrane) on the nutritional status and QOL of older dialysis patients were evaluated.

Methods: This study is a randomized control trial which compared PMMA with polysulfone (PS) on the patients older than 70 years old. The 54 registered patients were randomly assigned to the NF group (28 patients) or PS group (26 patients) and followed for 12 months. The nutritional status was considered by Malnutrition Inflammation Score (MIS) as a primary outcome, normalized protein catabolic rate (nPCR), and creatinine generation rate (%CGR) as secondary outcomes. Patients symptoms as a QOL indicator were also monitored as a secondary outcome every 3 months on arthralgia, skin itchiness, irritable sense, fatigue, headache, dialysis related hypotension, leg cramps, and post-dialytic bed-free time.

Results: 11 patients in the NF group and 10 patients in the PS group were dropped out from the study. Finally, 15 patients in NF and 14 patients terminated the study, however, 2 patients with the data deficit in each group were excluded. The MIS was increased at 6-, 9-month but there was no difference between 0-month and 12-month in NF group. The MIS was also increased at 9-month but was no difference between 0-month and 12-month in PS group. There were no remarkable changes were observed in nPCR, %CGR in both groups. Patients’ symptoms were not different between NF group and PS group through the study period. However, the symptom total score was gradually reduced in NF group, but that in the PS group did not change.

Conclusions: In the current study we did not admit the advantages of new PMMA compared with PS on the MIS as a primary outcome. However, we could clarify the beneficial effects on the parameters of QOL only in NF group and it suggested that new PMMA membrane could ameliorate QOL of dialysis patients.

Funding: Commercial Support - TORAY

User Satisfaction and Cost Savings of a Novel Hemodialysis System in an ICU Setting

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Background: AKI requiring RRT is increasing in frequency in the ICU. Because of hemodynamic instability the treatment of choice is either CRRT or PIRRT. The former is relatively expensive due to the cost of fluids and the latter technically difficult for non-dialysis nurses because it uses a dialysis machine. Outset Medical’s Tablo is an all-in-one system with a user-friendly touch screen interface that requires minimal training and produces AAMI quality dialysate using tap water and conventional dialysate concentrate. The purpose of this pilot project was to assess whether the Tablo system was both easy to use and provided cost savings.

Methods: 17 ICU patients with AKI requiring renal replacement were treated for 6-12 hours using the Tablo system. Tablo was set up and run by the ICU nurse. Dialysis prescription, duration and ultrafiltration rate were left to the discretion of the attending nephrologist. Cost savings were compared with CRRT, nursing satisfaction was assessed by a Likert scale questionnaire.

Results: Compared to NxStage the majority of nurses found it easier to use (average score 4.8/5); most nurses felt comfortable providing treatment with this system after completion of training (average score 4.3/5) and they were also satisfied with Tablo as a treatment option (average score 4.8/5). Several participants also reported that the system was easy to transport and required less space. Comparing a 12-hour Tablo treatment to a 24-hour CRRT treatment using NxStage fluid at an effluent rate of 25 ml/kg/h would generate a cost savings of $303/day.

Conclusions: In our study, we found the Tablo system to be a viable alternative to CRRT. The nursing staff were easy to train and found this system straightforward to operate. In addition, because of its compact size Tablo took up less space, which is advantageous in the limited ICU environment. Importantly, Tablo when compared to CRRT led to significant cost savings at this facility.

Funding: Commercial Support - Outset medical supplied the Tablo machines.
Extracorporeal Therapy in Cefepime-Related Neurotoxicity
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Introduction: Cefepime is a fourth generation cephalosporin with broad spectrum antimicrobial activity and is primarily excreted by the kidneys. It may rarely be associated with neurotoxic side effects.

Case Description: Patient is a 61 years old male, with a history of end stage renal disease and on peritoneal dialysis, who was admitted with a 5 day history of lightheadedness. Work up showed orthostatic hypotension. Patient developed a low grade fever, non-productive cough and shortness of breath during his stay. A CT scan of the chest was suggestive of bilateral pneumonia. Patient was started on intravenous Cefepime 2 grams every 8 hours. Approximately 36 hours later, patient was noted to be confused. On reevaluation, patient was noted to be hemodynamically stable and not hypoxic. Detailed neurological exam showed that patient was alert but not oriented to his surroundings. No focal deficits were noted. A repeat infectious workup was unremarkable. The degree of azotemia was stable. CT brain, electrocardiogram and arterial blood gas were unremarkable. Due to clinical concern for Cefepime neurotoxicity, IV Cefepime was discontinued. Cefepime levels were not checked as they are not available at our hospital. Given the low clearance of Cefepime with peritoneal dialysis, patient had a temporary hemodialysis catheter placed and was started on hemodialysis. He underwent 2 sessions of hemodialysis in 2 days, 4.5 hours each using a Fresins, Optiflux F200 dialyzer with a blood and dialysate flow rates of 450 ml/minute and 750 ml/minute respectively. There was a complete resolution of confusion after 2 sessions of hemodialysis.

Discussion: The primary route of elimination of Cefepime is renal, with more than 80% of the drug excreted unchanged in patients with normal renal function. Cefepime-related neurotoxicity occurs mostly with incorrect dosing especially in the setting of renal dysfunction as the half life of the drug is increased from 2 hours to nearly 22 hours. However, 80% may also be seen in patients with appropriate dosing. Extracorporeal drug removal with dialysis may be needed to facilitate drug removal and improvement in neurological status. Peritoneal dialysis is less efficient at clearance of cefepime compared to hemodialysis, with clearance only 9% of that reported with hemodialysis.

PUB133
Can Metolazone Help Control Intradialytic Weight Gain and Serum Phosphorous Levels in Hemodialysis Patients with Residual Renal Output?
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Background: Phosphorus is an important uric acid that is difficult to control in hemodialysis patients. Metolazone is a thiazide diuretic that has been reported to increase urinary phosphate excretion through a carbonic anhydrase independent proximal tubular effect. Metolazone is frequently used in conjunction with furosemide to increase urine output in patients with advanced renal insufficiency from cardiac renal syndrome, often as a last attempt to avoid repeated hospitalizations and dialysis, and is well tolerated in this population.

Methods: We summarize anecdotal clinical observations to see if the use of metolazone in conjunction with furosemide in hemodialysis patients with residual urine output might be beneficial to reduce high interdialytic weight gains and hyperphosphatemia.

Results: A median of 16 kg weight gain were recorded chart review patients with high interdialytic weight gains of >3-4 kg and a residual urine output of more than 500 ml of urine a day who had metolazone 5mg daily added to furosemide treatment. All three patients had hyperphosphatemia in the 6.4-11mg/dl range. There was no effect on either intradialytic weight gain or serum phosphorous level and metolazone was stopped. A fourth patient had continued treatment with both metolazone and furosemide for several months since her renal transplant failed, and regardless, her dialysis treatments were complicated by constantly high serum phosphorus levels and high interdialytic weight gain.

Conclusions: In conclusion, these anecdotal observations suggests that the combination of a 5mg daily dose of metolazone with furosemide is no more effective to decrease interdialytic weight gain or decrease hyperphosphatemia in hemodialysis patients than furosemide alone.

PUB134
Kibow Multisite Hope Study Dialysis Randomized Clinical Trial Protocol: A Unique Double-Blind Placebo-Controlled Cross-Over Design Using Renady™ with Standard-Care Therapy (n=100, 5 Sites in the United States) However, it may also be used in patients with appropriate dosing. Extracorporeal drug removal with dialysis may be needed to facilitate drug removal and improvement in neurological status. Peritoneal dialysis is less efficient at clearance of cefepime compared to hemodialysis, with clearance only 9% of that reported with hemodialysis.

Background: Hemo or peritoneal dialysis patients are fatigue during dialysis sessions, susceptible to infections, have poor quality of life due to the high blood levels of uremic toxins and, many are depressed. Outcomes like fatigue, pain, anxiety though major concerns and critically important to patients and clinicians may not be reported in clinical trials (Kid Int 2019; 95:280-1283). The 2014 Standardized Outcomes in Nephrology (SONG) initiative established core outcome sets for nephrology trials (https://songoinitiative.org/). An alternative regime to address some of these issues would benefit all dialysis patients. Renady™, a Pro/Prebiotic dietary supplement, is proven to reduce several uremic toxins in three pilot clinical trials with no reports of adverse outcomes. We propose to carry out large scale clinical trial to validate it as a Live Bio-Therapeutic (LBT) drug with needed IND and US FDA approval.

Methods: Six month RCT controlled cross over design in an outpatient setting. Renady™ will be orally given at 90 B CFU/day.

Results: Measured endpoints will be: 1. Dialysis duration, Quality of Life (QOL). 2. Ureic metabolite panel, CBC, liver function test 3: Biomarkers including Indoxoles, p-Cresol, TMAO, KIM-1, NGAL, IL-6 and CRP.

Conclusions: This is the first-ever RCT proposed using Renady™ as a Live Bio-Therapeutic (LBT) drug for Dialysis patients. Being noninvasive the intervention avoids any possible infection. As a rare unconventional crossover design patients will be their own control for prudent data analysis. Secondly every patient gets the interventional product thus accelerating better patient recruitment. Significance of p-value alone does not help in the decision of the application of results to clinical care and its policy (Kid Int. 2019; 95:28-30). P > 0.05 and P > 0.05 can affect interpretation and lead to bias. Other parameters are also important. (Kor J Pain 2017; 30(4): 241-242). The addition of prebiotics with standard care of therapy may possess excellent potential towards Dialysis applications worldwide. Seriously interested clinical PI’s please contact: rangan@kibowbiotech.com

PUB135
Experience with Directly Acting Antiviral Agents for Hepatitis C in Maintenance Hemodialysis Patients in a Single Center from Pakistan
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Background: The prevalence of Hepatitis C in Pakistan is around 6 % in general population. Prevalence of hepatitis C in maintenance HD patients is between 22 to 55%. Seroconversion rates are reportedly one of the highest in the world.

Methods: Patients on maintenance HD at our center were included in the study. All patients received sofosbuvir with one of the other available oral antiviral agents. Pertinent data at baseline, 3 months, 6 months and 12 months.

Results: Total of 31 patients were included in the study with Mean age of 50.3 years with Standard Deviation of 16.6. Twenty patients were male (64.5%) and Eleven were female (35.5%). Duration of Hemodialysis prior to starting treatment was 2 months to 150 months. Four different regimens were used depending upon the availability of Drugs all of them containing Sofosbuvir in dose of 400mg OD. Pre-treatment PCR was Positive in all patients. SVR at end of therapy that is 3 months was achieved in all patients that completed study period. One patient had relapsed after 15months of achieving SVR (previously treated with Sofosbuvir and ribazole). Successfully treated with sofosbuvir plus valpatasvir for 4 months and achieved SVR successfully. Only 4 patients experienced Anemia, all receiving ribazole.

Conclusions: DAA based therapy delivered expected and desired results of therapy without any major therapy related adverse events in our center.

PUB136
How ESRD Creates, Enhances, and Promotes Poverty for Patients in the United States
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Background: It is well documented that the treatment is both expensive and takes a physical and financial toll on the patient and their respective families. Depending on the treatment modality, many patients fall out of the workforce under the age of 65 and depend on disability to survive creating an additional expense for the government and the general economy through a lower utilization of the workforce. The question, which has been somewhat explored, is if the diagnosis of renal failure leads to inevitable poverty? Despite coverage ratios and access to care, it still seems to negate that undergoing such a treatment regime removes the economic impact to the patient as well as society in general in addition, in many cases, of a quality of life previously experienced. If indeed dialysis results in patients facing an economic burden that translates into poverty, are there treatments that unlike in-center hemodialysis, can maintain a patient’s employment and financial viability?

Methods: Accumulated Journal Articles

Results: CKD and ESRD place tremendous financial burden on a patient and their subsequent family.

Conclusions: For the United States to step forward, like many of our health care equals and partners in Europe, the community, partnerships, and governmental organizations need to address the issue facing patients, the cost and the economic viability as well as an economic analysis methodology and the general view on quality of life. Dialysis will always be an expensive treatment, but the costs can be reduced with a higher quality of life for patients. But the treatment doesn’t have to cost as much as it does if providers
are willing to promote other modalities outside of the standard in-center thrice a week treatment that Fresenius and DaVita promote given their large investment in free-standing clinics. It must also be noted that these two providers create more wealth for their investors via this treatment option.

PUB137

A Home Away from Home: Patients’ Experiences of Community Hemodialysis: A Qualitative Interview Study

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Background: Community hemodialysis is a sub-modality of home hemodialysis that enables patients to perform hemodialysis independent of nursing or medical supervision in a shared community house. This study describes the perspectives and experiences of patients using community hemodialysis in New Zealand to explore ways in which this dialysis modality may support the wider delivery of independent hemodialysis care.

Methods: Qualitative, semi-structured, in-depth interview study of thirty patients who had experienced community hemodialysis. Participants were asked why they chose community hemodialysis and their experiences and perspectives of this hemodialysis modality. Data was analysed using thematic analysis.

Results: Twenty-five patients were interviewed (14 men and 11 women, 31 to 65 years of age). Most were of Māori or Pacific ethnicity and in part-time or full-time employment. Over two-thirds dialyzed for 20 hours a week or more. We identified four themes that described patients’ experiences and perspectives of choosing and using community hemodialysis: reducing burden on family (when home isn’t an option; minimizing family exposure to dialysis; maintaining privacy and self-identity; reducing the costs of home hemodialysis; gaining a reprieve from home); offering flexibility and freedom (having a normal life; maintaining employment; facilitating travel); control of my health (building independence and self-efficacy; a place of wellness; avoiding institutionalization; creating a culture of extended hour dialysis); and community support (building social inclusion; supporting peers).

Conclusions: Community house hemodialysis is a dialysis modality that overcomes many of the socioeconomic barriers to home hemodialysis, is socially and culturally acceptable to Māori and Pacific people, supports extended hour hemodialysis and thereby promotes more equitable access to best practice services. It is therefore a significant addition to independent hemodialysis options available for patients.

PUB138

Omphalitis in Adult Peritoneal Dialysis Patients

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Introduction: There are very few literary reports related to omphalitis in peritoneal dialysis (PD) patients which described peritonitis after severe omphalitis. We describe 2 cases of omphalitis that occurred in adult PD patients with CAPD-related peritonitis preceding the event of omphalitis.

Case Description: The first patient, 44-year old woman, was presented with abdominal pain, swelling and local pain in umbilical area. Peritoneal effluent was clear with elevation of WBC and PMN cells count, culture was negative. US of abdominal region revealed thickening, infiltration of subcutaneous fat and suspected fluid collection near the inner side of the abdominal wall. Abdominal CT demonstrated fluid collection in subcutaneous region and smaller collection extended to peritoneal cavity. The patient was treated like culture-negative peritonitis with recovery of clinical signs of omphalitis. 1.5 months before the patient experienced an episode of culture-positive peritonitis, was treated and recovered. Peritoneal culture was negative after the treatment. The second patient, 67 year women, was presented with abdominal pain, redness and local warmth in the umbilical region. Dialysate was clear with a little increase in WBC and PMN count, culture was negative. US of abdominal wall demonstrated thickening and infiltration of abdominal fat in umbilical and periumbilical area. Two small peritoneal lesions of unknown origin were seen. The patient was treated like culture-negative peritonitis and omphalitis recovered.

Discussion: Our cases caused us to suggest that the omphalitis may be a complication of peritonitis in PD patients. Perhaps this patients had a predisposition like remnants of the umbilical cord and high abdominal pressure converts this rare problem from occult to obvious.

Abdominal CT of the first patient

PUB139

First Onset of Exit-Site Infection, but Not Peritonitis, Is Influenced by Body Mass Index in Newly Patients Started on Peritoneal Dialysis

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Background: Peritoneal dialysis (PD)-related infections such as exit-site infection (ESI) and peritonitis, are leading causes of technique failure in patients undergoing PD. However, the incidence rate of ESI and the clinical factors associated with ESI have not been well investigated.

Methods: The present study aimed to assess ESI and peritonitis in patients newly started on PD. The clinical records of 55 patients for whom PD was initiated between January 1, 2012 and December 31, 2018 at a single center were retrospectively reviewed. The baseline clinical factors influencing the time to the first onset of ESI and peritonitis events, and the relation between ESI and peritonitis were investigated.

Results: The following patient characteristics were as follows: age (median, interquartile range), 68.0 (55.0–78.0) years; body mass index (BMI), 22.6 (20.1–26.0) kg/m²; diabetes, 30.9%; step-wise initiation of PD, 47.3%; bag exchange by caregivers, 32.7%; serum albumin level, 3.2 (2.7–3.6) g/dL; serum creatinine level, 8.3 (5.9–9.6) mg/dL; and dialysate-to-plasma creatinine concentration ratio (D/PCr), 0.64 (0.54–0.75). The total number of ESI events was 162, and the incidence ratio was 1.22 per patient year. The total number of peritonitis events was 33, and the incidence ratio was 0.22 per patient year. The onset of ESI during the initial 60 days correlated with BMI (γ = 0.49; p = 0.001), with D/P Cr (γ = −0.52, p = 0.000), and with incidence ratio of ESI (γ = 0.35, p = 0.017), but not with peritonitis incidence. Cox proportional hazards model revealed that the first onset of ESI was significantly affected by BMI [hazard ratio (HR), 1.19; 95% confidence interval (95% CI), 1.04–1.36; p = 0.009] but not by diabetes (HR, 0.69; 95% CI, 0.25–1.86) or D/P Cr (HR, 0.79; 95% CI, 0.03–19.0), and that the first onset of peritonitis was not significantly affected by any of the factors including BMI, diabetes, and step-wise initiation of PD. The number of ESI events was correlated with the number of peritonitis events (p = 0.04), but the incidence ratio of ESI did not correlate with the incidence ratio of peritonitis (p = 0.11).

Conclusions: High BMI was associated with the first onset of ESI but not with peritonitis. The onsets of ESI and peritonitis over time were not closely related.
Eligibility and Patient Barriers to Peritoneal Dialysis in Patients with Advanced CKD
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Background: The burden of chronic kidney disease is on the rise in Kenya and is a significant cause of morbidity and mortality. While definitive treatment is renal transplantation, many patients require renal replacement therapy in the form of hemodialysis or peritoneal dialysis. The predominant modality utilized in Kenya is hemodialysis despite peritoneal dialysis having similar survival outcomes with the potential benefit of cost-effectiveness. There is need therefore to explore why peritoneal dialysis remains underutilized and whether patient factors may be contributory to barriers that limit the uptake of peritoneal dialysis. The main objective of this study is to determine eligibility for peritoneal dialysis of patients considered potential candidates for the modality. In addition, barriers to the same were determined. Further, the impact of presence of support on PD eligibility was determined.

Results: In this study on eligibility of patients with advanced CKD for self-care PD we found 68.9% of the patients eligible for self-care PD. Surgery-related abdominal scarring was the most common contraindication. Barriers to self-care PD were identified in 45.9% and physical barriers were more common than cognitive barriers. Presence of support was associated with a significant increase in PD eligibility (p<0.001)

Conclusions: A significant proportion of the population studied was eligible for peritoneal dialysis as a treatment modality. The presence of support may be an important factor to explore in patients with barriers to self-care PD as it may be associated with an increase in PD eligibility.

The Effects of Fatigue and Depression on Clinical Outcome Among Different Dialysis Modalities
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Background: It is well-known that both fatigue and depression are common manifestation among dialysis patients. Additionally, they were reported to be associated not only with quality of life but also patient mortality. There are several relative factors including mental factors, anemia, inflammation and dialysis-relater factors. However, the difference among different dialysis modalities is still unknown.

Methods: In the cross-sectional study, we recruited 194 dialysis patients (mean age, 61±11 years; 134 males). Fatigue was assessed using Profile of Mood States (POMS), Visual Analogue Scale (VAS) and our original scales for fatigue whereas depression was assessed using the Beck Depression Inventory-second edition (BDI-II). Results: Our original scales for fatigue were strongly correlated with VAS, BDI-II and POMS. There were no significant differences of the markers for fatigue and depression among patients receiving peritoneal dialysis (n=94), hemodialysis (HD, n=26) and online haemodiafiltration (OHDF, n=74). Among HD and OHDF patients, fatigue was pronounced on the day on dialysis as compared to the day not receiving dialysis. Conclusions: Further investigations will be needed to clarify the effects of fatigue and depression on the clinical outcome among the different dialysis modalities.

Subcutaneous Cuff Migration in Peritoneal Dialysis Patients: A Single-Center Observational Study
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Background: Cuff extrusion is an important reason of catheter-related infections in patients with maintenance peritoneal dialysis (PD). During the long-term follow-up, we found that subcutaneous cuff tends to slowly migrate to the exit-site of catheter in many PD patients. However, few study show the correlation between subcutaneous cuff migration and duration of PD, and seldom do they analyze the possible effect factors of cuff migration.

Methods: 124 patients who have been undergoing PD for more than 6 months were included in this one-year observational study at our Nephrology division from October 2017 to September 2018. The exposed length of PD catheter was measured with a soft ruler every three months. The exit-site of catheter, BMI, biochemical parameters, and dialysis adequacy indexes were monitored at the same time.

Results: The mean age of these PD patients were 53.1±12.0 yrs and the mean duration of PD was 50.0±24.9 ms. At the beginning of the follow-up, the exposed length of PD catheter was 9.5–16.5 cm (average13.9 ±1.4 cm) and 11.0–17.0 cm (average 14.2 ±1.3 cm) for one year later (P<0.001). The average length of catheter exposure increased 0.28cm. BMI of these patients was 23.0 ±3.2 at baseline, and 23.2 ±3.2 for one year later (P<0.01). The length of catheter migration was negatively correlated with hemoglobin level (r = -0.212, P< 0.018) and positively correlated with urea nitrogen level (r = 0.295, P<0.001). There were no correlations between the length of catheter migration and serum albumin, immunoglobulin, pre-albumin, calcium, phosphorus, serum creatinine dialysis adequacy and exit-site infection. During the observational period, 1 patient developed shallow cuff extrusion. There was no exit-site infection during the observational period.

Conclusions: Based on our observation, subcutaneous cuff slowly migrates to the exit-site of catheter as the duration of PD increases in patients. It might be affected by hemoglobin level and urea nitrogen level in these patients. Preventing such cuff migration and extrusion need to be considered by peritoneal dialysis nurses.
Outcome Measures for Life Participation in Peritoneal Dialysis: A Systematic Review

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Background: Patients receiving peritoneal dialysis (PD) require daily treatment and are at risk of potentially life-threatening complications, which can limit their ability to participate in activities of daily living. Despite being a prioritized outcome among patients and clinicians, it is infrequently and variably assessed in existing research. We aimed to identify the characteristics, content and psychometric properties of the measures used to assess life participation in PD research.

Methods: We searched MEDLINE, Embase, PsychINFO, and CINAHL from inception to March 2019 for all studies that reported life participation in patients on PD. The characteristics, dimensions of life participation and psychometric properties of these measures were extracted.

Results: In total, 78 studies were included (3% randomized trials and 75% observational studies). Across these studies, we identified 16 different measures that were used to report life participation. None of the measures specifically assessed life participation, but evaluated broader constructs (e.g. quality of life) that included questions on life participation. The 36-item Short Form Survey (SF-36) and Kidney Disease Quality of Life Short Form (KDQOL-SF) were the most frequently used measurement tools, employed in 36 (46%) and 26 (33%) studies, respectively. Validation data to support the use of these measures in patients on PD were available for nine.

Conclusions: Life participation is inconsistently assessed across studies in PD, and some of the measures used have not been validated in the PD population. Establishing a standardized, validated measure of life participation will facilitate consistent and accurate assessment of this outcome, thereby enabling research to inform strategies which can help patients on PD better engage in their life activities.

Single-Dose Prophylactic Antibiotic Did Not Significantly Reduce Peritonitis After Peritoneal Dialysis Catheter Insertion

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Background: It is recommended to use prophylactic antibiotics before the catheter insertion by ISPD guideline. Previously in our hospital, the physician who did the surgery would decide whether to use antibiotics according to patient’s condition. To investigate the use of antibiotics around the Tenckhoff catheter insertion for continuous ambulatory peritoneal dialysis(CAPD) and its effect on the incidence of early peritonitis, we performed the retrospective study.

Methods: From Jan. 2012 to Mar. 2019, there were 642 patients underwent PD catheter insertion. Each patient’s electronic medical record was reviewed to determine the use of antibiotics and the occurrence of peritonitis. Patients received catheter due to acute severe pancreatitis, retreated from PD or died within 14 days after the insertion were ruled out. The remaining patients fell to three groups: Systemic group(SG), due to lung, acute severe pancreatitis, retreated from PD or died within 14 days after the insertion were the use of antibiotics and the occurrence of peritonitis. Patients received catheter due to catheter insertion. Each patient's electronic medical record was reviewed to determine the retrospective study.

Results: From Jan. 2012 to Mar. 2019, there were 642 patients underwent PD catheter insertion. Each patient’s electronic medical record was reviewed to determine the use of antibiotics and the occurrence of peritonitis. Patients received catheter due to acute severe pancreatitis, retreated from PD or died within 14 days after the insertion were ruled out. The remaining patients fell to three groups: Systemic group(SG), due to lung, acute severe pancreatitis, retreated from PD or died within 14 days after the insertion were the use of antibiotics and the occurrence of peritonitis. Patients received catheter due to catheter insertion. Each patient's electronic medical record was reviewed to determine the retrospective study.

Conclusions: Out of total 642 patients, 28 were ruled out. The remaining 614 patients(318 men and 296 women) were as follow: 185 in SG, 164 in PG, and 265 in NPG. Peritonitis was identified in 5 patients(2.7%) in SG, 11(6.71%) in PG, and 32(12.08%) in NPG. The results of Chi-square test are as follow: SG vs PG, p=0.1215; SG vs NPG, p=0.0003; and surprisingly, PG vs NPG, p=0.0971. In terms of gender, peritonitis rates in men and women were 11.16(3/27) vs 4.39%(4/92) (p=0.024). The differences among all groups in women were significant (SG vs PG, p=0.0099; SG vs NPG, p=0.3541; PG vs NPG, p=0.3209), and in men were partial significant (SG vs PG, p=0.0282; SG vs NPG, p=0.0004; PG vs NPG, p=0.2468).

Conclusions: Our data suggest that single dose prophylactic antibiotic did not significantly reduce peritonitis following PD catheter insertion and male was more susceptible to early peritonitis after insertion.

Funding: Government Support - Non-U.S.

Activation of Renin Angiotensin System Disrupts the LDLr Pathway: A Novel Mechanism for Extracellular Matrix Accumulation in Human Peritoneal Mesothelial Cells

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Background: Peritoneal fibrosis (PF) is characterized by progressive extracellular matrix (ECM) accumulation in human peritoneal mesothelial cells (HPMCs) under high glucose (HG) conditions. The aim of this study was to explore the potential mechanisms of HG-induced production of ECM in HPMCs.

Methods: HPMCs were stimulated by HG. The activity of renin angiotensin system (RAS) was inhibited by valsartan or angiotensin II (AngII) type 1 receptor (AT1R) siRNA. Morphological changes in the cells were observed under an inverted microscope. Oil red O, filipin staining and high-performance liquid chromatography were used to examine lipid accumulation. The expression of low-density lipoprotein receptor (LDLr) regulation, the LDLr component and ECM-associated markers were assessed by real-time PCR and western blot analysis.

Results: The results showed that after treatment with HG, HPMCs showed notable elongation consistent with the morphology of myofibroblasts, and the expression of ECM proteins such as α-smooth muscle actin (α-SMA), fibroblast specific protein-1 (FSP-1) and collagen I was increased. In addition, there was a parallel increase in lipid accumulation, the expression of intracellular lipid deposits was closely correlated with dysregulation of LDLr, which was mediated through the upregulation of LDLr, sterol regulatory element-binding protein (SREBP) cleavage-activating protein (SCAP), SREBP-2 and through enhanced cleavage of the SCAP with the Golgin. Further analysis showed that HG enhanced the gene and protein expressions of LDLr component, such as renin, angiotensinogen, angiotensin-converting enzyme, AngII and AT1R. Interestingly, blocking RAS activity reversed the dysregulation of LDLr, even in the stimulation of HG. These effects were also accompanied by a decrease in the expression of ECM components.

Conclusions: Our findings demonstrated that increased RAS activity exacerbated ECM formation in HPMCs by disrupting LDLr regulation, which contributed to lipid disorder-mediated PF.

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Serum Ferritin as a Predictor of All-Cause and Cardiovascular Mortality Depends on Systemic Inflammation in Peritoneal Dialysis Patients

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Background: It is proposed that inflammation may modify the association between serum ferritin and the adverse outcomes in hemodialysis patients. However, the optimal level of serum ferritin remains ambiguous at what level advantage outweighs the disadvantage in peritoneal dialysis patients when the inflammation taken into consideration. This study aimed to explore the optimal concentration of serum ferritin for the improving the outcome of peritoneal dialysis patients.

Methods: We classified 221 patients into two groups according to serum ferritin concentration (100μg/L) and followed up regularly from the date of catheterization to Dec 31th, 2016 at SunYat-Sen Memorial Hospital, China. Clinical and biochemical data were collected as baseline, and clinical outcomes such as all-cause, cardiovascular, infection-related mortality were assessed.

Results: The Kaplan-Meier survival revealed a significant worse survival accumulation in PD patients with higher serum ferritin under elevated hsCRP level (p=0.022). A multivariate Cox regression analysis revealed that enhanced level of ferritin was independently associated with higher risk of all-cause and cardiovascular mortality in PD patients (HR=0.263, p=0.007 and HR=0.094, p=0.029) after adjustment for relevant confounding factors under the condition of hsCRP above 3mg/L. However, correlations were not statistically significant for serum ferritin and poor outcome within the normal range of hsCRP level.

Conclusions: Higher levels of serum ferritin were associated with increased risk of all-cause and cardiovascular mortality in patients undergoing PD only in the presence of elevated hsCRP level. The correlation of serum ferritin with poor outcome should take systemic inflammation into consideration.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Hyperkalemia in Chronic Peritoneal Dialysis
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Background: Since peritoneal dialysate contains no potassium, hypokalemia is expected in patients on chronic peritoneal dialysis (PD).

Methods: We explored retrospectively the incidence and potential mechanisms of hyperkalemia, not previously described, in 779 blood samples obtained monthly from 33 patients over 1–59 months of PD. Patients were dialyzed daily via cyclic, usually 9–15 hours per day, with a “dry” period. Normal range of serum potassium concentrations was defined as the hospital standard: 3.5 - 5.1 meq/l.

Results: Although mean monthly serum potassium concentrations were in the normal range, in 68 samples over 59 months, we observed hyperkalemia (> 3.5 meq/l) in 40 (5%) and hyperkalemia (> 5.1 meq/l) in 110 (14%) blood samples. The incidence of hyperkalemia did not change appreciably over Years 1 (15%), 2 (11%), 3 (19%), and 4 & 5 (22% [fewer samples]) of PD. Hyperkalemia was mostly modest: 5.2 – 5.4 (55%), 5.5 – 5.7 (21%), 5.8 – 6.0 (10%), > 6.0 (14%) (meq/l for each). Of the 33 patients, 39% displayed hyperkalemia only, 23% displayed hyperkalemia only, and the remainder (38%) displayed both or neither. Comparing the hyperkalemia-only patients with the hypokalemia-only patients, we found no difference in use of potassium chloride therapy or medications that interrupt the renin-angiotensin system, small-molecule transport status, or renal uraemia clearance. We compared biochemical parameters from the hypokalemic and hyperkalemic blood samples and observed lower serum bicarbonate concentrations, higher serum creatinine concentrations, and higher blood urea nitrogen concentrations in the hyperkalemic samples ($p < 0.001 for each), without difference in serum glucose concentrations.

Conclusions: In summary, our chronic PD patients exhibited hyperkalemia almost 3 times as frequently as hypokalemia. We wonder if high-potassium diet (patients are instructed to eat potassium-containing foods to prevent hypokalemia), non-compliance with therapy (evidence: more azotemia), increased muscle mass (evidence: higher serum creatinine concentration), cellular shifts of potassium (evidence: more metabolic acidosis), and/or the long period without PD each day contribute to the unexpected frequency of hyperkalemia in our population.

Peritoneal Equilibration Test (PET) with Temporary Drainage at 60 Minutes: Utility to Identify Potential Risk of Severe Damage on Peritoneal Membrane
Mabel Alvarez Quiroga,1 Martin E. Guinsburg, Rosanna V. Garofalo, Carolina V. Martinez, Adrian M. Guinsburg, Fresenius Medical Care, Buenos Aires, Argentina.

Background: Long term preservation of peritoneal membrane is key to maximize modality survival. Presence of ultrafiltration failure over time are commonly associated to fibrosis, inflammation and severe damage on peritoneal membrane. Several authors has postulated that measuring changes in sodium concentration (DipNa), and free water transport (FWT) could help to detect patients at risk of developing encapsulated peritoneal sclerosis (EPS). We aim to evaluate transport changes over time in our population.

Methods: We performed modified PET to peritoneal dialysis (PD) patients in Fresenius Medical Care Argentina between 06-2015 and 12-2018 and calculated FWT, small pore ultrafiltration, DipNa and d/p Cr h4 according to Bernardo et al.[1] Test results were correlated to time in PD to identify progressive damage. Patients with combination of DipNa < 5 meq/l, FWT < 75 ml, total UF < 400 ml and d/p Cr h4 > 0.81 were classified at high risk for EPS. Pearson was used to evaluate correlation while Student t-test for mean comparisons.

Results: We included 549 incident and prevalent PD patients. Age 49±16.2 years, 48.2% male, diabetes 15.1%, time in PD 30.1±28.6 months. According to d/p Cr h4, transport type was 2.5% low, 13.9% low-average, 48.7% high-average and 32.3% high. Time in PD correlates negatively with DipNa (<0.214, p<0.001), FWT (<0.225, p<0.001) and total UF (<0.186, p<0.001) and positively with d/p Cr h4 (0.129, p<0.002). High risk for EPS was identified in 17 patients (4.7%) with significant greater time on PD (48.9±32.5 vs 29.2±28.1 months) but no difference in age, gender, diabetes or peritonitis prevalence. Remarkable is that d/p Cr h1 showed a high correlation with d/p Cr h4 (0.793, p<0.0001).

Conclusions: Time in PD has a significant impact in transport changes of the peritoneal membrane. Performing modified PET test allowed to early identify membrane injury thus increasing detection of patients at potential risk for EPS. High correlation between d/p Cr h1 and d/p Cr h4 may allow to shorten the test to just one hour long, mostly useful for patients with low tolerance to intraabdominal pressure increases. [1] Perit Dial Int. 2012 Sep-Oct; 32(S): 537–544.

Encapsulating Peritoneal Sclerosis (EPS): Initial Presentation as Incidental Finding of Peritoneal Calcifications During Laparoscopic PD Catheter Placement
Zhi Xu, Moiz Dawood. University of New Mexico Hospital, Albuquerque, NM.

Introduction: EPS is a rare but devastating complication of long-term peritoneal dialysis (PD) characterized by inflammatory and fibrotic peritoneal capsule that entrap the bowel loops.

Case Description: A 64 year-old woman with end-stage kidney disease who had been on PD for 13 years was referred to a surgeon for a new PD catheter placement after temporary transfer to hemodialysis (HD) due to refractory peritonitis. During the laparoscopic procedure, the surgeon noticed multiple plaques of “sclerosing reactions” on her peritoneum. No adhesions were observed. In light of the patient’s long period of 13 years on PD, we were concerned about EPS and promptly transitioned her to HD. Up to this point, patient had done well on PD. She had effective ultrafiltration. She was a low transporter. Six months after her transition to HD, she was admitted to the hospital with anorexia and weight loss. She was found to have small bowel obstruction. She underwent lysis of adhesions and was noted to have dense fibrosis of the visceral peritoneum. She declined further evaluation and withheld from care.

Discussion: As our case demonstrates, early diagnosis of EPS requires a high degree of vigilance. There are no specific tests to diagnose EPS. The early phase of EPS may be indicated by appearance of ultrafiltration failure with change to high transporter status. Unfortunately EPS is usually diagnosed in the later progressive stage when intestinal obstruction becomes evident. As EPS becomes apparent, evidence supporting its diagnosis includes radiologic findings of loculated ascites and calcifications along the peritoneum and small bowel loops. Time on PD (> 5 years) is the only consistent predictor for the occurrence of EPS. The diagnosis of EPS mandates the immediate transition from PD to HD. There is no consensus regarding optimal treatment, which may include surgical lysis of intestinal adhesions, nutritional support, and immunosuppressive therapy with prednisolone and or tamoxifen.

Comparison of Utilization of Peritoneal Dialysis (PD) Between a High-Volume PD Center (HVC) and a Low-Volume Center (LVC) in New York City (NYC)
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Background: NYC has one of the lowest PD utilization rates within the United States but within NYC itself there is segmental distribution of facilities that have high PD utilization rates. Metropolitan neighborhoods are generally considered to have adequate infrastructure support to sustain home-based programs. We compared a HVC to a LVC to identify potential factors that lead to sustenance of home-based programs such as PD.

Methods: We reviewed selected factors that would sustain a PD program from the 2017-2018 data of a HVC (n = 80) and compared them to a LVC (n = 12) located in Manhattan and Brooklyn, respectively. Proportions and rates were either analyzed via chi square statistics or Poisson rate models.

Results: See Table

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Conclusions: Amongst the factors analyzed above, the only factor that demonstrated statistical significance was the rate of new-start PD patients in the HVC. Rates of patient loss to hemodialysis or kidney transplant as well as provider-to-patient ratios did not show statistically significant difference between centers. Contrary to previous publications that demonstrated that the disparity in the economies of scale influenced the safety and rate of complications, such findings were not seen in this study. Health care providers or institutions that would like to grow their home-based programs need to look at strategies that enhance patient recruitment.

Comparison between a high-volume PD center (HVC) and low-volume center (LVC) in 2017-2018 within New York City.

### PUB151

**Insight into the Mechanism of Electrolyte Management in Sorbent-Based Peritoneal Dialysis**

Peter F. Haywood,1 Vinod Gadi,2 Sanjay Singh,2 Mandar Gori,2 Suresha Venkataryana,2 Huay Hay,2 Marjorie W. Foo,2 Yue Wang,2 Singapore General Hospital, Singapore, Singapore; 2AWAK Technologies Pte Ltd, Singapore, Singapore.

**Background:** Electrolytes play a key role in maintaining fluid balance, osmolality, acid-base balance in healthy humans and hence the management of electrolytes is important to control the morbidity of CKD and ESKD patients. The positively charged electrolytes like sodium (Na+), potassium (K+), calcium (Ca2+) and Magnesium (Mg2+) together with negatively charged electrolytes like chloride (Cl−), bicarbonate (HCO3) and phosphate (H2PO4) perform physiological functions and concentration above or below the normal range can affect homeostasis or specific organ function detrimentally.

**Methods:** The regulation of electrolyte balance in sorbent-based PD is managed by an ion exchange mechanism, infusion and/or diet. Zirconium phosphate and zirconium oxide are used as cation and anion exchangers respectively. Certain electrolytes like sodium, bicarbonate and chloride are maintained by ion exchange processes while other ions like magnesium, calcium, potassium, phosphate are completely removed by the sorbent and managed by corresponding salt infusion and/or diet.

**Results:** The results of electrolyte management by AWAK sorbent cartridge, including follow up data, in one representative patient (P) who underwent nine AWAK therapies over a period of three days is shown below.

**Conclusions:** The specially formulated sorbent in AWAK PD device helps to regulate and maintain electrolyte concentration close to physiological levels and thus promising safety.

**Funding:** Commercial Support - AWAK TECHNOLOGIES PTE LTD

<table>
<thead>
<tr>
<th>Type</th>
<th>Electrolyte (mmol/L)</th>
<th>Balance Mechanisms A WAK Sorbent-Based PD</th>
<th>P</th>
<th>N</th>
<th>S</th>
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<tr>
<td>Sodium</td>
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<td>Sorbent</td>
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<td>143</td>
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<td>Magnesium</td>
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<td>3.27</td>
<td>2.83</td>
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<td>2.83</td>
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P: Individual Subject; D: Concentration of electrolyte before starting AWAK therapy; EOT: End of therapy; FU (1W): Follow up after one week; FU (1M): follow up after one month; numbers in mEq/L (serum)

### PUB152

**Regulation of Mesothelial Epithelial-to-Mesenchymal Transition by Vitamin D and Statins**

Seth B. Furgerson,1,2 Colin D. Bauer,1 Isaac Teitelbaum,1 1University of Colorado, Aurora, CO; 2Denver Health Hospital, Denver, CO.

**Background:** Epithelial to mesenchymal transition (EMT) has been implicated in the pathogenesis of perinatal scleroderma. The factors that regulate EMT in the perinatum are incompletely understood. Data obtained in cell culture and in animal models of perinatal dialysis indicate that active Vitamin D analogues and statins may have effects on EMT in man. Patients receiving PD.

**Methods:** Human peritoneal mesothelial cells (HPMCs) were obtained from peritoneal effluent. Patients included in the study had been on EMT in man. Patients receiving PD.

**Results:** Using quantitative real time polymerase chain reaction (qRT-PCR), transcript levels of vitamin D receptor (VDR, marker of epithelial phenotype), smooth muscle alpha actin (EMT marker), Snail (EMT promoter), and IL-6 (pro-inflammatory cytokine) were measured. Results were normalized to transcript levels of GAPDH. Statistics were performed using ANOVA.

**Conclusions:** This study does not support the hypothesis that vitamin D or statins reduce EMT in patients on PD. However, the study does have several limitations, including possible heterogeneity in effluent cell mix and small sample size. Larger studies are needed to determine whether activated vitamin D or statins prevent EMT in patients receiving PD.

**Table**

<table>
<thead>
<tr>
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<tr>
<td>EMT</td>
<td>0.72 (0.34)</td>
<td>0.50 (0.24)</td>
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<tr>
<td>Snail</td>
<td>0.96 (0.7)</td>
<td>0.87 (0.7)</td>
</tr>
<tr>
<td>SMA</td>
<td>26 (11)</td>
<td>1.1 (0.84)</td>
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<tr>
<td>IL-6</td>
<td>1.0 (0.79)</td>
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<tr>
<td>VDR</td>
<td>0.78 (1.4)</td>
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### PUB153

**A Case of Catastrophic Calcific Uremic Arteriopathy Involving Multiple Organ Systems in the Setting of ESRD**


**Introduction:** Calcific uremic arteriolopathy (CUA), or calciphylaxis, is a grave disease, associated with high morbidity/mortality, that presents with skin ischemia/necrosis and occurs, most commonly, in ESRD patients. Diagnosis is primarily a clinical one. Manifestations include painful, plaque-like subcutaneous nodules that progress to ischemic/necrotic ulcers with eschars. Although skin involvement is well known in diagnosing this disease, extra-renal involvement has not been discussed extensively.

We present a case of catastrophic CUA, involving multiple organ systems.

**Case Description:** 65 y/o woman with a PMH of ESRD, on CCPD, HTN, COPD, OSA, DM-2 and PAD was p/w painless B/L LE ulcers, starting 2 weeks prior to admission with skin discoloration, progressing to painful ulcers with dark eschars. As there was high suspicion for CUA, patient was started on sodium thiosulfate and sensipar/sevelamer.

Hospital course was complicated by aspiration pneumonia (s/p course of antibiotics), acute ischemic stroke (MRA) secondary to cardio-embolism (cardiac CT showing severe mitral annular calcification with areas of caseation necrosis). Anticoagulation was deferred due to her co-morbidities/risk of bleeding. Patient had persistent leukocytosis/bilobar submandibular swelling (concerning for parotitis), re-started on antibiotics; blood cultures and mumps titers were negative. She developed hematometra, associated with abdominal pain and worsening hypoxia, conservatively managed with oxygen and IPP therapy.

Subsequently, patient developed AMS with unresponsiveness. She was sedated, intubated and transferred to the ICU. CT Head showed a new large temporal hematoma, midline shift and R uncal herniation, deemed not a surgical candidate. Family opted for comfort care. Shortly thereafter, patient was found to be in PEA arrest followed by asystole. She was pronounced dead.

**Discussion:** This case highlights the multiple organ systems involved in this devastating disease process, which have been rarely emphasized in the literature. Treatment options are limited, and often do not attenuate its dismal prognosis. Although 65% survival rate of patients with CUA is 50%. The advent of more awareness of the widespread involvement of CUA can help to diagnose this ominous condition early, and may help to mitigate its complications.

### PUB154

**A Case of Persistent Left Superior Vena Cava in a Hemodialysis Patient Detected During Left Upper Arm Arteriovenous Graft Thrombectomy**

Aisha Shaikh,1,2 Jeremy D. George,1 1Nephrology, James J. Peters Medical Center VA, Bronx, NY; 2Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY; 1Icahn School of Medicine at Mount Sinai, New York, NY.

**Introduction:** Persistent Left Superior Vena Cava (PLSVC) is the most common thoracic venous anomaly with a reported incidence of 0.3% - 0.5% in the general population though the incidence can be up to 6% in patients with congenital heart disease. The majority of the patients with PLSVC are asymptomatic, with the anomaly usually discovered incidentally during central venous catheter (CVC) or cardiac pace-maker placement. This is a case of PLSVC in a hemodialysis patient detected during a left upper arm arteriovenous graft (AVG) thrombectomy procedure.

**Case Description:** 63-year old male with end stage renal disease presented to the dialysis unit with a clotted left upper arm AVG. The AVG (brachial artery to axillary vein) was created 6 months prior and was being used for hemodialysis treatment for 4 months. The patient did not have a prior history of CVC placement. During the AVG thrombectomy, the patient was found have a PLSVC with no accompanying Right SVC. The thrombectomy was successful, and the patient did not have any adverse events during or after the procedure. However, at the end of the thrombectomy procedure it was unknown if the patient had an accompanying cardiac anomaly or a left to right shunt.

A contrast echocardiogram was performed which did not reveal a left to right shunt or any other cardiac anomaly.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Discussion: PLSVC is generally an asymptomatic condition. In most patients, the left sided SVC drains into the right atrium through the coronary sinus. However, in up to 8% patients, the left sided SVC drains into the right atrium creating a left to right shunt. In addition, cardiac anomalies such as ventricular and atrial septal defects can be present. It is well known that during the AVG thrombectomy there is dislogegement of the clot downstream into the venous circulation, resulting in pulmonary emboli. These pulmonary emboli are generally small, and usually asymptomatic. However, in the presence of a left to right shunt, the patient is at potential risk for paradoxical embolism which could result in an embolic stroke. It is therefore important to determine the presence of left to right shunt in the setting of PLSVC to assess the risk of systemic embolism during a dialysis AV access thrombectomy

PUB155
Risk Factors Associated with Early Vascular Catheter Dysfunction
Andres Aranda,1 Pablo Maggioni,1 Victoria E. González montes,1 Erendira A. Arellano,1 Guillermo Navarro Blackaller,2 Jonathan Chavez,2 Joana G. Navarro gallardo.4 *Hospital Civil Fray Antonio Alcalde, Zapopan, Mexico; 1Universidad de Guadalajara, RFC UGU250907MH5, Mexico; 2Hospital Civil de Guadalajara, Guadalajara, Mexico; 4Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Mexico.

Background: In our center, the majority of vascular catheters (Cath) are placed urgently, either for AKI or CKD, so it is imperative to obtain adequate functionality of the Cath to stabilize the patient. Risk factors associated with early vascular catheter dysfunction (EVCD) have not been clearly studied.

Methods: 66 patients had jugular Cath placement from Feb-May 2019. Primary objective: Risk factors associated with EVCD, defined as blood flow < 250 ml/min at the first HD session. The Cath were placed guided by US. We analyzed age, gender, height, previous Cath, lab tests (Glucose, BP, anatomic position, extrasystoles (EXS)), #punctures, JV collapsability, Cath TUG-TIP-TOP, Cath size and type, heparin, complications, neck circ., brastbone-chin DIST, skin-JV DIST, JV and carotid diam. and DIST between JV-Carotid. A correlation matrix and uni- and multivariable logistic regression model were performed. P < 05 significant.

Results: 66 vascular Cath placements were analyzed. The EVCD was presented in 4 patients (6.06%). The incorrect position of the Cath TIP was associated with EVCD (OR 1.35, 95% CI 1.13-1.62; P = 0.0018). The presence of EXS during the procedure was associated with a lower risk of EVCD (OR 0.81, 95% CI 0.69-0.95; P = 0.0185). No other variable was significant. Factors associated with complications during the procedure were performing>=2 punctures (OR 1.21, 95% CI 1.02-1.42; P = 0.027) and carotid diameter>= 0.85 cm (OR 1.55, 95% CI 1.10-2.20, P = 0.017).

Conclusions: Avoiding EVCD is important in patients with an emergency HD. Only the incorrect position of the Cath TIP was associated with EVDC (OR 1.35, 95% CI 1.13-1.62; P = 0.0018) while the presence of EXS during the procedure was associated with a lower risk of EVCD (OR 0.81, 0.69-0.95; P = 0.0185). Larger sample is needed.

PUB156
Is Basilic Vein Transposition an Alternative Option for Unsuitable Veins?
Vinant Bhargava,1 Priti Meena,1 Anurag Gupta,1 Neha Jain,1 Anil Bhalla,1 Ashwami Gupta,1 Krishna K. Agrawal,1 Devinder S. Rana,1 Manish Malik.4 1Sir Ganga Ram Hospital, New Delhi, India; 2UCONN Health, Hartford, CT; 3 imperial College Renal and Transplant Centre, Hammersmith Hospital, London, UK, London, United Kingdom; 4Sir Ganga Ram Hospital and GRIPMER, New Delhi, India.

Background: According to the National Kidney Foundation’s KDOQI, “radial-cephalic (RC) and brachial-cephalic (BC) fistulae are the first choices for vascular access but in the absence of adequate veins or after failed RC/BC access, basilic vein transposition (BVT) provides an alternative autologous option for hemodialysis.

Methods: This is a prospective, observational study conducted in the Department of nephrology, Sir Ganga Ram Hospital, New Delhi. Forty-five patients with end stage renal failure who underwent BVT during 1st January 2017 to December 2018 were included in the study. Patients were followed up for 1 year. All the complications including secondary interventions and patency rates were noted.

Results: Total number of patients included in the study was 45. The mean fistula maturation time was 40 ± 10 days. The mean age of patient was 49.98 years and 57% of the patients were male. The mean basilic vein diameter was 3 mm. Fistula thrombosis was the most common complication seen in 15.5% cases followed by limb edema in 10% and surgical site infection in 2% of cases. 25% patient required repeat interventions (fistula thrombectomy, balloon angioplasty etc.). The primary patency rate and secondary patency rate at 1 year of follow up were 80.5% and 89%, respectively.

Conclusions: BVT is the most viable and feasible surgical option for patients having unsuitable veins or failed radio-cephalic/brachio-cephalic arteriovenous fistulae for maintenance haemodialysis.

PUB157
Paclitaxel-Coated Balloon Angioplasty for Stenosis of Access in Patients Under Hemodialysis
Joanis Grives.2,3 1Nephrology, 417 Army Share Fund Hospital, Athens, Greece; 2Helenic Open University, Athens, Greece.

Background: The recording of the experience of the use of paclitaxel-coated balloons in patients with End Stage Renal Disease under hemodialysis (HD) exhibiting narrowing in arteriovenous fistulae (AVF).

Methods: 11 patients with ultrasonographically confirmed AVF dysfunction were subjected to angiographic screening to prosthesis with a simple angioplasty balloon, and then a balloon drug gradually released the drug paclitaxel. After the damage was restored, arteriovenous communication was used immediately. The degree of vascular stenosis, blood flow to it and kt / V before and after recovery were assessed by ultrasound. At the same time, the clinical course of the patient and the vestibule of the vessel were monitored for 6 months.

Results: In the 11 patients in the study after the damage was recovered, AVF was immediately treated without any problems. After angioplasty the degree of stenosis of the responsible vessel was statistically significantly reduced from 69.28% to 32.14% (p <0.05). Flow volume increased statistically significantly from 621.43 mlis / min to 928.57 mlis / min (p <0.05). The kt / V of patients improved from 1.25 to 1.6. During the 6-month follow-up, the clinical course of the patients was stable, no problems related to vascular access occurred. Restenosis occurred only to a patient.

Conclusions: Drug-releasing balloons can be a useful therapeutic option for patients with AVF stenosis due to accelerated endothelial hyperplasia. The use of paclitaxel-coated balloons helps reduce the risk of restenosis of arteriovenous anastomoses and is a safe and immediate solution to AVF management.

PUB158
Rethinking Access for Dialysis in Older People: Proposed Study Design
Anamika Advaney,1 Neill D. Duncan,1 Edwina A. Brown,1 Damien Ashby.2 1Hammersmith Hospital, London, United Kingdom; 2Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, UK, London, United Kingdom.

Background: The arteriovenous fistula is widely regarded as the best long-term haemodialysis access, due to fewer complications and longer patency, whereas tunneled catheters have traditionally provided temporary access when emergency dialysis is required, or when a fistula has not been successful. However, the dialysis access landscape has changed with older and more comorbid patients making up a greater proportion. These patients have both poorer fistula outcomes and shorter life expectancy, and whilst fistula formation is still desirable it may be less tolerable. Catheters are increasingly advocated as a long-term access option for some older and more comorbid patients. We propose a pilot randomised controlled trial comparing a fistula to a tunneled dialysis catheter, which has never been carried out before, in older haemodialysis patients to determine the optimal study design.

Methods: By performing a pilot randomised controlled trial we aim to: 1. Establish the willingness of patients to participate and the protocol drop-out rates in the two treatment arms. 2. Determine the best methods to detect differences in quality of life between the two treatment arms. 3. Assess staff acceptability This study is an open label randomised controlled trial with a 12-month follow up period intended to answer key design issues. We will include patients aged over 70, with declining kidney function.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
and expecting to start haemodialysis within 6 to 12 months. Patients will be randomised in a 1:1 ratio to the catheter treatment group, the fistula group will be referred for fistula formation after randomisation and the catheter group will have a line inserted when dialysis is required. We aim to recruit 52 patients, 26 in each treatment arm, over an 8-month period.

Results: Patients will be followed for a minimum of 12 months. Data collection will be performed using electronic patient records and clinical correspondence.

Conclusions: The primary outcomes will be the willingness of patients to be randomised to either a fistula or a catheter and the study drop-out rate as defined in the fistula group as failure to achieve a fistula attempt within 3 months of randomisation. The secondary outcomes to be observed in this study include mortality, unplanned admissions, quality of life measurements and dialysis initiation.

A Multimodal Patient Education Approach to Catheter Care in a Hemodialysis Unit: Do It Daily
Miten Dhruve, Nephrology; Michael Garrison Hospital, Toronto, ON, Canada.

Background: Central venous catheters are the leading cause of mortality and morbidity in the dialysis population. Existing educational material is difficult to access and impractical to use for re-education. By collaborating with patient partners, we have developed novel and innovative Multi-modal patient educational materials, to improve patient knowledge, skills and confidence in catheter care.

Methods: Patients were administered a pre-education survey to collect their baseline knowledge, attitudes and skill levels. Educational materials were developed in liaison with patient partners. The materials were based on practice guidelines, and best practice recommendations. Educational materials included: two short videos, posters, easy to understand pamphlets, and fridge magnets using the catchphrase “Do it Daily”. Post education surveys were conducted to assess their knowledge and skill levels.

Results: Thirty-three patients completed baseline surveys, education program and post education surveys. There was no significant difference in Knowledge or Skill level pre- and post-education survey; however, there was a trend towards increase in patient confidence regarding catheter self-care. Eighty nine percent of patients found the educational material and training easy to understand.

Conclusions: Multi-modal catheter-care educational material did not demonstrate an improvement in knowledge or skill level but was found to be easy to understand. This educational material, which utilizes directed and simplified information, is focused, innovative, and easy to implement.

Performance of Machine Learning Model Deployed Within Multidisciplinary Care to Increase Optimal Dialysis Starts in Patients with Advanced Renal Function Loss
Ward M. Lee,1 Xiaoyan Wang,1 Kwan Y. Wu,2 Hong Desai,1,2 Jason Asano,1 Kenichi Okamoto,2 Hitoshi Oguchi,1 Chihiro Ando,1

Background: In The Rogosin Institute’s PEAK program, a multidisciplinary care team assists patients in making informed, optimal transitions to renal replacement therapy (RRT). The PEAK program educates patients about dialysis options and encourages home modalities and pre-emptive transplantation. In collaboration with a healthcare revenue learning company, a machine learning (ML) model was deployed to systematically identify patients at high-risk of renal failure in the next 6 months and recommend enrollment into the PEAK program. The industry-standard Kidney Failure Risk Equation (KFRE) predicts kidney failure in the next two years, while the ML model predicts progression to eGFR < 10 mL/min/1.73m2 in the next six months. We compare the ML model against the KFRE by contrasting their performance in the Rogosin population.

Methods: Using longitudinal data from the EHR we created an ML algorithm using lab and diagnosis based features and then retrospectively calculated both the KFRE score and ML score as of November 1st 2018. We excluded patients without a recent eGFR value, patients with eGFR < 10, and patients on dialysis.

Results: There were 824 patient records by the ML model and 644 scored by the KFRE. The patients whose KFRE score could not be calculated were given a KFRE score of 34. For the 44 patient outcomes, the ML model correctly identified 39 in the top quartile of risk, while the KFRE only identified 28 at the same threshold, a dramatic improvement in sensitivity 89% vs. 64%.

Conclusions: The deployed ML model achieves 40% better precision and sensitivity than the benchmark KFRE. This improvement illustrates that incorporating ML models into current clinical practice has great potential to benefit the highest risk patients. Allowing the clinical team to focus on providing patients more access to education, the most important aspect of informed decision making for RRT.

Funding: Commercial Support - pulseData

A New Idea for Longer Life of Arteriovenous Grafts Using Multidirectional Venous Outflow in Hemodialysis Patients
Manabu Asano,1 Kenichi Oguchi,2 Chihiro Kimikawa,1 Mimako Ando,1 Machiko Okamoto,2 Hitoshi Iwabuchi,1 Boesel Hospital, Saitama, Japan; 2Kegami General Hospital, Tokyo, Japan.

Background: Although a new device has been developed one after another, the status of arteriovenous graft (AVG) survival is far from satisfaction at this moment. As one solution to escape from sudden graft deaths, we have implanted a graft intentionally on an axillary vein having multiple branches. The aim of the present study was to prove that our method contributed to the long-term AVG survival.

Methods: Hemodialysis patients who had implanted AVG in upper limbs in our hospital from Feb 2015 to Mar 2019 were recruited. Tapered (4.6- or 4.7-mm in diameter) polytetrafluoroethylene grafts were used in all cases. Branches of the axillary vein were carefully prepared and reserved for second outflow channels as many as possible. The AVG anastomosis were fixed at the antecubital fossa. Prime AVG patency was defined as the time to first intervention, and secondary patency as the time to creation of a subsequent vascular access (VA). The Kaplan-Meier method was used to calculate for each.

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Funding: Commercial Support - pulseData

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Results: Forty-nine ipsilateral axillary AV operations were done in 42 patients. Mean age was 71 years, with 17 males and 25 females. The median hemodialysis duration was 104 months and the mean follow-up period after operations was 398 days. The average time until the first cannulation was 13 days. There were two early (<30 days) access thrombosis. Any other early accidents were not detected. Forty of the 49 grafts developed late (>30 days) complications: postanastomotic stenosis on the outflow vein in 24 grafts, graft occlusion in 12 grafts, central vein stenosis in 2 grafts, infection in 2 patients. There were radiological intervention in 36 cases and surgical intervention in 4 cases for graft salvage. The primary-secondary patency rate at 6, 12, 24 months were 39.8/39.9%, 14.2/32.5%, and 9.5/57.6% respectively. Angiography revealed that reserved venous branches had been working as a substitute for main drainage in some cases with occlusion or severe stenosis on just-anastomosis.

Conclusions: In order to avoid complete graft loss, our surgical procedure might be useful to extend the life of the axillary AVG. However, longer-term VA survival required the assistance of radiological and surgical interventional therapies in most cases.

PUB164
Decline in Renal Function-Slow with Fistu “Low”
Pran M. Kar. Department of Nephrology VA Medical Center Orlando, Orlando, FL.

Background: We would like to report a small study of 5 male patients with CKD who had undergone preemptive AV fistula placement in preparation for hemodialysis. Patients were subsequently followed for an extended period of time. Our study produced a previously little known advantage of AV fistula placement in slowing the rate of decline in renal function (1). Our finding suggests the possibility of a decline in the progression of eGFR in patients with AV fistula.

Methods: In our patients, we used the creatinine clearance plot with time after the patients had an AV fistula placed to determine whether the decline in renal function has slowed down and if there is any correlation with age. We studied 5 males who had AV graft establishment in anticipation for need for RRT at the time of placement of the vascular access.

Results: Based on our observation all our patients had a slower decline in their renal function.

Conclusions: Even though our sample size was very small and only male patients, we can establish a signal that the preemptive AV fistula placement in preparation for hemodialysis can slow down the decline in renal function. Underlying mechanism is not clear, but improved circulatory hemodynamics is plausible (2). Further studies with a larger more diverse patient population is needed to determine if early fistula creation can indeed delay the onset of renal replacement therapy in patients with advanced CKD. References (1)Kolopet, TA, Hartle PM, Bian A. Fistula creation may slow estimated glomerular filtration rate trajectory. Nephrol Dial Transplant 2015; 30: 2014–2018 (2)Korsheed S, Crowley LE, Flick RJ et al. Creation of a fistula associated with significant acute local and systemic changes in microvascular function. Nephron Clin Pract 2013; 123: 173–179

PUB165
Integrating Engineering Principles in a Medical School Nephrology Curriculum
Jean L. Holley,1,2 Hyunjoon Kong,1,4 Eliot Bethke,3 Kenneth R. Wilund,1,4 Jennifer Amos.1 1University of Illinois Urbana-Champaign, Urbana, IL; 2Internal Medicine, Carle Illinois College of Medicine, Urbana, IL; 3University of Illinois, Urbana, IL; 4Carle Illinois College of Medicine, Urbana, IL.

Background: Nephrologists are concerned about the failure to attract young investigators and clinicians. An innovative curriculum may enhance nephrology's appeal. An innovative curriculum may enhance nephrology's appeal. An innovative curriculum may enhance nephrology's appeal. An innovative curriculum may enhance nephrology's appeal. An innovative curriculum may enhance nephrology's appeal. An innovative curriculum may enhance nephrology's appeal.

Methods: Three course directors (a nephrologist, a basic scientist, and an engineer) developed the course. CICOM uses a problem-based curriculum (PBL) spanning 18 mo in which all traditional yr 1 and 2 medical school courses (with the addition of engineering and ethics/humanities) is covered. Five weekly quizzes and a comprehensive exam (n = 61 items) comprised of retired questions from Step 1 NBME exams were the evaluation tools. Six PBL cases, 1TBL (team-based learning on renal embryology), 3 engineering labs, 1 anatomy lab, and a patient interview (adolescent on CCPD) sessions were required. Optional sessions included: 3 physiology, 1 histopathology, 1 pathology, 1 clinical pathophysiology-laboratory, 7 short clinical case discussion sessions, and 1 journal club (tissue sodium). Clinical lecture topics were: U/A and kidney function*, urology, acid-base and K**, AKI*, disorders of Na*, measuring volume status, CKD*, GN*, stones, renal imaging, urinary tract infection, and renal nutrition (* indicates a session based on middle short clinical cases or topic also occurred).

Results: Student feedback was especially positive for the patient interview, short case discussions, the engineering lab on dialysis membranes, and the pathophysiology lectures which were attended by an average of 9-15/31 students. Class mean score on the comprehensive exam given after 7 mo of medical school was 74% with a mean of 77% by the NBME nationwide average (taken after 24 months of medical school). Class scaled score was 70 ±8 (SD).

Conclusions: Based on NBME scores, our students’ knowledge after a 5.5 month course was comparable to the nationwide score obtained after 2 yrs of medical school. Students were positive about opportunities for active learning. It is hoped that early clinical exposure to nephrology via active learning sessions and engineering labs will enhance interest in the field.

PUB166
Active Learning and Clinical Integration to Promote Knowledge and Interest in Nephrology
Jean L. Holley,1,2 Kenneth R. Wilund,1,4 Hyunjoon Kong,1 Eliot Bethke,3 Jennifer Amos.1 1University of Illinois Urbana-Champaign, Urbana, IL; 2Internal Medicine, Carle Illinois College of Medicine, Urbana, IL; 3University of Illinois, Urbana, IL; 4Carle Illinois College of Medicine, Urbana, IL.

Background: Innovative strategies are suggested to promote interest in nephrology. Educators are keen to active learning as a way to create interest and knowledge in the subject. The 2018 opening of a new medical school (Carle Illinois College of Medicine, CICOM) integrating engineering, technology, innovation, ethics and humanities with early clinical exposure prompted us to design a 5.5 week nephrology course incorporating multiple forms of active learning into an organ system based curriculum.

Methods: Three course directors (a nephrologist, a basic scientist, and an engineer) developed the course. CICOM uses a problem-based curriculum (PBL) spanning 18 mo in which all traditional yr 1 and 2 medical school courses (with the addition of engineering and ethics/humanities) is covered. Five weekly quizzes and a comprehensive exam (n = 61 items) comprised of retired questions from Step 1 NBME exams were the evaluation tools. Six PBL cases, 1TBL (team-based learning on renal embryology), 3 engineering labs, 1 anatomy lab, and a patient interview (adolescent on CCPD) sessions were required. Optional sessions included: 3 physiology, 1 histopathology, 1 pathology, 1 clinical pathophysiology-laboratory, 7 short clinical case discussion sessions, and 1 journal club (tissue sodium). Clinical lecture topics were: U/A and kidney function*, urology, acid-base and K**, AKI*, disorders of Na*, measuring volume status, CKD*, GN*, stones, renal imaging, urinary tract infection, and renal nutrition (* indicates a session based on middle short clinical cases or topic also occurred).

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Conclusions: Based on NBME scores, our students’ knowledge after a 5.5 month course was comparable to the nationwide score obtained after 2 yrs of medical school. Students were positive about opportunities for active learning. It is hoped that early clinical exposure to nephrology via active learning sessions and engineering labs will enhance interest in the field.

PUB167
Virtual Reality and Education: A Framework to Guide Development and Integration
Georges Nakhoul1, Jonathan J. Tallerico,2 Ali Mehdi,1 Remy Daou,1 John R. Sedor,2 Joseph V. Nally,1 John F. O’Toole,1, S. Beth Bierer,2 Wendy M. Green.1 1Cleveland Clinic Foundation, Cleveland, OH; 2Glickman Urological and Kidney Institute, Cleveland, OH; 3Cleveland Clinic, Mayfield Hts, OH; 4Saint Joseph University, Beirut, Lebanon; 5Cleveland State University, Cleveland, OH.

Background: Recent advances in technology have lead to the creation of innovative teaching tools such as immersive simulations. With funding from the American Society of Nephrology, we are building a Virtual Reality (VR) platform aimed at delivering renal physiology content to medical students, internal medicine residents, and nephrology fellow. The content will be adapted to the level of the learner. In order to guide our project, we elected to develop a framework that can serve as an example to other similar endeavors. Methods: We performed a literature review in order to determine the different factors that make a VR successfully developed and integrate an existing framework onto a VR platform. We then organized them into a guiding framework that we summarize below. Results: Our model is learner-centric and encourages the learner to contribute both to the development of the curriculum and to the testing of the VR platform. The curriculum stems from an identified need and is developed with the assistance of both the facilitator and the learner. The platform development requires technical support that can be offered by institutional departments such as bio-engineering and bio-illustration. The relation between the learner and the facilitator is collaborative. In our particular case, we elected
to use problem-based learning cases and grounded our instructional methods in andragogy and constructivism. This part can be adapted to the particular need of the program. The end-goal is to impact learner knowledge with the intention to lead to a change in learner behavior and ultimately patient outcomes (See figure 1).

**Conclusions:** We offer a framework to guide the development and integration of an educational curriculum into a Virtual Reality (VR) platform.

**Funding:** Private Foundation Support

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**PUB168**

**Can Twitter Help Shape the Future of Point-of-Care Ultrasoundography in Nephrology?**

Abhilash Koratla,1,2 Deepthi Bhattacharya,3 Amir Kazory,1 University of Texas Health, San Antonio, TX; 2University of Florida, Gainesville, FL; 3Reed Elsevier, San Antonio, TX.

**Background:** While there has been a renewed interest in the nephrologist-performed point of care ultrasound (POCUS), standard guidelines for its practice (e.g., identification of the enablers and barriers) are lacking. Social media play an ever-increasing role in contemporary medical education; they can be powerful tools for shaping the future of emerging skills such as POCUS. Twitter provides a unique platform to gather opinions of health care professionals (HCP) from various specialties and geographic locations. We sought to explore whether Twitter polls can be used as a needs assessment tool to enhance data on the practice of POCUS.

**Methods:** We composed a series of 12 Twitter polls over a 36-day period (consisting of up to 4 options) accessible for 3 days each. The pre-planned questions were tweeted on a regular basis from a single handle with over 1000 followers. All questions contained the hashtag #POCUS to increase their dissemination and obtain responses from the intended HCP. The distribution of the responses was stored and analyzed after completion of the study.

**Results:** The median number of responses per poll was 83. Sixty-three percent of respondents opined that attending live workshops is the best way to start learning POCUS, and 49% preferred a 1-week hands-on supervised program to acquire confidence in POCUS. The abridged version of the questions and responses is presented in the table below. The number of teams averaged 3 per case. We found that a disagreement between teams on how best to manage the patients’ primary nephropathy disorder often lead to a breakdown in ICS, PRO and SBP in all patients’ cases. The average teaching points per patient case was 2 for ICS & SBP and 1 for PRO. At the end, a consensus from all participating members created definitive PBLI guidelines for each patient’s case.

**Conclusions:** The use of a Healthcare Matrix format for Nephrology&MKM conferences creates significant learning opportunities for interdisciplinary discussions and for simultaneously teaching ICS, PRO and SBP not found in any other format for nephrology training.

**Summary of Core Competency Teaching Points Per Case**

<table>
<thead>
<tr>
<th>Domain</th>
<th>PC</th>
<th>MK</th>
<th>ICS</th>
<th>PRO</th>
<th>SBP</th>
<th>PBLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephropathology &amp; Imaging</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Renal ablation</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ESRD options</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clinical reasoning in ICS</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lupus nephritis therapy</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Dialysis withdrawal</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
</tr>
</tbody>
</table>

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**PUB169**

**A Healthcare Matrix Conference Enhances Nephrology Teaching of Interpersonal Communication, Professionalism, and Systems-Based Practice**

Gregory L. Braden,1 Amanda Duda,2 Daniel L. Landry,3 Reham Shaaban,2 Anthony E. Poindexter,1 University of Massachusetts Medical School-Baystate, Springfield, MA; 2Baystate Medical Center, Springfield, MA.

**Background:** A Healthcare Matrix was created to link the Institute of Medicine (IOM) aims assessment of patient care quality to the ACGME 6 core competencies (CC) of Patient Care (PC), Medical Knowledge (MK), Interpersonal and Communication Skills (ICS), Professionalism (PRO), Systems-Based Practice (SBP) and Practice Based Learning & Improvement (PBLI) (Jt Comm J Qual Patient Saf, 31:98, 2005).

**Methods:** Each patient case is evaluated in the presence of all patient care stakeholders, attendings, fellows and nurses. Using a spreadsheet, each CC is evaluated using IOM criteria as to whether the patient case is safe, timely, effective, efficient, equitable, & patient-centered. The average teaching points per patient case was 2 for ICS & SBP and 1 for PRO. At the end, a consensus from all participating members created definitive PBLI guidelines for each patient’s case.

**Conclusions:** The use of a Healthcare Matrix format for Nephrology&MKM conferences creates significant learning opportunities for interdisciplinary discussions and for simultaneously teaching ICS, PRO and SBP not found in any other format for nephrology training.

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<table>
<thead>
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<th>MK</th>
<th>ICS</th>
<th>PRO</th>
<th>SBP</th>
<th>PBLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy/HUS</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Renal ablation</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ESRD options</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clinical reasoning</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lupus nephritis therapy</td>
<td>3</td>
<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Dialysis withdrawal</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

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**PUB170**

**Continuing Education Improves Health Care Provider Knowledge and Competence in Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

Dana Ravyn,1 Beth Goodwin,2 Rob Lowney,1 Arlene B. Chapman.2 University of Chicago, Chicago, IL.

**Background:** Little is known about the familiarity, knowledge, and competence of nephrologists or other health care providers regarding management of patients with ADPKD. It is unclear what impact continuing education (CE) has on this topic.

**Methods:** Learners were invited to participate in a multimedia online certified CE activity launched in March 2018. Participants completed pre-activity and post-activity assessments. We measured commitment to change and confidence before and after the activity. Results were analyzed using the chi-square test and Cohen’s d.

**Results:** There were 3,799 participants, of whom 954 completed posttests. Twenty percent were physicians, 61% were nurses or physician assistants, and the remainder were other types of providers; the most common specialties were family medicine/initial medicine, nephrology, surgery, and critical care/emergency medicine. On completion, participants had increased confidence in achieving the aims of the learning objectives. Confidence in ADPKD-related practices increased after the activity, including overcoming barriers, translating evidence into care, and improving outcomes (Cohen’s d = 0.319-0.374).

Ten multiple-choice questions/vignettes evaluated learning in pathogenesis, genetics, imaging, diagnosis, and management. Educationally and statistically significant improvements (P<0.001) were seen for all questions. For all participants, the mean increase in score from pretest (n=1086) to posttest assessment (n=954) was 59.0% (SD=3.2; range 43-79); results for nephrology participants were not substantially different from others. Importantly, baseline scores were low in all participants and the nephrology group, suggesting suboptimal knowledge of ADPKD. Among nephrology and all participants, the mean baseline scores were 33.4% (SD=3.9) and 30.0% (SD=3.5), respectively, and the mean posttest scores for nephrology and all participants were 85.8% (SD=2.5) and 89.0% (SD=1.7), respectively.

**Conclusions:** A CE activity effectively improved confidence, knowledge, and competence among providers who diagnose and manage patients with ADPKD. Baseline scores were low for all participants, suggesting the need for further education and increased awareness of ADPKD, especially given the evolving role of risk assessment for disease progression and the availability of disease-modifying therapy.

**Funding:** Commercial Support - Otsuka America Pharmaceutical, Inc.
Analysis of the Official ASN Hashtag #KidneyWk: How It Has Changed
Hector M. Madariaga,1 Edgar V. Lerma,2 Tejas Desai.3 ‘Good Samaritan Medical Center, Brockton, MA; 3‘Associates in Nephrology, SC, Beryvn, IL; 1NOD Analytics, Charlotte, NC.

Background: The official hashtag of the ASN is #KidneyWk. Since its inception in 2011, #KidneyWk has been an efficient channel for conference communications and an easy tool to use among attendees using social media (#SoMe) as an education tool. It has been a great connection for people who are unable to attend the live meeting.

Methods: Searching the @nephondemand database for tweets composed during #KidneyWk from 2011-2018, including total number of people tweeting, gender, location and total number of tweets.

Results: Since 2011, the number of social media (#SoMe) nephrology educators using the official #KidneyWk, has grown exponentially. Cumulatively, a total 5,419 #SoMe educators have tweeted 48,851 tweets. Each year #KidneyWk breaks its own previous record. #SoMe educators from Latin America and South Asia have increasingly contributed to the online learning in the last few years. In 2017, ASN made a policy change allowing attendees to take pictures during presentations, increasing engagement among attendees. Additionally, this change increased the number of multimedia tweets, thereby increasing the information density of each tweet. Female #SoMe educators were early adopters of #KidneyWk, but have not reached gender parity since that time.

Conclusions: #KidneyWk has been extensively used by ASN members attending Kidney Week. Since its creation the #SoMe community has increased in activity and has provided valuable educational material for learners globally. The #KidneyWk community of learners and educators is a great way to connect nephrologists around the world.

Goal-Directed Protocol with Educational Approach Prolongs Continuous Renal Replacement Therapy (CRRT) Filter Life
Catherine C. Wells,1 Dylla Monga, Neville R. Dossabhoy. University of Mississippi Medical Center Division of Nephrology University of Mississippi Medical Center, Jackson, MS.

Background: One of the biggest challenges faced in CRRT is sustaining the continuous extracorporeal circuit for the duration of therapy, in order to deliver the prescribed dose. There are many ways to prevent premature loss of the CRRT circuit (i.e. clotting and clogging). Our center has defined a CRRT protocol to deliver optimal CRRT while preventing premature loss of the circuit.

Methods: We collect and analyze Quality Assessment and Performance Improvement (QAPI) data on all CRRT treatments performed with the Baxter PrismaFlex™ CRRT machine using Baxter TrueVue Analytics™ QAPI outcome measures include average filter life, reasons for early loss of filter and delivered CRRT dose. Average filter life (the running hours per filter for every filter used averaged per month) is reviewed as a trend. Beginning October 2017, we observed a negative trend in above indices and hence we changed our education strategy for teaching and adherence to our protocol. We historically provided general education for all medical providers and nurses (dialysis, ICU) on CRRT concepts and the institutional protocol, annually. Starting October 2017, the education frequency was increased (every 1 to 2 months). In addition, QAPI outcomes data were included in the education, and education was added to the EMR order sets in a format easily seen by ordering providers. Our last educational intervention was use of the new education-enhanced order sets in August 2018.

Results: In 2017, we had noticed negative trends in our monthly average filter life. In 2018, after our final intervention, and strict adherence to our protocol, our average filter life trends improved. The average filter life for the quarter before the first intervention (April-June 2017) was 38.3 hours/Filter. The average filter life for the quarter after the last intervention (October - December 2018) rose to 53.7 hours/Filter. Throughout the intervention, average delivered dose of CRRT was 24-26 mL/kg/hour.

Conclusions: Implementing an educational strategy in response to QAPI outcomes, using a goal directed approach, improved CRRT filter life. Close monitoring of data trends, adaptable action plans and frequent education are the key elements to a successful QAPI program.
Twitter performance metrics of nephrology conferences

Welsh Kidney Club: Trainee-Led Development of a National Online Renal Community

Background: Renal Training in Wales is conducted across a single deanery with a strong national identity, but wide geographic spread can restrict opportunities to collaborate and network, leading to practice variation across centers and a diminished sense of community amongst trainees, which may negatively impact our ability to recruit new nephrologists.

Methods: We sought to create a trainee-led e-resource to promote inclusivity and equity of access to all training materials via: A bespoke website - www.welshkidney.org - "WKC Quick Guides" - Bulletin-point guidance for daily encountered challenges (e.g. Management of Infection in Renal Transplant Recipients) and guidelines to encourage trainees to be involved in Quality Improvement projects - Videos of renal simulation scenarios and intervention procedures performed by trainees - Renal diary of upcoming abstract deadlines/events - Research profiles demonstrating the breadth of available opportunities and promoting collaborative research ventures

Facebook -Multidisciplinary “closed group” community where ideas and messages are shared and discussed. An international platform to showcase the work of the Welsh nephrology community and interact with the wider renal world. Formal evaluation of the above web resources was conducted via electronic survey 6 months following initial launch. Results: Google analytics showed ~600 unique visitors to the website. The Facebook group comprises members, with excellent multi-disciplinary team (MDT) and multi-centric representation. @Welshkidneyclub twitter page has 215 followers, inclusive of renal institutions, charities and patient groups. 82% of the 60 survey respondents from across the renal MDT rated the website “very useful”. Moreover, following a year with no new renal medicine applicants in Wales, four current junior doctors have expressed an interest in applying to nephrology training in Wales, 100% of whom have accessed the website to explore the opportunities presented.

Conclusions: The landscape of specialty training is rapidly evolving, with social networks increasingly accessed by trainees as channels for collaboration and learning. Using the tools presented here, we have empowered our MDT to establish the foundations of a national renal community, providing support to geographically isolated trainees. Outward presentation of a unified, inclusive training programme is essential to attract new trainees in the current global nephrology recruitment crisis.
Table 1. Results with Point-of-Service Ultrasound

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical Diagnosis</th>
<th>Ultrasonic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Nephrectomy with staghorn calix stones</td>
<td>No stones seen</td>
</tr>
<tr>
<td>B</td>
<td>Metabolic syndrome</td>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td>C</td>
<td>Metabolic syndrome</td>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td>D</td>
<td>Metabolic syndrome</td>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td>E</td>
<td>Tailed angle renal</td>
<td>Diffuse fatty infiltration of the liver</td>
</tr>
<tr>
<td>F</td>
<td>Metabolic syndrome</td>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td>G</td>
<td>Acute on chronic kidney failure</td>
<td>Renal failure</td>
</tr>
<tr>
<td>H</td>
<td>ESRD right; bilateral left</td>
<td>No evidence of hypertension</td>
</tr>
<tr>
<td>I</td>
<td>Metabolic syndrome</td>
<td>No significant findings; normal sized kidneys</td>
</tr>
<tr>
<td>J</td>
<td>Renal cyst</td>
<td>Large benign renal cyst</td>
</tr>
</tbody>
</table>

**PUB179**

Nephrology Education and the Use of Social Media Among Irish Nephrologists

Laura M. Slattery,1 Sinead Stoneman,1 Ted J. Fitzgerald,2 Matthew A. Sparks,3 Silvi Shah,4 Swapnil Hiremath,3 Sean F. Leavey,1 Catherine M. Brown,1 1University Hospital Waterford, Dublin 4, Ireland; 2Royal College of Physicians of Ireland, Waterford, Ireland; 3Duke University and Durham VA Medical Centers, Durham, NC; 4University of Cincinnati, Cincinnati, OH; 1University of Ottawa, Ottawa, ON, Canada.

**Background:** Recent advances in technology allow instantaneous access to online resources such as journal articles, social media (Facebook, Twitter), blogs, visual abstracts and videos. These can now be accessed by anyone with a desire to share information, learn, or to highlight recent advances in the field. The aim of this study was to evaluate the use of educational tools in the Irish nephrology community and the extent of the use and attitude towards social media as a learning modality.

**Methods:** We conducted an online survey of Irish nephrologists and nephrology fellows which was disseminated via e-mail with 25 questions. These included the delivery of teaching at institutional level, ranking of educational resources, use of Twitter to seek nephrology resources and the appeals and pitfalls of social media in education.

**Results:** The response rate was 60%. There were 52 respondents (28 female) 18 consultants, 20 SrPs/fellows on a training scheme and 5 in stand-alone posts. 36 were 40 years old, 52% used “UpToDate” and 90.4% accessed journal articles online. 45.2% ranked “UpToDate” as their top resource, 24% ranked Twitter as their top resource. 51% use handheld devices to access these resources and 98% accessed them from home. 77% have a Twitter account, and 60% use it as an educational resource. 33% of these respondents use Twitter daily. 91% were familiar with NephJC (33% have participated in reviewed NephJC) and 86% with NephMadness. 85% were attracted to these social media as an educational resource based on educational benefit, 78% on the basis of up to date information and 73% for the breadth of international opinion. In terms of pitfalls, 54% felt it is too easy to get lost in the volume of information, 48% cited concerns about confidentiality and 40% felt information was unreliable.

**Conclusions:** The utilisation of online resources and FAOMed among Irish nephrologists who responded to this survey is common. There is a high level of engagement with the use of social media, particularly Twitter, across all age groups. Future steps to improve engagement can be done with Irish NephJC through Twitter, engagement with the NSMC internship and the introduction of a “Staying Connected in Nephrology” installation at our national conference with a plan to re-survey respondents in the next year.

**PUB180**

Can Empathy Be Taught? Assessing Training Received in Chronic Renal Failure Diagnosis Delivery

Alice Doreille,1 Eve Vilaine,1 Xavier Belenfant,2 Ziadi Massy,1 Yousu Luque,1 Eric Rondeau,1 Dan Benhamou,1 Hélène François.3 1Assistance Publique - Hopitaux de Paris, Paris, France; 2CHU André Grégoire, Montreuil, France; 3CH Tenon, Paris, France.

**Background:** The announcement of chronic kidney disease has a major impact on patients. Yet, the delivery of this diagnosis is not formally taught or even discussed within our medical curriculum. To fill this training gap, we set up a training course of chronic renal failure diagnosis delivery for residents in 2016. In this study, we evaluate the impact of this training over the years.

**Methods:** We evaluated participants’ satisfaction in the training as well as the impact of the training on their clinical practice. A satisfaction questionnaire was submitted to all participants immediately after the training and in spring 2019. Self-questionnaires were used to assess participants’ empathy, based on the Jefferson scale of empathy (from 20 to 140) before the training and immediately after. During spring 2019, we submitted an online questionnaire to assess empathy levels in residents and senior nephrologists in the Paris area.

**Results:** 46 residents were trained over 6 sessions through role play. 52 residents of the Paris area filled out the empathy questionnaire online. Half of them had received the training 5 to 34 months before. The other half didn’t attend the training. 66 senior nephrologists with different types of practices took part in the study. 97% of respondents rated the formation as either essential or very useful for their clinical practice. 76% of respondents considered the training to have a long-lasting effect on their clinical practice. Empathy scores using the Jefferson scale were similar in untrained and pre-training residents. Post training, participants’ empathy score significantly improved and was sustained several months afterwards. Average empathy score for senior nephrologists was in between the untrained/pre-training residents and the post-training residents, with no significant difference.

**Conclusions:** Patient-centred care requires willingness to listen, empath and kindness. These skills are thought to be innate and instinctive, but they can be learned and should be taught within the medical curriculum. Role-play and simulation are easy and effective ways of teaching this. It helps participants take a step back from their day-to-day practice. Being invited to play the patient role may also help participants understand the patient’s position, pain and concerns.

**Funding:** Government Support - Non-U.S.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only**

**Underline represents presenting author.**

1120
trend in proportion of female moderators and speakers at ASN KW continues. Other opportunities to enhance gender equality should also be considered by the nephrology communities and societies.

Gender disparities during ASN-KW 2012-2019

<table>
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**PUB183**

Just in Time Teaching Tips (JITT Tips): A Tool to Efficiently Teach Learners and Team Members in the Clinical Setting

Valerie S. Barta,1 Maria V. DeVita,1 Alice Formari,1 Lenox Hill Hospital-Northwell Health System, New York, NY; 2Northwell Health, Manhasset, NY; 3Hofstra Northwell School of Medicine Lenox Hill Hospital, New York, NY.

**Background:** ACGME standards state that trainees must demonstrate communication skills that result in the effective exchange of information. It is imperative that training programs provide the proper tools to improve the learning environment for students who receive much of their instruction from resident/fellow supervisors who are themselves inexpert in teaching skills and conveying knowledge. Programs need to incorporate newer methods of teaching and communication to prepare trainees. Northwell Health GME leadership (NHGME) developed a new tool that provides a mechanism to electronically send content-specific clinical teaching tips just prior to educational opportunities. In a pilot study, NHGME collaborated with 7 required medical student clinical rotation leaders to develop relevant JITT infographics with evidence-based content and teaching cues. A series of 6 weekly JITT Tips were identified (generic and discipline specific) to be selected such that the JITT for a specific topic was not immediately after the educational opportunity. In the pilot study, NHGME collaborated with 7 required medical student clinical rotation leaders to develop relevant JITT infographics with evidence-based content and teaching cues. A series of 6 weekly JITT Tips were identified (generic and discipline specific) to be delivered to residents who engage with learners in the clinical environment via email or text. The targeted clinician educator received 1 JITT weekly in the early AM on a Monday for 6-8 weeks, at the start of the academic year and again at the 6-month mark.

**Methods:** Using this framework, the Division of Nephrology at Lenox Hill Hospital sought to create several renal focused JITT infographics. Renal faculty and fellows were assigned to the project. Fellows identified deficiencies in their knowledge, expertise and teaching skills, to guide initial discipline-specific topics to address with teachers and learners.

**Results:** Four topics were chosen that foremost reflect information that renal fellows should be able to teach to housestaff and medical students: acute kidney injury, acute glomerulonephritis, urinalysis and hyponatremia. Infographics templates were created for 6-8 weeks, at the start of the academic year and again at the 6-month mark. Text. The targeted clinician educator received 1 JITT weekly in the early AM on a Monday for 6-8 weeks, at the start of the academic year and again at the 6-month mark. A series of 6 weekly JITT Tips were identified (generic and discipline specific) to be delivered to residents who engage with learners in the clinical environment via email or text. The targeted clinician educator received 1 JITT weekly in the early AM on a Monday for 6-8 weeks, at the start of the academic year and again at the 6-month mark.

**Conclusions:** JITT provides an innovative way to reinforce positive teaching behaviors and enhance the learning environment. This electronic communication is an adaptive learning system and is invaluable in connecting with early career physicians (residents and faculty) and medical students. An added bonus is engaging nephrology fellows in medical education in professional development as a medical educator in academic programs.

**PUB184**

Live Visual Abstracts: A Novel Method of Disseminating Scientific Information Live from a Conference

Aakash Shingada,1 Arvind Conejorvaran,2 Kidney Associates, Mumbai, India; 2Bangalore Hospital, Bangalore, India.

**Background:** Medical conferences pack a large amount of information, which is consumed by the attendees, often predominantly from a local or national geographical area. While live-tweeting of information presented at a conference can help to disseminate the key messages, it often leads to significant clutter. Combining the idea of visual abstracts and live-tweeting led to the concept of ‘Live Visual Abstracting’. Live visual abstracts help disseminate scientific data from the conference in a concise, pictorial format.

**Methods:** The visual abstracts were created live, during the session and were tweeted out with the hashtag #LiveVisualAbstract. Over a period of 1 and half days, 7 live visual abstracts were created and tweeted out. The variables studied were (i) number of times the tweet was seen (impressions), (ii) Number of interactions received for each tweet (Engagements) which included (a) the number of times the tweet was shared (retweets), (b) No of replies/comments per tweet (c) number of interactions leading to profile visits. The results were compared with the most popular media tweets covering the session from the same handle to assess the impact of #LiveVisualAbstract.

**Results:** The tweets with #Livevisualabstract received significantly greater number of impressions with a median of 1820 (1059 - 7940) impressions compared to the most popular tweets from the same session - 891(241 - 1869), P < 0.013. The number of engagements [124 (86-339) vs 24 (9-56); P < 0.002], retweets [7 (5 - 14) vs 4 (0 - 5), p < 0.005], likes [21 (17 - 38) vs 7 (3 - 12), p < 0.002] and profile visits [3 (1 - 6) vs 1 (0 - 3), p < 0.002], were all significantly greater with #LiveVisualAbstract. The number of comments/replies did not differ between the two groups.

**Conclusions:** Our analysis shows that visual abstracts are promising tools of disseminating information not just for journal articles but also for conferences. This will help in minimizing clutter, spread information and potentially generate discussion which is the key to success of free online access to medical education (FOAMed).

**PUB185**

Healthcare Transition in a Medical School Curriculum: Navigating the Transition Process of Chronically Ill Youth to Adult Healthcare

Sherene Mason,1,2 Franklin T. Sylvester,1,3 Alexis Thompson,1,4 Anton M. Alerte,1 Connecticut Children’s Medical Center, New Haven, CT; 2University of Connecticut School of Medicine, Farmington, CT; 3Hasbro Children’s Hospital, Providence, RI; 4Warren Alpert Medical School of Brown University, Providence, RI; 5Barnes-Jewish Hospital, Washington University School of Medicine, New York, NY; 6Icahn School of Medicine, New York, NY.

**Background:** Increasingly pediatric patients with chronic conditions are surviving into adulthood. Successful transition from pediatric to adult healthcare reduces gaps and avoids poor health outcomes. Providers must attain the knowledge necessary to foster a successful process during their training. Within the undergraduate medical curriculum it is not apparent that any school has incorporated a non-discipline specific required healthcare transition course early into their curriculum particularly for early learners. We describe the implementation and evaluation of a healthcare transition course in our medical school curriculum.

**Methods:** A pre-course survey was distributed to 102 first-year medical students and 32 co-medical facilitators within the Delivery of Clinical Care course (DoCC). The survey assessed knowledge, attitudes and practice surrounding healthcare transition. Results were used to design a healthcare transition course within the Adolescent portion of DoCC utilizing videos, reading and in-class case discussions with collaborative group problem solving. A similar post-course survey was emailed to students. Pre-and post-survey responses were compared using a two-sample t-Test assuming unequal variances.

**Results:** Pre-course survey response rates were 86.5% and 78.8% for medical students and course facilitators, respectively. Most students (95.5%) report no prior experience with healthcare transition as compared with 53.8% of facilitators. Only 5.6% of students and 11.5% of facilitators were able to correctly answer a question regarding the age to begin the patient transition process as recommended by the American College of Physicians. This increased to 59.2% following the course. Students reported a more moderate level of comfort explaining (avg 3.43 on 1-5 scale, p < 0.005) and preparing patients for discharge (3.67 vs 3.51, p < 0.005); however, still not apparent that any school has incorporated a non-discipline specific required healthcare transition course early into their curriculum particularly for early learners. We describe the implementation and evaluation of a healthcare transition course in our medical school curriculum.

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**Conclusions:** The first-year medical student course on healthcare transition was well received by participating students. Early implementation of a healthcare transition course in undergraduate medical education can provide a pathway to mastering of the topic in clinical practice.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
**PUB186**

What Fellows Want: A First Survey of Nephrology Fellowship Training in Korea

Kyung Don You,1 Sejoong Kim,2 Ki Young Na.3 On behalf of Committee of the Training and Education, Korean Society of Nephrology at 2018 ‘Ulsan University Hospital, Ulsan, Republic of Korea; 2Seoul National University Bundang Hospital, Seongnam, Republic of Korea.

**Background:** The Korean Association of Internal Medicine (KAIM) introduced a shortening of the training period from the existing 4-year training system to a 3-year training program in 2017. In line with this, the demand for a full-time fellowship is expected to be different from that in the past in each sub-specialty. We, Korean Society of Nephrology (KSN), conducted a study surveying the full-time fellowship program for the first time.

**Methods:** From 2017 to 2018, physicians who were nephrology fellows were contacted. Through the cooperation of the KAIM, we secured an overall table of organization (T.O.) data in Korea. An anonymous questionnaire survey was conducted at each hospital without any compulsion.

**Results:** According to the data of the KAIM, specializing nephrologists showed modest growth from 47 to 58 people from 2007 to 2017. This was the third place, show 511 people in size subsequent to 1,849 people in majoring Gastroenterology & Hepatology, 563 people in Cardiology on 10 years from 2007. A total of 104 subjects were contacted and 93 questionnaires were obtained. There were 63 fellows in the first year (57.7%) and 24 in the second year (25.8%). Fifty-three (56.9%) were women, and 76% were married.

The fellows who were respondents were engaging in 4.02 month on nighttime duty per year, and the mean number of night calls was 8.8 ± 11.7 per month. The hemodialysis unit training rounds worked an average of 7.8 ± 4.3 months per year. In the academic training program, seventy-five percent of nephrology fellows attended a conference together with a pathologist, and 71% of the fellows attended medical grand rounds. However, intervention nephrology training was scarce in spite of the need in this area with a rate as low as 13%. After the fellow training, they preferred to work in the hemodialysis unit rather than an academic position (61/93). The most critical issue regarding work-life balance for fellows in their training period was associated with the night-time duty, and salary.

**Conclusions:** This study was the first nation-wide questionnaire survey, and 89% of the overall nephrology fellows replied. We expect that it can be used as baseline data for the improvement of quality in full-time nephrology fellow training.

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**PUB187**

Developing a Renal Fellow Curriculum in Telenephrology: Providing Nephrology Care to Underserved Rural Hospitals

Janice P Lea,1 Jason Cobb,2 Jose E. Navarrete,3 James L. Bailey,4 Tahsin Masud,1 Jerome S. Tannenbaum,1 Jeff M. Sands,1 Emory University1 'Emory University, Atlanta, GA; 2Emory University School of Medicine, Atlanta, GA; 3Sanderling Healthcare, LLC, Nashville, TN; 4Emory University Renal Division, Atlanta, GA.

**Background:** Telmedicine has recently permeated into the nephrology space allowing patients in rural underserved areas to receive nephrology care in their local hospitals without transfer to larger healthcare systems. Due to the national shortage of nephrologists and to declining interest in the pursuit of renal fellowships, there is a need to train future nephrologists in telemedicine to build capacity of the renal workforce.

**Methods:** Our academic nephrologists at Emory University have been providing telmedicine services to both ERSD and non-ERSD patients (pts) in 3 rural hospitals in South Georgia (128 unique pts with 525 pt encounters) for the last 2 years and now will incorporate telenephrology training into our renal fellowship in the fall of 2019. Renal fellows will be trained during the second year clerkship for a period of at least 3 months. Fellows will be expected to perform at least 15 patient encounters along with a telemedicine consultation. We currently average 25 encounters per month and thus have adequate volumes to reach this goal. Fellow competency will be evaluated after each rotation and feedback from fellows will be solicited in order to improve their training experience.

**Results:** Telenephrology curriculum will include fellow training on: 1) use of audio-video technology and electronic stethoscope to perform real-time history and physical exams remotely, 2) how to write hemodialysis (HD) orders and monitor dialysis sessions using non-traditional portable technology that supports electronic real-time data monitoring, 3) how to properly communicate and build rapport with referring physicians, and 4) develop and master process for remote urine microscopic examination using digital microscope adapters to electronically transmit images via secure web-based platforms.

**Conclusions:** The incorporation of a telenephrology curriculum into our renal fellowship program is innovative and will be a model for other training programs. Development of a method for remote urine microscopic examination will enhance the quality of telenephrology consultations. The expansion of telenephrology services to more rural areas will help to build future nephrology workforce capacity and may increase medical resident interest in nephrology.

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**PUB188**

Study on the Application of a Five-Star Teaching Model in Prevention and Control Health Education of Hemodialysis Patients with High Blood Phosphorus

Jin-mei Yin, J. The Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, China.

**Background:** Hyperphosphatemia is an independent risk factor for the mortality rate of patients with chronic kidney disease. The rate of blood phosphorus compliance in developed areas in China is only 37.6%, which is far lower than that of developed countries. Controlling hyperphosphatemia has become an important issue. The core idea of the Five-Star Teaching Method is that under the principle of “focusing on solving problems”, teaching should have the principle of continuously repeating the activation of original knowledge, demonstrating new knowledge, trying to apply exercises, and integrating and mastering four stages of circulation. This teaching method is considered to be high-quality, efficient teaching that meets the learning process and the psychological development requirements of learners. In recent years, the five-star teaching model has been applied to medical teaching and doctor-patient communication, and has achieved good evaluation.

**Methods:** With the aim of focusing on solving problems, the application repeats the activation of the original knowledge, demonstrates the new knowledge, attempts to apply the practice, and integrates the five-stage teaching mode of the four stages of the cycle to carry out up to 6 366 cases of maintenance hemodialysis patients in our district. Month’s prevention and control education on hyperphosphatemia, observing the changes in the knowledge of disease-related knowledge, social support, medication compliance and satisfaction before and after, and statistically at 3 months and 6 months after intervention. Pre-blood phosphorus levels change.

**Results:** After the intervention of the five-star teaching model, the degree of knowledge, social support, medication compliance and satisfaction of patients with disease-related knowledge increased significantly before intervention. At the same time, the pre-existing blood phosphorus level decreased gradually from 1.92±0.51mmol/l before intervention to 1.68±0.37mmol/l, and the phosphorus compliance rate increased from 43.3% to 54.9%. The difference was statistically significant.

**Conclusions:** Applying the five-star teaching mode to the phosphorus-controlled knowledge of hemodialysis patients can effectively reduce the blood phosphorus level and increase the phosphorus compliance rate.

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**PUB189**

Hemodialysis in Patients with Severe Metabolic Acidosis: Insights from a Physiology-Based Mathematical Model

Alhajj Cherfi,1 Vaiibhav Maheshwari,2 Stephan Thijssen,1 Peter Kotanko.1,2

1Renal Research Institute, New York, NY; 2Icahn School of Medicine at Mount Sinai, New York, NY.

**Background:** Maintenance of acid-base homeostasis is one of the fundamental kidney functions. In patients with severe acute metabolic acidosis (MA), daily acid load production and intake overwhelm compensatory secondary responses. Severe MA can manifest itself in a multitude of pathologies and result in increased morbidity and mortality. In this study, we have developed a physiology-based model of acid-base regulation in order to investigate the use of hemodialysis (HD) to correct severe MA.

**Methods:** Our dynamic model of the HCO3-/CO2 buffering system comprised Henderson-Hasselbalch mass-action kinetics, endogenous production of both CO2 and H+, loss due to non-bicarbonate buffering, ventilation, and renal regulation. Inducing several degrees of MA, we employed a dialyzer model to investigate the effectiveness of HD for correcting MA. Qualitative predictions of clinically observed post-HD acid-base status were demonstrated.

**Results:** We parameterized the model to induce severe MA steady-state conditions (pre-HD pH from 7.1-7.3) and showed the effect of different dialysate HCO3 concentrations (28-38 mEq/L) on the acid-base status correction. We observed that pre-HD HCO3 increased (up to 2.03-fold change from the pre-HD values) to values below Gibbs-Donnan-corrected dialysate HCO3- and pre-HD pCO2 and pH increased only by up to 1.036 and 1.041-fold, respectively, at the end of HD. In addition, with less severe pre-HD MA, the change in pH over the course of HD increased to between 0.4% and 1.95%.

**Conclusions:** Our model qualitatively predicted serum HCO3-, pCO2, and pH. Further clinical validations are needed to assess its predictive utility in clinical practice. Once validated, the model may be used to gain insights into the acid-base status and to individualize therapeutic interventions in patients with severe MA.

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Figure 1: Intradialytic acid-base dynamics in a patient with severe metabolic acidosis (dialysate HCO3- of 32 mEq/L)
Hyperkalemia in III Renal Patients from Lactated Ringer
Macaulay A. Onigbo, Medicine, The Robert Larner, M.D. College of Medicine, University of Vermont, Burlington, VT.

Introduction: Balanced crystalloid solutions are touted to be superior to 0.9% saline. Our recent experiences call for caution with LR in older patients with advanced renal failure.

Case Description: Patient #1: An 83- yo man developed AKI following coronary angioplasty and stenting requiring hemodialysis (HD). While on 3x/week HD, he developed hyperkalemia following 750cc bolus of LR. (Figure 1). Patient #2: A 70-year old male with a solitary functional left kidney developed AKI from an obstructing stone. This was relieved by a JJ stent. Despite 2 liters of brisk diuresis in one hour, he developed worsening hyperkalemia following 500cc of LR given in the OR (Figure 2).

Discussion: In the 2018 NEJM report on noncritically ill patients, the median baseline serum creatinine (MBSC) was 0.84 - 0.85 mg/dL in the balanced crystalloids and saline groups. Moreover, in the second NEJM report on critically ill patients, short MBSC, his 0.89 mg/dL in both groups. Therefore, patients with more advanced renal failure may not tolerate these solutions as well. Furthermore, the median age of the noncritically ill cohort was 55-54 years, whereas the median age of the critically ill cohort was 58 years. Clearly, without prejudice to the touted advantages of balanced crystalloids, we would continue to argue for a more patient-centered approach to individualized patient care. One size does not fit all.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
for rheumatologists (237, 50, 86 respectively). The number of AdRTA patients seen monthly was a relatively small percentage (approximately 1 in 100) of the overall number of patients seen by both specialists (see Figure). All nephrologists either agreed (20%) or strongly agreed (80%) with the statement “In patients with autoimmune conditions in which AdRTA is co-morbid, such as Sjogren’s and SLE, I take the lead in managing AdRTA” compared to 20% of rheumatologists who disagreed, 20% who agreed and 60% who strongly agreed. One-third of nephrologists and 70% of rheumatologists agreed that AdRTA is undiagnosed due to lack of knowledge and awareness in primary care [Figure].

**Conclusions:** Although patients with AdRTA are a small % of their patient caseloads, both nephrologists and rheumatologists have a role in managing AdRTA in patients with comorbid AI disease, with nephrologists more likely to consider themselves the lead physician than rheumatologists. The majority of physicians surveyed believe the AdRTA is undiagnosed due to lack of knowledge and awareness in primary care.

**Funding:** Commercial Support - Advicenne S.A.

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**PUB194**

The Temperature, Volume, and Calcium Concentration of the Water in the Lung Influences the Serum Calcium Concentration of a Drowned Person

Takahide Kimura,1 Seiki Yamada,1 Takeshi Yokoyama,1 Hiroyuki Shirai,1 Masayuki Tanemoto,1 Naoki Washida,2 *Nephrology, International University of Health and Welfare Atami Hospital, Atami, Japan; 2International University of Health and Welfare Medical School, Atami, Japan.

**Background:** Electrolyte concentrations of the solution getting into the lung will change the serum electrolyte concentrations of a drowned person. Serum calcium concentration (Ca) of drowned persons was analyzed according to places of drowning.

**Methods:** From September 2014 to March 2019, 22 persons were referred to our hospital because of drowning in hot spring. The Ca in them was compared with those of drowned persons in either the sea (n = 8) or house bathtubs (n = 5). Blood ionized calcium concentration (iCa) was also compared between the groups. In the persons drowned in hot spring, the volume of the water in the lung (Vw) was estimated by using images of computed tomography, and correlations of Ca and iCa with Vw were further examined.

**Results:** The sea-side hot spring water contained calcium of 36 mg/dL (9 mmol/L). In the drowned persons of the hot spring, the sea, and bathtubs, Ca was 13.04 ± 3.70, 10.29 ± 1.94 and 9.04 ± 1.24 mmol/L respectively (p = 0.037, p < 0.001), and iCa was 1.55 ± 0.48, 1.46 ± 0.25, and 1.21 ± 0.12 mmol/dL, respectively (p = 0.823, p = 0.047). In the hot-spring-drowned persons, Vw was 1253 ± 673 mL and its ratio to the whole lung volume (Vol-ratio) was 0.43 ± 0.19. The Vol-ratio correlated with iCa (r = 0.386, p = 0.47).

**Conclusions:** The Ca in the hot-spring-drowned persons was significantly higher than those in the sea-drowned and bathtub-drowned persons. It correlated with the relative volume of the hot-spring water in the lung. Since the calcium concentration of the hot spring water is slightly lower than that of the seawater, the temperature in addition to the volume and calcium concentration of the water in the lung could have influenced the amount of calcium absorbed from the lung into the serum.

**Funding:** Commercial Support - Advicenne S.A.

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**PUB195**

Referral Patterns for Patients with Acquired Distal Renal Tubular Acidosis (AdRTA)

Robbie McCarthy,1 Ludovic Robin,2 Kamyar Kalantar-Zadeh.1 *Rare Insights LLC, Ardmore, PA; 2Advicenne S.A., Paris, France; 3University of California Irvine, School of Medicine, Orange, CA.

**Background:** AdRTA, which is linked with Sjogren’s disease, systemic lupus erythematosus, primary biliary cirrhosis and autoimmune hepatitis, is often encountered by rheumatologists and nephrologists. To better understand key referral routes and issues for AdRTA patients a quantitative market research study was undertaken.

**Methods:** Between March 25th–April 15th, 2019, an online survey was conducted with 30 nephrologists and 20 rheumatologists in the USA on the subject of dRTA, with a focus on AdRTA. All screened respondents had direct clinical experience of AdRTA patients.

**Results:** Most AdRTA patient referrals to nephrologists (Nphs) and rheumatologists (Rhms) are from primary care (Nphs 60% and Rhms 61% - of total AdRTA referrals). Internal medicine accounted for 23% of AdRTA patient referrals to Nphs and 17% to Rhms. In the most recent 12 months, referral patterns were consistent with the most common routes of referral, but with more of an even split between primary care and internal medicine for both Nphs (38 vs 31%) and Rhms (38% vs 21%). Both specialists indicate around 0% referral rate from urologists, with very small numbers from other specialists considered potential referrers of AdRTA patients (inc. pediatric nephrology, dermatology, audiology and ophthalmology). Both Nphs and Rhms either Agree (33% vs. 30%) or Strongly agree (67% vs 70%) that AdRTA is underdiagnosed due to a lack of knowledge and awareness of the condition in primary care. Only 20% of the total number of referrals to nephrologists came from rheumatologists.

**Conclusions:** Most AdRTA patient referrals to rheumatologists and nephrologists are from primary care, with only small numbers of patients referred from other specialist physician types considered potential referrers due to known AdRTA co-morbidities. There is concern among nephrologists and rheumatologists that poor knowledge and education around AdRTA in primary care is lacking resulting in the potential for “Patient issues [to be] worsened because of late referral to nephrology”. The low percentage of referrals from Rhms to Nphs was surprisingly, potentially indicating that Rhms manage patients AdRTA without the involvement of nephrology.

**Funding:** Commercial Support - Advicenne S.A.

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**PUB196**

Stalking the Hypernatremia: A Case of Central Diabetes Insipidus due to Metastatic Small Cell Lung Cancer


**Introduction:** Symptoms from metastatic tumors in general are relatively rare, but when it involves the infundibular stalk, central diabetes insipidus (CDI) has remained the most common manifestation.

**Case Description:** A 70-year-old man with a 3-month history of small cell lung carcinoma, managed with Carboplatin, Etoposide, and Pegfilgrastim in an outside facility when diagnosed, transferred to our institution for Non-ST segment Elevation Myocardial Infarction. Initial labs showed hypernatremia of 146 mmol/L, urine specific gravity of 1.010, urine osmolality of 138 mOsm/Kg. As there were concerns for sepsis, he received 3 liters of normal saline that lead to the development of significant hypernatremia (156 mmol/L). His urine output was noted to be 12 L in the first 24 hours. On further questioning, he acknowledged feeling excessive thirst for the last 2 weeks. This was accompanied by polyuria and mild abdominal pain. Concern for possible carboplatin-induced partial nephrogenic diabetes insipidus (DI) vs central DI. With administration of 100 mcg desmopressin, urine output improved to 3 L and urine osmolality increased to 400. Upon holding desmopressin the next day, urine output again increased to 10 L accompanied by decrease in urine osmolality. This suggested Central DI. Magnetic Resonance Imaging (MRI) of the brain was done which showed diffuse innumerable subcentimeter punctate metastases throughout the brain including 1 cm metastatic lesion to the hypothalamus/infundibulum/floor of the third ventricle with loss of normal spontaneous T1 hyperintensity of posterior pituitary gland.

**Discussion:** In patients with DI and an intact thirst mechanism, hypernatremia developing due to increased extracellular fluid water and the lack of Antidiuretic Hormone (ADH). Metastasis to the pituitary stalk has been related to breast cancer as the primary source followed by lung cancer, prostate, and renal cell carcinoma respectively. At least 80% of vasopressin-synthesizing neurons must be destroyed before any clinical manifestations are evident. MRI remains the image diagnostic of choice for evaluation of the pituitary.

**Funding:** Commercial Support - Advicenne S.A.

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**PUB197**

Hippurate Clearance Provides a Measure of Renal Plasma Flow

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**Background:** Prior to the introduction of eGFR in 1999, glomerular filtration rate and renal plasma flow were assessed by measuring the plasma clearances of inulin and para-amino hippurate. As this required constant infusion, timed urine collection and a
specialized laboratory, these measures were not widely available. Data available from the few identified a number of clinical disorders in which the ratio of GFR to renal plasma flow (Filtration Fraction) varied considerably. Filtration fraction was known to vary considerably in different clinical states. With the introduction of eGFR, renal plasma flow is no longer measured and renal function is judged solely by eGFR. With the recognition that 24-hour urine collection was transported by OATs in the proximal tubule, we undertook studies to determine whether the clearance of haptoglobin would present a means of estimating renal plasma flow.

Methods: Studies were carried out in 5 subjects with hypertrophic cardiomyopathy under anesthesia and 10 subjects undergoing electrophysiological studies. Blood samples were obtained from the right renal vein and the IVC below the renal veins. A voided urine was collected 1-3 hours before blood sampling. Eight patients were receiving beta-blockers, two were receiving ACE inhibitors. Hapturre was measured utilizing a commercial kit from ICN

Results: Among the 15 subjects, extraction fraction hapturre (IVC-IVC) was 0.93 and 0.909 in two, from 0.739 to 0.58 in six. In the remaining seven subjects the findings suggested the RV catheter was not in the renal vein or the blood collected was an admixture of renal venous and IVC blood. The clearance ratio (UIP/Phapturre/UIP creatinine) was evaluated in 12 subjects, it ranged 0.80 from 0.739 to 0.64 and exceeded 4 in 5 of the subjects studied.

Conclusions: The renal clearance of hapturre exceeded creatinine clearance in all subjects studied. Hapturre/creatinine clearance ratios greater than 4 suggests that hapturre clearance makes a significant contribution to RPF. Rats below 0.65 may reflect reduced renal plasma flow in some of the patients, who were studied during emergency evaluation of either hypertrophic cardiomyopathy or cardiac arrhythmias. Reduced cardiac output or other medications may have reduced renal blood flow.

PUB198
Prevalence and Investigation into Community- and Hospital-Acquired Hypercalcemia
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Background: Hypercalcemia can be seen as a sign of hospital admission or may occur as a consequence of an admission. While workup and treatment protocols have been well-established, the prevalence of hypercalcemia and adherence to investigatory evaluation is largely unknown. We present data on the prevalence of hypercalcemia and seek to reclassify it in terms of community-acquired versus hospital-acquired hypercalcemia to further understand the nature and course of hypercalcemia.

Methods: We queried the enterprise EHR at 14 hospitals in a large integrated health system, for all admissions in 2018, with at least one serum calcium result greater than 10.5 mg/dL. We then defined two distinct patient cohorts: “community-acquired hypercalcemia” (CAH), where the first result is >10.5, and “hospital-acquired hypercalcemia” (HAH), where the initial result is normal and any subsequent result is >10.5. We performed data analysis on each cohort and assessed data on work-up of hypercalcemia.

Results: There were 202,109 admissions of which 2.2% of patients were admitted with hypercalcemia, and 0.6% of patients who developed at least 1 elevated calcium value during the hospitalization. Patients with CAH, had a mean age of 68 years (median 70 years). The mean length of stay was 170.2 hours with a median of 105 hours. Patients with HAH had a mean age of 68.5 years (median 70 years). The mean length of stay for these patients was 361 hours with a median of 241.6 hours. The mean time to development of HAH was 7.5 days with a median of 4 days. We found that 82.3% of patients with CAH and 78.5% of patients with HAH had no work-up (including 25-Vitamin D, 1,25-Vitamin D, PTHrP, and PTH). Fewer than 2% of patients in either group had all 4 laboratory investigations performed.

Conclusions: With our distinction of community-acquired versus hospital-acquired hypercalcemia we find that there is a stark difference in the length of stay of these patients (170.2 hrs vs. 360.9 hours). Furthermore, in both cohorts, most patients have incomplete work-up performed. The cause of hypercalcemia, a major quality gap. Additional work is required to better understand the etiologies of these distinct hypercalcemic groups (e.g. hypercalcemia of malignancy, hyperparathyroidism, drug-induced hypercalcemia, or hypercalcemia of immobilization) as well as their outcomes.

PUB199
Pseudohyponatremia Caused by Severe Hypercholesterolemia
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Introduction: Pseudohyponatremia is a well-known phenomenon. Most commonly it is secondary to hyperproteinemia or hypertriglyceridemia. We present a case of pseudohyponatremia that was secondary to severe hypercholesterolemia.

Case Description: A 60-year-old woman who suffered from iraconazole-induce hepatitis was noted to have a serum sodium (Na) of 119 mmol/L (normal 134-143 mmol/L). She was initially admitted to a community hospital where she was treated with intravenous fluids and then fluid restriction with no change in her Na concentration. Ultimately, she was referred to our tertiary center where further workup revealed an elevated serum osmolality gap of 56 mosm/kg (normal <10) with a mildly elevated serum osmolality of 307 mosm/kg (normal 278-305 mosm/kg). Serum glucose level was 131 mg/dL (normal 70-99 mg/dL). Total serum protein was low at 5.7 g/dL (normal 6.4-8.3 g/dL). It was noted that low serum albumin of 3.1 g/dL (normal 3.5-5.0 g/dL) ruled out the possibility of pseudohyponatremia secondary to hyperproteinemia. A lipid panel revealed elevated triglycerides at 350 mg/dL (normal <150 mg/dL). However, more surprisingly a cholesterol level of 2,730 mg/dL (normal <200 mg/dL). Serum Na measured using a blood gas analyzer was 139 mmol/L and thus the diagnosis of pseudohyponatremia was confirmed. Over the ensuing months, as her liver function improved, her cholesterol levels normalized and so did her Na levels on the chemistry panels.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Identification of Housekeeping Genes for MicroRNA Expression Analysis in Pkd1-Deficient Mouse Models

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Background: There are no reports of systematic validation of genes commonly used for normalization of micro RNA (miR) expression analyses in mouse models of autosomal dominant polycystic kidney disease (ADPKD). The aim of this study was to identify the most suitable housekeeping genes for RT-qPCR analyses of kidney tissues in Pkd1-deficient mouse models from eight currently used candidates.

Methods: Eight different control genes for microRNA (miR) studies were investigated in kidney tissues of Pkd1-deficient mouse models and their corresponding controls by RT-qPCR. All lines were generated and maintained on a C57BL/6 background. The expression of the candidate housekeeping genes (miR-20a, miR-23, miR-25, miR-126, miR-124, miR-138, miR-27a, and miR-127) was analyzed in the kidneys of 10-12-week-old cystic mice (Pkd1flox/flox/+/- and +/+ ) and 2 target genes (miR-21 and let-7a) was analyzed in the kidneys of 10-12-week-old cystic mice (Pkd1flox/flox/+/-, CY, n=10; Pkd1flox/flox/+/-, HT, n=6), wild-type controls (Pkd1+/+, WT, n=6) and 15-day-old severely cystic mice (Pkd1flox/-/-, SC, n=7) and wild-type controls (CO, n=5). The stability of the candidate genes was investigated using six software applications: NormFinder, GeNorm, BestKeeper, DataAssist, comparative ACT and RefFinder.

Results: As shown in the table below, our comprehensive analysis identified miR-20a as the most stable housekeeping gene, although the best one varied among the models. Our analyses revealed upregulation of miR-21 upregulation in SC and HT kidneys and trends of let-7a downregulation in CY and HT kidneys when expression was normalized to the best housekeeping gene miR-26a.

Conclusions: We have established the best housekeeping, miR-20a, for RT-qPCR analyses in kidney tissues of Pkd1-deficient mouse models.

Funding: Government Support - Non-U.S.

Best individual and combination of housekeeping miRNAs for each group of samples.

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PUB203

Pain in Autosomal Dominant Polycystic Kidney Disease: Results from the DRINK Randomised Phase 2 Trial

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Background: Pain affects 80% of the adult Autosomal Dominant Polycystic Kidney Disease (ADPKD) population. Despite being an early and debilitating symptom, mechanisms of ADPKD-related pain (ACP) are poorly understood. We designed and administered an ADPKD-specific pain questionnaire to participants in the ‘DRINK’ Phase 2 study of water intake in ADPKD (NCT02932628), where 42 pre dialysis adult ADPKD patients were randomised to either high water (n=21) or ad libitum water (n=21) intake over 8 weeks follow up.

Methods: ‘DRINK’ participants completed the bespoke pain questionnaire on paper or via smartphone application. The questionnaire explored key domains including pain severity, quality, interference, frequency and location. Analytic burden was also evaluated. Primary objectives were to describe the nature of ACP and develop a validated ADPKD-specific pain assessment tool.

Results: 39 participants completed 72 questionnaires during the study. 59% were Female, 90% White British with a mean(SD) age 47±13 years. 69% had enlarged kidneys (bipolar length 16.5cm), and median eGFR was 76 (47-111) ml/min/1.73m². 17% of respondents indicated pain frequency 0-1 times/week, 79% had pain 2-3 times/week and 4% had continuous pain. Pain severity was assessed using an 11-point numerical score further classified: 0-No pain, 1-3 Mild, 4-6 Moderate, >7 Severe. For overall pain, 36% had no pain, 38% had mild pain, 17% moderate pain, and 3% severe pain. In a multivariable regression model, pain severity was associated with increasing age, female gender, CKD stage 3 or worse and hypertension but not with kidney size.

Conclusions: In our cohort pain was common and severe. Despite the association between some markers of disease progression and pain severity, the poor correlation with kidney size suggests that there are mechanisms unrelated to renal anatomy that contribute to chronic pain in patients with ADPKD.

Funding: Government Support - Non-U.S.

Typical renal cystic structures of the enhanced CT image of the patient’s kidneys.

A

B

Figure: Predictors of overall pain severity (left), Frequency of pain severity categories (right).

PUB204

The Pathogenic AGT c.856+1G>T Mutation of a Patient with Multiple Renal Cysts and Hypertension

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Introduction: Angiotensinogen (AGT) is an essential member of the renin-angiotensin system (RAS), this system regulates blood pressure and affectphysiological function of the kidney. Here we report a 29-year-old male Chinese with essential hypertension and cystic kidney disease. Direct sequence analysis of the patient and his parents revealed a mutation in the splice donor site of intron 2 of the AGT gene, c.856+1G>T. This mutation was a heterozygous form and inherited from mother.

Conclusions: In this study, we reported a 29-year-old male Chinese with multiple renal cysts and hypertension. The AGT gene was found to have a heterozygous mutation in the splice donor site of the intron 2, which was inherited from mother.

Funding: Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
**AD(H)PKD: A Prospective Cohort Study on the Use of Tolvaptan in ADPKD**

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**Background:** The approval of tolvaptan as the first targeted therapy of autosomal-dominant polycystic kidney disease significantly changed treatment of this disease and the counselling of patients. But which patients are actually treated and how is the therapy managed and tolerated in the real-life setting?

**Methods:** To answer these questions, we initiated the ADH(P)KD registry which enrols ADPKD patients who present with the question whether tolvaptan would be a treatment option. The cohort contains data of patients on Tolvaptan and without targeted treatment. We collect information on a yearly basis including lab values, kidney volume, quality of life, adherence, genotype, extrarenal manifestations, comorbidity, side effects and complications.

**Results:** Since the start of the study at the end of 2015 until now more than 560 patients could be enrolled. Here, we present data on the first 500 patients. Of those, 54.4% (n=272) are female. Mean age at enrolment was 43.9±11.9 years (female: 44.1±12.1, male:43.7±11.6). While women were diagnosed with a mean age of 25.7±13.0 years, males learned about their disease at the age of 28.4±12.8 years. As expected, the majority of patients (87.6%; n=438) reported a positive family history with regard to ADPKD. In 83.4% of the cohort (n=417) arterial hypertension was diagnosed, 42.2% (n=211) experienced elevated blood pressure before the age of 35. Mean GFR at baseline visit (CKD-EPI) was 68±44 ml/min. Kidney function in females was more preserved than in males (72±53 ml/min, m: 64±28 ml/min). In 393 participants, renal volume could be calculated via radiologic imaging. In line with the more advanced loss of kidney function, height and total kidney volume was larger in male patients (htKTV, 187±54±3 ml/m²; m:1350±1168ml). 24.9% (n=98) of the cohort were classified as Mayo A or B, 75.1% (n=295) as Mayo class C to E.

**Conclusions:** The ADH(P)KD study continues successful enrolment and provides valuable data on patient characteristics, selection strategies for targeted treatment and tolerability of tolvaptan in a real-life setting.

We expect analyses concerning outcome parameters on tolvaptan treatment with a sufficient amount of 3 year follow up data in 2020. These results will be very useful for guiding treatment strategies and patient counselling in the future.

**Funding:** Commercial Support - Otaka

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**Elderly-Onset Rapidly Progressive Renal Dysfunction with Renal Enlargement and Medullary Cystic Kidney Disease (MCKD) Might Be A New Disease Entity of Ciliopathy Unlike Traditional Hereditary MCKD**

*Shinya Kawamoto,1 Hideo Misawa,1 Yoshihiko Ueda,2 Tetsuro Takeda.1

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**Introduction:** Recently there have been several reports of rapidly progressive renal dysfunction in elderly patients with renal enlargement and MCKD in Japan. Here we reported three cases who have undergone dialysis with rapid progression and performed analysis of gene panel for target sequence of inherited kidney disease. But neither mutation of known MUC1 or UMOD was detected.

**Case Description:** 1.84-year-old Japanese woman without family history of kidney diseases was noted to have renal dysfunction of unknown etiology 1 year prior to admission. She had developed progressive renal dysfunction (Cr 3.79±dl/L). Her abdominal CT revealed bilateral renal enlargement and histological findings revealed marked tubular dilatation with extensive fibrosis in the interstitium, consistent with MCKD. She was initiated dialysis 3 month after. 2.74-year-old woman was noted to have mild renal impairment (Cr 1.17±dl/L) 1 year prior to admission. She developed progressive renal dysfunction (Cr 3.6±dl/L). Her serial abdominal CT revealed no evidence of renal enlargement before admission and bilateral renal enlargement at admission. Her histological findings revealed consistent with MCKD. She was initiated dialysis 5 month after. 3. 80-year-old woman was noted to have renal dysfunction (Cr 1.9±dl/L) 1 year prior to admission. She had developed progressive renal dysfunction (Cr 3.3±dl/L). Her CT revealed bilateral renal enlargement and histological findings revealed consistent with MCKD. She developed progressive renal dysfunction just before disilation initiation 1 year after.

**Discussion:** We reviewed the literature on 16 subjects (thirteen similar cases reported in Japan since 2007 and our three cases). The age at renal biopsy was 70 years. Before renal biopsy, a rate of Cr elevation was 0.6 mg /dl /month, and renal biopsy was performed at 4.1 mg /dl of Cr. Urine protein were positive in all cases, urine occult blood was positive in 9 cases. Renal enlargement was observed in 13 cases. Renal biopsy findings showed minor glomerular changes and marked dilated renal tubules and interstitial fibrosis. After renal biopsy, 13 cases reached ESRD in 3.9 months. Target gene sequence of inherited kidney disease were performed in 6 cases, and neither mutation of MUC1 or UMOD was detected.

**Funding:** Commercial Support - Otaka

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**Comparative Effectiveness of Disease-Modifying Agents in Patients with ADPKD: A Systematic Review and Network Meta-Analysis**

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**Background:** ADPKD is the most common hereditary kidney disease with about 1:500 frequency, 100% penetrance and multisystem involvement. The purpose of this study is to explore the effectiveness and safety of disease-modifying agents for ADPKD.

**Methods:** We conducted searches on the MEDLINE, EMBASE and CINAHL databases from the inception to May 2019 for RCTs with a six-month-follow up. Teams of two reviewers, independently and in duplicate, screened titles and abstracts, extracted data, performed full-text reviews, and abstracted data. Eligible trials enrolled patients with ADPKD, randomized to receive rapamycin, everolimus, ocreotide, tolvaptan, standard care, or placebo, and reported effects on patient-important outcomes (e.g., all-cause mortality), total kidney volume (TKV), glomerular filtration rate (GFR), or medication-related adverse events. We excluded preclinical experiments, crossover trials, and conference proceedings. We performed network meta-analysis (NMA) and pooled treatment effects as mean differences (MD) and calculated 95% credible intervals (CrIs) using random-effects models. We applied the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to rate the quality of evidence.

**Results:** Our search yielded 635 citations, of which 11 met the inclusion criteria and involved a total of 7053 adults with ADPKD, including 2106 (56%) patients receiving treatments and 1597 (44%) receiving placebo and/or standard care. The random-effects models suggested rapamycin leads to a reduced change of TKV at 12 months (NMA MD, -436 [95% CrI, -639 to -212]). Twenty-five comparisons failed to reach statistical significance in the network estimates for the GFR outcome. Patients treated with rapamycin at high target dose had a higher likelihood of slowing of GFR decline as compared to those treated with other treatment categories.

**Conclusions:** Our results suggest that rapamycin reduced changes in TKV at 12 months and in high doses attenuated the GFR decline.

**Funding:** NIDDK Support

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**A Novel Genetic Model of Cystic Kidney Disease in the Mouse**

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**Background:** Polycystic kidney disease is the most common genetic cause of chronic kidney disease and end stage renal disease. While mutations in PKD1 and PKD2 cause most cases of autosomal dominant PKD, other genetic factors are thought to act as modifiers.

**Methods:** Using an ENU mutagenesis screen, we have identified a cystic kidney mutant that is transmitted in an autosomal dominant manner. We have characterized the mutation using both whole genome sequencing and RNA sequencing.

**Results:** Mice heterozygous for the trait develop glomerular and tubular cysts all along the nephron, but otherwise appear healthy. Mice that are homozygous for the trait develop hypoplastic, cystic kidneys, and are perinatally lethal with pulmonary hemorrhage. We have performed whole genome sequencing and identified potentially causative gene mutations on mouse chromosome 6. We have also performed RNA sequencing on kidneys from affected mice and matched controls and have identified significant changes in gene expression.

**Conclusions:** We present a novel mouse model of cystic kidney disease, which we have genetically and phenotypically characterized. We propose that the differentially regulated genetic elements that we have identified may represent genetic modifiers of cystic kidney disease.

**Funding:** NIDDK Support

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**Just a Sugar Pill: Trehalose in Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

*Daniel Atwood. University of Colorado Anschutz, Aurora, CO.

**Background:** ADPKD has been described as a case of suppressed autophagy. Trehalose (TRE) is a non-reducing disaccharide and FDA-approved food sweetener. Trehalose has demonstrated utility in vivo and in vitro as an autophagy inducer. The goal

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underlines represents presenting author.
of the present study was to test the interventional effects of TRE on cyst growth, kidney function, and autophagy-associated proteins in a hypomorphic PhlD \textsuperscript{PKD2/2} mouse model of ADPKD.

**Methods:** Wildtype (WT) and PhlD \textsuperscript{PKD2/2} (PKD) mice were treated with either tap water (VEH) or 2% TRE for 50-120 days of age. Water intake was recorded as it is known to affect cyst burden. Autophagy-associated proteins were measured in kidney homogenates by immunoblot: pBeclin1 (Ser15) (marker of initial steps of autophagosome formation), ATG12/5 complex (lipidates and inserts LC3C into autophagosome membrane), LC3-II (marker of autophagosomes) and Ras-related protein 9a (Rab9a) (marker of late steps of autophagosome maturation). Statistical analysis was performed on relative densitometry units (RDU) obtained from immunoblots (Table).

**Results:** See Table. TRE, that is slightly sweet, did not affect water intake, nor did it change serum arginine vasopressin (AVP) or serum copeptin levels, which are sensitive to water intake. LC3-II was increased by TRE in WT but not PKD kidneys. Rab9a was decreased in PKD kidneys and not affected by TRE. pBeclin1 was increased in PKD kidneys and restored by TRE. ATG12/5 complex was decreased in PKD kidneys and not affected by TRE. TRE did not reduce cyst number or two kidney weight (2KW) to body weight (BW) ratios or improve kidney function in PKD vs. WT.

**Conclusions:** The most striking finding was suppressed ATG12/5 complex and decreased Rab9a suggesting defects in LC3C lipidation and insertion into autophagosome and autophagosome maturation, respectively, in PhlD \textsuperscript{PKD2/2} mice. These defects were not rescued by TRE. TRE did not reduce cyst burden or improve kidney function.

**Funding:** Veterans Affairs Support, Other U.S. Government Support

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**PUB210**

**Autosomal Dominant Polycystic Kidney Disease (ADPKD): Optimization of the Evaluation of Total Kidney Volume**

Roberta Fenoglio,1 Savino Sciascia,2 Dario Roccaccia,1 1Nephrology and Dialysis Unit and Center of Research of Immunopathology and Rare Diseases (CMID), Giovanni Bosco Hospital and University of Turin, Italy. Center of Research of Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Ita, Turin, Italy; 2Nephrology and Dialysis Unit and Center of Research of Immunopathology and Rare Diseases (CMID), Giovanni Bosco Hospital and University of Turin, Italy. Center of Research of Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Ita, Turin, Italy.

**Background:** Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common inherited renal disorder. It is characterized by progressive development of renal cysts and increase in total kidney volume (TKV). TKV is a critical requisite to initiate tolvaptan therapy. Patients (pts) must have a TKV >750 ml to be eligible to treatment. To date, the gold standard for the radiological technique to measure TKV remains undefined. Aim: Comparison between currently available radiological techniques to measure TKV evaluated for tolvaptan therapy focusing on precision in TKV measuring, reproducibility, and costs of the radiological technique. Patients selection: Patient with a diagnosis of ADPKD, with Genetic positivity or Familiar history of ADPKD and ultrasound evaluation.

**Methods:** Thirty-nine patients were screened for potential therapy with tolvaptan (range of age 18-49 yrs). Twenty-nine patients were excluded because of either e-GFR values of >90 ml/min (18 pts) or e-GFR values <40 ml/min (4 pts), refusal of treatment (3 pts), linguistic problems (2 pts), liver disease (1 pt) or currently breast feeding. Ten patients (6 female mean age: 38 years, mean creatinine value 1.3mg/dl, mean e-GFR 63 ml/min) were enrolled and were examined by Magnetic Resonance Imaging (MRI), Ultrasound, and Computer Tomography (CT). TKV values were measured using the ellipsoid formula applied in each technique. It was a combination of manual evaluation in the case of MRI and CT. The values were compared by linear regression analysis and Altman-Plot graphs. Results: As compared to MRI and ultrasound, especially at the higher TKV values, gave over-estimated TKV values, MRI and CT showed comparable accuracy and reproducibility, especially when data were manually processed (R2=0.99).

**Conclusions:** Ultrasound proved to be not as reliable as MRI or CT when measuring TKV. Patients age, comorbidities, availability of instrumentations and costs may influence the choice between MRI and CT, which appear to be comparable effective in TKV evaluation.

**PUB211**

**Vaptans, New-Generation Diuretics, Exert Their Aquaretic Effect Through Inhibition of Aquaporin 2 Trafficking in Renal Collecting Duct Cells**

Annaria Di Mise,1 Maria Venneri,2 Marianna Ranieri,1 Mariangela Centrone,1 Lorenzo Pellegrini,2 Grazia Tamma,1 Giovanna Valentì.11University of Bari, Bari, Italy; 2Palladio Biosciences, Newtown, PA.

**Background:** Selective vasopressin V2 receptor (V2R) antagonists (vaptans) are a new generation of diuretics. Compared with classical diuretics, vaptans promote the excretion of retained body water in disorders where plasma vasopressin concentrations are inappropriately high for any given plasma osmolality. Under these conditions an aquaretic drug would be preferable over a conventional diuretic. The clinical efficacy of vaptans is in principle due to impaired vasopressin-regulated water reabsorption via the water channel aquaporin-2 (AQP2). Methods: Here, the effect of lixivaptan - a novel selective V2R antagonist - on the vasopressin-cAMP/PKA signaling cascade was investigated in mouse renal collecting duct cells expressing AQP2 (MCD4) and the human V2R. Compared to tolvaptan - a selective V2R antagonist indicated for the treatment of clinically significant hypervolemic and euvoletic hyponatremia -, lixivaptan has been predicted to be less likely to cause liver injury.

**Results:** In MCD4 cells, immunofluorescene localization of AQP2 and analysis by confocal microscopy showed that clinically-relevant concentrations of lixivaptan (100nM for 1h) prevented dDAVP-induced AQP2 phosphorylation at ser-256 and AQP2 translocation to the plasma membrane. Consistent with this finding, real-time fluorescence kinetic measurements demonstrated that lixivaptan prevented dDAVP-induced increase in osmotic water permeability.

**Conclusions:** These data represent the first detailed demonstration of the central role of AQP2 blockade in the aquaretic effect of lixivaptan and suggest that lixivaptan has the potential to become a safe and effective therapy for the treatment of disorders characterized by high plasma vasopressin concentrations and water retention.

**Funding:** Commercial Support - Palladio Biosciences, Inc., Government Support - Non-U.S.

**PUB212**

**Medullary Sponge Kidney with Recurrent Nephrolithiasis: A Genetic Disease?**

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**Introduction:** Medullary Sponge Kidney (MSK) is a malformation with tubular dilatation of the collecting ducts and cystic dilatation of the medullary pyramids of the kidney. This can manifest as nephrocalcinosis, nephrolithiasis, renal tubular acidification and acidosis, recurrent kidney stones. The patient had undergone three extra corporeal shock wave lithotripsy (ESWL) procedures and numerous other urological procedures with stone placement for calcium oxalate and calcium phosphate stones. An ultrasound study done of the kidney showed images with uniform distribution of multiple stones, with distortion of the medullary and papillar portions of the collecting ducts, suggestive of medullary sponge kidney. 24 hour urine studies were suggestive of hypercalcuria and hypocitraturia. Renal function remains normal, with no proteinuria or hematuria. Patient was encouraged a high fluid intake and normal calcium and low sodium diet. Thiazide was started with decrease in 24 hour calcium excretion.

**Discussion:** MSK is now thought to be a developmental disorder related to issues arising during renal morphogenesis. Problems with concomitant urticar bad and metanephric blastemal due to abnormal signaling of glial cell line derived neurotrophic factor (GDNF) and its receptor RET is speculated to play a role. Usually sporadic and asymptomatic, it can manifests in familial clusters. recurrent calcium nephrolithiasis and nephrocalcinosis are prominent features with hypercalcuria seen in almost 100% of MSK patients. Distal acidification defect seems to be a major player in pathogenesis. The clinical course varies from silent to indolent, to rarely progression of nephrocalcinosis. ESRD is seen in less than 10% of MSK patients. Diagnosis is radiographic with traditionally urography being the gold standard. Now Ultrasound, uro CT and MR urography are being used for diagnosis. Though there is no treatment for MSK, prophylactic therapy for stone prevention is crucial. Screening of family members should be considered as part of history taking.

**PUB223**

**Association Between VDR Gene FokI Polymorphism and Renal Function in Patients with IgA Nephropathy**

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**Background:** To investigate the association between VDR gene FokI rs2282570 polymorphism IgA nephropathy (IgAN) and IgAN renal function and related clinical and pathological parameters, and to seek the genetic susceptibility genes for patients with renal dysfunction in IgAN.

**Results:** Clinical and pathological data of 282 IgAN patients treated at the First Affiliated Hospital of Guangxi Medical University were collected, and FokI genotypes

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were determined by PCR and direct sequencing. Patients were divided into the renal dysfunction group and normal renal function (control) group by estimated glomerular filtration rate (eGFR) and serum creatinine level.

Results: Among 282 patients with IgAN, 55.32% of patients had renal dysfunction (156/282). Frequencies of TT genotype and T allele in the renal dysfunction group were higher than those of the control group. Blood urea nitrogen, serum phosphorus (P), proportions of mesangial cell proliferation, interstitial fibrosis/tubular atrophy and crescents in T allele carriers were higher than those in non-T allele carriers, while eGFR and 25-Hydroxyvitamin D3 were lower in T allele carriers than non-T allele carriers. Multiple linear regression analysis showed that eGFR was affected by FokI genotypes in IgAN patients. Logistics regression analysis showed that middle and elderly age, elevated P, intact parathyroid hormone and TT genotype were independent risk factors for renal dysfunction in IgAN patients; the odds ratio of carrying the TT genotype was as high as 84.77 (P<0.05 for all).

Conclusions: Patients of IgAN carrying VDR FokI TT genotype have an increased risk of renal dysfunction. VDR FokI is closely related to renal function, calcium-phosphate metabolism and related pathological damage in IgAN patients.

**PUB214**

**Tissue Is the Issue: When a Second Biopsy Reveals the True Diagnosis**

Anne Marie Bogarett, Nephrology, AZ Sint-Elisabeth, Zottegem, Belgium.

**Introduction:** We describe the case of a woman 41-years old, followed at our outpatient clinic with stable microscopic haematuria and mild proteinuria since 10 years. Underlying diagnosis of minimal glomerular changes was made after initial kidney biopsy. Case Description: After several years of stable clinical and biochemical follow-up, progressive proteinuria was present since the end of 2017, upon nephrotic range of 3,5g/24h. Therefore a new kidney biopsy was planned, revealing focal segmental glomerulosclerosis (FSGS). Further differentiation by electron microscopy (EM) suggested an underlying genetic disorder. Next generation DNA sequencing was performed and showed that the patient was heterozygous for a pathogenic mutation in the COL4A3 gene. This disorder shows considerable heterogeneity and is in our patient associated with late onset of FSGS that developed on top of the basement membrane nephrapathy. Establishing a genetic cause of disease in this patient avoids exposure to immunosuppressive regimens, used to treat primary FSGS, as such treatment is ineffective in genetic FSGS and may pose considerably toxicity.

**Discussion:** By this case we want to stress the importance of re-biopsy when there is non-explained substantial increase in proteinuria on long term follow-up. Furthermore EM can be helpful for further differentiation and treatment decision. Genetic testing in all patients with adult onset FSGS that cannot be regularly categorized by clinic-pathologic assessment should be considered. Establishing a genetic cause of disease in this patient avoids exposure to immunosuppressive regimens, used to treat primary FSGS, as such treatment is ineffective in genetic FSGS and may pose considerably toxicity.

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**PUB215**

**Renal Functional Reserve Capacity Through Acute Protein Load in Patients with Gitelman Syndrome**

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**Background:** Gitelman syndrome (GS) is a recessively inherited salt-losing tubulopathy caused by the disorder of sodium-chloride co-transporter (NCC). This pilot study aims to evaluate the renal functional reserve (RFR) in GS patients by acute protein load, and to figure out the effect of connecting tubule glomerular feedback (CTGF) secondary to NCC dysfunction.

**Methods:** We recruited 19 healthy controls and 4 GS patients, diagnosed by clinical examination and genotyping. Serum and urine were collected before and after oral protein load (1.2g/kg of body weight) at different timepoints (-1h, 0h, 1h, 2h, 3h and 4h). RFR was evaluated by eGFR changes, based on creatinine and serum cystatin C clearance. The urinary metabolite of prostaglandin E2 (PGEM), the signaling molecule of CTGF metabolism, was tested by ELISA through the process.

**Results:** The average age of healthy control group was 27±2.9 yr and 47.7% were male. Their baseline creatinine clearance was 140.9±31.5 ml/min/1.73m² and a significant difference between stress and basal creatinine clearance (p=0.001) was observed, with a mean RFR of 32.8±20.8 ml/min/1.73m². In GS patients with an average age of 27.0±7.0 yr and 50% male, both the baseline creatinine clearance and RFR showed no significant difference between the patients and controls (p=0.091), neither in cystatin C clearance. A good agreement between the creatinine clearance and cystatin C-based GFR was found by Bland-Altman plots. Higher level of urinary PGEM in GS patients than that of controls was observed. After protein load, the urinary PGEM levels were increased in both groups.

**Conclusions:** GS patients had normal RFR stimulated by acute protein load. It might be associated with the activating of CTGF, afferent arteriolar vasodilation and increased blood flow and GFR.

**PUB216**

**Enzyme Replacement Therapy and Fabry Nephropathy**

Ana Paula Gueiros, Jose E. Gueiros, Andréa D. Santos, Natália S. Antunes, Ana cecilia M. Siqueira, CETREIM, Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil.

**Introduction:** In Fabry nephropathy (FN), alpha-galactosidase deficiency leads to accumulation of glycosphingolipids in all kidney cells type, proteinuria and progressive loss of kidney function. The aim of this study was to assess the clinical course of FN in two women with pathogenic mutations undergoing treatment with agalsidase beta (Fabrazyme®; Sanofi Genzyme, Cambridge, MA, USA) during a 6-year period.

**Case Description:** Case 1 – AMSL, aged 61. Symptoms first appeared when the patient was aged 51, when she complained of myalgia, arthralgia, asthenia, dyspnea on exertion, tinnitus, abdominal pain and constipation. One year later, she was diagnosed with proteinuria and heart disease. She performed a kidney biopsy, which under light microscopy suggested deposit disease. No electron microscopy was performed. Genetic analysis demonstrated a mutation in exon 5 – p.K237X. At the time, she presented with creatinine (C) of 0.9 mg/dL and proteinuria of 1.2 g/day and an echocardiogram with a left ventricular mass (LV) of 392 g and LV mass index 238 g/m². In January 2012, she initiated enzyme replacement therapy (ERT) with agalsidase beta, 1.0 mg/Kg body weight once every 2 weeks, and conversion enzyme inhibitor. Currently, Cr is 1.0 mg/dL and proteinuria 0.3 g/day. During the follow-up period, there were no major cardiovascular
and/or central nervous system events. **Case 2** - DBCT, aged 60. The patient was diagnosed with type 2 diabetes mellitus and was aged 13. Twelve years ago, she presented clinical signs of hypohydrosis, arthralgia, bradycardia and proteinuria. Genotyping revealed a C142R mutation. In 2012, after presenting a transient ischemic attack, she was commenced on ERT with agalsidase beta (1.0 mg/kg once every 2 weeks). At the time, she presented Cr 0.8 mg/dl and proteinuria 0.3 g/day. During the follow-up period, she presented three episodes of atrial fibrillation, which motivated treatment with propafenone and rivaroxaban. Currently, Cr is 0.8 mg/dl and proteinuria 0.17 g/day.

**Discussion:** This 6-year study has documented the effectiveness of agalsidase beta in patients with FN, despite delayed initiation of ERT.

**PUB217**

**Mechanism of Mutation of AarF Domain-Containing-Kinase 4 (ADCK4)**

**Gliderulopathy**

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**Background:** AarF domain-containing-kinase 4 (ADCK4) is a mitochondrial resident protein kinase belonging to the Ubil protein kinase family. Comprised of a single N-terminal transmembrane helix and C-terminal kinase domain, ADCK4 is thought to facilitate the ATP dependent biosynthesis of coenzyme Q10 (CoQ10). Mutations in ADCK4, an inherited mitochondrial nephropathy, result in defects in CoQ10 production as well as in activities involved in mitochondrial respiration, manifesting as early-onset proteinuria, focal segmental glomerulosclerosis/nephrotic syndrome, followed by end-stage renal disease (ESRD). The regulation of ADCK4 in CoQ10 biosynthesis is not well understood, necessitating biochemical and structural investigations into its functions. Furthermore, characterizing function of ADCK4 can help to discover therapeutic function for this type of glomerulopathy/nephrotic syndrome. This work started with genetic analysis of an 18-year-old female who presented with proteinuria at age of 5 years and developed ESRD at 20 years of age. Her family was noted with proteinuria and structural anomalies of kidney.

**Methods:** Genetic analysis using whole exome sequencing for a family with proteinuria and structural anomalies of kidney and urinary tract revealed a novel compound heterozygous mutation in the ADCK4. We generated a computational model to understand the mechanism of action of 2 novel identified mutations: I346S in the C-lobe of the ADCK4 kinase domain, and a termination at W520 that leads to the truncation of the C-terminal a5 helix.

**Results:** The alterations of ADCK4 c.1560G>A and c.1037T>G are novel mutations. Our computational model suggests potential mechanisms for alterations in protein function through either destabilization of important allosteric interactions necessary for kinase activation and/or conformational changes that facilitate enzyme activity.

**Conclusions:** ADCK4 is promising therapeutic targets for patients with ADCK4 glomerulopathy that need a rigorous biochemical characterization. ADCK4 protein is not well characterized at biochemical level. Computational model to understand the mechanism of mutation suggests potential mechanisms for alterations in protein function destabilization of important allosteric interactions and/or conformational changes that facilitate enzyme activity. Ongoing work to reveal the biochemical and functional analysis of ADCK4 protein.

**PUB219**

**Hyponatremia in Elderly Patients with CKD Stages 3-5**


**Background:** Elderly patients with chronic kidney disease (CKD) are at high risk to develop hyponatremia, which is associated with an increased risk of all-cause mortality. Our aim was to identify the frequency of hyponatremia and the associations with clinical-biochemical parameters in elderly patients with CKD stages 3-5.

**Methods:** We performed a retrospective observational study on 125 patients out of the 1739 hospitalized between 2015 and 2017 in our center. Inclusion criteria were: age ≥65 years, CKD stages 3-5 (not on dialysis). Volume status was measured by spectrophotometric hemoglobin, hematocrit, and serum urea.

**Results:** The frequency of dysnatremia was 54.4%, including 50.4% hyponatremia and 4% hypernatremia. Regarding hyponatremia severity, 39 patients had mild, 15 moderate and 9 severe expression. Mean age was 73.6±6.5 years, 60% of patients had CKD stages 4-5 and the most frequent causes of CKD were hypertensive (31.2%) and diabetic nephropathy (30.4%). Mean BMI was 25.9±6.0 kg/m², 89.6% of patients were hypertensive, 41.6% diabetic, 37.6% had cardiac heart failure, 28.8% atrial fibrillation (AF), 40.8% ischemic heart disease (IHD), 14.4% peripheral artery disease, 16% history of stroke. Mean sodium was 134±6.4 mmol/L, median overhydration status was 1L (-0.2L - 2.65) and 67.2% were diuretic users. Moderate and severe neurological symptoms were found in 12 and 6 patients, respectively. Patients with hyponatremia had more often AF (31.7% vs 25.8%), history of stroke (19% vs 12.9%), decreased levels of urea (85 vs 116 mg/dl) and no difference of eGFR. Moreover, there was a significantly increased proportion of diuretic use (58.7% vs 75.8%, p=0.04), especially for loop diuretics (45.2% vs 54.8%, p=0.01), but a significant proportion of patients was treated with loop+aldosterone antagonist diuretic (15.9% vs 4.8%, p=0.03) in the hyponatremia subgroup. By multivariate logistic regression analysis, diuretic treatment reduced the risk of hyponatremia by 39% (OR=0.61; 95% CI 0.38-0.98, p=0.04) and the combination of loop and aldosterone antagonist therapy increased the risk 5.4 times (OR=5.43; 95% CI 1.35-28.9; p<0.01).

**Conclusions:** We showed that hyponatremia was frequent in elderly patients with CKD stages 3-5 and associated with cardiovascular comorbidities. Also, the diuretic treatment was an independent factor for hyponatremia.

**PUB220**

**Epithelial Trophic Cytomegalovirus Causes Abortive Infection in Cultured Podocytes**

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**Background:** Cytomegalovirus (CMV) is a herpesvirus with broad tropism, allowing for infection of virtually all tissues. Clinical manifestations include retinitis, hepatitis, and kidney dysfunction, particularly in renal allografts. In native kidneys, CMV is associated with collapsing focal segmental glomerulosclerosis (FGS). We investigated CMV infection of podocytes due to their central role in glomerular function.

**Methods:** Human urine-derived podocytes were cultured in collagen type I-coated flasks. Immunochemistry confirmed the presence of podocyte cell markers including podocin, nephrin, followed by cell differentiation. Cells were exposed to two CMV laboratory strains, TB40 or Tbow, both which were engineered to express green fluorescent protein (GFP). GFP expression was analyzed by flow cytometry. RT-PCR of the early CMV gene product UL123 was performed. In order to test for a productive infection, conditioned media was added to a renal pigmented epithelial cell line (ARPE) that are highly susceptible to CMV infection.

**Results:** Cultured podocytes demonstrated the capacity of infection when exposed to an epithelial trophic strain of CMV (TB40) as seen by GFP expression in up to 3% of cells and by RT-PCR for CMV gene expression, but not when exposed to a fibroblast tropic strain (Tbow). ARPE cells exposed to cell media from infected cultured podocytes did not become infected with CMV.

**Conclusions:** Cultured human podocytes are susceptible to infection by an epithelial cell media strain in vitro and this process appears to be abortive, as the infection is not transmitted to other cells. Future studies will assess cytotoxic effects following CMV infection including changes in podocyte function. Studies of CMV infection of podocytes may provide mechanistic information about CMV-mediated glomerular injury, including collapsing FSGS.

**Funding:** Private Foundation Support
Thrombotic Microangiopathy vs. Class IV Lupus Nephritis in Systemic Lupus Erythematosus

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Background: The kidney is often involved in systemic lupus erythematosus (SLE). Lupus nephritis is the kidney manifestation predominantly as lupus nephritis or as vascular involvement with the severest form being thrombotic microangiopathy (TMA). The objective of this study was to capture the clinical and prognostic characteristics of TMA compared to class IV lupus nephritis in SLE patients.

Methods: We conducted a retrospective analysis of kidney pathological reports and laboratory data in 89 SLE patients. Renal prognosis was determined as the need for dialysis. All data were collected at the time when the biopsy was taken. Quantitative data were reported as mean and standard deviation, while categorical data were reported as frequency and percentage.

Results: Among 89 SLE patients screened, 27 met the inclusion criteria. Eight had TMA without evidence of ISN/RPS lupus nephritis and 19 had class IV lupus nephritis. No significant difference between the two groups according to age, gender or race. Patients in TMA group had significantly higher lactate dehydrogenase levels (718±499 vs. 264±107 U/L, P = .009), serum C3 (100.6±39.3 vs. 65.8±27 mg/dL, P = .049), white blood cell count (1474.7±793.3 vs. 5807.9±2053.2 ×10^3/μL, P = .004), fasting glucose level (121.5±39.8 vs. 92.1±19.4 mg/dL, P = .02), and total bilirubin (0.6±0.5 vs. 0.3±0.1 mg/dL, P = .007). Patients in TMA group had significant lower platelet count (158.4±88.6 vs. 231.1±105.2 ×10^3/μL, P = .03), albumin (2.8±0.5 vs. 4.0±0.3 g/dL, P = .001), haemoglobin (86.8±11.6 vs. 166.6±45.9 mg/dL, P = .03), subepithelial deposits (P = .001), intramembranous deposits (P = .001), mesangial deposits (P = .001), and lambda deposits (P = .015) and albumin deposits (P = .002). All TMA patients had negative Anti-DNA antibody titers. After a median follow up time of 53 weeks, renal prognosis in TMA patients was worse (P = .002). Among the TMA patients, 3 were dialysis dependent (37.5%), compared with none in class IV lupus nephritis patients. Mortality occurred in 2 TMA patients during the period of follow up.

Conclusions: Renal prognosis in TMA-associated SLE is worse than in class IV lupus nephritis. Laboratory findings can be suggestive, but renal biopsy remains superior for discrimination between the two groups.

Renal Biopsy Performed to Diagnose Sarcoidosis but Diagnosed IgA Nephropathy: A Case Report

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Introduction: Renal disorder attributed to sarcoidosis generally causes tubulointerstitial damage. We herein report a case in which renal biopsy was performed for sarcoidosis diagnosis but was diagnosed as IgA nephropathy.

Case Description: We encountered a 69-year-old female with persistent proteinuria and hematuria. Her history included facial palsy and neurosarcoidosis diagnosed by bronchoscopy (CD4/CD8 ratio: 7.22) and CT findings (filar lymph node swelling) 5 years prior to visiting our hospital. She was treated with prednisolone (PSL) 50 mg and her symptoms improved. PSL was gradually tapered and discontinued. She had no proteinuria and no hematuria 2 years previously (Cr 0.68 mg/dL). She was diagnosed with renal disorder (Cr 0.92 mg/dL, proteinuria 1+, hematuria 3+) 1 year previously, and she subsequently visited our hospital. CT showed lung hilar region lymph node swelling and multiple mottled shadows in the liver. Laboratory findings included the following results: ACE 36.5 U/ml, 1,25(OH)2-vitamin D 67.4 pg/mL, soluble IL-2 receptor 2230 U/mL, proteinuria 0.46 g/day, and urine β-2 MG 9450 µg/L. We suspected recurrence of sarcoidosis and renal biopsy was performed for diagnosis. Mild to moderate increase of mesangial cells and matrix was observed in most glomeruli. Although tubulointerstitial injury was partially observed, epithelial cell granuloma, which is characteristic of sarcoidosis, was not observed. IgA and C3 deposition in mesangial areas was observed in immunofluorescent analysis. Based on these findings, we diagnosed the patient with IgA nephropathy, not sarcoidosis, for the kidney lesion. Hepatic biopsy was then performed for definitive diagnosis, which showed epithelioid cell granulomas. The patient was finally diagnosed with sarcoidosis. She was subsequently treated with PSL 30 mg and her renal function and urinary findings improved.

Discussion: We experienced an interesting case that suggested IgA nephropathy diagnosed by renal biopsy and sarcoidosis diagnosed by liver biopsy. It is very rare for sarcoidosis to accompany IgA nephropathy. We speculate that IgA nephropathy occurred secondary to immune abnorality caused by sarcoidosis.

Antithrombin III, Fibrinogen, Factor XIII, Protein C, Protein S, Echocardiogram, Doppler Ultrasound

Purtscher-Like Retinopathy: A Cure for Underlying Thrombotic Microangiopathy

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Introduction: Purtscher-like retinopathy (PLR) is a retinal disorder characterized by acute visual loss and retinal findings including cotton-wool spots and intraretinal hemorrhages. PLR is a rare ophthalmological manifestation of systemic thrombotic
microangiopathy (TMA). We describe a patient who presented to the hospital with PLR and was subsequently diagnosed as having atypical hemolytic uremic syndrome (aHUS) with multiple organ involvement.

Case Description: A 36-year-old woman presented with a sudden onset of blurred vision, marked dyspnea, and decreased urine output. Vital signs were stable on admission. Fundoscopy revealed multiple bilateral peripapillary yellow-white patches like cotton wool spots, intraocular hemorrhages, and macular edema suggestive of PLR. She was found to have worsening anemia (Hb 6.8 g/dl), thrombocytopenia (platelet count 40,000/mcmm³), and oliguric acute kidney injury (serum creatinine 8.3 mg/dl; unknown baseline renal function). The patient had been on dialysis for one at month 1, 3 and 6 respectively, including one patient who incorporated proteinuria. Hematrua disappeared at month 3 in all patients. Creatinine did not change over time. Treg did not change, while Th17 decreased in all patients, showing a change in the Th1/Th17 profile. The u-NAG increased in 3 patients during the induction phase y developing all during the maintenance phase.

Discussion: The sequential MNL therapy seems to be effective in IgAN patients; this effect was associated with a change in the inflammatory and pro-inflammatory profile. The changes in u-NAG were associated with benefits in proteinuria, which suggest that the treatment influences lysosomes activity.

PUB228

The Efficacy and Safety of Bortezomib-Based Treatment in Patients with Monoclonal Gammopathy of Renal Significance: A Single-Center Case Series Study

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Background: Monoclonal gammapathy of renal significance (MGRS) is still an understudied disease. Bortezomib-based treatment has been shown to be effective in this population. However, the majority of relevant reports in China were single case reports. We presented our own experience managing a series of MGRS patients by bortezomib-based treatment.

Methods: This retrospective study enrolled patients who had been diagnosed as MGRS and received bortezomib-based treatment in our division from January 2016 to January 2019. The diagnosis of MGRS was re-confirmed according to the updated International Kidney and Monoclonal Gammapathy Research Group consensus definition. Charts were retrospectively reviewed for demographic and clinical information. Serum creatinine and urinary protein were measured after each treatment to evaluate the renal outcome. Treatment-associated adverse events were also recorded. The outcomes were described using the summarized impact analysis (SIA) and a Kaplan-Meier analysis. The study was approved by the institutional review board.

Results: Nine patients (male/female=7/2) were included, with a median age of 68 years (range, 49–73 years). All had been confirmed to have an abnormal plasma cell origin-stained pathologic clone by bone marrow flow cytometry. Median treatment duration was 5 range, 1–7) months. The overall response rate of 33.3% (3/9), including one case of complete response and two cases of partial response. There were three episodes of severe infection, leading to an incidence of 3.3% (3/94).

Conclusions: Bortezomib-based treatment achieved a renal response rate of 33.3% in the treated nine MGRS patients. Incidence of adverse events was 7.3%, all being infection. A tailored and clone-targeted approach would be the core of future management.

Funding: Government Support - Non-U.S.

PUB229

A Prescribed Chinese Traditional Medicine, Shen Ping Decoction, Inhibits Multiple Protein Kinases Activated by PDGF in Human Mesangial Cells

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Background: A prescribed Chinese traditional medicine, Shen Ping decoction (SP), has been used in China to treat IgA nephropathy (IgAN) successfully for decades, reducing proteinuria and hematuria. Our previous work showed that SP inhibits mesangial cell (MC) proliferation, phosphorylation of PDGFR-β, Akt and ERK1/2, induced by PDGF or pathogenic IgA1-containing immune complexes. Furthermore, SP inhibited phosphorylation of EGFR induced by PDGFR-β and Akt, suggesting that SP was a potent inhibitor of mesangial cell proliferation. The aim of the current study was to elucidate the molecular mechanisms of SP against MC proliferation and survival.

Methods: We used a high content screening approach to identify potential targets of SP. We validated these targets using immunoblotting. We used a lentiviral shRNA expression system to target Akt and EGFR. We used a co-culture model of MCs and human umbilical vein endothelial cells (HUVECs) to simulate the in vivo microenvironment. We evaluated the effects of SP on MC proliferation and survival.

Results: SP inhibited the proliferation of MCs and HUVECs in a dose-dependent manner. SP downregulated the expression of Akt, EGFR, and PDGFR-β in MCs. SP also inhibited the phosphorylation of Akt and EGFR in MCs. SP reduced the formation of capillary-like structures in a co-culture model of MCs and HUVECs. SP also inhibited the migration and invasion of MCs in a Transwell assay.

Conclusions: The results of this study suggest that SP inhibits MC proliferation and survival by regulating the Akt and EGFR pathways. These findings support the use of SP as a potential therapeutic agent for the treatment of IgAN.

Funding: This study was supported by the National Natural Science Foundation of China (81870908, 81670943), and the Shanghai Municipal Commission of Health and Family Planning (2017SHJX023).

PUB227

IgA Nephropathy: Role of Interleukin-17, a Novel Pilot Sequential Treatment

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Background: IgA Nephropathy (IgAN) is the most common glomerulonephritis; however, it is refractory (r-IgAN) in some cases. The new pathogenic data in particular interleukin-17 (IL-17) opening a new field to explore more effective treatments. We design an MNL Therapy (multicytokine normalization levels therapy) to control sequentially the possible genes (Th1, Th17, Treg lymphocytes), cytokines (IL-17 inhibition) and liposomal actions controlling (other N. Objective: To evaluate the efficacy of the sequential administration of the paricalcitol and secukinumab on the proteinuria and creatinine in patients with r-IgAN).

Methods: This is a pilot trial treatment report. Changes in proteinuria (24-hours-collected), plasma creatinine and urine N-Acetyl-B-D-galactosaminidase (u-NAG) during the follow-up (induction phase: month 0 to 1 and maintenance phase: month 2 to 6). Evolutions of the hematuria, peripheral blood Th17, Treg (% of CD4) cells were also evaluated.

Results: Four patients were included. As whole proteinuria decreased 28, 45 and 33% in month 1, 3 and 6, respectively, including one patient who increased proteinuria. Hematuria disappeared at month 3 in all patients. Creatinine did not change over time. Treg did not change, while Th17 decreased in all patients, showing a change in the Th1/Th17 profile. The u-NAG increased in 3 patients during the induction phase y decreasing all during the maintenance phase.

Conclusions: The sequential MNL therapy seems to be effective in IgAN patients; this effect was associated with a change in the inflammatory and pro-inflammatory profile. The changes in u-NAG were associated with benefits in proteinuria, which suggest that the treatment influences lysosomes activity.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Conclusions: The inhibitory effects of the Chinese traditional medicine SP on multiple tyrosine-kinase activity-mediated signaling pathways by PDGF may provide a mechanistic explanation for SP activities in IgAN. Future studies are needed to identify and compare the responses in SP and then test them as targeted therapy of IgAN.

Funding: NIDDK Support, Private Foundation Support

PUB230
Production of Human Podocyte PLA2R Protein with Application of Anti-PLA2R ELISA in Patients with Membranous Nephropathy

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Background: Anti-phospholipase A2 receptor (PLA2R) autoantibodies could be found in 60–85% patients with idiopathic membranous nephropathy. It’s believed that these autoantibodies attacking on the auto-antigens, membrane-form PLA2R upon the podocyte, form immune complex and then cause podocyte damage. To investigate the entities of these autoantibodies, we conduct a study to manufacture the recombinant human PLA2R protein with extracellular domain (soluble-form PLA2R).

Methods: The cDNA of extracellular PLA2R was cloned into specified vector, then transfected into Freestyle 293 system. After expression, protein is undergone purification with affinity chromatography. Recombinant protein was examined by Western blot, SDS-Page to confirm the protein properties. Finally, these recombinant proteins would be used as coating protein to detect plasma anti-PLA2R autoantibodies which are confirmed by commercial ELISA-kit (Euroimmun).

Results: According to the Western blot and SDS-Page, the recombinant proteins have accurate molecule weight. Recombinant human PLA2R protein can be used to detect plasma anti-PLA2R autoantibodies. Comparing to commercial ELISA-kit, the titers trends of autoantibodies are highly correlated (r=0.89).

Conclusions: We successfully manufactures recombinant human PLA2R protein. Entities of the protein was carefully examined. This recombinant protein could be applied as in-house anti-PLA2R ELISA assay. Furthermore, the recombinant protein could help us to investigate the feature of anti-PLA2R autoantibodies from patient’s sample in further studies.

PUB231
The Role of Secretary IgA in the Pathogenesis of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most frequent primary glomerulonephritis, characterized by glomerular deposition of IgA-containing immune complexes (IC). Disregulation of mucosal immune system is recognized as a major cause of development of IgAN. Secretary IgA (SIgA), which is the dominant in external mucosal secretions, is characterized as the ‘first line defense’ of mucosal areas. Previous reports have shown that the serum level of SIgA is elevated in Dutch IgAN patients, and higher serum SIgA is associated with creatinine clearance and proteinuria. In addition, mesangial deposits of SIgA were detected in about 15% of IgAN patients, and observed a colocalization with IgA, MBL, and C4d. Currently, a strong evidence has demonstrated that galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1-containing IC are essential effector molecules in IgAN. In present study, we analyzed the association of SIgA and Gd-IgA1 in the pathogenesis of IgAN.

Methods: We measured serum SIgA in patients with IgAN (n=37), disease controls (n=5) and healthy controls (n=5) by ELISA. The associations between serum level of SIgA and Gd-IgA1 or IgA-IgA1 immune complexes. Moreover, serum SIgA did not correlate with any clinical parameters and pathological phenotypes.

Conclusions: Serum level of SIgA was not elevated in Japanese patients with IgAN. Moreover, serum level of SIgA did not correlate with Gd-IgA1 and disease severity of IgAN. Thus, it is suggested that SIgA is not involved in the pathogenesis of IgAN.

Funding: Government Support - Non-U.S.

PUB232
The Pharmacogenomic Association of FCGR2B-231T with Response to Treatment in Lupus Nephritis

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Background: To determine FCGR2B-I232T polymorphisms is related to susceptibility, activity and treat response to lupus nephritis (LN) of Chinese.

Methods: FCGR2B-I232T polymorphism was determined by sequencing in LNPatients and 196healthy individuals from China. The disease activity index was calculated using theACR SLE Disease Activity Index (SLEDAI) and pathologicclassificationwere according to international Society of Nephrology/Renal Pathology Society 2003 classification.

Results: The CC genotype was associated with increased occurrence of LN (P= 0.022, odds ratio [OR] 2.388, 95% confidence interval (95%CI) 1.115-5.075). Patients with homozgyous FCGR2B-I232TCCT variant showed higherSLEDAI-2K (P = 0.035), indicated by higher incidence of thrombocytopenia (p=0.03), anemia (p=0.02) and Class IV (p=0.005), higher AI index (p=0.042), lower level of C3 (p=0.011). As toremission scores in the CC genotype and TT/CT genotype, the non-responder with CC genotype were much more than TT/CT genotype (p=0.025, OR=3.95, 95%CI 1.198-9.061). The patients who used the IV CYC therapy with CC genotype was more difficult to remis (p=0.012, OR=19, 95%CI 1.198-9.061).

Conclusions: The FCGR2B-I232T polymorphism associated with susceptibility to lupus nephritis. Additionally, LN patients homozgyous for FCGR2B-I232T show more severe clinical manifestations. The finding that the homozgyous FCGR2B-I232TC genotype was associated with complete response in the LN patients, especially the IV CYC therapy, implies that FCGR2B-I232T may be broadly involved in disease pathogenesis and response to therapy.

PUB233
Clinical and Pathological Features and Renal Outcomes of Lupus Nephritis in Elderly Patients

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Background: Lupus nephritis (LN) is one of the most common and severe complications of systemic lupus erythematosus (SLE). Renal involvement is the second cause of death in patients with SLE. There are many risk factors associated with poor renal outcome, however, it has not been defined exclusively. The retrospective analysis is to describe the clinical and pathological characteristics and renal outcomes of LN in elderly patients.

Methods: The clinical features of patients with LN from Jan 1, 2012 to Dec 31, 2017 in Center of Kidney Disease of 2nd Affiliated Hospital, Nanjing Medical University were collected and analyzed. SLE patients without renal biopsy were excluded. All LN patients were pathologically classified according to the 2003 International Society of Nephrology/ Renal Pathological Society (ISN/RPS) classification system.

Results: Among the 34 patients with biopsy-proven lupus nephritis, there were 32 (94%) females and 2 (6%) males, with an average onset age of (44±12) years old. The major damage was the mesangial glomerulosclerosis in 1647% patients and acute kidney injury (AKI) accrued in (824%) patients. The incidence of blood system involvement, malar rash, pleurisy, arthritis and fever was 91%, 47%, 41%, 29% and 26% respectively. The highest positive rate of serum autoantibody was ANA(100%), and the following was Anti-Sm(53%) and Anti-dsDNA(53%). The incidence of low serum C3 was 91%. All patients were pathologically classified based on ISN/RPS 2003 classification, only 412% patients with class II and 1(3%) patient with class III, 29(85%) patients with class IV, V, III+V or IV+V. 13(38%) patients with class IV, 3(9%) patients with class V, 5(15%) patients with class III+V and 5(53%) patients with class IV+V. These 34 patients with an average follow-up time of 1.2-6 years (median duration was 4 years), 22 (64.7%) patients were in completely remission, 9 (26.5%) patients were in partly remission, 3 (8.8%) patients relapsed.

Conclusions: The patients diagnosed with LN in our center have an older onset age. Proliferative lupus nephritis was the most common renal damage type in our center, and the renal outcome was favorable. In addition to the proven clinical risk factors and treatment regimens, compliance of patients and socioeconomic factors are also important factors affecting prognosis.

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PUB234
NSAID-Related Minimal Change Disease and Interstitial Nephritis with Tertiary Lymphoid Organ Formation

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Introduction: Interstitial nephritis (AIN) and minimal change disease (MCD) are known complications of NSAID exposure. Intense inflammatory infiltrates occasionally lead to formation of tertiary lymphoid organs (TLOs) which are unencapsulated nodular aggregates consisting of a core of B-cells, surrounded by T-cells and azoephores. TLO’s have been described in chronically rejected kidney allografts, IgA nephropathy and lupus nephritis. We report a case of TLO formation in NSAID induced AIN with MCD. Case Description: A 69-year-old African American male was admitted with fatigue, arthralgia and oliguria. Medical history was notable for remote right nephrectomy, prostate cancer, hypertension, and gout. The patient reported daily ibuprofen use (1200-1800mg/d) for 3 months prior to admission for shoulder pain. Admission blood work showed serum creatinine 11.4 mg/dl and serum albumin 1.8 g/dl. Urinalysis showed new 3+ proteinuria, 12 RBCs and 9 WBCs. A 24-h urine collection measured 11.5 g protein. Renal work up was negative. Renal ultrasound was normal. Kidney biopsy was performed. The histopathology sample revealed one core with normal glomeruli and mild focal interstitial infiltrate another core with near-total obliteration of renal architecture with a patchy dense lymphoid infiltrate with germinal centers separated by plasma cell rich infiltrate admixed with eosinophils. IF was negative. EM showed diffuse podocyte foot process effacement.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The patient was advised to avoid NSAIDS and was treated with oral prednisone 40mg/d for 6 weeks followed by a short taper. Serum creatinine improved to 1.3 mg/dL ("baseline") and proteinuria reduced to less than 30 mg/g following cessation of steroids.

Discussion: The above findings illustrate novel histopathology in NSAID induced nephrotoxicity and highlight the importance of chronic antigen stimulation in its pathogenesis. The functional significance of TLO’s remains undefined, and it is unclear whether the presence of TLO’s serve a pathologic or protective role.

Methods: A 14wk repeat-dose safety and pharmacokinetic/pharmacodynamic (PK/PD) study in non-human primates (NHP) (Cynomolgus monkey) was performed by biweekly intravenous (i.v.) administration of BION-1301 at three different dose levels. To support a potential change in route of administration, a 4wk repeat-dose NHP bridging study was conducted with weekly subcutaneous (s.c.) administration of BION-1301 at three different dose levels.

Results: In both the 14wk i.v. study and the 4wk s.c. study, BION-1301 was evaluated for safety, PK and PD. For PK and PD, BION-1301 levels, uncomplexed APRIL levels and immunoglobulin levels (IgA, IgG, IgM) were quantified in serum. Immunophenotyping was performed on peripheral blood to assess the impact of BION-1301 on the B cell compartment.

Conclusions: Results of these extended nonclinical pharmacology and toxicology experiments add to the BION1301 safety, PK, PD assessments reported earlier (Dulos et al, ASN 2018) and inform the ongoing clinical program to develop BION1301 for the treatment of IgA.

Funding: Commercial Support - Aduro Biotech Inc.

PUB237

The Deposition of Immunoglobulin A on the Glomerular Loop Correlates with Severity Both Clinically and Pathologically in a Patient with IgA Vasculitis with Nephritis

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Background: Immunoglobulin A vasculitis with nephritis (IgAVN) is considered to be systemic form of IgA nephropathy (IgAN). Both IgAN and IgAVN are defined by the presence of IgA in dominant glomerular deposits. However, the pathologic significance of the difference in glomerular location of IgA and other immunoglobulin deposits is remain unclear. In this study, we focused on the deposition of IgA on the glomerular loop and investigated.

Materials and Methods: We conducted a retrospective study of 37 adult patients of biopsy-proven IgAVN. We divided 37 IgAVN patient into two group: IgA deposition on the glomerular loop group (n = 11) and non-IgA deposition on the glomerular loop group (n = 26). We compared in terms of clinicopathological feature and renal prognosis in each group.

Results: 37 adults IgAVN patients (male:22, female:15) were analyzed. IgA deposit on the glomerular loop group of 11 patients. The onset age of IgAVN was predominantly higher in IgA deposition on the glomerular loop group. (48.2±17.9 vs 35.6±14.9) The average proteinuria was 3.39±2.57 g/day in the IgA deposition on glomerular loop group and 1.43±1.56 g/day in non-IgA deposition on glomerular loop group. (P=0.0036) In historical findings, there were many cases of crescent formation predominated in the IgA deposition on glomerular loop group. (P = 0.039) There was no significant difference in eGFR value at the time of renal biopsy. (eGFR: 69.8±25.6 vs 87.2±32.5 P = 0.082) Renal function was predominantly worse in the IgA deposition on glomerular loop group in half a year after treatment. (eGFR: 49.5±16.9 vs 83.9±23.2 P = 0.0004) However, there was no significant difference between the two groups in the initial dose of steroid and in combination with steroid pulse.

Conclusions: We have clearly shown that deposition of IgA on the glomerular loop correlates with severity both clinically and pathologically. These results suggested that these deposition may play a key role in the pathogenesis of IgAVN, and also suggested that the selection of therapy for IgAVN might be affected.

PUB238

Nephrotic Syndrome in the Elderly: Not Always What It Seems

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Introduction: Polypharmacy is defined simply as the use of multiple medications by a patient. Older adults are especially impacted by polypharmacy. The use of greater numbers of drug therapies has been independently associated with an increased risk for an adverse drug event (ADE).

nephrotic syndrome due to minimal change disease or membranous nephropathy. Given the increased use of medications in the elderly and risk for an ADE, it is of utmost importance to be vigilant of the possible side effects of NSAIDs in this population.

PUB239

Eosinophilic Granulomatosis with Polyangiitis Renal Disease
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Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic necrotizing vasculitis affecting small to medium sized vessels, characterized associated with asthma and eosinophilia. EGPA renal disease is prevalent in approximately 25%. Presentation includes focal and segmental necrotizing crescentic glomerulonephritis (NCGN), eosinophilic interstitial infiltrates or obstructive uropathy caused by vascular involvement of the ureters. The aim of our study is to analyse the prevalence, clinical manifestations and outcomes of EGPA patients with renal involvement.

Methods: We retrospectively analysed 142 patients with EGPA according to the criteria of the American College of Rheumatology or Chapel Hill Consensus 2012 definition. We selected patients with renal involvement defined by the presence of (A) Renal insufficiency serum creatinine (Scr) > 97 μmol/L, or (B) haematuria and/or proteinuria (>1+ in urinalysis) or (C) obstructive uropathy.

Results: Of eleven (7.74%) patients with renal involvement, three presented with rapidly progressive kidney injury with Scr >290μmol/L, 6 with Scr greater than >117μmol/L and two had normal Scr [44-97μmol/L]. Renal biopsy performed in 6 patients, demonstrated 3 NCGN, 2 had both NCGN and tubulointerstitial nephritis (TN) with eosinophil infiltrates, and 1 had TN with normal Scr alone. All had eosinophilic arteriolar necrosis, NCGN with eosinophil infiltrates or obstructive uropathy.

Conclusions: At the end of follow up 2 patients were renal transplant recipients, 5 had chronic kidney disease (CKD) and 4 maintained normal kidney function. Although renal involvement in EGPA is less frequent than in others AAV, it must be taken into account due to its potential to lead to end-stage renal failure. ANCA positive patients may present with NCGN leading to CKD. Furthermore, ANCA negative patients, may have manifestations such as TN with eosinophil infiltrates or obstructive uropathy.

PUB240

Clinical and Pathological Manifestations of ANCA-Associated Vasculitis Superimposed on Rheumatoid Arthritis
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Background: Patients with rheumatoid arthritis can have renal disorders, most of which are mild. However, ANCA-associated vasculitis may be superimposed on rheumatoid arthritis, with severe organ damage, especially renal failure. We try to investigate characteristics of ANCA associated vasculitis combined with rheumatoid arthritis.

Methods: Patients with concurrent rheumatoid arthritis (RA) and ANCA associated vasculitis (AAV) were identified by searching medical database of the Peking Union Medical College Hospital, Beijing, China from January 2000 to December 2018. We excluded patients exposed to TNF-α inhibitors. Data on age, sex, involved organs, laboratory tests, renal pathology at the diagnosis of AAV, and therapeutic regimens of both RA and AAV were retrospectively retrieved and analyzed. To further explore whether there was any difference in clinical features and renal pathology between AAV patients with and without concurrent RA, we conducted a 1:4 matched case-control study. 36 controls were matched to 9 cases having renal pathology according to age and sex.

Results: 15 patients in our hospital and 27 patients from literature with concurrent RA and AAV were identified. They were 54 ± 17 years old at the diagnosis of AAV, and 29 (69.9%) of them were women. AAV was diagnosed 6(2,12) years later than RA. Kidney was the most frequently involved(80.9%). Those with renal involvement had an average baseline serum creatinine of 290 (148, 471) μmol/L. Patients with RA were more likely to have AAV proved by renal biopsy than those without RA (15.0% vs 1.5%, p=0.001). AAV patients with concurrent RA were more likely to be asymptomatic(33.3% vs. 2.8%, P=0.02) and presented lower eGFR [23.9±15.5 vs 34.3±24.3 ml/min (1.73 m²), p=0.049] at diagnosis as compared with those with AAV alone. However, the two groups did not differ in the percentage of global sclerotic and cellular crescentic glomeruli (global sclerotic glomeruli 37.3±23.5% vs 26.9±24.0%, p=0.26, cellular crescentic glomeruli 23.1±18.7% vs 34.0±18.4%, p=0.11).

Conclusion: AAV was more frequent in patients with RA than those without RA. AAV superimposed on RA were more likely to be asymptomatic and with worse renal function.

PUB241

Use of Rituximab in Fibrillary Glomerulonephritis
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Introduction: Fibrillary glomerulonephritis (GN) is a rare glomerular disease characterized by glomerular deposition of randomly arranged non-amyloid fibrils. The prognosis of fibrillary GN is poor, with up to 50% of patients progressing to end-stage renal disease within 2 years of diagnosis. The optimal treatment is unknown. Cases with fibrillary glomerulonephritis are presented who were treated with Rituximab with different outcomes.

Case Description: Patient 1 is a 72 years old male with 9 g proteinuria and biopsy proven fibrillary GN. He received 4 doses of weekly IV Rituximab 375 mg2 mg with subsequent reduction in proteinuria to 1.2 g. Two years later, proteinuria increased to 5 g. Due to a concern for recurrence, patient was given 2 doses of IV Rituximab 1 g each, separated by 2 weeks. Renal function since then, has remained stable on 6 month follow up with a serum creatinine around 1.8 mg/dl, while proteinuria decreased to 1.4 g. Patient 2 is a 68 years old female with 3.6 g proteinuria and biopsy proven fibrillary GN. Serum creatinine on diagnosis was 2.0 mg/dl. She received 2 doses of IV Rituximab 1 g each, separated by 2 weeks. Six months later proteinuria worsened to 4.6 g and she progressed to end stage renal disease. No evidence of monoclonal gammapathy was noted in either patient. Both patients received intravenous corticosteroids as premedication with Rituximab along with Lorsartan 100 mg daily.

Discussion: Due to the rare nature of this disease, no controlled trials have been conducted. Steroids and different cytotoxic drugs have been used in fibrillary GN without any proven benefit. Rituximab, a monoclonal anti-CD20 antibody directed against B cells has been used as a treatment due to the characteristic presence of polyclonal immunoglobulin deposits in the mesangium and glomerular basement membrane. There are reports of B-cell reconstitution with subsequent reapparance of detectable CD19+ cells may be responsible for relapse in fibrillary GN. Data on Rituximab therapy for fibrillary GN are outcomes have been inconsistent. However, it provides an option to consider as untreated fibrillary GN will most likely result in progression of disease. More data is needed to prove its efficacy in this disease, and to assess the need to consider Rituximab administration as soon as CD19+ cells become detectable, despite the absence of clinically evident relapse.
**PUB243**

Infection and Glomerular Disease: The Patient and Caregiver Perspective

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**Background:** Individuals with glomerular disease (GD) comprise ~7% of the ~30 million Americans with chronic kidney disease. Both GD and immunosuppressive (IS) treatment place these patients at increased risk for infection. Patient and caregiver perspectives on the impact of infection on quality of life and vaccination behavior have not been previously described. Herein we present results from an electronic survey of the membership of NephCare Kidney International (NKI), a KD focused patient and family support network.

**Methods:** A 22 question web-based survey comprised of 20 close-ended and 2 open-ended questions was sent to members of NKI in the Fall of 2019. The survey was promoted with two social media posts and within an NKI newsletter. Quantitative and qualitative analyses were performed.

**Results:** We received 262 responses from 3171 e-mail invitations (response rate 8.3%). Fifty four percent (n=139) of responses were from parents of children with GD < 18 years of age and 46% of responses (n=123) were received from adult GD patients. The majority of respondents (95%) reported prior IS exposure, including steroids (95%), calcineurin inhibitors (76%), MMF (41%), rituximab (26%), and cyclophosphamide (19%). The majority of parental respondents (65%) and nearly half of all adult respondents (45%) reported being very concerned about acquiring an infection. Since diagnosis, 56% of parents and 47% of adults with GD reported a 2 emergency room visit or hospitalizations for treatment of infection. The majority of respondents (58%) reported more frequent infections since GD diagnosis, and 44% reported more infections while taking IS medications. Respondents reported that infections resulted in frequent interruption in social activities (29%), exercise (25%), and attending school (33%) or work (20%). Flu vaccination during the 2018-2019 season was reported by 76% of parental respondents and 64% of adult GD patients. Reasons for not receiving the flu vaccination included fear of reaction/relapse, perceived contraindication due to IS medications, and perceived provider recommendation.

**Conclusions:** Individuals with GD and their caregivers are concerned about infections, report frequent infection-related healthcare visits and interruption in activities. Infection remains a preventable and under-studied complication of GD deserving of additional study.

**PUB244**

Sequential Therapy for Remission Induction in Severe ANCA-Associated Glomerulonephritis

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**Background:** The introduction of combination therapy with glucocorticoids (GC) and cyclophosphamide (CYC) or rituximab (RTX) has resulted in remission rates exceeding 90% in patients with ANCA associated vasculitis (AAV). However, early treatment related mortality remains a major concern and has driven the search for safer induction regimens exploring minimizing or avoidance of GC and CYC. Most trials have excluded patients with severe renal disease. We report the outcomes of AAV patients with severe renal disease treated with sequential therapy (ST) starting with GC and oral CYC followed by transition to RTX.

**Methods:** Patients with new or relapsing severe AAV who presented with severe renal disease and/or RPGN were identified. RPGN was defined as at least a 20% decrease in e-GFR over a 2 week period along with hematuria and proteinuria. Induction treatment included pulse GC for 3 days followed by oral prednisone tapered to 5 mg by month 6, oral CYC adjusted for GFR until improvement in BVAS and serum creatinine at which point, CYC was stopped and induction dose of RTX was given. Use of Plasma Exchange PLEX was allowed. The primary outcome was complete remission defined as BVAS of zero by 6 months (6M). Descriptive data are presented as median with range and mean with SD.

**Results:** Nine patients met the inclusion criteria. Median age at diagnosis was 63 years. Majority were females, MPO ANCA positive and had a new diagnosis. The mean nadir (SD) e-GFR was 12 (5) with 3 requiring dialysis. Median BVAS at the time of diagnosis was 15. All patients received (ST) and 3 received PLEX. Median exposure to oral CYC was 35 days. The mean (SD) e-GFR and median BVAS were 26(12) and 3 respectively at the time of switching to RTX. The median prednisone dose at 6 months was 5 mg. The median follow up was 44 months. All patients achieved remission. One patient reached ESRD. The mean daily (SD) e-GFR in the remaining 8 patients at last FU was 37(27) and the mean (SD) e-GFR rise at 1 year was 26(25). Adverse events included 2 patients with pneumonia and 3 with bone marrow suppression. There were no deaths.

**Conclusions:** Sequential therapy with GC and CYC followed by RTX is effective for patients with severe renal disease. Therapy related adverse events comparable to other studies and further modification in ST with decrease in GC dosage should be explored.

**PUB245**

Multicenter Review of Types of Glomerular Diseases in the Emirate of Abu Dhabi: Six Years of Experience

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**Background:** Glomerulonephritis (GN) is a rising paramount renal disease that varies in etiology from inherited or acquired factors. Its severity can range from asymptomatic depictions to end stage kidney disease (ESKD). This study was done to look at the patterns of biopsy-proven glomerulonephritis based on data from a multicenters in Abu Dhabi.

**Methods:** This study is a retrospective a cross sectional study. Included kidney biopsy were from all patients above the age of 18 years, over a six-year period from 2010 till 2015, who had diagnosis of glomerular disease other than diabetes mellitus. The number of reviewed biopsies was 416.

**Results:** The most common type of glomerulonephritis among the study sample were the IGA GN (22.8) followed by the FSGS (20.4%) followed by the SLE (19.7%). The least common types were Pauci Immune (1.7). There was female preponderance in lupus nephritis and pauci immune GN. The nationality comparison did not reveal a predominant GN among Emirati nationals. The age relationship to GN types showed that the majority (82.9%) of SLE patients, MCD (74.5%) and non-categorized (71.4%) patients are young between the age of 18 to 39 years. On the other hand, 57.1%, 25% and 16.7% of patients with Pauci immune, other GN types and MPGN respectively are 60 years and older.

**Conclusions:** This study shows the histopathological variety of glomerular disease in Abu Dhabi. It could be a driving point to help understand GN better in the region.

**Funding:** Government Support - Non-U.S.

**PUB246**

Incidence and Risk Factors of Serious Infections in ANCA-Associated Vasculitis with Renal Involvement

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**Background:** Infection is one of the most commonly encountered problems in patients with ANCA-associated vasculitis (AAV) and contributes significantly in morbidity and mortality. We investigated the incidence, type and risk factors for serious infections and compared the incidence of non- prophylaxis with prophylaxis with trimethoprim–sulfamethoxazole in patients with AAV.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

*Underline represents presenting author.*

1136
Proteinuria Could Not Be a Surrogate Prognostic Marker in IgA Nephropathy

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Background: ACE-I/ARBs have been widely used for treatment of IgA nephropathy (IgAN), however, there is no study showing outcome of long-term ACE-I/ARBs treatments in IgAN children with persistent mild proteinuria.

Methods: Out of 253 patients with IgA nephropathy and IgAN nephrotic syndrome, 215 patients were followed up for at least five years in a tertiary center. Data on age, sex, disease and treatment characteristics and the type of serious infections were collected. Serious infections were defined as infectious episodes requiring hospitalization.

Results: Of the 215 patients the average age of diagnosis was 71.6 years (SD 10.9) and 43% were women. A total of 17 serious infections were identified in 11 patients during a median follow-up of 2.6 years (incidence: 19.6 per 100 patient-years). Pneumonia (47%) and urinary tract infections (18%) were the most frequent types of infection. More than half of the infections (65%) were recorded during induction treatment (Rituximab, RTX), Cyclosporine (CYC) or combination treatment CYC+RTX and the remaining of them (35%) during the maintenance treatment (RTX or Mycophenolate Mofetil (MMF)). The majority of patients (76%, 16/21) received prophylaxis with trimethoprim–sulfamethoxazole. Among those who developed a serious infection (11/21) the induction treatment was cyclophosphamide (CYC) or combination treatment CYC+RTX and the remaining of them (5%) during the maintenance treatment.

Conclusions: One in two patients with AAV had renal involvement experienced at least one serious infection during follow-up, with more frequent infections of the respiratory and urinary tract. The incidence of serious infection is particularly high during the first six months, and combination induction treatment CYC+RTX and the failure of prophylaxis with trimethoprim-sulfamethoxazole are identified as risk factors.

Efficacy and Safety of the Combined Induction Therapy with Rituximab and Low Steroid Doses in Glomerulonephritis

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Background: Proteinuria and acute renal dysfunctions are the main objectives for glomerulonephritis control. The autoimmune component of the primary glomerulonephritis (PG) is steadily assuming. The efficacy of the Rituximab and the low steroids doses (combined therapy: CT) in these diseases is not well known. Moreover, if there are differences in the effect of the CT among PG and secondary glomerulonephritis (SG) has not been evaluated. Objectives: Primary outcome: To evaluate the risk of death and or transplant in primary glomerulonephritis (PG) vs second glomerulonephritis (SG). Secondary outcome: The changes in the proteinuria (median±p25-p75), 24-hours collected and estimated glomerular filtration rate (eGFR) (mean) during 24 months of follow-up. Potential differences between PG and SG were also assessed. Lethal infection was recorded as safety issue.

Methods: A retrospective study in a third level hospital was conducted. Rituximab (1g every two weeks for two doses) and methylprednisolone 120-250 mg /Xdt and subsequently, prednisone 30 mg/d was tapered and discontinued at month 3. Study period: From May 2008 to November 2018. eGFR was calculated using the CKD-EPI formula.

Results: Forty consecutive patients were included. PG: 14(32%) and SG: 306(68%) who were followed up 44 months. 102(25%) patients died or needed CRRT. No differences in the primary outcome were observed between PG and SG (3 versus 7 patients, respectively P = 1). As a whole, eGFR increased from basal to month 12 (8.6 ml/min/1.73m2, P=0.01) and decreased from month 12 to 24 (4.8 ml/min/1.73m2, P=0.01), no differences between PG and SG were observed. Proteinuria decreased from basal to month 24 at the PG [from 4.0 (2.7-6.1/g/d) to 0.21(0.1-7.9),P=0.01] and at SG [from 4.0 (3.4-3.1) to 0.45(0.0-6), P=0.01]. Six patients died, two of them (4.5%) due to a fatal infection and corresponded to SG.

Conclusions: The CT showed efficacy without differences between the two glomerulonephritis types, which may represent a new therapeutic option in those patients. Fatal infections were seen in the secondary glomerulonephritis group.

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposition Disease: Our Experience

Umesh Lingare, Nephrology, Institute of nephrology, Bangalore, India.

Background: PGNMID is a rare disease affecting the native kidneys and transplanted kidneys. Here we present four cases of PGNMID that illustrate the challenges of diagnostic approach and highlight the allologin outcome after treatment with BORTEZOMIB. Patients with PGNMID may show an initial response to therapy with ACE-I/ARBs, but in post transplant patients, their native kidney biopsy was reevaluated to determine the recurrence disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema after 7 months disease being immune complex mediated MPGN presented with edema.
PUB251
ANKA-Associated Crescentic Glomerulonephritis Can Be Concurrent with Another Immune Complex-Mediated Glomerulopathy: One Health Center Experience
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Background: Autoimmune disorders are known to trigger multiple systemic diseases. There are relatively few reports for a potential overlapping syndrome including ANKA associated crescentic glomerulonephritis (CGN) and another type of immune complex disease (ICD) in the kidneys. Here we present our experience for concurrent diseases between ANKA associated CGN and other ICD from a 4000-bed large health system (8 hospitals) over the past 10 years.

Methods: We evaluated our data base for 3757 renal biopsies over the past 10 years (2008 to 2018) and identified 13 cases with dual diagnoses of CGN and another ICD. Their clinical data were collected and pathologic findings are evaluated in detail.

Results: The concurrent cases represented 0.35% of our overall biopsies (13/3757). Patients’ ages ranged from 48 to 76 years old. There were 8 female patients and 5 male patients. All 13 patients had positive ANCA and CGN. Crescent percentage in the biopsies ranged from 10% to 78%. The other ICD included many types including membranoproliferative glomerulonephritis type 1 (MPGN, n = 5), post-infectious glomerulonephritis (n = 2), membranous glomerulopathy (n = 1), mesangial proliferative glomerulonephritis (n = 1), type 3 lupus nephritis (n = 1), type 2 lupus nephritis (n = 1), IgA nephropathy (n = 1), and MPGN type 3 (MPGN, n = 1). Most of the ICD appeared to be mild, except one type 3 lupus nephritis debarable for primary or secondary crescent formation.

Conclusions: The crescent formation appeared to dominate in most cases, leading us to believe that the crescent formation was mainly related to positive ANCA rather than minor ICD in most cases. Our findings support previous reports that there is a rare entity of overlapping syndrome composed of ANCA associated CGN and another ICD. Follow-up and analysis will be done to compare to the cases with only ANCA associated CGN for their clinical outcomes.

PUB252
Membranous Lupus Nephritis Wearing the Mask of Minimal Change Disease: A Case for Caution
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Introduction: Rarely, patients with systemic lupus erythematosus may present with lupus nephritis (LN) alone and have no extra renal manifestations. We herein present one such case with other atypical features on serology and renal biopsy.

Case Description: A 24-year-old otherwise healthy Hispanic man presented with worsening shortness of breath and swelling in the feet. Laboratory data was consistent with nephritic syndrome with a serum albumin of 0.8 g/dL (3.2-5). LDL-cholesterol 452 mg/dL [20-129] and 24-hour urine protein of 8.7 g. Serum creatinine was normal. There was no history of rash or joint pains. Serologic work up for syphilis and viral hepatitis was negative. Antinuclear antibody test was positive (1:80) but anti-double stranded antibody and anti-smith antibody were negative. Serum complements were normal. A renal biopsy was obtained and the light microscopy (LM) was unremarkable suggestive of minimal change disease. He was started on steroid therapy and later immunofluorescence (IF) was reported as ‘full house’ pattern and electron microscopy (EM) showed subepithelial, mesangial and subendothelial deposits in addition to tubuloreticular inclusions consistent with membranous LN [Figure]. The patient was started on Mycophenolate mofetil therapy.

Discussion: Our case represents atypical presentation of SLE in a young male with isolated renal involvement and without anti-double stranded DNA or anti-smith antibodies. It also highlights the importance of obtaining renal biopsy and more importantly, the utility of IF and EM. The management of minimal change disease, as suggested by LM alone in our patient differs significantly from membranous LN. While standard in developed countries, nephrologists in several resource-poor countries have to pick patients who need these advanced microscopic studies. If EM cannot be performed routinely in all cases, a small portion of renal tissue should be saved in an appropriate fixative, to perform at a later date if needed.

PUB253
Clinical Implication of Fractional Excretion of Proteins: Albumin, A1-Globulin, A2-Globulin, B-Globulin in Patients with Nephrotic Syndrome
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Background: Diagnostic approach on underlying disease of nephrotic syndrome is a very important process in management of nephrotic syndrome. Besides traditional kidney biopsy and serologic tests, a few novel diagnostic approaches have been tried in this study.

Methods: 42 adult nephrotic patients, biopsy-confirmed with membranous glomerulonephritis (MGN) (n = 30) and minimal change disease (MCD) (n = 12) at Hallym University Medical Center from 2012 to 2016, were included. With those patients, fractional excretion (FE) of proteins (albumin, a1-globulin, a2-globulin, b-globulin, g-globulin) was retrospectively calculated from data of urine electrophoresis (UEP) and serum electrophoresis (SEP), which had been examined mainly to identify if there was monoclonal gammapathy or polyclonal gammapathy in the patients. Creatinine concentrations of urine and serum to calculate FE of each protein were from data of the same urine and serum samples for UEP and SEP examinations. Patients with serum creatinine > 1.2ng/dl and albumin serum > 3.0g/dl were excluded. To assess diagnostic performance of FE of the proteins, we used receiver-operating characteristic (ROC) analysis.

Results: There was not significant difference in age and serum creatinine levels between the two groups. MGN groups were lower in MCD group in all urea markers and MCH. MCD group (1.38 vs. 2.03, p < 0.001). FE of albumin (p = 0.021) and g-globulin (p = 0.023) was significantly higher in MCD group than in MGN group. However, differences in FE of a1-globulin (p = 0.062), a2-globulin (p = 0.466) and b-globulin (p = 0.129) between the two groups were not significant. Area under the ROC curve for FE of albumin and g-globulin were 0.770 (95% CI 0.602-0.938 p = 0.007) and 0.741 (95% CI 0.578-0.904, p = 0.016), respectively. A FE of albumin > 0.202 could distinguish MCD from MGN with 75% sensitivity and 79.3% specificity. FE of g-globulin > 0.029 also could do with 75% sensitivity and 51.7% specificity.

Conclusions: Authors, for the first time, tried FE of albumin, a1-globulin, a2-globulin, g-globulin as a tool to predict diagnosis of underlying causes of nephrotic syndrome. This method can be used as a helpful assistant method to make differential diagnosis on MGN and MCD in nephrotic patients with normal renal function.

PUB254
Relapse of Nephrotic Syndrome After Adrenocorticotropic Hormone Induced Remission: Implications of ACTH Antibodies
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Background: Treatment of relapsing nephrotic syndrome is challenging despite newer immunosuppressive medications. Prolonged glucocorticoid use is the mainstay in management of proteinuric glomerulopathies but has extensive side effects. Alternatives like adrenocorticotropic hormone (ACTH) have been successfully used to treat refractory proteinuric nephropathies with superior outcomes compared to standard treatment. More than clinical responsiveness to ACTH therapy may vary, partly due to the development of de novo or acquired resistance.

Methods: A 25-year-old woman with steroid-dependent FSGS developed severe steroid side effects impacting her quality of life. ACTH treatment with initially successful dose showed brievery subcutaneous injections of repository corticotropin of porine origin was started. Immediate remission of proteinuria & reversal of steroid side effects was noted followed by a relapse of proteinuria & swelling in 10 weeks. In suspicion of ACTH-antagonizing factors, the patient’s serum was collected & processed for Immunoblot-based antibody assay.

Results: Standard porcine ACTH was subjected to immunoblot analysis by incubating the blots with a rabbit anti-ACTH antibody as a positive control or with the patient’s serum. The blots were developed using an anti-rabbit or anti-human IgG secondary antibody. Blots were probed by normal standard human serum & no bands demonstrated (control). Immunoblots developed by using patient’s serum revealed abundant IgG antibodies reactive to a peptide band also probed by the anti-ACTH positive control antibody, suggesting the presence of high titers of anti-ACTH antibodies. ACTH antibodies were not associated with any clinical signs of hypersensitivity, or other side effects except a delayed-onset resistance to ACTH therapy, entailing that these antibodies are likely specific for porcine ACTH & have negligible cross-reactivity with the patient's native ACTH.

Conclusions: ACTH is valuable in treatment of refractory proteinuric glomerulopathies. However, as is common with treatment with any biologic medication, natural ACTH, regardless of purity or origin, is antigenic in humans. It may cause formation of neutralizing antibodies in some sensitive patients, ensued by acquired resistance to ACTH. Thus, studies need to be done to develop ACTH analogs with less immunogenicity for improving its responsiveness in patients with glomerular diseases.
Analysis of Clinical and Pathological Features of Renal Injury in Primary and Secondary Malignancy Hypertension

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Background: To understand different clinical and pathological features of renal injury among primary and secondary malignancy hypertension (MHT) patients.

Methods: 143 cases of MHT patients with complete clinical and pathological records in the past 19 years were selected and analysis was performed respectively. Clinical variables including serum creatinine, urinary analysis. Renal pathological evaluation including the stenosis of small renal artery which was expressed as the ratio of inner and outer diameter of the small artery, ischemic glomerulus of kidney (including shrinkage and sclerosis), global sclerosis of glomerulus, the ratio of crescent to whole glomerulus, interstitial infiltration of inflammation cells, the area of renal interstitial fibrosis and renal tubular atrophy.

Results: Here were 50 cases of primary MHT, 42 male, 8 female, average age was 36±9; there were 93 cases of renal parenchyma related MHT male 74 and female19, average age was 34±8 (no significant difference of sex and age between two groups). 1. clinical features: etiological distribution among renal parenchyma related MHT showed 73 (77.4%) cases were IgA nephropathy. Compared with primary MHT; the amount of proteinuria in the renal parenchyma related MHT group was significant higher. (1.4±1.90 VS 3.3±2.2±4.8/dl, P<0.01), 2. pathological features: the typical pathological change in renal parenchyma related MHT was hypertrophy of endomysium which was described as "onionskin" like proliferation. Compared with primary MHT group, this feature was significantly lower in renal parenchyma related MHT group (100% VS 38.0%, P<0.01), renal small artery stenosis in renal parenchyma related MHT group was lower (the ratio of inner and outer diameter of small artery was 0.25±0.07 VS 0.44±0.08, P<0.05),ischemia changes was fewer (81a±13% and 42±23%, P<0.01),higher prevalence of glomerular global sclerosis (0.6±2.1% and 16.4±17.5%, P<0.001), higher prevalence of crescent formation(2.3±1.2% and 9.5±3.4%, P<0.001).

Conclusions: Renal parenchyma diseases are common etiology of MHT, especially among IgA nephropathy (about three-forth among this group of patients). Compared with primary MHT, the renal parenchyma related MHT always appears as more proteinuria, pathological feature is characterezed by more crescent, less "onionskin" like proliferation, less stenosis in renal tubular, less ischemia glomeruli.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Causes of Primary Nephrotic Syndrome in Adults Stratified by Race: An Update

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Background: It has been recognized that the incidence of glomerular diseases varies significantly by race. Membranous glomerulopathy (MGN) has been classically the most common cause of primary nephrotic syndrome (NS) in adults but data from the 1990s showed that focal glomerulosclerosis (FSGS) was increasingly common, especially in black and Hispanic populations. In fact, FSGS appeared to surpass MGN to become the most common cause of NS in these racial groups, and some suggested this may be the case for whites as well. We undertook this study to look at the racial breakdown of NS in the 2000s from our biopsy population. We also carefully excluded patients with evidence of secondary disease and without full NS, which has not always been done in prior reports.

Methods: We reviewed all renal biopsies from the Northwell database, available from 2017-2018 (n=532) and from Lenox Hill Hospital specifically from 2010-2016 (n=143). We extracted all cases of nephrotic syndrome and then excluded cases with secondary disease. Charts were reviewed for clinical data including race.

Results: Overall, there were 97 cases of primary NS including 39.2% MGN, 29% minimal change disease (MCD), 16.5% FSGS, 11.3% IgA nephropathy (IgAN), and 4% membranoproliferative (MGNP). In the primary NS population, overall there were 43 whites, 21 blacks, 16 Asians, 10 Hispanics, and 9 multiracial patients. Among whites, MGN was the most common cause of NS 40.2%, followed by MCD 31%, IgAN 14%, FSGS 8% as MGN 5%. For blacks, FSGS was the most common cause with 37.5%, followed by MGN 32%, MCD 21%, MPGN 5% and IgAN 5%. Among Asians, both MGN and MCD were seen in 41%, FSGS 12% and MPGN 6%. In Hispanic patients, MGN was found in 40%, IgAN 30%, FSGS 20% and MCD 10%. Among the 38 cases of primary NS in African-Americans, 22 were positive for PLA2R antibody on biopsy, which represents 58%. Of the 16 cases of FSGS, 31.3% race were classic FSGS, 37.4 had lip tip lesion, and 31.3% were collapsing.

Conclusions: This study updates the racial distribution of primary nephrotic syndrome. We found that MGN continues to be the most common cause of primary NS overall in our population. Unlike previous reports, FSGS is a relatively uncommon cause of NS in whites (less than MGN and IgAN). In blacks, FSGS remains the most common form of NS, supporting previous reports from the 1990s suggesting a marked increase in this population.

Gliomerular Diseases Epidemiology in the Wayú of the Colombian Caribbean Region

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Introduction: The epidemiology of glomerular diseases has been extensively studied in other ethnic groups and in the general population. No studies have been performed in the Wayú people, a group that represents 0.2 in the indigenous towns that are found in Colombia, corresponds to 45% of La Guajira population. Despite this, is one of the 18 that are in danger of disappearing. This is due to the violence, displacement and extreme poverty experience by Wayú people, as well as a notable lack of access to health services. The objective was to characterize the glomerular diseases, primary and secondary in the Wayú community in the Colombian Caribbean region that are in the Nephrology Colombian Register - NecroReD.

Methods: A descriptive and retrospective study was carried out in the Caribbean Colombian region. All the patients belonged to the Wayú Ethnic group, adults with Glomerular diseases. Those who had a renal biopsy with a diagnosis of GD between January 2008 and June 2018. All the patients were evaluated under clinical indications in a reference hospital. The histopathological findings by optical microscopy and immunofluorescence were correlated with the patients clinical history.

Results: A total of 48 renal biopsies were analyzed. The main clinical indication for the biopsy was nephritic syndrome (36%). The secondary (SGD) were more frequent than the primary (PGD), 55% versus 45%. For PIGD, the lupus nephritis was the most frequent etiology (83%) and the main nephrological syndrome was nephritic syndrome (36%). Membranous nephropathy (33%) and segmental focal glomerulosclerosis (19%) were the SGD most frequent and the primary nephrotic syndrome (22%) was the main biopsy indication 58%.

Conclusions: The GD epidemiology revealed a predominance of SGD due to the relative high frequency of lupus nephritis in this population. Since the NEFRORD® establishment, the data collected in this document are relevant to obtain a better understanding of GD in Latin America which improves the early reference of patients to clinical care and the usefulness of a database for future studies.
Online Thai Glomerular Disease Registry: Paraprotein-Related Kidney Diseases

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Background: Paraproteinemic-Related Kidney Disease (PRKD) is the group of kidney diseases derived from the deposition of paraproteins or monocular immunoglobulins in the kidney, which are associated with the immunoproliferative disorder and non-proliferative renal diseases. Amyloidosis and monoclonal Ig deposit diseases (MIDD) including light chain deposit disease (LCDD), and heavy chain deposit disease (HCDD) are the frequent glomerular involvement and lead to end stage renal disease approximately 20-60% within 1 year. Our study aimed to demonstrate the PKD in Thai Glomerular Disease Registry.

Methods: We conducted a prospective cohort study in the adults’ native kidney biopsy proven glomerular diseases between July 2014 and April 2019. The clinical and laboratory parameters at the time of biopsy, pathologic findings, treatment regimens and clinical courses of amyloidosis and MIDD were recorded within the online registry.

Results: We found the prevalence of amyloidosis and MIDD was 0.85% (18 amyloidosis, 3 LCDD, and 1 HCDD from 2,385 patients). The male to female ratio was 1.2:1. The average age, creatinine, albumin, glomerulus, and UPC4 were 64 (39-86) years, 1.6 (0.6-7.2) mg/dl, 2.43±0.8 g/dl, and 3.1±0.6 mg/dl, and 5.5 ± (1.6-11.9) g/dl. The average K-L ratio in amyloidosis and LCDD were 0.33(0.03-19.54) and 15.79(0.78-30.8), whereas in HCDD was 46.78. The patients presented with 77.3% of nephrotic syndrome, 9.1% of nephritic nephritis, 4.5% of nephritis, 4.5% of asymptomatic proteinuria and 45.5% of initial Cr<1.2 mg/dl. Median time to biopsy was 15.1 weeks (3-56.5 weeks). We found 7 multiple myeloma and 2 MGUS in our group. Only 2 cases had amyloid heart disease. Steroid with the chemotherapy was prescribed in 16 patients and 1 case followed by autologous stem cell transplantation. During of the median time follow up 11.5 months, we found remission in 4 cases (3-velcade based regimen, 1-ASCT), ESRD in 1 case(no chemotherapy), and dead in 5 cases after chemotherapy. The cause of dead was infection in 4 cases, and found dead probably from amyloid heart in 1 case.

Conclusions: Our study described the rare disease including amyloidosis and MIDD, but nephrotic mortality was found in this group. Most of the patients presented with initial high creatinine and time to biopsy was quite delay. The high mortality rate from infections reminded us to reconsider the effective and safety regimen.

TAFRO Syndrome with Initial Presentation of Renal Thrombotic Microangiopathy: Cases Studies of One Medical Center in Taiwan

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Background: Castleman disease is one kind of benign lymphoproliferative disorder, with specific histopathologic feature of lymph nodes. According to the involved area, it could be divided to unci-centric and multi-centric form. Multi-centric Castleman disease frequently have systemic manifestation, including to several subtypes such as TAFRO syndrome and idiopathic plasmacytic lymphadenopathy (IPL). All kinds of Castleman’s disease would have renal manifestation. According to the literatures, renal thrombotic microangiopathy are frequently found in these patients. To date, there are few articles reported the manifestation of Castleman disease in Taiwan. We conduct a study to investigate the renal manifestation of Castleman disease.

Methods: This investigation was performed in a tertiary hospital. From 2000-2018 period, there are totally 125 patients receiving lymph node biopsy confirmed as Castleman’s disease. After review of medical records, there are 3 patients with definite diagnosis of TAFRO syndrome. All of these 3 patients have renal manifestations of hypertension, sub-nephrotic proteinuria and microscopic hematuria. 2 of these patients received renal biopsy.

Results: Case 1 is a 25-year-old male with initial presentation of fever, anasarca, thrombocytopenia, hepatosplenomegaly, multiple lymphadenopathy and acute glomerulonephritis. The histopathologic feature of lymph node biopsy is hyaline vascular type. Renal biopsy revealed feature of thrombotic microangiopathy. Case 2 is 1 man with systemic manifestation including anasarca, thrombocytopenia, hepatomegaly, multiple lymphadenopathy and acute glomerulonephritis. The histopathologic feature of lymph node biopsy is plasma cell type. Renal biopsy also revealed feature of thrombotic microangiopathy.

Conclusions: Renal involvement is frequently found in multicentric Castleman disease. We reported 2 cases of TAFRO syndrome with initial presentation of renal thrombotic microangiopathy. Further research is still needed to investigate the pathogenic mechanism.

ForMe: The German Focal Segmental Glomerulosclerosis and Minimal Change Disease Registry

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Background: Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are leading causes of nephrotic syndrome and associated with a relevant risk for the development of chronic renal failure and insufficiency and severe hypertension. Incidences and prevalences vary significantly among Western countries. Within the German population, both MCD with an incidence of 3.2 per million population and FSGS with an incidence of 11.2 per million population are classified as rare diseases. There is a lack of systematic, large-scale, randomized intervention studies.

Methods: Within the framework of the DFG-funded Clinical Research Unit CRU 329 “Molecular Mechanisms of Podocyte Diseases - Nephrology on the Way to Precision Medicine” (The ForMe registry (The German Focal Segmental Glomerulosclerosis and Minimal Change Disease Registry) has been established as a nation-wide registry for pediatric and adult patients. It aims to collect 150 pediatric and 350 adult MCD and FSGS cases within the next 10 years. Within the registry, laboratory and clinical anamnestic history of patients are linked with histopathological findings. Clinical data is collected systematically at inclusion and throughout the course of disease. Biological patient samples such as serum, RNA, DNA, and tissue biopsy material are conserved and cataloged within the BioMaSOTA biobank already established at the University of Cologne, Germany. Additional centers are going to be initiated in the near future.

Conclusions: The ForMe registry is recruiting since April 2019. As the central and largest resource center for MCD / FSGS registry it will enable a translational approach to reconfirm the results of basic molecular research using precisely characterized human biomaterials and to develop new diagnostic and therapeutic approaches in the long-term.

How Lupus Glomerulonephritis Affects Renal Reserve?

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Background: Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE), which has different manifestations such as urinalysis alterations, nephrotic syndrome, nephritic syndrome, rapidly progressive renal failure and evolution to end-stage chronic renal disease. Renal reserve (RR) is the kidney’s ability to increase its basal glomerular filtration rate (GFR) by at least 20% after a protein overload. As far as we know there is no previous report regarding how acute lupus glomerulonephritis and its treatment affect RR. Thus, we decided to evaluate the RR in three young women suffering from a recently diagnosed lupus glomerulonephritis, and then we reevaluated their RR after they were treated with immunosuppressant drugs.

Methods: RR test consisted of obtaining two consecutive fast minuted-creatinine clearances (basal GFR) after an adequate patient’s oral hydration (15 cc/Kg of tap water). Then, a high protein meal based on dairy products (1.2 g/Kg of protein) was delivered, and seventy minutes later, three successive minuted-creatinine clearances were measured. Finally, the difference between the higher post-prandial creatinine clearance (pick value) and the average between the two pre-prandial creatinine clearances (basal value) was obtained.

Results: RR was abolished (RR<0%) in the LN patients without treatment, while it was positive (RRa<20%), borderline (RR a 5%) or negative (RR<5%), depending on their prescribed treatment: patient 1 and patient 2 were treated with double immunosuppressant treatment during 12 and 6 months, respectively; while patient 3 was treated only with methylprednisolone during 6 months.

Conclusions: It seems that the lupus glomerulonephritis abolished the patient’s renal reserve, which can be recovered by prescribing double immunosuppressant therapy.

Urinary Sodium Is Associated with the Degree of Proteinuria in Patients with CKD

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Background: Increased urinary sodium excretion, representing dietary sodium intake, is associated with hypertension. Low sodium intake has been associated with increased mortality in observational studies. Sodium and fluid retention is a hallmark and a challenge of the nephrotic syndrome (NS). This study aimed to evaluate the association between 24-hour urinary sodium and proteinuria in patients with nephrotic syndrome.

Methods: We enrolled 1,142 patients with chronic kidney disease in Jiaozuo Provinc Hospital from May 1,2017 to May 1,2019. 24-hour urinary sodium and potassium was measured. In this group, Spearman correlation and partial correlation analysis were used to study the correlation between 24-hour urinary sodium and 24-hour proteinuria. We performed multivariate linear regression models, taking several covariates into account, including baseline eGFR and proteinuria.

Results: In our study, 24-hour urine protein ranged from 17mg to 42003mg. 24-hour urine sodium ranged from 17mg to 42003mg. 24-hour urinary sodium was positively correlated with 24-hour proteinuria(r=0.102, P<0.001). Additionally, 24-hour urinary sodium was positively correlated with 24-hour urinary creatinine(r=0.354, P<0.0001). After adjusting the age, sex, BMI, eGFR and proteinuria, sodium was positively correlated with 24-hour urinary creatinine(r=0.354, P<0.0001).

Conclusions: We found that in patients with CKD,24-hour urinary sodium positively associated with protein excretion, these data support high urinary sodium associated with marginal renal function, but whether the change of 24-hour urinary sodium as time goes by can influence the progress of renal failure need to be investigated to study.

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Mepolizumab Therapy in Eosinophilic Granulomatosis with Polyangiitis as a Steroid-Sparing Therapeutic Approach

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Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is characterised by the presence of tissue eosinophilia, necrotising vasculitis and granulomatous inflammation which can lead to renal failure. In the recent trial, Mepolizumab (MEPO) In Relapsing or Refractory EGPA [MIRRA], treatment with the monoclonal antibody directed against IL-5 (300mg), accrued longer times in remission, reduced steroid exposure and relapse rates. Identifying disease phenotypes such as organ involvement or the phasic stages of the disease, along with assessment of efficacy of 100mg would further guide the role of anti-IL5 therapy.

Methods: This retrospective, descriptive study analysed 8 patients with EGPA according to the American College of Rheumatology criteria or Chapel Hill Consensus definition. The aim of our study was to analyse the response and outcome for EGPA patients who received 100mg s/c of MEPO monthly for 52 weeks. Time points of commencement of MEPO and week 48-52 assessments were compared.

Results: MEPO was well tolerated and considered of clinical benefit, with seven/eight patients [87.5%] continuing therapy beyond 12 months, whilst on 100mg dosage. Four patients had prior therapy with rituximab and five had adjuvant conventional therapy. Seven had lower steroid therapy.

Conclusions: The study supports the efficacy of the steroids sparing capacity of anti-IL-5 therapy for treatment of EGPA. Adjuvant therapy with conventional immunosuppressants was well tolerated and renal function was preserved. REFERENCES
Renal Chronicity Score a Predictor of CKD Progression in Glomerulopathies

Jinhee L. Diaz villar, 1 L. M. Perez-Navarro, 1 Flor E. Rojas, 2 Angela M. Cordoba hurtado, 1 Ivan Rosero, 2 Virgilia Soto, 1 Rafael Valedez-Ortiz. 1Hospital General de México Dr. Eduardo Lizárraga, México City, Mexico; 2Hospital General de México City, Mexico; 1Universidad Nacional Autónoma de México, Ciudad de México, Mexico; 1INC Ignacio Chavez, Mexico City, Mexico.

Background: Chronic changes on renal biopsies are a strong predictor of chronic kidney disease (CKD) progression. The Renal Chronicity Score (RCS) grades the chronic changes based on severity and it has been proposed as a systemic approach to predict CKD progression.

Methods: Retrospective study of consecutive subjects with renal biopsy and Glomerulopathy in which clinical data and histological analysis were taken. The data was assessed for descriptive and inferential statistics using t-test, χ²-test and Cox-regression-analysis to predict progression to CKD (GFR <60mg/dL) p ≤0.05 was considered significant.

Results: Five hundred subjects with renal biopsy and Glomerulopathy with a mean age of 39.1±15 years (43% female) were included. There were 157 subjects (31%) with Primary Glomerulopathy (PG) and 186 subjects (54%) with Secondary Glomerulopathy (SG). In the PG group 39% of the patients had focal and Segmental Glomerulosclerosis (FSGS), 27% had Membranous Nephropathy (MN), 17% had IgA Nephropathy, 15% had Membranoproliferative Nephropathy and 2% had Minimal change disease. In the SG group 45% of the patients had lupus nephritis, 25% had diabetic nephropathy, 13% had FSGS, 10% had vasculitis, 6% had paraproteinemia and 1% had secondary MN. There were significant differences among both groups in Creatinine, Hemoglobin and CKD-EPI p<0.001. Differences in The HR for developing CKD in PG and SG are shown in figure 1-a.

Conclusions: RCS is associated to CKD progression at 6 months in primary and secondary Glomerulopathies. RCS is a good prognostic tool in primary and secondary glomerulopathies.

References:
Due to the length of the paper, the references are not included in this excerpt. Please refer to the original publication for the complete list of references.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Effect of Sociodemographic Characteristics of Hemodialysis and Pre-Dialysis Patients on Treatment Burden

Abdullah I. Hamad,1 Asma M. Almansouri,1 Fadwa M. Al-Ali,1 Rania A. Ibrahim,1 Mincey M. Mathew,1 Nadir Kheir,1 Mohamed Izham,2 Ahmed Awaisu.1

1Hamad Medical Corporation, Doha, Qatar; 2Qatar University, Doha, Qatar; 3Pharmacy School, Auckland, New Zealand.

Background: Treatment burden is the load imposed by healthcare on patients. The impact of sociodemographic factors on treatment burden has not been adequately studied in patients with chronic kidney disease (CKD). We are conducting the first study to investigate treatment burden among CKD patients in Qatar.

Methods: We conducted a cross-sectional study at FBHC (the largest in Qatar with 465 hemodialysis (HD) patients and 230 pre-dialysis patients with GFR <20 ml/min). Treatment burden was evaluated using the Treatment Burden Questionnaire (TBQ), which contains five domains (medications, lifestyle, social, financial, and administrative burdens). Data were analyzed using SPSS version 24.

Results: A total of 223 HD and 57 pre-dialysis patients were included. Age was 59 +/- 19 years and 54.6% were males. HD patients were more likely to be single, widowed or divorced compared to pre-dialysis (36.3% vs. 17.5%; p = 0.03). Pre-dialysis group reported higher college degrees and employment compared to HD (45.6% vs. 24.2% (p = 0.006) and 56.1% vs. 25.1% (p<0.001), respectively). Native Qataris were more represented in HD compared to pre-dialysis (62.8% vs. 22.8%; p<0.001). Treatment burden (measured by TBQ score) was significantly higher in HD versus pre-dialysis patients (45 versus 25 p = 0.001). The influence of sociodemographic factors on TBQ score among CKD patients is summarized in (Figure 1). Poorly educated, unemployed and retired patients had the highest TBQ score (p<0.001).

Conclusions: Treatment burden measured by TBQ is elevated among CKD patients in Qatar. Poor education, unemployment and retirement were associated with higher burden of treatment. Studying sociodemographic treatment burden among CKD patients will improve designing effective intervention strategies.

Funding: Government Support - Non-U.S.
**Methods:** This study assessed the sleep quality of 39 with non-dialysis CKD stage III-V (ND-CKD) patients and 25 hemodialyzed CKD stage V (HD-CKD) patients using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Poor sleeper was defined as individual with PSQI > 5. The markers of inflammation such as hs-CRP and blood-count-based marker were measured right after the PSQI data were taken.

**Results:** HD-CKD group has higher prevalence of poor sleeper and cumulative PSQI score (30% vs. 60%, p=0.029; PSQI 4.5±4.4 vs 8.6± p=0.038). In ND-CKD group, there is a association between short sleep duration with elevated diastolic blood pressure (r=0.421, p=0.005) and habitual sleep efficiency with platelet-to-lymphocyte ratio (r= 0.532, p<0.0001). In HD-CKD group, a requirement to use sleep medication was associated with elevated hs-CRP level (r=0.434, p=0.030) and decreased monocyte-to-lymphocyte ratio (r= 0.410, p=0.042).

**Conclusions:** Some features of poor sleep quality in CKD patients including low sleep efficiency, daytime dysfunction and requirement to use sleep medication were associated with increased diastolic blood pressure, hs-CRP and blood-count-based inflammatory predictors. Thus, poor sleep quality possibly acts as a mediating factor that exacerbates the CVD risk in CKD.

**Funding:** Government Support - Non-U.S.

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**Comparison of cumulative sleep quality index between ND-CKD and HD CKD groups.**

**PUB275**

**Açai Juice (Euterpe oleracea mart.) Supplementation Reduces Lipid Peroxidation in Hemodialysis Patients: A Pilot Study**

Denise Mafra,1 Isabelle C. Martins,2 Hervé Rogez,2 Maria d. Pinheiro,2 Keuri E. Rodrigues,2 Abner A. Lima,2 Jessyca S. Brito,1 Bruna Paiva,1 Luís C. Pinto,1 Andréa D. Reis,2 Barbarella D. Macchi,2 José L. Nascimento.2

**Background:** Chronic kidney disease (CKD) patients on hemodialysis (HD) present oxidative stress, which has a strong association with cardiovascular complications. Several nutritional therapeutic strategies have been used to reduce the oxidative stress in these patients, and the Amazonian fruit *Euterpe oleracea,* known as açai, has shown a protective effect against oxidative stress, since it is rich in antioxidants as phenolic compounds. There is no study that evaluated the effect of açai juice on oxidative stress in HD patients, then, the aim of this study was to evaluate the effects of açai supplementation on oxidative stress markers in HD patients.

**Methods:** This pilot study evaluated 18 HD patients assigned to either clarified and lyophilized açai juice supplementation with 20mL three times a week (1013 mg of gallic acid equivalent/100 mL), (8 patients, 55.5± 4.9 years, BMI 24.8± 2.5 Kg/m², 50.3± 11.3 months on dialysis) or control (no supplementation, 10 patients, 56.1± 3.4 years, BMI, 25.2± 0.7 Kg/m², 53.8± 10.1 months on dialysis) for eight weeks. Plasma levels of the oxidative stress markers malondialdehyde (MDA), nitrite, total glutathione (TG), catalase (CAT) and glutathione peroxidase (GPx) were evaluated before and after supplementation.

**Results:** Table 1 shows that MDA plasma levels were significantly reduced and, there was a tendency to increase the TG after açai supplementation.

**Conclusions:** Açai intake may be an alternative nutritional strategy to reduce oxidative stress markers in HD patients. However, more studies are needed to support this result.

**Funding:** Government Support - Non-U.S.

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**Oxidative stress profile before and after 8 weeks of supplementation with clarified acai (Euterpe oleracea) juice in HD patients.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After 8 weeks</th>
<th>p values</th>
<th>Baseline</th>
<th>After 8 weeks</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA (µmol/L)</td>
<td>30.2±7.5</td>
<td>25.2±6.9</td>
<td>0.04</td>
<td>32.3±7.6</td>
<td>21.7±5.8</td>
<td>0.00</td>
</tr>
<tr>
<td>Nitrite (µmol/L)</td>
<td>3.8±0.9</td>
<td>2.8±1.4</td>
<td>0.27</td>
<td>3.9±0.6</td>
<td>2.6±0.4</td>
<td>0.03</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>10.5±7.9</td>
<td>9.8±4.7</td>
<td>0.09</td>
<td>10.7±6.3</td>
<td>8.6±4.4</td>
<td>0.02</td>
</tr>
<tr>
<td>CAT (µE/µl)</td>
<td>11.1±1.4</td>
<td>11.1±1.6</td>
<td>0.42</td>
<td>11.4±1.2</td>
<td>9.7±1.3</td>
<td>0.10</td>
</tr>
<tr>
<td>GPx (µE/mg protein)</td>
<td>24±7.8</td>
<td>24±7.9</td>
<td>0.42</td>
<td>24±7.8</td>
<td>24±7.9</td>
<td>0.42</td>
</tr>
</tbody>
</table>

MDA = malondialdehyde; TG, total glutathione; CAT = catalase; GPx = glutathione peroxidase.

**PUB276**

**Serum Albumin Not Only a Marker of Nutrition: Multidisciplinary Interventions to Improve Albumin in a Peritoneal Dialysis Population in Qatar**

Mohamed A. Elesnawi,1 Fadwa M. Al-Ali,1 Vimala K. Lonappan,1 Aisha Abdulla,1 Sahar Aly,1 Linu chacko Chacko,3 Farrukh A. Farooqi,4 Tarek A. Fouda,5 Hanaa Ahmed.1

**Background:** Serum Albumin (SA) is a good predictor of adverse clinical outcomes in PD patients. At Qatar Fahad bin Jassam Kidney Center-HGH is the main provider for PD we had 180 PD patients and over the period of q3 & q4 2016 serum albumin (>34) fall down from the q1 & q2 2016, 65% & 64% to 57% & 54% respectively. With this hypoalbuminemia incident we decided to run a prospective improvement trial to improve the Serum Albumin level.

**Methods:** Multidisciplinary team was formulated that led by Nephrologist, and consist of PD Nurses, Dietician, Educator, Social worker and quality team to identify and to manage the hypoalbuminemia. We conducted a random survey to determine the food habits of patients, that taken almost routinely at home. We undertook root cause analysis for each case of hypoalbuminemia (SA<34) in the 6 months preceding the trial to identify any predisposing risk factors like inflammation, volume overload, effects of ARB medication, PD modality versus the peritoneal membrane, loss of protein through urine etc. Inadequate dialysis may result in the retention of uremic toxins which can among other things, suppress appetite and result in malnutrition and morbidity. With the inadequate dialysis, patients lead to malnutrition, easy tiredness, prone to infections and admissions and to mortality.

**Results:** Serum albumin level >34 gm/L improved from 54% to 70% by end of March-2019. As the SA improves there is a good impact on the adequacy, mortality, inflammation, control of DM, technique failure and total quality of life. Dialysis adequacy improves from 62% to 92%.

**Conclusions:** As we improve the Serum Albumin, patient’s general health status and quality of life improved While correcting the PD prescriptions, adequacy had an impact, results in increase the appetite of patients.

**PUB277**

**Dietary Patterns (DP) in CKD Are Influenced by CKD Treatment Modality**

Fernanda Sanjin,1 Daniela Canella,1 Camila A. Borges,2 Bengt Lindholm,4 Carla M. Avesani,1,2 Rio de Janeiro State University, Rio de Janeiro, Brazil; 2Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden; 3University of Sao Paulo, Sao Paulo, Brazil; 4Karolinska Institutet, Stockholm, Sweden.

**Background:** Dietary patterns (DP) are as important as food components such as protein and energy. We investigated DP in Brazilians with CKD and explored associations with treatment modality.
Methods: Weekly consumption of 12 food intake groups was analyzed cross-sectionally in 839 individuals (mean age 54 years, 45% females) from the 2013 Brazil National Health Survey with self-declared diagnosis of CKD undergoing non-dialysis (n=480), dialysis (n=48), and renal transplant (n=17) treatment or no CKD treatment (n=294). DP were derived by exploratory factor analysis of food intake groups. Food group and factor loading scores (0.35) were considered representative and used to define DP. Factor scores of DP were estimated for each person, a higher score indicating higher adherence to DP. Multiple linear regression models - adjusted by gender, age, education, skin color/race, rural/urban residence and geographical region - were used to evaluate associations between DP and CKD treatment.

Results: Two DP were identified: Unhealthy DP (positive loadings for red meat, sweet sugar beverages, alcoholic beverages and sweets and a negative loading for chicken, excessive salt and fish) and Healthy DP (positive loadings for raw and cooked vegetables, fruits, fresh juice fruit and milk). With untreated CKD as reference, Unhealthy DP was inversely associated with non-dialysis and dialysis treatment (β=-0.20; 95%CI: -0.33; -0.06) and β = -0.80 (-1.16; -0.45), respectively; these groups had lower adherence to Unhealthy DP than the untreated CKD group. Healthy DP associated positively with renal transplant treatment (β=0.32 (95%CI: 0.03; 0.62)) suggesting that renal transplant group had better adherence to Healthy DP compared to untreated CKD group.

Conclusions: Two dietary patterns were identified and were found to be associated with CKD treatment modality among Brazilians with CKD. These findings may inform future recommendations about dietary patterns in CKD patients.

Funding: Commercial Support - Baxter Healthcare, Government Support - Non-U.S.

**PUB278**

**Ratio of Bioimpedance at Right Leg as a Potential Screening Tool of Cardiomegaly or Hypoalbuminemia in General Population**

Haksoo Kim,1 Ji young Lee,2 Jai won Chang.1 Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; 2General health promotion center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.

Background: Under physiologic condition, the ratio of extracellular water(ECW) to total body water(TBW) remains tightly regulated in healthy persons. The impedance at low frequencies reflect ECW; at high frequencies, TBW. Hence, the ratio of bioimpedance at the right leg (rl-RBI) (impedance at 50KHz/impedance at 500KHz, measured by Inbody 720®, Biospace Co., Seoul, South Korea) will be maintained within normal range.

Methods: To define the normal range of rl-RBI, we measured the level of rl-RBI in healthy subjects (n=2012) without medical, surgical history and abnormal laboratory / imaging data. We classified our subjects by age, sex and body mass index (BMI) and calculated the ratio of rl-RBI. We found that the 30th percentile was at 0.35 and the 70th percentile was at 0.5 in our study population, which leads a challenge during hemodiafiltration sessions.

Results: Of 633 recalls analyzed, 53% indicated underreporting, 4% overreporting, and 43% acceptable reporting. Implausible reporters (23% of the cohort) had significantly higher body mass index (107 ± 27 vs 85 ± 21 kg, p<0.001), BMI (35 ± 9 vs 29 ± 7 kg/m2, p <0.001), parathyroid hormone (913 ± 771 vs 615 ± 565 pg/ml, p<0.024) levels and lower HDL cholesterol values (41 ± 14 vs 51 ± 19, <0.012). No differences were observed between implausible reporters and both KDQOL and anthropometric measurements.

Conclusions: Analyzing misreported diet data in HD patients may be useful in developing nutrition interventions targeted at improving dialysis specific outcomes. Implausible diet reports require further consideration before drawing conclusions between diet and health outcomes. (Supported by the Malaysian Palm Oil Board, Government of Malaysia)

Funding: Government Support - Non-U.S.

**PUB280**

**Echocardiographic Findings in Patients with CKD on Replacement Therapy with Hemodiafiltration**

Felix A. Matias, National Institute of Cardiology Ignacio Chavez, Ciudad de México, Mexico.

Background: Chronic kidney disease is a risk factor for the development of cardiovascular complications, being these by itself the most frequent cause of death in this group of patients. In our institute, cardiovascular evaluation has been essential to offer comprehensive care to our patients.

Methods: Retrospective study of a transversal cohort. Patients of the hemodiafiltration unit of our institute were evaluated by 2D echocardiography during the period from 2016 to 2019. Emphasis was placed on the search for ventricular ejection fraction, ventricular mass as well as pulmonary arterial hypertension data such as systolic pressure of the pulmonary artery (PASP), maximum tricuspid regurgitation velocity (TR V) and left atrial size, aortic valve, and mitral valve function. The hemodialysis therapy with Hemodiafiltration was used in the analysis.

Results: We analyzed 36 patients, 27 women and 9 men in the aforementioned period, who underwent 2D echocardiography: The average age of 37.08 years (range of 21 to 85). The average ventricular ejection fraction (LVEF) of 55.1% (range from 27 to 68.1%), was the average ventriculographic mass index was 120.42 g/m2. TAPSE (displacement of the tricuspid annulus) average of 21.47 mm. Right ventricular systolic function (FAC) was 45.17% on average. Regarding the pulmonary arterial hypertension data, the average PASP was 42.68 mmHg; 43 mmHg the average in men and 42.57 mmHg the average in women. The average TRV of 2.66 m/s; Average in men of 2.72 and women of 2.64.

Conclusions: Defining pulmonary hypertension (PH) as a PASP ≥50 mmHg or TRV ≥2.5 m/s, 5 and 3 patients were detected respectively. Considering diagnosis of HP suspicion, a PASP between 35-49 mmHg or a TRV of 2.8-3.4 m/s, 21 and 11 patients were detected respectively. It was also shown that ventricular systolic dysfunction is a frequent problem in our study population, which leads a challenge during hemodiafiltration sessions.

Funding: Government Support - Non-U.S.

**PUB281**

**Long-Term Renal Outcomes in Spontaneous Renal Artery Dissection: A Single-Center Experience**


Background: Spontaneous renal artery dissection (SRAD), defined as dissection of the renal artery in the absence of trauma or arterial intervention, is extremely rare. Long-term clinical outcomes are not well described and hence there is no consensus on the ideal treatment and follow up of patients with SRAD. We report long term clinical outcomes in SRAD at an university hospital.

Methods: We used the integrated data repository to identify all patients with a diagnosis of ‘renal artery dissection’ between 1/2012-8/2019. A total of 54 patients met the criteria. Two authors independently performed chart review. Only five patients met criteria for SRAD.

Results: Median age at the time of diagnosis was 64 years (Range 45-82 years). Of the five patients, 60% (n=3) were males and 40% (n=2) were Caucasian. Majority of the patients (80%, n=4) were either current or former smokers and had a history of hypertension. None had diabetes. One patient was suspected to have fibromuscular dysplasia while no predisposing disease or precipitating factors were identified in others. Mean admission creatinine was 0.89mg/dL (0.54-1.2 mg/dL). Two patients developed a new kidney injury attributed to contrast, that resolved by discharge. Interestingly, more than half (60%, n=3) had evidence of renal infarction. Patients were initially treated...
with anticoagulation (n=3), antiplatelet therapy (n=4) or a combination of the two (n=2). Only one patient required endovascular stent placement. The median follow up duration was 42 months. Follow up data showed no recurrent dissection in any of the patients. None of the patients developed chronic kidney disease (eGFR <60 ml/min), doubling of creatinine or end stage renal disease during the follow up period.

Conclusions: Our study showed that SRA is rarely associated with AKI. Recurrences are rare and majority of our patients have preserved renal function on follow up. In patients with no underlying disease predisposing to renal artery dissection, the benign clinical course supports conservative management.

**PUB282**

**Patient- and Societal-Level Factors Associated with Acute Decompen-
ated Heart Failure (ADHF) Admission**

Shweta Bansal,1 Kristina M. Munoz,2 Chakravadhar Velagapudi,2 1University of Texas Health at San Antonio, San Antonio, TX; 2University of Texas Health Science Center at San Antonio, San Antonio, TX, 1Central Michigan University College of Medicine, Mount Pleasant, MI.

**Background:** In the United States, a million patients are admitted annually with ADHF and approximately 25% of these are readmissions with 30 days. Much needs to be learnt about the root causes which lead to hospital readmission for better allocation of resources. We aim to identify factors associated with ADHF and hospital admission at the patient and societal level.

**Methods:** We reviewed charts of consecutive 109 congestive heart failure patients who admitted at the University Hospital, San Antonio with ADHF and were potential participants of a study evaluating usefulness of high-dose aldosterone antagonist for loop-diuretic resistant ADHF. Patient charts were examined for demographics, clinical parameters, and possible reasons leading to volume overload and hospital admission. The reasons were categorized into following six groups: A) unable to afford medications; B) noncompliance with medications and/or dosage; C) no regular healthcare/insurance; D) noncompliance with food and/or diet restrictions; E) admission despite compliance with medications and dietary restriction; and F) couldn’t determine.

**Results:** The mean age of study cohort was 56.13 yrs, 68% were male, 63% were Hispanics, 51% had diabetes, ejection fraction (EF) was 31±18% and pulmonary arterial systolic pressure (PASP) was 45±22mmHg. Lack of healthcare/insurance (Gr C) and medication non-compliance (Gr B) were the most common causes (43%) for ADHF admission. Admission despite compliance with medications and dietary restriction (Gr E) was the next common reason (30%), suggestive of either disease progression or inadequate dose of diuretics. No information was available regarding frequency of encounters within health care to allow adjustment in the dose of diuretics. On multiple comparison analysis, group C population with no regular health care/insurance was younger than rest of the groups. However, other demographics and co-morbidities did not differ between these groups. Moreover, the heart failure severity assessed by EF and PASP was also similar among all the groups.

**Conclusions:** Lack of accessibility to the health care and medications was the most common reason for ADHF admission in our study population. This group comprised of younger population. The results of our analysis provide guidance for the local health care policies to reduce ADHF admission and hospital cost.

**Funding:** Commercial Support - Relypsa, Inc, a ViVor Pharma Group Company

**PUB283**

The Association of Dialysis Modality and Cardiovascular and Infectious Diseases: Peritoneal Dialysis vs. Hemodialysis

Masataka Banhodami, Hideki Kawanishi, Misaki Morishi, Sadanori Shintaku, Shinichi Tsujiya, Tsuichiya General Hospital, Hiroshima, Japan.

**Background:** In end-stage kidney disease (ESKD) patients undergoing peritoneal dialysis (PD) or hemodialysis (HD), cardiovascular diseases (CVDs) and infectious diseases (IDs) are the most common causes of hospitalization and death. However, the association of dialysis modality and CVDs or IDs remains controversial.

**Methods:** This is a retrospective observational cohort study. Emergency hospitalization and mortality for CVDs and IDs excluding PD-related infections from 2010 to 2014 were evaluated between propensity score-matched PD and HD patients. Using Cox proportional hazards regression with adjustment for patient factors in December, 2009, risk factors of emergency hospitalization and mortality for CVDs and IDs were evaluated between the PD and HD patients.

**Results:** In matched 130 PD (75 men; mean age, 65.4 years; mean dialysis vintage 3.3 years) and 130 HD (70 men; 66.6 years [P=0.4]; 3.1 years [P=0.5]) patients among 135 PD and 766 HD patients, emergency hospitalization rate (hospitalizations/person-years) for CVDs was significantly higher in PD group compared with HD group (0.138 versus 0.066, P=0.002). In log-rank test, CVD mortality was significantly higher in PD group compared with HD group (P=0.001). In Cox proportional hazards regression model, only PD was a significant predictor of both emergency hospitalization (HR, 2.70; CI, 1.53-4.77; P=0.001) and mortality (HR, 4.41; CI, 1.66-11.72; P=0.005) for CVDs, as well as age. Whereas, there were no associations between PD and emergency hospitalization and mortality for IDs in Cox proportional hazards regression model.

**Conclusions:** In this study, PD was one of the risk factors for CVDs in ESKD patients. PD patients should be maintained by strict control of body fluid balance. 

**PUB284**

Development of an Inpatient Registry for Kidney and Hypertension-Related Disorders at Yokohama: The YCU-Kidney and Hypertension Registry

Tsuchiya, M., Moriishi, T., Yamauchi, S., Uchida, M., Tsuchiya, M., Hirota, H., Tsuchiya, M., Wakui, Y., and Tsuchiya, M. 1Yokohama City University, Yokohama, Japan; 2Yokohama City University Graduate School of Medicine, Kanazawa-Ku, Japan.

**Background:** Patient registry has been increasingly important as a strategy to promote evidence-based research and to improve the patient care. Since Yokohama City University Hospital is one of the leading hospitals in Kanagawa Prefecture, a representative and well-known urban area in Japan, it should important to develop such a registry in the hospital. Thus, we started to construct an inpatient registry of kidney and hypertension-related disorders at Yokohama City University Hospital (YCU-Kidney and Hypertension Registry) from the beginning of 2018.

**Methods:** The categories of YCU-Kidney and Hypertension Registry include a series of inpatient information including the patients ID, age, sex, type of hospitalization (scheduled or emergency), purpose of hospitalization, renal biopsy (+/−), cause of kidney and hypertension-related disorders, and content of treatment including dialysis therapy (+/−). During the first year (from January to December 2018) of the YCU-Kidney and Hypertension Registry, total of 445 inpatients were registered, and all of data for information of the categories were securely stored in the electronic health record system (SS-MIN2) of Yokohama City University Hospital.

**Results:** We presently are able to securely access the saved data and to analyze the updated trends regarding the detailed information of inpatients who were admitted to the YCU hospital due to kidney and hypertension-related disorders. We will present that more than half of the inpatients were derived from emergency admission at Yokohama City University Hospital which is located in an urban area in Japan, and will also present the detailed information about these inpatients in the YCU-Kidney and Hypertension Registry.

**Conclusions:** We intend to continue and expand the information recorded in the YCU-Kidney and Hypertension Registry, to improve the outcome measures including patient report type of outcome such as QOL and also to perform file case studies sorted out by diseases.

**Funding:** Government Support - Non-U.S.

**PUB285**

Serum Hepcidin and Cardiovascular Events in ESRD

Kristin Danielson Pists, Olof Heimbürger, Peter Stenving, Abdul Rashid T. Qureshi, Bengt Lindholm, Peter F. Barany, Karolinska Institutet, Stockholm, Sweden.

**Background:** Hepcidin, the central regulator of iron metabolism, has recently been suggested to play a role in the development of cardiovascular disease in patients with end-stage renal disease. We investigated whether hepcidin increases the risk for cardiovascular mortality in 234 patients with end-stage renal disease (ESRD).

**Methods:** 234 study subjects with ESRD stage CKD5D-ND were included in the cohort. Median age was 55 (30-68) years, 62 % were male, 35 % had CVD as baseline, 29 % had diabetes and median estimated glomerular filtration rate was 6.1 (3.8-10.3). The following parameters were assessed: hepcidin (the sum of all isoforms), high sensitive CRP (hs CRP), presence of cardiovascular disease (CVD), and Framingham’s CVD risk score. Patients were stratified into four groups based on their median level of hepcidin and median level of CRP (group 0: low hs CRP + low hepcidin; group 1: low hs CRP + high hepcidin; group 2: high hs CRP + low hepcidin; group 3: high hs CRP + high hepcidin).

**Results:** During a median follow-up of 42.5 (7.8-60) months, 57 patients died. In competing risk analysis, in crude analysis group 2 (SHR 2.07 95% CI 1.02-4.21) associated with all-cause mortality. When we adjusted for other confounders it lost its statistical significance.

**Conclusions:** The patients with high hs CRP + low hepcidin were associated with increased all-cause mortality in CKD patients in crude analysis.

**Funding:** Government Support - Non-U.S.

**PUB286**

Hyperaldosteronism and Fibromuscular Dysplasia: Two Potential Causes of Secondary Hypertension and Hypokalemia in One Patient

Wahid N. Saeed,1 Tiana Jespersen,2 Brian Y. Young,3 1UC Davis Medical Center, Sacramento, CA; 2University of California Davis, Sacramento, CA; 3CHMG, Fresno, CA.

**Introduction:** Hypertension (HTN) is common, affecting nearly 30% of U.S. adults, with 5-10% of these cases due to secondary HTN. Potential causes of secondary HTN include renal artery stenosis, from either atherosclerotic disease or fibromuscular dysplasia (FMD), and hyperaldosteronism. Here, we present a hypertensive, hypokalemic patient with both an aldosteronomia and FMD.

**Case Description:** A 59-year-old woman presented with an over 10 year history of HTN necessitating metoprolol, losartan and spironolactone, and hypokalemia requiring

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**Underline represents presenting author.**

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potassium supplements. Her cardiologist initially pursued imaging with concurrent CT abdomen showing a 2.1 cm right adrenal nodule and renal duplex ultrasound showing 60% stenosis and beading of the right main renal artery consistent with FMD. Carotid artery duplex showed bilateral 50-70% stenosis from FMD. Nephrology consultation was asked to help diagnose and manage. Spironolactone was discontinued for 4 weeks and serum aldosterone (30 ng/dl) and plasma renin activity (< 0.1 ng/ml/hr) were drawn, with the elevated ratio highly suspicious of primary hyperaldosteronism rather than FMD as the cause of HTN. Salt challenge was deferred due to profound, persistent hypokalemia despite amiloride and potassium repletion. Adrenal vein sampling showed lateralization to the right adrenal, underlying right adrenalectomy and her blood pressure and potassium normalized shortly after. She was off all medications within 2 weeks and remains stable 9 months post operation. She has not required any intervention for FMD and is undergoing conservative monitoring with her vascular surgeon.

**Discussion:**

This case history and physical with attention to specific clinical clues remains the mainstay approach to diagnosing secondary HTN. HTN and hypokalemia can point to either a primary (e.g. adrenal adenoma or hyperplasia) or secondary (e.g. renovascular) hyper-aldosterone state. Initial workup should begin with biochemical diagnostics to direct imaging studies rather than vice versa. Given its physiologic relevance, beginning with interpretation of the aldosterone to renin ratio better directs and expedites a therapeutic plan, including in patients with a concomitant adrenal nodule and renovascular disease.

**PUB287**

**Eosinophilic Granulomatosis with Polyangiitis Cardiac Disease**

Allyson C. Egan,1 Teresa Bada Bosch,2 David R. Jayne,1 1Renal Medicine, University of Cambridge, Cambridge, United Kingdom; 2Hospital Universitario 12 de Octubre, Madrid, Spain; 1University of Cambridge, Cambridge, United Kingdom.

**Background:** Eosinophilic granulomatosis with polyangiitis (EGPA), is characterized by disseminated necroting small vessel vasculitis with extravascular granulomas, amongst patients with the prodrome of asthma and tissue eosinophilia.1,2 The French Vasculitis Study Group five-factor prognostic score (FFS) associates cardiac disease with a poorer prognostic group.1,2 Histological findings in 7/9 cardiac transplant recipients, had evidence of EGPA in explanted native hearts despite ongoing immunosuppression.2

**Methods:** This retrospective, descriptive study analysed 18 patients with EGPA according to the ACR criteria or Chapel Hill Consensus 2012 definition. Identification of cardiac disease was based upon abnormalities in clinical condition, cardiac enzymes, ECG, ECHO and in some cases cardiac MRI. The aim of our study was to analyse the outcomes of patients with cardiac disease.

**Results:** All 18 EGPA patients were asthmatic and 15 were ANCA negative. At the time of mean follow-up 61.7 ± 33.8 months, percentage survival in the cohort was 100%. Two patients had evidence of thrombo-embolic disease. Pulmonary and ENT involvement were common with cardiac disease, unlike renal disease. Table 1.

**Conclusions:** In accordance with literature, cardiac disease was found predominantly in ANCA negative patients. Therapy with conventional immunosuppression and biologic therapies had a favourable outcome. Early diagnosis of cardiac involvement is essential in guiding management decisions and prognosis. 1 Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): evolution in classification, etiopathogenesis, assessment and management. A.Mahr et al Curr Opin Rheumatology, (2014) 2 Eosinophilic granulomatosis with polyangiitis Cardiac Disease.

**Table 1: Data of patients with EGPA cardiac disease**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All [n=18]</th>
</tr>
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<tbody>
<tr>
<td>Gender ratio M/F</td>
<td>11/7</td>
</tr>
<tr>
<td>ANCA positive/negative</td>
<td>15 negative/3 positive</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>47.8 ± 11.4 years</td>
</tr>
<tr>
<td>Time from asthma to EGPA</td>
<td>Mean follow-up 61.7 ± 33.8 months</td>
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</tbody>
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**Involvement No. %**

| Heart | 10/18 [100%] |
| ENT | 12/15 [80%] |
| Pulmonary | 12/15 [80%] |
| Peripheral nervous system | 10/17 [60%] |
| Constitutional | 9/17 [52%] |
| Skin | 8/15 [53%] |
| Bowel | 4/16 [25%] |
| Renal | 3/18 [18%] |
| DAH | 3/18 [18%] |

**Cardiac Manifestations**

| Cardiomyopathy | 6/18 [33%] |
| Myocarditis | 10/18 [55%] |
| Pericarditis | 3/18 [17%] |
| LUS dysfunctions | 1/18 [5%] |
| Myocardial infarction | 1/18 [5%] |
| Cor pulmonale | 1/18 [5%] |

**Immunosuppressors**

| Steroids | 14/18 [100%] |
| Cyclophosphamide | 12/15 [80%] |
| Rituximab | 10/15 [67%] |
| Azathioprine | 6/15 [40%] |
| Mycophenolate mofetil | 4/15 [26%] |
| Methotrexate | 2/15 [13%] |
| Mepolizumab | 1/15 [6%] |

**Acknowledgements:** *Mean [SD]*

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

**PUB288**

**Modification of the Effects of Intensive Systolic Blood Pressure Control on Risk of AKI by Baseline Body Mass Index**

Adhish Agarwal,1 Guo Wei,1 Robert E. Boucher,2 Tom Greene,1 Shriniwas Bednani,2 1University of Utah, Salt Lake City, UT; 2University of Utah School of Medicine, Salt Lake City, UT.

**Background:** The results of the Systolic Blood Pressure Intervention Trial (SPRINT) suggest increased risk of acute kidney injury (AKI) with intensive (INT) systolic blood pressure (SBP) control. It is unknown whether this effect persists across the body weight spectrum. We evaluated whether baseline body mass index (BMI) modified the effects of SPRINT intervention on risk of AKI.

**Methods:** SPRINT randomized 9361 high-risk non-diabetic participants with a SBP of 130 mm Hg or higher to either INT SBP target of < 120 mm Hg or standard SBP target of < 140 mm Hg. We used SPRINT BioLINCC data for our analysis. After excluding participants with a baseline BMI of <18.5 or > 50 Kg/m2 (N= 9191), we evaluated the effects of INT SBP control on risk of AKI during the mean 4.1 years follow-up period in four strata (defined by baseline BMI of < 25, 25 to < 30, 30 to < 35, and ≥ 35 Kg/m2) and across baseline BMI as a linear variable using Cox proportional models. SPRINT defined ‘AKI’ as episodes of acute kidney injury or acute renal failure during the study period noted on admission or during a hospitalization reported in the hospital discharge summary and was either a primary or main secondary diagnosis. Results: The mean age was 67.9 ± 9.4 years, 35.3 % were female, and mean baseline BMI was 29.8 ± 5.4 Kg/m2. There were 1682, 3599, 2413, and 1497 participants in the four baseline BMI strata. Increased risk of AKI with INT SBP control persisted across the BMI spectrum as shown in the Figure. The effect of INT SBP control on AKI did not differ significantly between different baseline BMI levels (P-linear/categorical interaction 0.37/0.93).

**Conclusions:** INT SBP control increases risk of AKI across the BMI spectrum in high-risk patients without diabetes.

**Figure:** Spline Curve and Forest Plot (with Hazard Ratios) for risk of AKI with INT SBP control across baseline BMI spectrum in SPRINT

**PUB289**

**Impact of Ambulatory Blood Pressure Monitoring (ABPM) on Blood Pressure Control and Medication Load in the Outpatient Clinic**

Tarig Ahmed,1 Neil K. Agarwal,2 Sumeet Aggarwal,1 Zaiauddin Ahmed. 1Drexel University College of Medicine, Philadelphia, PA.

**Background:** Utility of 24-hour ambulatory blood pressure monitoring (ABPM) is used for assessment of complex hypertension is established. Whether or not ABPM leads to changes of blood pressure, control, and medication load is unknown.

**Methods:** We retrospectively reviewed 35 charts of patients who received ABPM from a single outpatient nephrology office. Of the 35, 9 charts were excluded due to lack of follow up data. We collected demographic information: Age, Gender, Ethnicity, Diabetic status, CKD stage, Indication for ABPM. ABPM data Including: Average daytime pressures, Average nighttime pressures, total average pressures, nocturnal dipping, hypertensive load. Blood pressure readings for the 3 office visits prior to and after ABPM were recorded. Anti-hypertensive regiments prior to and after ABPM were recorded. Anti-hypertensive regiments prior to and after ABPM were recorded. We calculated pill burden by taking patients dose and dividing it by the maximum dose of the respective medication.

**Results:** Of the 26 patients (20 Female, 6 Male), 18 were African American, 5 were diabetic, 12 had CKD stage 3 or greater, and mean age was 55.7±17.5 years. The mean pre-ABPM systolic blood pressure (pre-SBP) was 139.2±14.6 mmHg, mean post-ABPM systolic blood pressure (post-SBP) was 134.8±17.1 mmHg. The mean systolic difference was 4.3±5.0mmHg (p=0.3931). The mean pre-ABPM diastolic blood pressure (pre-DDBP) was 85.7±11.5 mmHg, mean post-ABPM diastolic blood pressure (post-DDBP) was 80.3±12.9 mmHg. The mean diastolic difference was 5.4±3.4mmHg (p=0.3209).

When comparing ABPM, we found that there was no significant change of blood pressure or pill burden after ABPM. Further studies are needed to evaluate the impact of ABPM on blood pressure and patient outcomes.
Can Cocaine Use Be Diagnosed in ESRD Patients Using Hemodialysis Effluent?
Sourab Dhujel, Sheetal Koul, Wayne A. Satz, Avrum Gillespie.

**Background:** Cocaine use is a common cause of drug-related emergency department visits. Cocaine use can be difficult to diagnose in End Stage Renal Disease (ESRD) patients as denial is common and patients can’t produce a urine specimen. Benzoylcegonine, cocaine’s major metabolite, is a small water-soluble molecule and is detectable in the hemodialysis (HD) effluent using a reagent assay for urine. We utilize hemodialysis effluent as an alternate specimen to urine and blood in ESRD patients and report our results of testing hemodialysis effluent in patients with suspected cocaine use.

**Methods:** A retrospective chart review was conducted between 9/1/16 and 2/28/19 in an urban Philadelphia hospital. We identified hospital admissions that contained both an ICD diagnosis code of ESRD and an order for Urine Drug Screen. For each admission we collected age, race/ethnicity, sex, admission diagnoses, and whether the specimen was urine or HD effluent. Data were analyzed using independent t-test, Fisher’s exact test, and chi-square analyses.

**Results:** We identified 1103 ESRD patients with 3306 admissions for whom cocaine use was suspected. Only 264 (24%) had a drug screen submitted for analysis. Of these 264 patients, the average age was 55 years old (± 12), 39% were female, 73% black, 17% Hispanic, 5% white, and 5% other. Eighty-two patients (31%) had effluent sent. Twenty-four of these patients had at least one admission with a positive cocaine test. For 14 patients (58%) their HD effluent was always positive, 4 (17%) were positive between 75%-50% of the time, and 6 (25%) were never positive. Hyperkalemia and volume overload/pulmonary edema were common admitting diagnoses in both groups; however, chest pain was more common in the cocaine positive HD effluent group and altered mental status in the cocaine negative HD effluent group. There were no racial/ethnic differences in HD effluent cocaine positivity. More females were in the cocaine positive effluent group than males (61% vs 39%, p = 0.01).

**Conclusions:** Our data demonstrates the difficulty in collecting urine drug specimens in ESRD patients. Utilizing hemodialysis effluent for testing ESRD patients suspected of cocaine use appears to be a promising tool. Future studies are necessary to validate this simple test which could be used to find the prevalence of cocaine use related morbidity among ESRD patients and examine differences in cocaine use.

**PUB291**

Presentation of 17 Cases of Monoclonal Gammopathy with Renal Involvement: To Unify a Diagnosis in Retrospect
México, Mexico

**Background:** Monoclonal gammopathies consist of a heterogeneous group of disorders characterized by clonal proliferation of immunoglobulins produced by clones of plasma cells or B lymphocytes. Renal diseases associated with monoclonal gammopathy are different in their pathogenesis, kidney biopsy findings and presentation clinical.

**Methods:** In a period of 10 years, from June 2008 to February 2018, 17 cases with a histopathological diagnosis of renal involvement due to monoclonal gammopathy were identified in a single institution.

**Results:** The average age of presentation was 57.2 years. The histopathological findings of renal biopsy were 7 cases of cast nephropathy (myeloma kidney) of which 6 were positive lambda and 1 positive kappa, 1 case of glomerulopathy with nodular and nodular pattern with focal active extracapillary proliferation. In cases of amyloidosis, 6 cases presented with a glomerular, interstitial and vascular pattern, 1 case with involvement restricted to the vascular compartment and 2 with glomerular and vascular involvement. 5 patients required hemodialysis at the onset of the disease; 37.5% of cases of multiple myeloma. Of the patients diagnosed with amyloidosis 2 of them presented as nephrotic syndrome, 3 patients with predominance of heart failure, 1 patient with the combination Nephrotic syndrome plus heart failure, 1 patient presented with peripheral neuropathy and 2 patients with dysautonomia. During follow-up, 14 patients died or lost track of the institute; 1 patient is in remission of amyloidosis, 1 patient is in a bone marrow transplant protocol and one patient is on maintenance hemodialysis twice a week.

**Conclusions:** In the cardiology institute, renal and cardiac involvement are more frequently recognized as a form of initial presentation of monoclonal gammopathies, however, they are often underdiagnosed. The kidney is the affected organ where the disease is diagnosed. It is necessary the early recognition of these pathologies in our population to improve the prognosis of our patients.

**PUB292**

Obstructive Uropathy with Uremia due to Advanced Cervical-Uterine Cancer
Héctor R. Ibarra-Sifuentes, Raymundo Vera, Jose L. Avila Velazquez, Michelle Morales sandino, Giovanna Y. Arteaga Muller, Mara C. Olivo.

**Background:** Cervical-uterine cancer (CUC) is a worldwide public health problem. Advanced CUC affects nearby regional structures causing obstruction. Rarely, obstructive uropathy can cause acute kidney injury (AKI), which leads to uremic syndrome with urgent treatment such as ureteral stent placement, nephrostomies and hemodialysis, as saving life modalities are required.

**Methods:** A retrospectively analysis of the AKI patients characteristics due to obstructive uropathy caused by advanced CUC presenting to the emergency department of Hospital Universitario Monterrey, located in Monterrey, Mexico, during May 2014 to January 2019.

**Results:** 28 patients were analyzed with 45±1.1 as mean age (Table1). The main comorbidities were Diabetes Mellitus 5 (18%), and Hypertension 5 (18%). The mean evolution period was 22±20 years. 60% had metastatic CUC. The most common presenting symptom was general malaise and weight loss in 57% and 46%, respectively. The mean Blood Urea Nitrogen and Creatinine was 87±60 mg/dL and 6.9±6.5 mg/dL, respectively. 46% of the patients underwent JJ stent placement, and 39% required nephrostomies. The mean hospitalization period was 6.64±7.64days. 10 patients (36%) died, with a mean survival of 6±6 months, no difference in mortality between treatments arms (long-rank test: 0.950).

**Conclusions:** Advanced CUC and obstructive uropathy presenting with AKI is a common public health problem on developing countries. They have a long period of evolution, the main symptoms are general malaise and weight loss and unfortunately had a short mean survival of 6 months. Integral clinical assessment is a crucial priority.

<table>
<thead>
<tr>
<th>Age, years (SD)</th>
<th>Blood Urea Nitrogen (mg/dL)</th>
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<tbody>
<tr>
<td>47.1±15.38</td>
<td>22.56 (±20.34)</td>
</tr>
<tr>
<td>22.56 (±20.34)</td>
<td>86.76 (±69.02)</td>
</tr>
<tr>
<td>86.76 (±69.02)</td>
<td>12.46 (±4.8)</td>
</tr>
<tr>
<td>12.46 (±4.8)</td>
<td>Precalculous nephropathy, (%)</td>
</tr>
<tr>
<td>11 (58.8)</td>
<td>Postcalculus nephropathy, (%)</td>
</tr>
<tr>
<td>10 (55.5)</td>
<td>Survival, months (age)</td>
</tr>
<tr>
<td>6.64 (±7.64)</td>
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</table>

BUN, Blood Urea Nitrogen

**PUB293**

Severe Hypercalcemia: New Etiologies and Nephrological Management in a Reference Hospital
Jose L. Lerma, Miguel Sánchez-Jáuregui Castillo, Elena Ruíz, Jesús Martín-Centellas, Manuel Heras Benito.

**Background:** Hypercalcemia is a metabolic disorder that can cause malignant ventricular arrhythmias, intestinal motility problems, decreased level of consciousness, neuromuscular irritation and, in very advanced situations, death. Although in its mild forms it is very frequent and causes mild symptoms, its severe forms are expressions of serious pathologies, and can be the initial analytical data or the consequence of aggressive therapies or vitamin poisonings or prescription errors. It is interesting to evaluate the etiologies, and the Nephrologist therapies of a Reference University Hospital since it may be useful for future approaches Aims: 1. Establishing etiology of severe hypercalcemia 2. Evaluating specific Nephrological/dialytic treatment and follow up.

**Methods:** Salamanca University Hospital Nephrology Service was consulted about severe hypercalcemia which was collected prospectively during a 36-month interval. A total of 31 patients (12 men, 19 women) presented Ca≤11.5, with a maximum of 19.5. Therapy and results were followed up. Statistical Analysis:SPSS 15.0
Results: Tumoral: 19/31 (61.3%) were related to neoplasms with direct bone involvement (multiple myeloma MM) or metastasis (Ca Mamma, Lymphomas, Ca prostate). In some very frequent cancers, such as breast cancer, it was the first manifestation that led to hospital admission, diagnosis and subsequent treatment. Most frequent causes were Hematological Neoplasms, especially MM(first rank with a total of 5 cases) followed by Non-Hodgkin lymphomas, and implied a poor prognosis as expression of highly advanced metastatic bone disease. Mortality: 22% Hemodialysis was done in 4 patients (12.9%). Biphosphonates :100% Non tumoral 12/31 (38.7%) Calcifieded Intoxiation (n=5; 16.1%), saterogenetic (n=4) and miscellaneous (n=3). Hemodialysis 0%. Biphosphonates 100%. Mortality: 15% Non tumoral 21% Renal Failure: 15%

Conclusions: 1) Severe Hypercalcemia is a serious increasing metabolic disorder that needs Dialytic Management in some cases. 2) Main etiology is neoplasms (61.3%), of hematological origin (38.7%), and solid tumor (bone metastasis). 3) Vitamin D intoxication (calcifeded) was an treatment underestimated reversible cause (16.1%), especially in patients with previous CKD or liver dysfunction. 4) Severe Hypercalcemia Management requires a multidisciplinary approach (Nephro-oncology)

PUB294
Lung Cancer and Renal Failure
Robertta Fenoglio, Savino Sciascia, Dario Roccatello. Nephrology and Dialysis Unit and Center of Research of Immunopathology and Rare Diseases (CMID), Giovanni Bosco Hospital and University of Turin, Italy, Center of Research of Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Ita, Turin, Italy.

Background: Since there are few epidemiological studies in the literature regarding cancer patients (pts) with renal failure (RF), studying the possible renal co-morbidities is expected to improve the management of these pts. Aim of the Work: to evaluate the relationship between RF and pt survival in patients with lung cancer.

Methods: We analyzed the data of pts receiving a diagnosis of lung cancer between 1/1/2015 and 30/6/2018 who underwent therapy and were followed-up for at least 3 months or until diagnosis or death and the new prevalence of RF was examined by comparing different formulas for calculating the glomerular filtration rate (GFR) and matching any possible correlation between them.

Results: We analyzed 277 pts. GFR<60 ml/min was detected in about 60% of cancer pts diagnosed, while in the middle-advanced stage, the prevalence of RF was much lower (10%). We obtained significant differences in the GFR depending on the various formulations that were used. The Cockcroft-Gault formula tends to overestimate the number of pts with GFR ≥60ml/min in a statistically significant manner as compared to CKD-EPI and MDRD (p<0.001). The new onset was significantly more frequent in pts undergoing first line treatment with cisplatin as compared to carboplatin (p=0.001). The data also showed a worsening of RF even in some pts who were treated with new therapeutic protocols based on the use of so-called targeted therapies. The available literature data concerning these drugs is based on case reports or full case-series. The average survival of our pts series was 18.2 months. Pts whose renal function worsened during or after treatment showed significantly reduced survival (p=0.02). No difference was observed between pts with RF at diagnosis and pts with normal renal function. These results can be explained by the systematic procreation of nephrotoxic drugs in patients at risk, and further reinforce the indication for personalized therapies.

Conclusions: RF is frequent in pts with lung cancer and shows consistent prevalence during follow-up. The conventional measures of GFR do not provide univocal data, thus emphasizing the need to use highly performing formulations. Accurate screening for risk factors and devising customized protocols can drastically reduce the impact of these factors on the survival of patients.

PUB295
Renal Parameters at Diagnosis of Multiple Myeloma in a Predominant Minority Population

Background: Although multiple myeloma may occur in all races, the incidence tends to be higher in Blacks of African descent. This abstract describes the broad range of renal abnormalities at the time of diagnosis in a mostly African American population.

Methods: Electronic medical records of all patients who had confirmed diagnosis of multiple myeloma (MM) in 2018 in a large inner-city public teaching hospital were reviewed. Inclusion criterion was initial diagnosis at the institution and prior to initiation of chemotherapy. The international staging system (ISS) was determined and the range of values for the institution was used to define abnormalities.

Results: 186 subjects met the criteria for the analysis. Percentage of African Americans, Hispanics and Caucasians was 57, 16, and 18 respectively. Males: Females=50% vs 44% with non-African Americans having more males. Serum creatinine was a 1.5mg/dl in 28% and there was no gender or racial differences. Renal impairment was independent of race, MM duration or hypertension but 76% occurred in those with ISS III (P<0.001). Hypercalcemia (25% vs 7%) and quantified proteinuria of ≥ 500mg/24 hours (55% vs 14%) were statistically significant in those with and without renal impairment at presentation. Hypernatremia of < 135mEq/L was present in 35% of all subjects but in 43% in those with ISS III. Low Anion gap <5 was present in 27% of subjects but contrary to previous reports there was no differences among the various immunoglobulin subtypes.

Conclusions: In a predominantly African American population, abnormal renal parameters abound at presentation of multiple myeloma but they seem to be determined more by the disease nature rather than demographics or preexisting co-morbidities.

PUB296
Contrast Medium Increases DNA Radiation Damage and Delays DNA Damage Repair in Kidney
Shu Fujino, Shigehiro Doi, Toshiki Doi, Ayumu Nakashima, Takao Masaki. Hiroshima University Hospital, Hiroshima-Shi, Japan.

Background: Contrast-induced nephropathy (CIN) is a well-recognized cause of acute kidney injury in the clinical setting; however, no effective treatment for CIN has yet been established. Furthermore, contrast medium (CM) has also recently been shown to contribute to radiation-induced DNA damage in lymphocytes. In this study, we investigated the effect of CM on DNA damage and DNA repair in irradiated kidneys and kidney-derived cells.

Methods: For the in vivo study, male mice (8 weeks old) underwent unilateral nephrectomy. One week later, the renal artery was clamped for 30 min and ioxholo (Ihx) was injected via the right retrobulbar sinus (CIN mice). The mice were then irradiated with 10 Gy of radiation (CIN-IR mice) and kidneys were harvested 24 h after radiation. DNA damage markers (γH2AX, pATM, 53BP1, RAD51), the oxidative stress marker, γH2AX-2′-deoxyguanosine, and the macrophage marker F4/80 were examined by immunohistochemistry and western blotting. For the in vitro study, expression levels of DNA damage markers (γH2AX, pATM, 53BP1, RAD51) were examined in human renal tubular epithelium (HK-2) cells treated with ioxholo (Ihx-HK2), 1 Gy of radiation (IR-HK2), or both (Ihx-HK2), using immunofluorescence.

Results: γH2AX, pATM, 53BP1, and RAD51 expression levels were significantly increased in CIN-IR mice compared with control, IR, and CIN mice. Expression of 5-hydroxy-2′-deoxyguanosine and F4/80 were also increased in CIN-IR mice. The numbers of RAD51 foci were significantly increased in Ihx-HK2 compared with Ihx-HK2 and IR-HK2 at 1 h after radiation. γH2AX and 53BP1 foci were also increased in Ihx-HK2 and IR-HK2 24 h after radiation.

Conclusions: CM increases DNA radiation damage and delays DNA damage repair, as well as increasing levels of oxidative stress and inflammation.

PUB297
Targeting Nuclear Receptor Interacting Protein 2 Blocks Podocyte Injury and Proteinuria
Qing Hou, Xiuxen Zhai, Zhao-hong Chen, Zhihong Liu. National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China.

Background: Podocytocpytosis results in proteinuria and frequently progresses to chronic kidney disease; here we reported that targeted knockout of Nuclear Receptor Interacting Protein 2 (NRIP2) completely blocked podocyte injury and proteinuria.

Methods: NRIP2 was identified as the most centralized hub gene, arising from glomerular transcriptional profiles of renal biopsies from patients with podocytocpytosis.

Results: NRIP2 was upregulated and expressed, but not restricted, in glomerular podocytes. Genetic knockout of Nrip2 completely blocked podocyte injury and loss, and proteinuria in Adriamycin and Paromycin Amino Nucleoside nephropathy mice. Podocyte-specific induction of NRIP2 resulted in podocyte injury and glomerulosclerosis in zebrafish. Mechanistically, NRIP2 was required for β-catenin signaling activation via retaining nuclear β-catenin.

Conclusions: This work clearly identifies NRIP2 as a potential therapeutic target and a critical retention factor of nuclear β-catenin in podocytocpytosis.

PUB298
Biphasic MIF and SDF1 Expression Promotes CD44-Mediated Glomerular Parietal Epithelial Cell Migration in Focal Segmental Glomerulosclerosis
Naoko Itô, Kazuo Sakamoto, Michio Nagata. University of Tsukuba, Tsukuba, Japan.

Background: Focal segmental glomerulosclerosis (FSGS) is commensured with local syneciae by glomerular parietal epithelial cell (PEC) activation, including its migration and adhesion to glomerular tuft with podocyte detachment. However, the molecular signaling that mediates podocyte injury and PEC activation remains unknown. In FSGS, podocyte-specific NRIP2 knockout or hypoxia in HK-2 cells has been known as a marker of PEC activation, and it may be implicated in progression of segmental sclerosis. In the present study, we focused on the roles of CD44 and two chemokines, migration inhibitor factor (MIF) and stromal cell-derived factor 1 (SDF1), during podocyte injury-driven PEC activation.

Methods: NEP25/1MB2 mice, the toxin-induced podocyte injury model, were used (n=5). The glomerular expression of MIF, SDF1, CXCR4 and CD44 was assessed by immunostaining sequentially on day 0, 4, 8 and 12. Using immortalized mouse PEC (PEC), in vitro study was conducted by real-time PCR, western blotting, and migration assays. PEC and CD44 and SDF1 or CXCR4 expression, or both, was promoted by CIN mice and in vitro study used hypertonic and hypoxia as stimuli.

Results: In the early stage of podocyte injury (on day 4), podocytes expressed MIF and SDF1. As podocytes were detached (on day 8 and 12), PECs expressed CD44 with MIF and SDF1 and CXCR4. In vitro, MIF and SDF1 individually induced CD44 and CXCR4 on PECs, and promoted their chemotaxis and endothelial cell migration.

Conclusions: Biphasic expression of MIF and SDF1 in podocytes and PECs, and roles of these chemokines in PEC activation in vitro suggested that CD44-mediated PEC migration might be initiated by MIF and SDF1 and sustained through their paracrine and autocrine effect.
Post-Translational Regulation of Endothelial-Derived CCN Proteins in Response to Uremic Serum from Haemodialysis Patients

Mark E. Dockrell, South West Thames Institute for Renal Research, Surrey, United Kingdom.

Background: Non-traditional risk factors play an important role in cardiovascular disease (CVD) observed in renal patients. Vascular smooth muscle cells (VSMC) dedifferentiation is a key step in neointimal hyperplasia. Endothelial cell derived CCN2/CTGF and CCN3/Noggin play opposing roles in regulating VSMC dedifferentiation and migration modulating neointimal hyperplasia. We aim to investigate the expression and alteration in the CCN protein axis in human endothelial cells in response to uremic serum donated by haemodialysis patients.

Methods: Blood samples were obtained from consented haemodialysis patients (n=10) and healthy control subjects (n=6). Serum was prepared and stored at -80°C. Human Umbilical Vascular Endothelial Cells (HUVEC) from a mixed donor pool were cultured in supplemented growth medium on collagen IV. Cells were incubated in serum-free media containing 10% v/v patient serum (PS) and 10% v/v control subject serum (CS). After 24 hours, media was removed, cells lysed and RNA extracted. RNA was subject to reverse transcriptase followed by real time QPCR. Relative gene expression was calculated by ∆∆Ct analysis. Following 72 hour incubation of HUVEC in the conditions above, media was removed, centrifuged and stored. Cells were lysed and lysates prepared for PAGE Western Blotting.

Results: There was no significant difference in TGFβ1 or CCN2/CTGF RNA expression. Although serum significantly reduced CCN3 RNA, there was no difference between PS and CS treated cells. There was no measurable difference in LDI between cultures with any of the protocols. Although there was some variation in the protein expression from cells exposed to sera from different patients, there was still an overall significant increase of between 35 and 70% in the intact 36:36Kda CTGF from cells treated with PS compared to both CS and sf (p<0.05). PS treatment induced a significant reduction in CCN3 protein in CS treatment (40-65% reduction, p<0.05). The endothelial cell treated with PS compared to both CS and sf (p<0.05). PS treatment induced significantly decreased CCN3 protein than CS treatment (40-65% reduction, p<0.05). The endothelial cell treated with PS compared to both CS and sf (p<0.05). The endothelial cell treated with PS compared to both CS and sf (p<0.05). The endothelial cell treated with PS compared to both CS and sf (p<0.05).

Conclusions: From our data, we conclude that serum from haemodialysis patients induces dedifferentiation of VSMC in culture in favor of VSMC differentiation and migration potentially driving vascular calcification in these patients.

Fundring: Private Foundation Support

A Case Report of Podocytic Infloring Glomerulopathy with Bladder Tumor

Xiaoru Dou, Jianyi Pan, Jiayi Chen, Jinhong Chen. Shunde Hospital of Southern Medical University, Foshan, China.

Introduction: Podocyte infloring glomerulopathy (PIG) is a recently described condition with pathologic entity characterized by diffuse podocyte infloring into the glomerular basement membrane (GBM) associated with ultra-structurally demonstrable microspherulter aggregates. The clinical features, significance, and pathogenesis of this condition are still not well delineated because only a few cases have been documented to date, almost all from Japan. Here we reported a case of PIG associated with bladder tumor in a Chinese woman.

Case Description: A 76-year-old Chinese woman was admitted to our hospital with gross hematuria, edema, massive proteinuria, hypoalbuminemia, hyperlipidemia, and kidney dysfunction. Laboratory test of urine exfoliative cytology suggested poorly differentiated cancer cells, indicating a diagnosis of bladder tumor. Renal biopsy was performed to determine the cause of proteinuria and kidney dysfunction. Histological examination of the biopsy specimens showed mild segmental mesangial hyperplasia in the glomeruli. Immunofluorescence staining did not show glomerular deposition of immunoglobulins, light chains, or complement components. Electron microscopy showed slightly and irregularly thickened glomerular basement membrane (GBM) with irregular membranous structures in the GBM, suggesting podocytic infloring glomerulopathy. There were no electron-dense deposits in the GBM, while various findings indicated podocyte injury.

Discussion: This patient was the first report of PIG with bladder epithelial cancer in the world. The pathogenesis of the disease remains unclear, and the therapeutic strategy on this disease needs to be further studied in the future.

The Spectrum of Clinical and Histopathological Diagnosis in Patients with Rapidly Progressive Renal Failure: An Indian Experience from a Tertiary Center

Neha Jain,1 Amrut Gupa,2 Devinder S. Rana,3 Anil Bhalla,4 Ashwani Gupta,1 Marish Malik,2 Vinant Bhagava,2 Niraj Patel,2 Sabina Yusuf.1

Background: Rapidly progressive renal failure (RPRF) is defined as progressive renal impairment over a period of a few weeks. The underlying etiology may be a primary renal disease or a systemic disorder. The data on RPRF from the Indian subcontinent is sparse. We aim to study the clinical profile and the histopathological findings on renal biopsy of patients presenting with RPRF at our center.

Methods: Consecutively presenting patients with renal failure of recent onset and rapidly progressing over the duration of weeks to less than 3 months with normal sized kidneys on ultrasound were included after informed consent. Kidney biopsy was performed under ultrasound guidance. Light microscopy and immunofluorescent staining of renal biopsies were performed using a variety of antibodies. Immunofluorescence staining was performed using a variety of antibodies. Immunofluorescence staining was performed using a variety of antibodies. Immunofluorescence staining was performed using a variety of antibodies. Immunofluorescence staining was performed using a variety of antibodies.

Results: A total of 2680 biopsies were performed. Indications for renal biopsy were as follows: nephrotic and nephritic syndromes, rapidly progressive glomerulonephritis, asymptomatic hematuria and renal failure of unknown etiology. Renal biopsy was performed percutaneously by using an automated gun under ultrasound guidance. Light microscopy and immunofluorescence studies were used.

Background: Histopathological analysis of renal parenchyma is the gold standard diagnostic tool in renal medicine. We report our experience on renal biopsy and the histopathological patterns of renal diseases presented to Teaching Hospital Kandy.

Methods: This retrospective study included adult patients who had native renal biopsy during a period of 9 years & 4 months, from January 2010 to April 2019. A total of 1150 biopsies were performed. Indications for renal biopsy were as follows: nephrotic and nephritic syndromes, rapidly progressive glomerulonephritis, asymptomatic hematuria and renal failure of unknown etiology. Renal biopsy was performed percutaneously using an automated gun under ultrasound guidance. Light microscopy and immunofluorescence studies were used.

Results: A total of 2680 biopsies were examined; sample included 1332 males and 1348 females (age 12 – 88 years). Primary glomerulonephritis (GN) was reported in 1096 (40.9%) cases, secondary GN in 988 (36.9%), tubulo-interstitial disease in 382 (14.2%) and chronic kidney disease of unknown etiology (CKDu) in 214 (8%) cases. Among primary GN; Focal segmental glomerulosclerosis was the commonest seen in 11.41% biopsies, followed by minimal change disease in 10.11%, immunoglobulin A nephropathy in 9.14%, membranous GN in 5.7%, membranoproliferative GN in 3.76% and immunoglobulin M disease in 0.55% biopsies. Among secondary GN, lupus nephritis (LN) was the commonest seen in 15.45%, followed by diabetic nephropathy in 7.27%, post-infectious GN in 7.1%, renal vasculitis in 4.25%, hypertensive nephropathy in 1.52%, amyloidosis in 0.85%, myeloma nephropathy in 0.22% and thrombotic microangiopathy in 0.18%. Among biopsies demonstrating tubulo-interstitial disease, chronic interstitial nephritis was the commonest seen in 8.05%, followed by acute interstitial nephritis in 4.4%, acute tubular injury in 1.64% and acute tubular necrosis in 0.14% cases. CKDu was commoner among males than females with a count of 174 (6.49%) & 40 (1.49%) respectively. Mean age of CKDu patients was 44.3 years.

Conclusions: Nephrotic syndrome was the leading indication for renal biopsy. LN and FSGS were the predominant histological patterns. Among females LN stands as the commonest pathology. CKDu shows a significant prevalence among middled aged men.
Spot urine protein/creatinine ratio to 24 hour urine protein (uPCR) according to urine creatinine level

**Conclusions:**

- uPCR tends to overestimate proteinuria based on urine creatinine level.
- The ratio of uPCR to 24HU protein was 6.8 ± 0.1 for concentrated group, 105.3 ± 73.1 mg/dL for reference group, and 0.3 ± 682.9 mg/dL for diluted group, respectively.
- The overestimation of proteinuria increases when urine creatinine is less than 50 mg/dL.

**Background:**

Proteinuria is an important indicator of prognosis in kidney disease. Spot urine protein/creatinine ratio is widely used because it is considered to be able to replace 24 hour urine protein. Previous studies tested the accuracy of spot urine protein/creatinine ratio using the specific gravity of urinalysis. However, in present study, we investigated whether urine creatinine affects proteinuria quantification without other tests.

**Methods:**

We reviewed patients who underwent 24 hour urine protein (24H) urine protein and spot urine protein/creatinine ratio (uPCR) simultaneously at Gachon University Gil Medical Center between June 2002 and June 2018. The subjects were 1,286 patients and 31 patients with membranous nephropathy were excluded. One thousand five hundred fifty-four samples were reviewed.

**Results:**

The mean of 24H urine protein was 1.4 ± 2.4 g/day (range 0.006-22.7 g/day), and the mean of spot urine protein and creatinine were 165.4 ± 315.4 mg/dL (range 0.1-5500 mg/dL) and 105.3 ± 73.1 mg/dL (range 0.3-682.9 mg/dL), respectively. The ratio of uPCR to 24H protein (uPCR/24Hprotein) was 6.8 ± 6.7. When the patients were divided into three groups (concentrated group 0-50 mg/dL, reference group 50-200 mg/dL, diluted group 200-500 mg/dL), the spot urine protein/creatinine ratio (uPCR) was 18.6 ± 146.7 (p = 0.003 vs. reference group), 4.0 ± 26.7, and 4.1 ± 12.6 (p = 0.088 vs. reference group), respectively.

**Conclusions:**

- Overestimation of proteinuria in urine sample with low urine creatinine levels was found.
- Spot urine protein/creatinine ratio was significantly higher in patients with low urine creatinine levels.
- The ratio of uPCR to 24H protein (uPCR/24Hprotein) was significantly lower in patients with low urine creatinine levels.
- Spot urine protein/creatinine ratio is considered to be able to replace 24 hour urine protein.

**Key:**

- TH - Thursday
- FR - Friday
- SA - Saturday
- OR - Oral
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of glomerular basement membrane. Follow up between 1 month and one year is available, proving that the finding improved to variable extent with lipid lowering agents and renal function parameters are stable.

Discussion: Since the first report of LPG in 1989, approximately 150 cases and 15 different Apolipoprotein E gene mutations in a heterozygous form have been described to play a causative role. Exact pathogenetic mechanism remains to be defined, however abnormal intraglomerular lipid trafficking may be the underlying factor. Though most cases of Lipoprotein Glomerulopathy are of Asian ancestry, mostly Japanese, it has never been described in Indian subcontinent. Kidney biopsy is very important in diagnosis of LPG. Majority of lipid thrombi within glomerular capillaries with high index of suspicion in dyslipidemic patients may play a crucial role and chances of missing the disease can be minimized.

PUB307
Prevalence and Risk Factors in Preterm Infants with Nephrocalcinosis
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Background: Nephrocalcinosis is a relatively common clinical condition in preterm infants, and the prevalence of nephrocalcinosis in premature infants ranges from 7% to 41% in different studies. Nephrocalcinosis in preterm neonates are known to be affected by multifactorial etiologies such as low gestational age, low birth weight, bronchopulmonary dysplasia, fluid restriction and other various causes. The aim of this study was to evaluate the prevalence and the risk factors of nephrocalcinosis in Korean infants born preterm.

Methods: We retrospectively analyzed the medical records of 27 preterm infants who were admitted to a neonatal intensive care unit from January 2015 to December 2016 and diagnosed as having nephrocalcinosis during hospitalization and 1-year follow-up. The diagnosis of nephrocalcinosis was made by the medical history and renal ultrasonography.

Results: The prevalence of nephrocalcinosis in Korean infants born preterm is 4.1%. The median age at the time of diagnosis was 72 days (17 - 548 days), and the male-to-female ratio was 1:1.1. The median gestational age was 28.8 weeks and body weight at birth was 1149.4±693.5 grams. The risk factors of nephrocalcinosis included patent ductus arteriosus (n=13, 48.1%), bronchopulmonary dysplasia (n=11, 40.7%), the use of vitamin D (n=23, 85.2%), and diuretics (n=5, 18.5%). The serum levels of calcium and phosphorous at the time of diagnosis were 10.3±1.0 and 5.7±1.1 mg/dL, respectively. The hospitalization period was 119.3±63.4 day, and 1 patient died during follow-up. Although nephrocalcinosis persisted in 8 patients during the first year of life, only 3 patients visited the pediatric nephrology clinic or outpatient nephrology.

Conclusions: The prevalence of nephrocalcinosis in Korean infants born preterm was relatively low. Nephrocalcinosis in preterm infants might be associated with impaired renal function in the future, and the cooperation between the neonatologists and nephrologists is necessary. Future research for interventions to prevent nephrocalcinosis in preterm infants is crucial.

PUB308
Hypernatremia and Neurological Outcomes in Children
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Background: Hypernatremia in hospitalized children is associated with increased mortality and neurological insult, particularly in children with rapid fluctuations in serum sodium level. Current clinical guidelines recommend a reduction of 0.5mmol/L per hour or less, to reduce known complications of cerebral edema, seizures and increased mortality. Recent evidence amongst adults with hypernatremia found no difference in mortality between those who received more rapid or less rapid correction, however there are no large scale trials in the paediatric population. The aim of this study is to examine the association between the rate of correction of hypernatremia, neurological outcomes and all-cause mortality in children.

Methods: A retrospective review was conducted over a three year period from May 2016 until May 2019 in a large tertiary academic pediatric hospital. Eligible participants were identified through interrogation of the electronic medical record (EMR). All patients aged 6 months – 18 years seen at the Royal Children’s Hospital with a serum sodium result demonstrating moderate to severe hypernatremia (defined at least as one serum level of 150mmol/L or greater) were included in the analysis. Demographic and clinical data were collected. The relationship between rate of serum sodium correction and neurological injury and mortality was assessed using multivariate logistic regression. Outcomes including mortality, cerebral oedema, seizures, encephalopathy, myelolysisis and decreased level of consciousness were determined using direct chart review.

Results: A total of 145 children met the inclusion criteria. Over the three year study period, 33% had a serum sodium level of 150mmol/L or greater and were included in the study. 51.2% of included patients were male, and the median age was 4.2 years. The majority of children had a sodium level in the range of 150-160mmol/L (n=198, 59%). 118 children (33%) had a sodium level between 160-169mmol/L, and 21 children (6%) had a sodium level of 170mmol/L or greater. The most common primary admission units of the cohort were cardiac services (21.3%), neurosurgery (18.1%), and general medicine (16.2%).

Conclusions: Hypernatremia remains a common and concerning occurrence in our hospital setting. Our analysis may add to further defining the relationship between rate of sodium correction, neurological outcomes and all-cause mortality outcomes.

PUB309
Malignancy After Pediatric Kidney Transplantation: A Single-Center Experience
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Background: Malignancy has become a major burden in transplantation patients with more potent immunosuppressants and longer graft survival. Although there is cumulating cases with malignancy after pediatric kidney transplantation(KT), reports regarding incidence, manifestations, and prognosis are rare. We aimed to investigate the incidence, manifestations, and outcomes of malignancy after pediatric KT in our center.

Methods: We retrospectively reviewed medical records of 143 patients aged under 18 years old who had KT between January 1990 and January 2019 at Asan Medical Center.

Results: Patients had KT at an mean age of 13.2 ± 4.4 years (range, 1.4 – 18.0 years), with mean follow up period of 11.7 ± 7.8 years. In total, 11 patients (7.7 %) had malignancy after KT. Malignancy was diagnosed after a mean period of 7.0 ± 5.9 years (range, 0.5 – 20.6 years) after transplantation. Mean age at diagnosis of malignancy was 20.7 ± 6.1 years. Eight patients out of 11(72.7 %) were diagnosed as post-transplant lymphoproliferative disease(PTLD), and other three patients had papillary thyroid cancer, mucopidermoid cancer of hard palate, and T-cell acute lymphoblastic leukemia(ALL), respectively. PTLD was diagnosed within 4.3 ± 3.3 years (range, 0.5 – 9.8 years) after KT. Three patients with PTLD (37.5 %) expired. Among 3 patients with malignancy other than PTLD, one patient with mucopidermoid cancer showed progression despite surgical resection and chemotherapy. Other two patients were cured without recurrence. Four patients (57.1 %) among the survivors who were all diagnosed with PTLD are currently under follow up with preserved renal function which did not deteriorate during the treatment of malignancy. Details of the cases are described on the attached table.

Conclusions: PTLD was the most common malignancy after KT in children, occurring at 5.6 % of patients within average of 4.3 ± 3.3 years after KT in our center. Careful follow up is needed especially regarding the possibilities of PTLD after KT in children.

PUB310
Estimated Neprhon Number in Japanese Children with Wilms Tumor
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Background: It has been postulated that an inherited nephron loss would lead to the development of chronic kidney disease (CKD) in later life. Consistent with this hypothesis, recent studies have reported that low birth weight is associated with an increased risk of CKD. However, the effects of birth weight and nephron number in children on development of noncommunicable CKD in adult age have not been elucidated. We, therefore, estimated nephron number in living children with Wilms tumor.

Methods: We evaluated the children with Wilms tumor at Jikei University Hospital who underwent an enhanced CT scan and nephrectomy. Nephron number was calculated by multiplying cortical volume of a healthy side by the glomerular density in a nephrectomy sample, as like Figure 1.

Results: Two children operated on at the age of 16 months (CASE1) and 11 months (CASE2) old for Wilms tumor were identified. The estimated number of nephrons was 843,390 per kidney in CASE1, and 1,021,397 per kidney in CASE2 (Table 1).

Conclusions: These results suggested the possibility of being able to estimate nephron number in living children with Wilms tumor. Further studies involving much larger numbers of subjects are required to determine the role of nephron number in children.
Coping Strategies Employed by Families of Paediatric Patients with Chronic Kidney Disease

Methods

To our knowledge, this is the first review focusing on identifying Coping strategies of different nature are employed by caregivers to manage their negative emotions. The Information presented would serve as a basis for healthcare professionals to better understand these caregivers and develop person-centred support structures for them to cope with their negative emotions.

Table 1. Patients Characteristics.

<table>
<thead>
<tr>
<th>Geographical age</th>
<th>Birth weight (kg)</th>
<th>Serum Cr (mpL)</th>
<th>Neutrophil number (10⁹/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASU</td>
<td>40 weeks (29°)</td>
<td>2,318</td>
<td>0.17</td>
</tr>
<tr>
<td>CASU</td>
<td>60 weeks (18°)</td>
<td>2,071</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Figure 1: How to calculate neutrophil number.

**PUB311**

**Positive Emotions of Caregivers of Children with CKD: A Qualitative Systematic Review**

**Background:** Negative emotions such as distress, fear, and anxiety are commonly experienced by caregivers of children with Chronic Kidney Disease (CKD). However, the caregiving process may also bring about positive emotions. This study aims to explore and summarize positive emotions of the caregivers.

**Methods:** A systematic review was performed using the PRISMA guidelines to identify qualitative research studying experiences of caregivers (ages 1 to 18) with CKD. Databases (PubMed, PsycINFO, Embase, Scopus, Cochrane) and grey literature (Google Scholar) were searched for relevant articles. The initial search yielded 17,493 title and abstracts. With an agreed upon selection criteria by the authors, 14 papers were included. Qualitative research studies documenting, for a rate of 0.82 episodes/year in first cohort and 0.34 episodes/year for recent cohort. Younger age at insertion was significantly associated to mortality change (p=0.047 and 0.044). Two patients died not associated with peritonitis.

**Conclusions:**: Peritonitis rates were higher than national rates in the earlier cohort (0.82 episodes/year vs. 0.32 episodes/yr). Younger age was associated to mortality change. Younger children in dialysis have higher risks of morbidity. Decreasing infection rate may be associated with implementation of catheter care protocol, shorter dialysis vintage and restarting of local transplant program. Close monitoring of infection rates and trends result in better outcomes for patients on dialysis.

**PUB313**

**Decreasing Rates of Peritonitis Among Children Undergoing Peritoneal Dialysis in Puerto Rico**

**Background:** Peritonitis is a life-threatening complication of peritoneal dialysis (PD). From 2006-2016, higher than expected peritonitis rates (0.82 episodes/year vs. 0.5 episodes/year) were reported among children receiving PD in Puerto Rico (PR). Peritoneal PD catheter care interventions were developed to address this disparity.

**Methods:** Retrospective chart review of patients undergoing chronic PD in PR from 2006-2018. Patients with incomplete data were excluded. Peritonitis defined as peritoneal WBC>100cells/mm³ and polymorphonuclear cells-50% and peritoneal fluid culture. Demographic(age, sex), clinical, and outcome (peritonitis rate, change of modality and death) variables recorded. High peritonitis rate defined as >0.5 episodes/yr. Associations were assessed using Fisher exact test.

**Results:**: 53 patients underwent PD, 32 were included. Age at initiation 9yrs(6days-20yrs), 50% males. Time on dialysis 865 patient-months. 57 peritonitis episodes documented, for a rate of 0.82 episodes/year in first cohort and 0.34 episodes/year for recent cohort. Younger age at insertion was significantly associated to mortality change (p=0.047 and 0.044). Two patients died not associated with peritonitis.

**Conclusions:**: Peritonitis rates were higher than national rates in the earlier cohort (0.82 episodes/year vs. 0.32 episodes/yr). Younger age was associated to mortality change. Younger children in dialysis have higher risks of morbidity. Decreasing infection rate may be associated with implementation of catheter care protocol, shorter dialysis vintage and restarting of local transplant program. Close monitoring of infection rates and trends result in better outcomes for patients on dialysis.

**PUB314**

**ESRD in a Pediatric Population in a Southern Algerian Province**

**Background:** End stage renal disease (ESRD) in pediatric population is a major challenge for medical and paramedical staff. In Algeria, the number of children reaching ESRD is increasing. The pediatric ESRD in Algeria are few. The statistical data are collected but there is no operable national register. The objectives of this study: To estimate the prevalence and the annual incidence of ESRD in the pediatric population of Ghardaia and to determine the epidemiological characteristics of dialyzed children.

**Methods:** In this retrospective study, we included all patients under the age of 19 years at the time of the ESRD, living in Ghardaia, treated at least 03 months by hemodialysis (HD) or peritoneal dialysis (DP) during the period between 01/01/2005 to 12/31/2018. Information was collected from the medical files, interrogation of patients and their parents.

**Results:**: Thirty (34) children were included. The average age was 12 years (1-19), sex ratio (M/F) was 0.88 (16/18). The average annual incidence of eESRD in our series was: 12 p/mn / yr. and The prevalence is : 135 p/mn (Per million age related population). The frequency was high for patients between 10 and 14 years of age (44%) Congenital abnormalities of kidneys and urinary tract (CUT) were the first cause of ESRD in our study (26%) hereditary nephropathies (23%) primary Glomerular nephropathy (20%), 17% congenital abnormalities, 2% nephrotic syndrome was the chief of wire. In 30 % of the cases, etiology was not found; this is mainly due to delayed diagnosis Hemodialysis is the first treatment method for incident (61%) and prevalent (67%) patients. It was in most cases urgent (70%), anemia was predominantly present at the time of dialysis (89%). A very high mortality rate (23%) was founded mainly due to dialysis insufficiency, A very low school enrollment (45%) and significant retardation of growth (73%). 15 % was regularly followed in pediatrics during years of dialysis The transplant rate (9 %) is very low, only 3 patients has been transplanted.

**Conclusions:**: Our study is of the few works on the pediatric ESRD in southern of Algeria; we were able to raise the following remarks: - A high incidence and prevalence of pediatric ESRD compared to Europe or the USA - Delayed diagnosis of chronic kidney disease detrimental to patient survival - Very limited access to specialized therapies (urological surgery, genetic tests)
Myasthenic Crisis (MC) Precipitated by Omalizumab (Om) Therapy

Background: Om is a recombinant humanized antibody (human/mouse) that blocks binding of IgE to its high affinity receptor on mast cells. It is approved for the treatment of severe allergic asthma and atopic dermatitis. Several reports have suggested that MC has also been described with the use of Om or its constitutive ingredients. Proposed mechanisms may include immune cross-reactivity, impurities in the Om molecule, and direct myasthenic effects. Of note, Om is humanized glycosylated monoclonal antibody (Ab) of IgG1, with a reported incidence of MC in the broad-spectrum antibiotic era of 0.002%. The study included 22 patients (biopsy-proven) who had an episode of MC. The results show that MC is more common with Om although it can also occur with other monoclonal antibodies.

Results: The study included 22 patients with MC. Of note, MC was associated with Om or its constitutive ingredients. The study found that the incidence of MC in patients with Om treatment is 0.002%. The study also found that MC is more common with Om although it can also occur with other monoclonal antibodies. The study also found that MC patients are more likely to have a history of allergic asthma or atopic dermatitis.

Conclusions: The study suggests that MC is more common with Om and other monoclonal antibodies. The study also found that MC patients are more likely to have a history of allergic asthma or atopic dermatitis.

PUB316
Factors Predicting Ertapenem-Induced Neurotoxicity in Hemodialysis Patients

Background: Ertapenem is a carbapenem antibiotic that is frequently utilized in hemodialysis (HD) patients. Studies have suggested that HD patients may be at increased risk for neurotoxicity with ertapenem. The study included 2,960 patients on HD with a mean follow-up of 2 years. The study found that the incidence of neurotoxicity in HD patients with ertapenem was 0.25%. The study also found that the use of ertapenem in HD patients was associated with an increased risk of neurotoxicity.

Results: The study included 2,960 patients on HD with a mean follow-up of 2 years. The study found that the incidence of neurotoxicity in HD patients with ertapenem was 0.25%. The study also found that the use of ertapenem in HD patients was associated with an increased risk of neurotoxicity.

Conclusions: The study suggests that HD patients may be at increased risk for neurotoxicity with ertapenem. The study also found that the use of ertapenem in HD patients was associated with an increased risk of neurotoxicity.

PUB317
Cost-Effective Therapeutics for Patients with ESRD: A Guide for the Practicing Nephrologist

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Urea pocket card or mobile app. In conclusion, our case report suggests that high level of vigilance is required while using newer M Abs as reversible side effects such as MC can occur with use of MC. We describe a case of full blown MC due to Om is limited to ocular myasthenia gravis (MG). We discuss the potential mechanisms of MC formation of acetylcholine receptor (AChR) or muscle specific tyrosine kinase (MuSK) and categorized by drug class. Interestingly, 72% of spousal donors were women (10,062 vs 3,745), 68% of life partners donors (375 vs 169), 62% of parent to child (7,309 vs 4,573), but only 56% of child to partner donors (375 vs 169). Logistic regression analysis demonstrated that women vs men donating was significantly associated to AKI and specially AIN, however the relationship between bacteremia, AKI, and mortality was not observed in the study. The study suggests that women donate more kidneys than men and is not associated to a higher concordance rate of severe AKI compared to men. The study also found that women donate more kidneys than men and is not associated to a higher concordance rate of severe AKI compared to men.

Results: The study included 112,700 living donor (LD) kidney transplants reported to UNOS/OPTN between 1998 and 2018 were analyzed. Only adult donors were included in the analyses. The time period was divided into 3-year intervals to adjust for yearly fluctuations. Logistic regression models were used to test the odds for women to donate a LD kidney adjusted for possible risk factors.

Conclusions: The study shows that women are more likely to donate kidneys than men and is not associated to a higher concordance rate of severe AKI compared to men. The study also found that women donate more kidneys than men and is not associated to a higher concordance rate of severe AKI compared to men.

Background: It has previously been reported that women donate more kidneys than men. It was thought that socioeconomic factors might play a role, with men historically acting as “breadwinners”, but this role has changed over the past 20 years. We examined gender patterns and associated factors in living donation from 1998-2018.

Methods: All 112,700 living donor (LD) kidney transplants reported to UNOS/OPTN between 1998 and 2018 were analyzed. Only adult donors were included in the analyses. The time period was divided into 3-year intervals to adjust for yearly fluctuations. Logistic regression models were used to test the odds for women to donate a LD kidney adjusted for possible risk factors.

Results: Overall, 60.5% of all living donors were women. Beginning in 2007, the odds ratio (OR) of female donation was progressively higher compared to 1998-2000 (OR: 1.07, 95% CI: 1.04-1.10) (2007-09, CI: 1.04-1.10) to 1.144 in 2016-18 (CI 1.091-1.200). Except for over 70 years of age, the OR for women vs men donating was significantly higher for all age groups, with highest being the 40-50 yr group (1.621, CI 1.557-1.687). No racial differences could be detected. When donor relationships were examined in a subgroup analysis, 72% of spousal donors were women (10,062 vs 7,345), 68% of life partner donors (357 vs 169), 62% of partner to child (7,309 vs 4,573), but only 56.8% of child to partner donors. We describe a case of full-blown MC due to Om is limited to ocular myasthenia gravis (MG). We discuss the potential mechanisms of MC formation of acetylcholine receptor (AChR) or muscle specific tyrosine kinase (MuSK) and categorized by drug class. Interestingly, 72% of spousal donors were women (10,062 vs 3,745), 68% of life partners donors (375 vs 169), 62% of partner to child (7,309 vs 4,573), but only 56% of child to partner donors. When donor relationships were examined in a subgroup analysis, 72% of spousal donors were women (10,062 vs 3,745), 68% of life partner donors (357 vs 169), 62% of partner to child (7,309 vs 4,573), but only 56% of child to partner donors.

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1154
Acute Pancreatitis Risk After Kidney Transplantation: Propensity Score Matching Analysis of a National Cohort

Ya-Wen Chang, Tung-Min Yu, Ming-Ju Wu. Taichung Veterans General Hospital, Taichung, Taiwan.

Background: Data for elucidating post-kidney transplantation (KT) acute pancreatitis (AP) risk are limited and no large-scale cohort study has investigated the impact of AP after KT.

Methods: Data from Taiwan National Health Insurance (NHI) Research Database (NHIRD) were calculated through the method of propensity score matching to compare the pancreatitis risk in patients with and without KT.

Results: The overall pancreatitis incidence rates were 1.71 and 0.61 per 1,000 person-years in the KT and non-KT groups, respectively and corresponding adjusted HR (aHR [95% CI]) for pancreatitis was 2.42 (1.43–4.10) in the KT group. In the multivariable model, AP risk was higher in transplant patients with alcohol-related illnesses (aHR: 3.85, 95% CI: 1.36–10.9), gall stone disease (aHR: 3.43, 95% CI: 1.45–8.14), or past history of pancreatitis (aHR: 9.94, 95% CI: 4.98–19.8). Of note, recurrent AP risk was significantly higher in the KT group (aHR: 9.77, 95% CI: 3.33–28.7). Patients with post-KT AP demonstrated shorter patient and allograft survival than did those without (both P < 0.001), respectively.

Conclusions: In conclusion, KT recipients are very likely to be associated with AP. Moreover, their inferior outcomes are strongly associated with post-KT AP.

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116.9 (±105.6) months and the GFR was 59.95 (±13.1) mL/min/1.73m². Blood vitamin C was adequate in the majority of patients taking PPI and insufficient in all patients in the control group. Blood levels of vitamin B12 (98.2 and 90.9%) and folic acid (92.5 and 95.5%) were adequate in most patients of both groups (p<0.05). The food intake recall was used to quantify the intake of macro and micronutrients, and no significant difference between the groups was found, except for vitamin C intake, which was higher in the group taking PPI (86.23 ± 116.0 mg) compared to the control group (42.57 ± 29 mg) (p<0.001). Regarding BMI, 51.8% of the patients taking PPI were eutrophic and the remainder obese; in the control group, 36.3% were eutrophic, 54.5% obese, and 9% underweight. The results of micronutrients were similar between groups.

Conclusions: The findings of this study suggest that the intake of PPIs by renal transplant patients does not impair the nutritional status based on vitamin B12, vitamin C, and folic acid serum levels or based on body composition.

**PUB323**

Multidisciplinary Reconciliation of Renal Transplant Recipients’ Medications: A Single-Center Experience

Mohammad Zaitoun,1 Weam Elnazer,2 Hany El Hennawy,3 Ahmed Mahedy,4 Khalid Al-Asheikh,2 1Pharmacy Department, Armed Forces Hospitals Southern Region, Khamis Mushait, Saudi Arabia; 2Nephrology Center, Armed Forces Hospitals Southern Region, Khamis Mushait, Saudi Arabia; 3Transplantation Surgery Unit, Armed Forces Hospitals Southern Region, Khamis Mushait, Saudi Arabia; 4Internal Medicine Department, Banka Faculty of Medicine, Banha, Egypt.

**Background:** Transitions of healthcare increase the risk of medication errors. Besides, renal transplant recipients are at increased risk of errors due to frequent medication modifications and administration of multiple high alert medications. This study aimed at describing a single center experience in renal transplant recipients’ medications reconciliation and its impact in preventing medication errors.

**Methods:** A prospective observational study was conducted from Jan. to May 2019. Multidisciplinary medication reconciliation process was implemented in the renal transplant unit of the armed forces hospitals southern region, Saudi Arabia. A clinical Pharmacist reviewed the best possible medication history (BPHM) list, developed by admitting physician and nurses, versus admission medications within 24 hours of admission. Upon discharge, clinical Pharmacist reviewed discharge medications against pre-admission BPHM and medications administered within 24 hours. For Post-discharge, clinical Pharmacist conducted medication reconciliation of first outpatient clinic prescriptions against discharge ones. Physicians were contacted to resolve any detected discrepancies.

**Results:** Twenty-four patients were transplanted during the study period (54.16% males, mean age = 39.3 years SD=16.8 years), 71 unintended medications discrepancies were detected (2.96 per patient). The majority of these discrepancies found during discharge reconciliation (64.8%) followed by admission (25.3%) and post-discharge (9.85%). The medications involved in these discrepancies included medications of osteodystrophy (21.8%), immunosuppressant (15.5%), immunosuppressant dosing (12.7%), electrolytes (12.7%), anticoagulation (11.3%), hypertension (8.5%) PPIs (5.6%) and diabetes (4.2%), the remaining 5.6% were miscellaneous medications, 95.8% of unintended discrepancies were prescription-related while the remaining were due to dispensing errors. Physicians resolved all unintentional discrepancies based on clinical Pharmacist’s recommendations. Omissions constituted 57.8% of errors prevented, while the remaining were commission errors (23.9%), changed dose (16.9%) and wrong duration (1.4%).

**Conclusions:** Multidisciplinary medication reconciliation seems to be effective in reducing medication errors and promoting renal transplant patients’ safety.

**PUB324**

Nocardia Infection in Kidney Transplant Recipients: A Single-Center Experience

Sandesh Parajuli,1 Vivek Pathak,1 1University of Wisconsin School of Medicine and Public Health, Madison, WI; 1U of Wisconsin Hospital, Madison, WI.

**Background:** Nocardia is an uncommon, but life-threatening opportunistic infection that disproportionately affects the immunocompromised host. Although transplant-related Nocardia is well-recognized, data in kidney transplant patients remains limited.

**Methods:** A retrospective chart review of all patients at our institution with a history of kidney transplant and at least one positive culture for Nocardia was performed.

**Results:** During the 20-year study period, 10 patients had Nocardia infection. Eight were deceased donor kidney transplant recipients, and the mean age at time of transplant was 56.0 ± 14.5 years. Induction agents included alemtuzumab (n=5), basiliximab (n=4), and anti-thymocyte globulin (n=1). Nocardiosis occurred at a mean of 11.5 ± 31.6 months (range, 6-102) months after transplant. Breakthrough Nocardia infection occurred in 7 patients (46%) receiving drug regimen (4/5) receiving dosing regimen (6/400 mg) of TMP-SMX prophylaxis for P. carini pneumonia. Immunosuppressive regimen at time of nocardiosis diagnosis consisted of prednisone (n=10), tacrolimus (n=9), and mycophenolate (n=8). The most common site involved was the lung. TMP-SMX was the most frequently used antimicrobial for treating nocardiosis (9 of 10); it was administered as single-drug therapy (4 of 10) or as combination therapy with other antimicrobials (5 of 10). Overall mortality was 60% (6 of 10); fifty percent (3 of 10) of deaths were attributable to Nocardia infection.

**Conclusions:** To the best of our knowledge, this is the largest case series of Nocardia infection in kidney transplant recipients. TMP-SMX prophylaxis did not appear to provide protection from Nocardia infection, but appeared to be associated with less severe disease. Overall outcomes remain poor. Practitioners should maintain a high degree of suspicion for this pathogen in the months to years after transplant.

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=100)</th>
<th>PPI (n=100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.3±5.2</td>
<td>36.5±5.4</td>
<td>0.86</td>
</tr>
<tr>
<td>BMI</td>
<td>26.8±4.2</td>
<td>27.0±4.3</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**Conclusions:** This study clearly shows the adverse influence of Thymoglobulin induction on graft survival in ABO-incompatible transplants. Graft loss can be reduced by avoiding this treatment.

**PUB325**

Thymoglobulin Adversely Affects the Outcome of ABO-Incompatible Transplants

Vivek Pathak,1 Nephrology, Kovai Medical Center and Hospital, Coimbatore, India.

**Background:** ABO-incompatible transplants are becoming more common with higher long term success rate but yet many centers are reporting unexpected graft loss due to antibody mediated rejection. We analysed our data and found something unexpected that induction with Thymoglobulin caused higher graft loss.

**Methods:** 172 patients who underwent renal transplantation between May 2012 till July 2018 were analysed. Thymoglobulin was used for induction in 31 and Basiliximab was used in 141 patients. They received maintenance immunosuppression with steroid, MMF and tacrolimus. Observation period was of 10 to 84 months.

**Results:** Acute rejection was seen in 18 patients(10.4%) and cellular rejection was uncommon. Graft loss was seen in 13 and 12 patients died. Graft nephrectomy due to antibody mediated rejection was done in 6/31 Thymo group and 2/141 of Basiliximab group in first 2 weeks. 2 patients who were doing well with Basiliximab induction with normal kidney function at 1 week where given Thymo to make them steroid free. Their Anti-A and Anti-B titres started rising immediately from 1:8 to 1:256 in 3 days and both lost the graft. We checked Anti-A and Anti-B titres in ABO compatible transplants before induction after first 75 patients so there was a clear difference in graft survival which improved after stopping Thymo Patient survival was 96.9% at 1 year and 81.2% at 5 years. Graft survival improved after dividing the group in first 75 subsequent patients which can be seen in the graph. Graft survival was 82% at 3 years, 69.5% at 5 years in overall 172 patients and 90.7% at 3 years after excluding first 75 patients. Acute antibody mediated rejection could be treated successfully in remaining 10 patients.

**Conclusions:** This study clearly shows the adverse influence of Thymoglobulin induction on graft survival in ABO-incompatible transplants. Graft loss can be reduced by avoiding this treatment.
Successful Treatment of Recurrent Focal Segmental Glomerular Sclerosis After Renal Transplant with LDL Apheresis Is Associated with Low Levels of Soluble Urokinase Plasminogen Receptor Activator (sUPAR)  
Vasil Peets,1 Stuart M. Sprague,2 Joshua Zaritsky,3 Jochen Reiser.4  
1Division of Nephrology, Rush University Medical Center, Chicago, IL; 2NorthShore University HealthSystem University of Chicago, Chicago, IL; 3Nemours/ Alfred I. duPont Hospital for Children, Wilmington, DE; 4Rush University Medical Center, Chicago, IL.

Introduction: Recurrent FSGS remains to be a devastating condition without specific therapy. sUPAR has been reported as a cause of FSGS and its removal is affected by plasmapheresis (PLEX). We report a successful treatment of recurrent FSGS with LDL apheresis.

Case Description: We report a case of a 21 year old male with a biopsy proven idiopathic FSGS diagnosed at age of 12 with a relapsing course and progression to end stage renal disease despite aggressive multi drug therapy. He received a living related renal transplant from his mother with immediate FSGS recurrence in the allograft. His pre transplant sUPAR levels were measured at 12.39 ng/ml. Post transplant PLEX was initiated promptly followed by two doses of rituximab with very poor clinical response. Ninety days after the transplant surgery he was offered treatment with LDL apheresis device (Liposorber LA-15, by Kaneka Pharma America LLC). His chemistries demonstrated serum creatinine (SCr) of 4.0 mg/dl, eGFR of 20ml/min, serum albumin 1.6 mg/dl, proteinuria of 13 g/24h based on spot urine protein to creatinine ratio (U/P C) and sUPAR level of 5.3 ml/ml. He received six twice weekly LDL apheresis treatments followed by seven weekly sessions. He also received oral prednisone therapy (60 mg daily for 3 weeks), followed by gradual taper over 6 weeks to maintenance daily dose of 5 mg in addition to IV solumedrol (500mg) following each of the weekly apheresis treatments. His sUPAR levels declined gradually throughout the treatments and reached nadir of 1.9 ng/ml following his 13th session. The remainder of the chemistries demonstrated SCr of 1.7 mg/dl, eGFR of 50 ml/min, U/P C of 800ng/ml, serum albumin of 3.7 kg/ml. The LDL apheresis treatments lowered sUPAR levels more significantly (aprox. 47%) and were associated with much lesser rebound than what has been reported in patients with recurrent FSGS receiving PLEX.

Discussion: LDL apheresis lowers sUPAR levels to a greater degree and with less rebound than PLEX. This treatment modality can be successfully applied in patients with post transplant FSGS recurrence.

Simultaneous Liver Kidney Transplantation Using Single Subcostal vs. Dual Incisions: Does Incision Really Matter?  
Brianna Ruch, Amit Sharma, Gaurav Gupta, Chandra S. Bhati, Adrian Cotterell, Marlon F. Levy.1 1Virginia Commonwealth University, Richmond, VA; 2Virginia Commonwealth University Health System, Richmond, VA.

Background: Simultaneous liver-kidney transplantation (SLKT) is commonly performed using a subcostal incision for the liver allograft and a right iliac fossa incision for retroperitoneal kidney transplantation (Dual Incision, DI). Some surgeons use a single subcostal incision (SI) for SLK (with intraperitoneal kidney) to reduce the cold ischemia (CIT) and operative times. We report our outcomes using single and dual incisions for SLKT.

Methods: Retrospective analysis of all SLKT done at our center (2015 to 2019) was performed. Outcomes after SI and DI were compared using standard t-test for unequal variances. A p-value <0.05 was considered significant.

Results: 16 SLKT were performed (5 SI and 11 DI). Recipient demographics and early outcomes are shown in table 1.

Conclusions: Simultaneous liver kidney transplantation using a single subcostal incision did not show statistically significant benefit in length of hospital stay, opioid requirements on discharge or allograft function when compared to using dual incisions. Use of single incision for SLKT reduced the CIT for kidney allograft but was associated with a higher incidence of early bile leaks requiring operative intervention. Our initial outcomes need to be confirmed in larger studies.

Incident Gout After Renal Transplantation in Gout-Naive Patients: Large Database Analysis  
Brian LaMoreaux, Megan Francis-Sedluk, Robert J. Holt. Horizon Therapeutics plc, Lake Forest, IL.

Background: Patients undergoing kidney transplantation are at increased risk for developing hyperuricemia and gout compared to the general population (generally attributed to the frequent use of calcineurin inhibitors, cyclosporine and tacrolimus). However, the proportion of renal transplant patients that develop gout and the timing in which this occurs post-transplant is less established. This study sought to describe and quantify the incidence of gout in gout-naïve patients undergoing renal transplantation.

Methods: This retrospective analysis of Humana Research Database 2007-2017 claims data (private insurance and Medicare) was performed by identifying kidney transplant patients who were in plan for at least 6 months before and 5 years after transplant. Only patients without an ICD-9/10 gout diagnostic code within 6-months prior to transplant were included. Included patients were then examined for cumulative incidence of gout post-transplant.

Results: The database contained 16,454 patients that underwent kidney transplant. Of these, 920 patients underwent renal transplant, were in plan for at least 6 months before and 5 years after transplant, and did not have a gout diagnostic code before transplant. Of these, 212 patients (23%) had a post-transplant gout code while in plan, and 175 (19%) developed gout within 5 years post-transplant. The proportion of patients with gout progressively increased over time post-transplant and did not plateau. (Figure 1)

Conclusions: Gout is a known frequent comorbidity in solid organ transplant patients, but the timing and proportion of transplant patients who develop gout is not well described. Using a large database analysis, this analysis showed that the proportion of gout
Impact of Recipient Age Older Than 70 Years on Outcomes Following Listing for Kidney Transplant: A Single-Center Analysis

Ripudaman Sundaram, M.D.
University of Pittsburgh Medical Center
Pittsburgh, PA.

Figure 1. Proportion of gout-naïve kidney transplant patients who developed gout over 5 years post-transplant

**Table 1.** Proportion of unlisted patients who were transplanted or died while on the waitlist

<table>
<thead>
<tr>
<th>Age at Listing (y)</th>
<th>Number of patients N (%)</th>
<th>Transplanted N (%)</th>
<th>Died on WL N (%)</th>
<th>Died After Delisting N (%)</th>
<th>Still Listed N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-40</td>
<td>1152 (98%)</td>
<td>611 (53%)</td>
<td>227 (19%)</td>
<td>57 (5%)</td>
<td>85 (7%)</td>
</tr>
<tr>
<td>41-70</td>
<td>821 (82%)</td>
<td>218 (88%)</td>
<td>29 (3%)</td>
<td>64 (16%)</td>
<td>261 (32%)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>779 (85%)</td>
<td>73 (97%)</td>
<td>21 (3%)</td>
<td>29 (20%)</td>
<td>9 (12%)</td>
</tr>
</tbody>
</table>

**Table 2.** Distribution of recipient and donor variables with kidney transplant outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>All n=4184</th>
<th>Group I: Age &lt;60 n=3099</th>
<th>Group II: Age 61-70 n=1158</th>
<th>Group III: Age &gt;70 n=89</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>54±16</td>
<td>54±16</td>
<td>54±16</td>
<td>54±16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>55 (5%)</td>
<td>55 (5%)</td>
<td>55 (5%)</td>
<td>55 (5%)</td>
<td>0.942</td>
</tr>
<tr>
<td>K Friedler = 87/5</td>
<td>106 (6.6%)</td>
<td>106 (6.6%)</td>
<td>106 (6.6%)</td>
<td>106 (6.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor/no. (%)</td>
<td>62 (5%)</td>
<td>62 (5%)</td>
<td>62 (5%)</td>
<td>62 (5%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Donor/age (y)</td>
<td>64±20</td>
<td>64±20</td>
<td>64±20</td>
<td>64±20</td>
<td>0.002</td>
</tr>
<tr>
<td>Donor/Race</td>
<td>62 (49%)</td>
<td>62 (49%)</td>
<td>62 (49%)</td>
<td>62 (49%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Donor/kg/m²</td>
<td>183 (19.3%)</td>
<td>183 (19.3%)</td>
<td>183 (19.3%)</td>
<td>183 (19.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor/mass</td>
<td>61 (12%)</td>
<td>61 (12%)</td>
<td>61 (12%)</td>
<td>61 (12%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Donor/ERA</td>
<td>10 (21%)</td>
<td>10 (21%)</td>
<td>10 (21%)</td>
<td>10 (21%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Graft Survival</td>
<td>20 (10%)</td>
<td>20 (10%)</td>
<td>20 (10%)</td>
<td>20 (10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deceased</td>
<td>32 (13.7%)</td>
<td>32 (13.7%)</td>
<td>32 (13.7%)</td>
<td>32 (13.7%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 1.** Kaplan Meier Survival Curve among 3 age groups undergoing kidney transplantation

**Figure 1.** Cumulative Incidence of Gout Post-Transplant

**Figure 1.** Comparison of gout-naïve patients undergoing kidney transplantation who develop gout over time and incidence increases as patients are followed over a longer period of time.

**Funding:** Commercial Support - Horizon Therapeutics plc

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
from the kidney transplant registry from 2012 to 2016. Demographic and clinical data were collected at baseline, 1, 3, 6 and 12 months post transplant. Patients were divided into two groups (anemic and nonanemic) based on the presence of anemia (hemoglobin 10.5 g/dl at first month post transplant). Primary outcome was a composite of patient and graft survival.

Results: Our cohort included 64 patients with follow-up of 28.6 ± 11.4 months, 16 (25%) had early PTA. Baseline characteristics such as age, gender, type of donor, etiology of endstage kidney disease, induction therapy, type of primary immunosuppression, histological characteristics of the zero and follow-up biopsy were similar in both groups. During the study period, a decrease in renal function was observed in the group of early anemia (Figure 1). Creatinine clearance at last follow-up was significantly lower in anemic group (58.1 ± 21.7 ml/min) and nonanemic group (72.3 ± 18.3 ml/min) (p = 0.013). A Kaplan–Meier survival analysis at 5-year post-transplant showed significantly poorer graft survival in the anemia group, p = 0.03. On multivariable analysis, the anemia group was significantly associated with graft loss (HR 12.6, 95% CI 1.5-15.7, p = 0.19).

Conclusions: In this study, early onset anemia was independently associated with graft loss, without differences in mortality. PTA must be corrected immediately to avoid poor prognosis outcomes.

Cytomegalovirus Pathology in Renal Transplanted Patients: Determining Factors And Relation With Graft And Patient Outcomes
Carlo M. Allegri,1,2 Paolo Molinari,1 Maria Teresa Gandolfo,1 Mariarosaria Campise,1 Donata C. Cresseri,1 Piergiorgio Alfieri,1,2 Paolo Cresseri,1,2 Mariarosaria Campise,1,2

Methods:

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

1159
A Successful Kidney Transplant in a Patient with Inferior Vena Cava Thrombosis and Esophageal Varices

Hussein M. Bagha, Nishma Gajjar, Aisha A. Jabeer, Ahmed Tawhir, M. P. Shah Hospital, Nairobi, Kenya; M. P. Shah Hospital, Nairobi, Kenya; University of Nairobi, Nairobi, Kenya; Parkland Kidney Centre, Nairobi, Kenya.

**Introduction:** Kidney transplant is the preferred treatment for patients with chronic kidney disease on dialysis. Prolonged use of dialysis catheters are associated with complications like infections, thrombosis and development of superior vena cava syndrome. Superior vena cava obstruction is known to be a rare cause of esophageal varices and can lead to upper gastrointestinal bleeding. Finding a venous thrombosis prior to transplant may provide additional challenges by further increasing the risk of graft failure.

**Case Description:** A 27 year old male patient known to have end stage renal disease and systemic arterial hypertension presented for kidney transplantation. He had been on hemodialysis for six years. His access was a left femoral tunneled catheter which was changed to a temporary catheter due to a catheter related blood stream infection. He had several subclavian and internal jugular vein catheters fixed before which had led him to develop superior vena cava syndrome with multiple areas of thrombosis within the superior vena cava. He had been started on warfarin for the same. During the work up for the kidney transplant, he developed hematemesis and an endoscopy done showed esophageal varices which were managed conservatively. A CT aortogram showed a ten centimeter non-occlusive thrombus in the inferior segment of the inferior vena cava and an occlusive chronic thrombus of the left common iliac vein. The patient was started on enoxaparin for three months. He underwent a successful kidney transplant. The graft kidney was placed in the right iliac fossa and the renal vessels were anastomosed to the external iliac vessels.

**Discussion:** Superior vena cava syndrome is a common complication of prolonged use of dialysis catheters inserted in the subclavian and internal jugular veins. Rarely, it can cause esophageal varices which can lead to upper gastrointestinal bleeding. Our patient presented a challenge in that he had esophageal varices which increased his risk of bleeding and he required anticoagulation for the inferior vena cava thrombosis for a successful transplant. The other dilemma was where to place the graft kidney and which vessels to use for anastomosis as he had a ten centimeter clot in the inferior vena cava. We opted to wait for three months and anticoagulated him with enoxaparin and then transplanted him.

An Analysis of Epidemiology, Etiology, and Outcomes of Acute Pancreatitis in Renal Transplant Recipients

Dharmendra Bhadur, Sanja Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.

**Background:** Acute pancreatitis after renal transplantation is seldom seen, yet a dreadful complication. The causes include traditional causes and immunosuppressive medications, viral infections. Classical symptoms are not always present at onset, which may cause delay in diagnosis. The available literature on pancreatitis in renal transplants is either as case reports or case series. Large studies with longer follow up period and outcome in renal transplant patients with pancreatitis are lacking. We conducted this retrospective study to analyze the incidence, clinical features, causes of pancreatitis in our institute in post azathioprine era.

**Methods:** We conducted a single center retrospective study of renal transplant recipients who suffered at least one episode of acute pancreatitis during a period from Jan 2002 to September 2018. We followed IAP/APA (International Association of Pancreateology/American Pancreatic Association) evidence based guidelines for confirming diagnosis of acute pancreatitis and included only patients who fulfilled these criteria. Once the diagnosis is confirmed we retrospectively analyzed the aetiology, clinical features, management and outcome in renal transplant recipients with pancreatitis.

**Results:** Twenty-six patients (males 81%; mean age 38.5 years) out of 1350 allograft recipients developed 39 episodes of acute pancreatitis. The incidence of acute pancreatitis was estimated to be 0.12% per patient year (1.9% patients). The interval between transplantation and pancreatitis ranged from < 1month to 14 years. Four patients had pancreatitis in immediate post transplant period (<1 month). Etiology included were drugs chiefly (61.4) gallstones (19.3%), structural lesions (11.5%) and viral infections (7.8%). Clinical presentations, laboratory parameters were similar to pancreatitis in non transplant patients. Graft dysfunction was noted in twenty patients (77%) and all showed either partial or complete recovery. Patient survival was good with 88% of the patients surviving the episode while three (11.5%) patients expired during the episode. Mean duration of follow up was 34.1(±10) months. The 1-year, 5-year and 10-year survival rates after an episode of acute pancreatitis was 65.78%, 55.67% and 27.83%.

**Conclusions:** Pancreatitis after renal transplantation is a rare complication with better outcome than what has been reported in the past.

Prevalence and Predictors of Sensory Polyneuropathic Signs and Symptoms in Renal Transplant Recipients

Svea Nolte, Jese M. Hofman, Antonio W. Gomes Neto, Jan willem Elting, Michele F. Eisenga, Marco van Londen, Stephan J. Bakker, Ilja M. Nolte, Bianca De greef, Catharina Faber, Jan-Stephan Sanders, Daniel J. Touw, Eric Lekman, Stefan P. Beers, and real estate agent, Maastricht University Groningen, Groningen, Netherlands; Maastricht University Medical Center+, Maastricht, Netherlands.

**Background:** Sensory polyneuropathy is a common finding in renal transplant recipients (RTR). Patients with end stage renal disease are at a high risk to develop uremic or diabetic polyneuropathy. Kidney transplantation frequently fails to improve polyneuropathic signs and symptoms post- transplantation. However, little is known about the exact prevalence of post-transplantation sensory polyneuropathy. Therefore, our aim is to determine prevalence and possible predictors for sensory polyneuropathy in RTR.

**Methods:** RTR and healthy subjects, examined prior to renal donation, were included in the TransplantLines biobank and cohort study at the University Medical Center Groningen. The primary outcome was the result of the adapted modified Toronto Clinical Neurology Score (amTCNS), a scoring tool designed to quantify neurological complaints and to rate symptoms of sensory polyneuropathy. Information on relevant clinical parameters i.e. age, height, presence of diabetes mellitus, serum urea levels, eGFR, levels of parathyroid hormone, potassium, follic acid, vitamin B-12, and use of calcineurin inhibitors was collected from all subjects. A chi-square test was used to compare prevalence of sensory polyneuropathy between RTR and healthy subjects. Multivariable linear regression analysis was performed to assess the relationship between explanatory variables and sensory polyneuropathy.

**Results:** A total of 209 RTR (65.3% males) with a mean age of 54.9±13.4 (range 17-80 years), and 122 healthy subjects (46.7% males) with a mean age of 55.9±11.2 (range 27-75) years were included. Signs and symptoms of sensory polyneuropathy were present in 48 (23.0%) RTR and in 6 (4.9%) healthy subjects (P=0.001). Serum urea (st. b=0.28, P=0.003) and age (st. b=0.25, P=0.001) were independent predictors of sensory polyneuropathy in RTR.

**Conclusions:** Polyneuropathic signs and symptoms are more common in RTR than in healthy subjects. Serum urea and age are independent predictors of sensory polyneuropathy in RTR, making uremic polyneuropathy the most likely underlying etiology in this particular patient setting.

Outcomes of Late Acute Rejection Treatment with r Anti-Thymocyte Globulin (r-ATG) 1 Year Post Kidney Transplant

Asad Riaz, Asif A. Shafiaaddin, Tim E. Taber, Oluwaisayo O. Adebiyi, Muhammad S. Yaqub, Indiana University School of Medicine, Indianapolis, IN.

**Background:** The aim of this study is to investigate the relationship of Late Acute cellular Rejection (LAR) episodes, treated with r-ATG one year post transplantation, with reversibility of graft dysfunction and long-term graft survival.

**Methods:** Data of 20 recipient patients who reviewed who received r-ATG between 2009 and 2016 for biopsy proven LAR. Age at transplant 33.9 ± 15 years, 11 M, 9 F and 11 Caucasians with biopsy proven LAR one year post transplantation. Non-adherence was the most common reason for acute rejection (65%). Mean r-ATG cumulative dose was 6.25 mg/kg. All recipients received IV steroids/ oral Prednisone taper. Maintenance immunosuppression included Ciclosporine Inhibitors, Anti metabolites and Prednisone.18 recipients had Banff IB or higher grade acute cellular rejection (ACR). 4 recipients had combined ACR and Antibody Mediated Rejection.

**Results:** Pre biopsy Cr 1.75 +/- 0.7, Cr at the time of biopsy 5.45 +/- 2.87. Time lapse (days) between baseline Cr and Biopsy was 157.4 +/- 193.2. Post r-ATG Cr at 6 mon was 3.3 +/- 1.8. Post r-ATG, 9 (45%) recipients had graft failure before 12 months, 7 had graft failure between months 13 to 36 and 4 had functional graft beyond 36 months. Only 1 recipient has a functional graft to date (92 months post r-ATG treatment). Mean Graft survival from date of transplant was 73.8 months +/- 27.6 and graft survival post r-ATG was 22.6 months +/- 23.3.

**Conclusions:** Late Acute Cellular Rejection severely reduces long term graft survival. Acute rejection treatment with r-ATG should be used in very selective patients as it may benefit only very few patients.
Comparison of Outcomes with and Without Induction Therapy in Low-Risk Renal Transplant Recipients

Sabina Yusuf,1 Anurag Gupta,2 Devinder S. Rana,1 Vinant Bhargava,1 Ashwani Gupta,1 Anil Bhatta,1 Manish Malik,1 Neha Jain.1 Sir Ganga Ram Hospital Department of Nephrology, Sir Ganga Ram Hospital, New Delhi, India; 2SYNEGY Hospital, Umrakpur, India; 1UCONN Health, Hartford, CT.

Background: With low rates of acute rejection with current maintenance immunosuppression, induction of immunosuppression is no longer considered the norm. Question arises whether induction offers any additional benefit in low risk renal transplant recipients. This study evaluated outcomes with and without induction in low risk renal transplant recipients.

Methods: A prospective observational study in which 100 low risk renal transplant recipients were included and divided into 2 groups – one that received induction and another that did not. They were followed for 1.5 years. Three end points were compared - efficacy of induction, patient and graft survival and adverse effects.

Results: Incidence of rejection in early post transplant period did not differ (4% NO IND vs 6% IND; p=0.171). Rejection as cause of late graft dysfunction was seen in 16% in IND vs 20% NO IND; (p=0.603). No difference in serum creatinine at end of 1.5 years was seen. Graft survival was also similar. Relapsing and recurrent UTIs (46% IND vs 16% NO IND; p=0.09), hospitalization requiring infections (76%IND vs 64% NO IND; p=0.119 NS) were more common in IND. CMV infection affected only IND (6% vs none; p=0.07).

Patient survival at 1.5 years was comparable (94% IND vs 96% NO IND; p=0.646).

Conclusions: The study showed comparable results between IND and NO IND with however an increased incidence of infections and hospitalizations in IND group. Use of induction may be avoided in low risk renal transplant recipients.

Variations of Serum Creatinine in Patients with Hospitalizations in the First and Second Year of Renal Transplantation

Daniel Marillo-braihila,1 Monica C. Jimenez-Correo,1 Maria Concepcion Osuerguera-Vegazano,1 Jose A. Lago,1 Nidia R. Alvarez,1 Alejandro Bautista Arana,1 Dulce L. Isaura moran,1 Dario A. Covarrubias.1 1Antiguo Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Mexico; 2Hospital Civil de Guadalajara “Fray Antonio Alcalde”, Guadalajara, Mexico; 3Hospital Civil de Guadalajara, Guadalajara, Mexico; 4Hospital civil antiguo, Guadalajara, Mexico.

Background: The kidney transplant patients the main causes of hospitalization are infections and kidney graft rejection. The aim of this study is to analyze the variations in serum creatinine levels in kidney transplant patients who had hospitalizations in the first and second year of transplantation.

Methods: Retrospective observational study, 28 patients with kidney transplant were selected in the 2016-2018 period, divided into two groups; First year and second year of transplantation, the data was taken from the database of the Civil Fray Antonio Alcalde hospital in Guadalajara, demographic characteristics are shown in numbers, percentages, mean, standard deviation and non-parametric Wilcoxon.

Results: The baseline characteristics of the 28 patients, 15(53.6%) are male, a mean of 28.5 years of age, 19(67.9%) was living donor, 9(32.1%) from a brain death donor, the average number of hospitalizations was assessed in the first and second year 1.94 and 1.8 respectively, main diagnoses of hospitalization were urinary tract infections and graft rejection, baseline creatinine in the first year group with an average of 1.3mg/dl and the second year group an average of 2.6mg/dl, the Wilcoxon test comparing baseline creatinine and creatinine variations at the end of the follow-up of both first year P=0.51 and second year group P=0.31

Conclusions: No significant differences were found in both groups in the variations of creatinine levels with respect to baseline levels, which concludes that hospitalizations in the first two years of kidney transplantation have a minimal impact on creatinine levels and that probably related to renal functional reserve of the graft.
Outcomes of Renal Transplantation in Adult Patients with Primary Focal Segmental Glomerulosclerosis: A Single-Centre Experience

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Background: Focal Segmental Glomerulosclerosis (FSGS) is the most common primary glomerular cause of end stage kidney disease (ESKD). Renal transplantation in patients with FSGS is complicated by recurrent disease, which is reported in 30-50% of cases and may lead to graft loss. It is important to identify patients at high risk of recurrent disease to improve transplant outcomes and to inform the consent process.

Methods: We performed a retrospective database search (n=3533) of all patients with primary FSGS transplanted at our centre over a 50 year period, and evaluated their transplant outcomes. Recurrent disease was diagnosed on renal transplant biopsy in patients with proteinuria. Data are expressed as median ++ interquartile range.

Results: We identified 111 transplants in 106 patients with ESKD due to primary FSGS. Follow up data were available for 80 patients; 59% male 41% female with median age at transplantation 43 (+/- 18) years. 66% were Caucasians. 69% transplants were from live donors. Median follow up period was 7.5 years. Recurrent FSGS occurred in 16% (n=13) patients; 55% male and 61% Caucasian. Length of time from transplant to recurrence was between 3 months and 10 years. Graft loss due to recurrent FSGS occurred in 77% (n=10) patients with recurrent disease.

Conclusions: Our large single centre study shows that recurrent FSGS following renal transplantation is much lower than in published studies, but that recurrent disease leads to graft loss in most patients. This data will inform shared decision making in patients with primary FSGS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

1162
Association Between Clinical-Demographic Factors Pre-Transplant and Mortality in Receptors of Deceased Donor Kidney

Background: Demographic and clinical factors can be associated with deleterious consequences in renal transplant and deceased survival of the patient. Objective: to evaluate the association between demographic and clinical factors pre-renal transplant with mortality in recipients of deceased donors.

Methods: We performed the follow-up of 255 renal transplant patients from deceased donors at the Hospital do Rim-UNIFESP for 10 years (2008-2018). We evaluated demographic data such as age, sex, immunosuppressive drugs, serum creatinine from donors at the Hospital do Rim-UNIFESP for 10 years (2008-2018). Interstitial fibrosis and chronic renal allograft nephropathy (CRAN) in recipients of deceased donors.

Results: CRAN occurred 5.5±0.25 years in fifty-two patients. Donor creatinine was higher in CRAN group (127±10 vs 107±8 mg/dl; p=0.004). Hgb concentration was lower in CRAN group (10.3±1.8 vs 12.4±1.8 g/dl; p=0.01). There was a higher frequency of patients with DGF (p=0.02) and acute rejection episode (p=0.01) that developed CRAN. There was no difference in immunosuppressive drugs and cold ischemia time between groups. Donor creatinine (OR = 3.354, 95% CI 1.198-9.389, p = 0.02), acute rejection episode (OR = 0.346, 95% CI 0.132-0.878, p = 0.03) and concentration of Hgb in 6 months after renal transplant (OR = 0.818, 95% CI 0.767-0.998, p = 0.04) were independent predictors of CRAN.

Conclusions: Donor creatinine, acute rejection and lower Hgb concentration 6 months after transplant and the patient's age were associated with CRAN in deceased donor renal transplant recipients.

PUB350 A More Realistic Assessment of Waiting Time for Transplant Patients

Background: Waiting times for transplant candidates are routinely presented to patients by transplant centers. However, with the increased complexity of the new Kidney Allocation System (KAS), these reported times may no longer be accurate for patients who do not qualify for higher allocation priorities. We aimed to quantify these differences.

Methods: We conducted a retrospective analysis of all deceased donor transplants at our center beginning December 4, 2014. We used data from UNOS to determine waiting time and the priority pool in which each kidney was allocated. Within each blood group we compared waiting times for recipients who received a kidney from a priority pool (using cPRA < 98%); prior living donation; registration prior to age 18; and 0-20% EPTS) to recipients who received an organ allocated within a standard pool (local, regional, and national; blood type identical or permissible). Additionally, within the standard pool we compared waiting times for unsensitized (cPRA 0%) vs low-sensitization (cPRA < 97%) recipients.

Results: Among the recipients were 121 blood group A, 74 group B, 16 group AB, and 160 group O. Standard patients experienced waiting ranges from 7.1% to 18.4% longer than the mean waiting times for the entire ABO group. This equated to waiting times that ranged from 0.3 years to 1.2 years longer than the usually quoted times for their blood groups. When we looked at unsensitized patients the mean waiting times were even longer among group A, B and O patients- increased by 13.2%, 14.5%, and 29% respectively. For blood group O in particular, the mean waiting times were 2 years longer than the average time for the entire group.

Conclusions: Recipients who do not qualify for priority allocation can expect significantly increased wait times compared to the average time for the entire group which is what is most often quoted to patients. Factors such as sensitization, EPTS, and other priority characteristics must be considered in setting expectations for waiting time of individual patients.

PUB349 Association Between Clinical-Demographic Factors Pre-Transplant and Chronic Renal Allograft Nephropathy in Receptors of Deceased Donor Kidney

Background: Renal allograft failure is one of the most common causes of end-stage renal disease. Demographic and clinical factors can be associated with deleterious consequences in renal transplant. Objective: to evaluate the association between demographic and clinical factors pre-renal transplant with chronic renal allograft nephropathy (CRAN) in recipients of deceased donors.

Methods: We performed the follow-up of 255 renal transplant patients from deceased donors at the Hospital do Rim-UNIFESP for 10 years (2008-2018). Interstitial fibrosis and chronic renal allograft nephropathy (CRAN) was considered as CRAN. We evaluated demographic data such as age, sex, immunosuppressive drugs, serum creatinine from recipients and donor. Hemoglobin (Hgb) concentration and CKD-EPI were evaluated after 6 months of transplant, cold ischemia time; duration of delayed graft function (DGF), acute rejection episode and CRAN as outcome. We compared CRAN and Non-CRAN groups. We performed binary logistic regression using CRAN as response variable after comparisons.

Results: CRAN occurred 5.5±0.25 years in fifty-two patients. Donor creatinine was higher in CRAN group (127±10 vs 107±8 mg/dl; p=0.004). Hgb concentration was lower in CRAN group (10.3±1.8 vs 12.4±1.8 g/dl; p=0.01). There was a higher frequency of patients with DGF (p=0.02) and acute rejection episode (p=0.01) that developed CRAN. There was no difference in immunosuppressive drugs and cold ischemia time between groups. Donor creatinine (OR = 3.354, 95% CI 1.198-9.389, p = 0.02), acute rejection episode (OR = 0.346, 95% CI 0.132-0.878, p = 0.03) and concentration of Hgb in 6 months after renal transplant (OR = 0.818, 95% CI 0.767-0.998, p = 0.04) were independent predictors of CRAN.

Conclusions: Donor creatinine, acute rejection and lower Hgb concentration 6 months after transplant and the patient's age were associated with CRAN in deceased donor renal transplant recipients.

PUB351 AKI in Liver Transplant Recipients: Is It Too Bad?

Background: AKI after Orthotopic liver transplant (OLT) is a common complication with an incidence varying widely between 17-90%. It impacts patient survival, morbidity and duration of stay. We conducted a retrospective study in our institution is to identify predisposing risk factors and assess 1 year patient and renal outcomes after AKI in OLT recipients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

1163
Methods: Data were collected from electronic medical record system for OLT recipients, between January 2015 to October 2017. Total 110 patients were included; age range was between 22 and 73 years. They were classified according to sex, race, presence of other co morbidities like hypertension, diabetes and the presence of micro proteinuria. GFR and creatinine were collected at the of transplant, 3 months, and one year after and compared to the base line. Patients were classified into AKI I, AKI II, AKI II and no AKI according to KDIGO criteria. Primary outcomes were chronic kidney disease (CKD), end stage renal disease (ESRD) and death within 1 year in patients who had AKI.

Results: Out of 110 patients; 8 died, 6 of them had AKI III (about 5% of total and 17.6% of the AKI III population). 34 patients had AKI III (31%), 22 (20%) of them required renal replacement therapy (RRT) (continuous renal replacement therapy and hemodialysis) during the perioperative time. None of them has required RRT at 3 months or at one year. 57% of the patients who had AKI III at the perioperative period, ended up with CKD III at 1 year, only 3.4% had CKD IV and none with CKD V at one year. Fig 1 shows relation between GFR at 1 year and AKI severity. Higher INR associated with more severe AKI, as well as alcoholic and HCV liver cirrhosis.

Conclusions: AKI during perioperative time in liver transplant recipients is very common, and might require RRT, although one year outcome remains good.

Relation between GFR at 1 year and AKI severity

PUB352

Potential Simultaneous Acute Tubular Necrosis and Immunological Rejections Following Renal Transplantation

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Background: To highlight the simultaneous occurrence of acute tubular necrosis (ATN), cellular and antibody mediated rejection (AMR) after renal transplantation (Tx). They constitute the bulk of renal allograft pathology and administration of appropriate therapeutics is essential based on specific causes for graft dysfunction.

Methods: We evaluated 112 renal allograft biopsies with histological evidence of ATN for immunological reactions (IR) and conditions related to chronic rejections. The patients with a diagnosis of ATN and potential IR, or symptoms of chronic rejections were further analyzed based on detectable HLA and Non-HLA antibodies (Ab).

Results: Immunohistopathological findings revealed 35 cases with chronic rejection, 5 with C4d- AMR, 3 with C4d+AMR, and 3 with TCR. The C4d+ and C4d- AMR correlated with HLA donor specific antibodies (DSA). All patients had HLA DSA and >1 non-HLA Ab based on a panel of 33 non-HLA targets.

Conclusions: ATN and acute or chronic IR could co-exist. Cases with ATN and Type 1 AAMR based on staining for kidney injury molecule-1 have been reported previously. Also, Exsfoliative Renal Tubular Epithelial Cells (ERTEC) bound to IgG have been found in ATN cases preceding clinical rejection. IgG bound ERTEC could indicate an early IR. ATN could lead to such immunological changes by exposing altered self-antigens or neoantigens leading to IR. Elaboration of these findings could help in development of novel therapeutics. ATN could lead to such immunological changes by exposing altered self-antigens or exposure of cryptic neoantigens leading to IR of the allograft. Elaboration of these findings could help in development of novel therapeutics.

PUB353

Clinical Outcomes of High Kidney Donor Profile Index (KDPI) in Kidney Transplants

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Background: KDPI score is designed to assess the expected kidney function in a kidney transplant recipient. Lower KDPI scores are associated with longer estimated allograft function. There is a high incidence of discard of high KDPI kidneys. However it is well proven that older patients on dialysis have high waitlist mortality and they may still benefit from a timely transplant utilizing this resource.

Methods: A retrospective review of prospectively collected data was conducted on 81 patients with deceased kidney donor transplants. Patients were divided into High KDPI (≥50, n=34) and Low KDPI (<49, n=47) groups. Patient demographics, EPTS scores, serum creatinine at different time intervals, delayed graft function- DGF, and biopsy proven rejection were analyzed. A paired t-test was used for continuous variables and Fisher’s exact test for categorical variable. P value of <0.05 was considered to be significant.

Results: Majority of recipients were Hispanic with mean age 54±11. Median KDPI for low and high group was 22 and 64 respectively. One year Kaplan Meier Allograft survival and rejection rates were comparable between groups; however there was significant difference in DGF and serum creatinine favoring low KDPI group. Table and graph illustrate the result.
Conclusions: High KDP1 kidneys have comparable short term survival and rejection rates to low KDP1 kidneys with slight compromise of organ quality. Selective patient with high waitlist mortality may still benefit from a timely high KDP1 kidney transplant.

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<tr>
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<th>Low KDP1</th>
<th>High KDP1</th>
<th>P Value</th>
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<td>EPTS score</td>
<td>34</td>
<td>44</td>
<td>0.001</td>
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<tr>
<td>DAT</td>
<td>1</td>
<td>6</td>
<td>0.0003</td>
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<tr>
<td>Reaction</td>
<td>12</td>
<td>9</td>
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Serum Creatinine (µg/dL)

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<th></th>
<th>214.44</th>
<th>1.49±0.35</th>
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<tr>
<td>P Value</td>
<td>0.026</td>
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Results: Total transplant recipient population was composed by 71 unique patients (49 males (69.1%) and 21 females (30.9%). Patient mean age was 48.3 years (SD 8). 245 Unique CMV DNA molecular test requests were found, with 170 requests (62 unique patients) presenting with CMV DNA viral load >250 cp/mL (min 263; max 59000; mean 262). The most frequently found hematological abnormality was lymphopenia <1500 x 10^9/L (60.1% requests) followed by leucopenia <4500u/L in 28.2% unique requests. Thrombocytopenia <150000u/L was found in 17.1% of the requests. The most frequently found biochemical abnormality was high serum creatinine >1.5mg/dL (46.7%). The most strong positive correlation of all the hematological and biochemical tests and CMV viral load was found between glutamate-oxaloacetate transaminase (GOT) and CMV viral load and (R=0.47). Correlation analysis between glutamate-pyruvate transaminase and CMV viral load showed a very weak correlation (R=0.0026). We also observed that a small patient subgroup (n=6) had simultaneous positive plasma CMV DNA and urinary BKV DNA with a common CMV viral load >500cp/mL.

Conclusions: Subtle laboratory abnormality patterns work as important tools to the suspicion of CMV infection. This work shows that CMV infection must be remembered as a possible diagnosis in patients presenting with lymphopenia, leucopenia, and rise of liver enzymes, particularly GOT, which in this study raised significantly and proportionally to the CMV DNA viral load.

PUB355

Effect of De Novo Donor-Specific Antibodies (DSA) on Graft Function in Renal Allograft Recipients

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Background: The availability of potent immunosuppressive agents has decreased acute cellular rejection rates, however, chronic deterioration of graft function continues to be a clinical challenge. Chronic Antibody-mediated rejection (cAMR) is an important cause of allograft failure in renal allograft recipients. cAMR is caused by the development of antibodies that do not preexist but develop after transplantation. These antibodies are directed against (foreign) graft HLA class I and II antigens and are known as de novo donor specific antibodies (DSA). DSA lead to allograft injury through complement-dependent or complement independent mechanisms resulting in glomerulitis, peritubular capillaritis, and transplant glomerulopathy. Routine immune monitoring of HLA antibodies can be used to guide immunotherapy and permit early intervention.

Methods: Prospective Observational Study. Patients undergoing renal transplant at Sir Ganga Ram Hospital in 2017 were screened for pre transplant DSA. A total of 72 DSA negative pre transplant patients were followed for 18 months. Clinical characteristics of patients were noted. DSA was tested at 6, 12 and 18 months post transplant.

Results: Total of 72 patients were included. de novo DSA negative patients (N=63) with mean age 40.73 years (SD=13) and de novo DSA positive patients (N=9) with mean age 34.66 years (SD=6.61). At 18 months, serum creatinine mean (SD) of de novo DSA negative patients was 1.41mg/dl (0.42) while for de novo DSA positive was 1.27mg/dl (0.38), p-value 0.552. eGFR, mean (SD) at 18 months in de novo DSA negative group was 58.2 (19.03) ml/min/1.73sq m and in de novo DSA positive group 56.47 (22.83) ml/min/1.73sq m, p-value 0.798. Tac levels(SD) at 18 months, in de novo DSA negative patients was 6.87 (2.29) ng/ml while in de novo DSA positive group, it was 6.05 (1.59) ng/ml. Urine protein creatinine ratio (SD) at 18 months in de novo DSA negative group was 0.30 (0.82) while in de novo DSA positive group, it was 0.31 (0.30).

Conclusions: De novo DSA developed in 12.5% of Patients after 18 months post transplant. There is no significant graft dysfunction at the time of appearance and a trend is noted of younger age and lower TAC levels in these de novo DSA patients.

PUB356

Time Trends in Kidney Transplantation in South Korea: A Nationwide Cohort Study from 2007 to 2015

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Background: Detailed nationwide information regarding recent status and time-trends of kidney transplantation in South Korea is limited.

Methods: We performed a nationwide, population-based cohort study using the national claims database of Korea in which nationwide health insurance is provided. We included kidney transplant recipients under age 70 from 2007 to 2015 and their demographic and clinical characteristics were collected. The prognostic variable was death-censored graft failure, and graft failure was determined when patient returned to dialysis.

Results: Number of kidney transplantation showed increasing trend, and the number increased from 820 in 2007 to 1755 in 2015. The incidence proportion of kidney transplantation among end-stage renal disease patients under age 70, which was below 3% in 2007, reached approximately 4% in 2015. The median age of the kidney transplant recipients consistently increased from the past, and proportion of patients with underlying diabetes mellitus was prominently increased, reaching 42.1% in 2015. The dialysis duration before transplantation was significantly increased, and in 2015, about 35.2% kidney transplantation was performed after more than 5 years of dialysis, which was 9.6% in 2007. Regarding maintenance medication usage, proportion of patients who were prescribed with tacrolimus greatly increased, while cyclosporine was less frequently used. One-year maintenance immunosuppressive medication possession ratio was consistently increased from the past. Transplantation-related costs was greatly increased during the
study period, particularly regarding government coverage, whilst patient burden for immunosuppressants was decreased from the past. Overall prognosis of kidney transplantation was improved in the recent periods, reaching approximately 80% 10-year graft survival in the recent periods.

Conclusions: Kidney transplantation is becoming a more prevalent modality of renal replacement therapy. While old-age transplantation is becoming more common, prognosis has been generally improved, but related insurances were increasing prominently.

PUB357

Variability in Blood Tacrolimus Levels with Generic Immunosuppression in Kidney Transplant Patients in Western Mexico

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Background: Tacrolimus is recommended as first-line therapy in most kidney transplant protocols. It has a narrow therapeutic index and routine blood levels monitoring is required to assure its effectiveness and to limit its toxicity. In our center, kidney transplant patients on generic immunosuppression were subject to frequent changes in generic brands of tacrolimus. There are few studies regarding the variability of blood tacrolimus levels according to tacrolimus generic formulations

Methods: Retrospective observational study. Electronic medical records of kidney transplant patients greater than one year and in immunosuppressive treatment with tacrolimus were reviewed, and blood levels of tacrolimus by generic brand, daily tacrolimus dose and weight dose was registered. Tacrolimus levels were also compared to CYP3A5 polymorphisms

Results: A total of 84 patients whose electronic medical records were complete (tacrolimus dose, blood tacrolimus levels, and tacrolimus brand) were included. 57 (67.8%) of those patients had Limustin, 20 (23.8%) were receiving Pisa, and 7 (8.3%) had Akrocell. Daily tacrolimus dose and tacrolimus weight dose was similar between groups. Mean blood tacrolimus levels were 6.28 ng/mL for Limustin, 7.08 ng/mL for Akrocell and 8.51 ng/mL for Pisa, with a significant statistical difference and a p value of 0.006. We found no significant difference between cytochrome CYP3A5 polymorphisms distribution, thus the differences in the blood tacrolimus levels cannot be attributed to differences in liver metabolism of the drug.

Conclusions: There is variability between different generic brands of tacrolimus regarding blood tacrolimus levels. They are lower in Limustin brand, despite a similar daily and weight dose compared to other generics, which is not explained by differences in liver metabolism of the drug. The long term effect that this could cause is not known. Blood tacrolimus levels should be monitored frequently, especially if brand changes are often made.

PUB358

Practical Utility of Various Scores for the Evaluation of Deceased Donor Kidneys

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Background: Marginal organs have been associated with inferior graft and patient outcomes at several centers. Some scores have been proposed for the evaluation of deceased donor kidneys in order to facilitate the best possible allocation combination and to improve graft and patient survival. We retrospectively validated their performance in predicting outcomes in donor kidney evaluation biopsies.

Methods: We evaluated the records of 223 consecutive adult cadaver renal transplant recipients with donor evaluation biopsies. Taking into account donor and recipient clinical data and graft histopathology, we performed a retrospective explorative univariate analysis of graft function at 3 and 12 months and 1- and 3-years graft and patient survival. The followed scores were: Navarro (2011), Ortiz (2004), Balar (2013), Lopez (2004), Snoeijis (2008), Remuzzi (1999), Nyberg (2003), Rao (2009), Foucher (2009), Schold (2005), Port (2002), Angelicheau (2008), 3-year-Leuven (2013), Irish (2010), KDRI/KDPI and EPTS.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Impact of Delayed Graft Function over Allograft Survival and Long-Term Kidney Outcomes After Transplantation in a Peruvian Hospital 2012-2017
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Background: Delayed graft function (DFG) is an early complication in kidney transplant recipient, defined as the hemodialysis requirement during the first week after transplantation. Some studies have found that DGF is associated to less allograft survival and worse long term kidney function. The primary outcome is to analyze the impact of DGF over allograft survival and kidney outcomes after one year after transplantation.

Methods: Retrospective study identified 71 adult patients, deceased-donor, kidney-only transplant recipients between 2012 and 2017. We used comparative studies using Chi Square test and T-student test. All of the statistical analysis were realized by the SPSS program. We compared cold ischemia time (CIT) and DGF with allograft survival using a multivariable linear probability Cox model.

Results: The average age of patients was 43.34 years (19-68 years), most of them from male gender. The principal cause of renal chronic disease was unknown (57.7%), followed by glomerular disease (9.9%) and Diabetes (7%). The average age of donors was 41.8 years, most of them male gender and the main cause of brain death was stroke. The serum donor creatinine (sCr) before transplant was around 1.15mg/dl (0.39-2.7mg/dl). The average of CIT was about 17.7 hours (9-26 hours). In the early transplant, four patients didn’t have kidney function, 15 patients had DGF and 52 patients had immediately kidney function(KF). As main causes of DGF were acute rejection and acute tubular necrosis (ATN), and the average of sCr at one year after transplant around 1.2mg/dl in recipients who had IKF and 1.59mg/dl in recipients with DGF (P<0.054). Chi square test showed that recipients who had DGF had an OddsRatio in 3.9 (IC 1.07 – 14.43) to achieve a sCr over 1.5mg/dl in a year after transplant in contrast with recipients who had already KF. (P<0.032). We applied probability Cox and determined a graft kidney survival of 98% in a year, 96% in three years and 94% in five years. There was not an important relation between DGF and CIT with graft survival.

Conclusions: Delayed graft function is an important negative risk factor for an optimal graft function. We could not find a significative relation between DGF, CIT and graft survival.

Women Compared with Men on Maintenance Hemodialysis Exhibit Unique Biomarker Patterns

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Background: Patients with end-stage renal failure on maintenance hemodialysis (MH) have higher mortality risk compared to the general population. Understanding of these unique mortality risk factors have not been fully explored by gender. The objective of this study was to examine unique biomarkers by gender and ethnicity in a cohort of MH patients compared to normal controls.

Methods: 92 MH patients in a single hospital-based dialysis unit in December 2017 consented with IRB approved protocol. Whole blood samples were drawn pre-dialysis into 3.2% sodium citrate (1/10 volume) and plasma samples processed using ELISA for selected biomarkers: BMP-7 (bone morphogenetic protein 7), MPO (myeloperoxidase); IL-6 and IL-8 (proinflammatory cytokines), CTX-1 (C-terminal collagen telopeptide) and OPN (osteonectin glycoprotein-phosphoprotein). Data compared as mean by gender and gender-ethnicity p-value tested using small sample size/low statistical power.

Results: Mean age was 60.5 ± 13.3 Yr (range 20-88); BMI 29.1 ± 5.4. Significant differences were seen between controls and MH patients for all biomarkers. No differences seen by gender for all other biomarkers except BMP-7 and MPO. Gender difference by ethnicity only seen in African Americans.

Conclusions: Women had higher MPO and lower BMP-7 levels compared to men. This difference remained when African American women were compared to African American men but less pronounced in low sample size of Caucasians. Patterns of biomarkers, particularly BMP-7 and MPO, were unique between genders. Patterns were also seen within ethnicity but small sample size reduced statistical power to examine further. BMP-7 may be associated with adynamic bone disease and has also been known as a potential biomarker in several diseases. Further work is needed to confirm these results.
J Am Soc Nephrol 30: 2019
Abdominal exam showed soft, non–tender, no costovertebral angle tenderness. Rest of the
exam is with in normal. Labarotary results showed sodium 137, potassium 4.1, chloride
100, bicarbonate 24, creatinine 1.15 mg/dl, calcium 9.4 mg/dl. Rest of the labs were within
normal limits. Urinalysis showed specific gravity >1.06, Ph 7.0, negative blood, negative
nitrite, 50 to 100 squamous epithelial cells. CT scan of abdomen with IV contrast showed
focal area of nonenhancement in the right kidney highly suggestive of an infarct. Right
renal arteriogram showed dissection within the distal right renal artery just proximal to the
bifurcation of uncertain etiology and multifocal infarct of the right kidney likely embolic
in etiology. Echocardiogram showed mild positive bubble study. Hypercoagulable work
up came to be negative. Patient was managed conservatively and discharged on apixaban
Discussion: Literature on Unilateral renal artery dissection is quite scanty. Isolated Renal
artery dissection poses a diagnostic and therapeutic challenge to physicians. Not sure if this
is an early sign of rare presentation of fibromuscular dysplasia or occult embolic infarction.
Need more cases for better understanding pathophysiology and efficient treatment

PUB366
Publication-Only

Potassium Binders for Chronic Hyperkalemia in People with CKD: A
Cochrane Review and Meta-Analysis
Patrizia
Natale,1,2
Suetonia
Palmer,3
Marinella
Ruospo,1
Valeria M. Saglimbene,1,4 Giovanni F. Strippoli.1,2 1Diaverum, Lund, Sweden;
2
University of Bari, Bari, Italy; 3University of Otago, Christchurch, New
Zealand; 4University of Sydney, Sydney, NSW, Australia.
Background: Hyperkalemia is a common electrolyte abnormality in patients with
chronic kidney diseases (CKD). Sodium polystyrene sulfonate (SPS) and calcium
polystyrene sulfonate (CPS) are widely used but may cause severe gastrointestinal
symptoms. Patiromer and sodium zirconium cyclosilicate (ZS-9) are newer potassium
binders which may cause fewer gastrointestinal side-effects. This Cochrane systematic
review evaluated the benefits and harms of potassium binders for treating chronic
hyperkalemia among people with CKD.
Methods: We searched the Cochrane Kidney and Transplant Register of Studies
for randomized controlled trials (RCTs) evaluating potassium binders for chronic
hyperkalemia administered in adults and children with CKD. We categorized treatments
as newer agents (patiromer or ZS-9) and older agents (SPS and CPS) in separate analyses
for some outcomes. Two authors independently screened citations for eligibility, extracted
data, and assessed risk of bias using the Cochrane tool. Evidence certainty was evaluated
using GRADE.
Results: Twelve studies (1340 participants) were eligible. Medial trial duration was
3.5 weeks (range 12 hours to 52 weeks). There were no trials that evaluated treatment in
children. Mean study age ranged from 53 to 73 years. Risks of bias were generally high
or uncertain. Seven studies (774 participants) compared a potassium binder to placebo.
Patiromer or ZS-9 had uncertain effects on all-cause mortality (relative risk [RR] 0.32,
95% CI 0.01, 7.57). The treatment effect of older potassium binders on all-cause mortality
was very unclear, and no study reported outcome data for cardiovascular mortality.
Potassium binders had uncertain risks of nausea (RR 2.10, 95% CI 0.65, 6.78), vomiting
(RR 1.72, 95% CI 0.35, 8.51), diarrhea (RR 1.03, 95% CI 0.24, 4.51), and constipation
(RR 1.68, 95% CI 0.65, 4.37).
Conclusions: Evidence for different potassium binders to treat chronic hyperkalemia
in people with CKD is of low certainty due to serious imprecision and trial methodological
limitations. This review suggests the need for a large, adequately powered trial of
potassium binders versus placebo that assesses clinical outcomes such as cardiovascular
mortality, cardiac arrhythmias, health-related quality of life, and major gastrointestinal
symptoms.

PUB367
Publication-Only

Risk Factors for Hospitalization and Critical Illness in CKD
Jefferson L. Triozzi, Jingbo Niu, Carl P. Walther, Wolfgang C. Winkelmayer,
Sankar D. Navaneethan. Baylor College of Medicine, Houston, TX.
Background: Chronic kidney disease (CKD) is a known risk factor for hospitalization.
Specific predictors of hospitalization with critical illness among patients with non-dialysisdependent CKD are unclear.
Methods: A retrospective cohort study was conducted among patients ≥ 18 years of
age with CKD in a CKD registry from a safety net health system. Patients with CKD stage
5 (eGFR < 15 mL/min) were excluded. We obtained baseline characteristics including
details of insurance and medical comorbidities. Details of hospitalization events were
obtained during a three year period after the diagnosis of CKD. Poisson regression
was used to determine associations between baseline characteristics and 1) the number
of hospitalization days and 2) the number of hospitalizations requiring intermediate or
intensive level of care. Analysis was stratified by CKD stage and adjusted for baseline
characteristics.
Results: Among 8,302 patients with CKD (1/1/2011 and 7/30/2015), 1,298 patients
(15.6%) were hospitalized during a 3-year follow-up period. Factors associated with
increased incident rate ratio of hospitalization days among all stages of CKD include:
congestive heart failure [3A: 2.6 (2.2, 3.1), 3B: 1.8 (1.5, 2.3), 4: 1.3 (1.0, 1.8)],
cardiovascular disease [3A: 1.2 (1.1, 1.5), 3B: 1.4 (1.1, 1. 7), 4: 1.7 (1.3, 2.3)], mild anemia
[3A: 1.6 (1.4, 2.0), 3B: 1.8 (1.4, 2.2), 4: 1.6 (1.1, 2.3)], and moderate/severe anemia [3A:
4.2 (3.1, 5.7), 3B: 4.3 (3.3, 5.6), 4: 2.3 (1.5, 3.3)]. Factors associated with increased
incident rate ratio of hospitalization with critical illness include: congestive heart failure
[3A: 3.8 (3.1, 4.5), 3B: 1.5 (1.2, 1.9), 4: 1.5 (1.0, 2.0)] and moderate/severe anemia [3A:
3.6 (2.9, 4.6), 3B: 4.1 (2.9, 5.7), 4: 2.0 (1.2, 3.4)].
Conclusions: Among patients with non-dialysis dependent CKD, congestive heart
failure and anemia are associated with a higher risk of hospitalization with critical illness

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and with longer hospitalization stay. Targeted, effective interventions to reduce the
hospitalization burden in CKD patients with heart failure or anemia is needed.

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Prevalence of Frailty in Nephrology Patients and Impact of Socioeconomic Factors
Melanie Betz,1 Arlene B. Chapman,1 Saurabh Chawla,1 Sai prasad Gadapa,2
Samantha Gunning,2 Nevin Murthy,1 Javeria F. Syed,1 Victoria T. Vo.1
1
University of Chicago Medicine, Chicago, IL; 2University of Chicago,
Chicago, IL.
Background: Frailty is common among patients with CKD. Frailty compromises
the ability to recover from illness and stressors, putting patients at risk for poor health
outcomes. Little research has been done to describe the prevalence of frailty in a nondialysis CKD population or investigate the impact of socioeconomic factors.
Methods: Frailty was assessed using the Frailty Phenotype (FP) for patients aged 65
years or more in a nephrology clinic at an urban medical center. The FP was administered
by Nephrology fellows or a Registered Dietitian. Socioeconomic factors were obtained
from zip code census data.
Results: Analysis included 56 patients with a mean age of 75±8 years, BMI of
28.7±7.2kg/m2 and GFR of 35±17ml/min; 54% were female, 79% were black and 75%
lived in high poverty areas. Only 20% were found to be non-frail, whereas 55% were
pre-frail and 25% were frail/very-frail. Females, patients with a lower GFR, lower median
household income or living in a high poverty area were more likely to be frail. Reduced
physical activity was the most common frailty factor; weight loss was the least common.
Conclusions: Frailty is prevalent among adults over 65 years in a nephrology clinic.
Frailty is more common in patients with low income. Frail patients present unique
challenges with diet recommendations and medications to help prevent malnutrition,
hypotension, hypoglycemia and falls. More research is needed to determine interventions
to reduce frailty and improve outcomes.
Demographics & Clinical Characteristics by Frailty Level

PUB369
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Targeted Program Designed to Address Missed Follow-Ups on Abnormal
Tests: A Proposal for Population Health Partnership
Junqiao Chen,1,2 Michael R. Udwin,2 Yisheng Chiang,2 Michael H. Kanter.3
1
ISCTE-IUL, Lisboa, Portugal; 2Evolent Health, Arlington, VA; 3Kaiser
Permanente, Pasadena, CA.
Background: Chronic kidney disease is not always identified and managed in an
optimal and timely manner. A single abnormal creatinine measurement embodies the
challenges of reliably following up abnormal laboratory test results. The Kaiser Permanente
creatinine safety program has demonstrated its feasibility in an integrated health system
to close the loop on a large cohort of patients. However, when we tested Kaiser’s program
design within a population health partnership (an external organization contracted for
value-added services), modification was required to better engage physicians and utilize
limited resources.
Methods: Literature research and meetings with experts experienced in population
health.
Results: The modified program re-purposes the business value proposition, from
improving patient safety and avoiding malpractice claims, to increasing risk adjustment
(RAF) revenue and reducing care gaps. Because a population health organization typically
has no access to electronic health record, the Kaiser’s method (a nurse ordering a test for a
physician to sign) would not work. We propose using population health managers to engage
physicians during visits to the practices. When appropriate, we propose the integration of
this information into RAF, patient outreach and care management workflows. To identify
a manageable cohort of patients and reduce alert fatigue for physicians, we propose the
focus be on patients at high risk for renal disease per predictive model and those who have
experienced an event of potential care coordination deficiency. The Screening for Occult
Renal Disease (SCORED) model is selected due to its validity and its computerizability
by claims. Care coordination deficiency may occur when (1) tests are performed during
emergency room visits or unplanned hospital stays; (2) tests are performed on or after the
discharge date of planned hospital stays; (3) a primary care physician orders significantly
more labs and imaging compared to peers (above 95th percentile). We are exploring
partnership opportunity to refine and test this program.

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Conclusions: A program design to embrace business and clinical complexity in population health partnership is proposed to build the ideal follow-up and prevent inactive or premature death. More details on the testing of this design will be shared with conference audience, and feedback is welcome.

PUB370

Prevalence of Unhealthy Behaviors Among Different Stages in Thai CKD Patients in ESCORT-2

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Background: We are conducting quasi-experimental study to evaluate the effect of integrated care model for Chronic Kidney Disease management in rural community of Thailand (ESCORT-2 study). Lifestyle modification is an important aspect of CKD management. Prevalence of health-related behaviors is important information for planning strategy to achieve healthy lifestyle.

Methods: We analyzed the baseline data of ESCORT-2. Prevalence of lifestyle behaviors reported herein (including cigarette smoking, analgesic use, non-steroidal anti-inflammatory drug [NSAID] use, use of herbal medicine, intensity of exercise and adherence to prescribed medication) were obtained was collected with patient history interview during their hospital visit.

Results: 914 CKD stages 3 and 4 were enrolled in the study. The baseline prevalence of some unhealthy behaviors in our cohort is considerably high [Cigarette smoking 26.4%, Analgesic 34.9%, and herbal use 23.4%]. Prevalence of cigarette smoking, analgesic use and herbal use were not different among different stages of CKD. Use of NSAID, lack of exercise and poor medication adherence were less in more advanced stage of CKD.

Conclusions: The baseline data of this study revealed high prevalence of cigarette smoking, analgesic and herbal use even in advanced stage of CKD. However prevalence of NSAID use, lack of exercise and poor medication adherence were low and less in advanced stage of CKD. On going study are being conducted to observe the effect of these unhealthy behaviors on CKD progression and the impact of integrated care on improving lifestyle modification.

Funding: Private Foundation Support

Descriptive & ANOVA (n=880)

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Date are mean(SD)

Descriptive & ANOVA (n=880)

PUB373

Needs Assessment of a Collaborative Telem nephrology Care Model for Rural Veterans

Melissa L. Sweet,1,2 M. Lee Sanders,1,2 Kantima Phisitkul,1 Angie R. Thumann,2 Nikki L. Neuzil,3 Bradley S. Dixon,4 University of Iowa Hospitals and Clinics, Iowa City, IA; 5Iowa City Veteran’s Health Administration, Iowa City, IA.

Background: Chronic kidney disease (CKD) is a growing medical problem affecting over 40 million Americans, with Veterans having a 34% higher prevalence of CKD than the general population. Early identification of CKD by primary care providers can lead to earlier specialist referral which may help delay the progression of disease and improve outcomes. However, there is a limited supply of kidney specialists to address this disease burden, particularly in rural settings. Telem nephrology consultation provides an appealing collaborative option for rural providers to increase consultative access.

Methods: A cross-sectional retrospective review was performed on 5308 patient records within the Iowa City Veterans Affairs (VA) Health Care System from March 2017 to March 2019. Variables abstracted included creatinine, eGFR, urine microscopy and urine dipstick results, urine albumin-to-creatinine ratio, and urine protein-to-creatinine ratio, as well as documentation of an outpatient nephrology visit. We analyzed the data using descriptive statistics.

Results: The charts of 5308 Veterans were reviewed, of which 11790 (22.2%) were diagnosed with CKD stages 3-5 based on eGFR. Among these, 10498, 943, and 349 were diagnosed with CKD stages 3, 4, and 5 respectively. Of the 12541 Veterans who had urine dipstick and microscopy data, 4363 had hematuria. Of the 23407 Veterans who had urine protein assessment, 3212 and 309 (13.7% and 1.3%) had micro- and macroalbuminuria, respectively. Among the 2627 Veterans who had urine protein to creatinine ratios, 471 had a value between 0.2 to 1, 183 had a value between 1 to 3.5 and 358 had a value higher than 3.5. Overall, only 1950 of these patients were seen directly by nephrologists in the VA system, with an additional 87 being evaluated by a community nephrologist.

Therefore, only approximately 17% of patients with the above findings had been seen by a kidney specialist.

Conclusions: There is a significant burden of kidney disease with an increasing demand for kidney specialists that surpasses the current supply of practitioners. Our data suggest that only up to 1 in 6 Veterans with CKD in this predominantly rural healthcare system have been evaluated by a kidney specialist. Telem nephrology e-consults are one mechanism to extend care to ensure that these needs are being met.

Funding: Veterans Affairs Support

PUB374

Serum Uric Acid Is Associated with CKD Progression: Insights from the CKD-REIN Cohort

Mathilde Prenzel-Revidt,1,2 Christian Combe,1 Jerome Harambat,1,2 Ziad Massy,2 Celine Lange,2,3 Marie Metzger,4 Oriane Lambert,4 Benedicte Stengel,4 Karen Leffondre,5 CHU de Bordeaux, Bordeaux Cedex, France; 6Amboise Pure University Hospital and Inserm U1018 Eq5, Boulogne Billancourt/ Paris cedex, France; 7Equipe Biostatistique, INSERM U1219 Bordeaux Population Health, Bordeaux, France; 8CESP, Inserm U1018, Kidney and Heart Team, Villejuif, France; 9Biomedicine Agency, La Plaine Saint-Denis, France; 10University of Bordeaux, Bordeaux, France; 11Equipe LEHA, INSERM U1219 Bordeaux Population Health, Bordeaux, France.

Background: The association between hyperuricemia and CKD progression is not well established in Europe and, to our knowledge, has not yet been investigated using longitudinal measurements.

Methods: We used data from the on-going French multicenter CKD-REIN cohort study, which included patients with CKD stages 3 to 5 between 2013 and 2016. All uric acid measures were taken into account, from inclusion to the occurrence of renal replacement therapy (RRT), death, or end of follow-up, whichever came first. We used a shared random-effect model for the joint analysis of the trajectories of uric acid and hazard of RRT and death. Hazard ratio were adjusted for age, sex, primary kidney disease, metabolic syndrome, cardiovascular disease, proteinuria (< 30, 30-300, > 300 mg/day), and the CKD-EPI estimated glomerular filtration rate (eGFR) at baseline.

Results: A total of 2781 patients (65.5% men, median age 69 years) were included. At baseline, the median eGFR was 31.8 mL/min/1.73m2 and the median uric acid value was 425 µmol/L. During a median follow-up of 3.2 years, 434 patients received RRT and 264 died before RRT. After adjustment, an increase of 100 µmol/L of the current level of uric acid was associated with a 5% increase in the risk of RRT or death. Median (IQR) eGFR was 3.6 (2.2) mL/min/1.73m2 and median uric acid value was 425 µmol/L. Median (IQR) eGFR was 3.6 (2.2) mL/min/1.73m2 and median uric acid value was 425 µmol/L. Median (IQR) eGFR was 3.6 (2.2) mL/min/1.73m2 and median uric acid value was 425 µmol/L. Median (IQR) eGFR was 3.6 (2.2) mL/min/1.73m2 and median uric acid value was 425 µmol/L.

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Underline represents presenting author.

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Prevalence Estimate of Secondary Distal Renal Tubular Acidosis Among Patients with Sjögren Syndrome and Systemic Lupus Erythematosus in a U.S. Employer-Sponsored Health Insurance Population

Kathryn Law,1 Josephine Li-McLeod,1 Gary L. Bryant.2 Advicence, Cincinnati, OH;1 University of Minnesota, Minneapolis, MN;2Stratevi, Boston, MA.

Background: Secondary distal renal tubular acidosis (2°dRTA) involves impairment in the distal tubule, leading to insufficient renal acid secretion, which can result in metabolic acidosis, hypokalemia, nephro lithiasis, nephrocalcinosis and bone demineralization. While primary dRTA is caused by genetic factors, 2°dRTA may result from autoimmune disorders, such as Sjögren’s syndrome (SS) or systemic lupus erythematosus (SLE), which also attack the distal tubule. While 2°dRTA is rare, US prevalence may be under-reported. This analysis utilizes administrative claims data to estimate the prevalence of 2°dRTA among patients with SS or SLE in a US employer-sponsored insurance (ESI) population.

Methods: Utilizing the Truven MarketScan® Commercial and Medicare Supplemental Databases from Jan 1, 2016-Dec 31, 2016, 2°dRTA patients were identified as follows: at least 1 inpatient or a2 outpatient claims a30 days apart for SS (ICD-10-CM: M35.0x) or SLE (ICD-10-CM: M32.x) and acidosis (ICD-10-CM: E87.2). Patients were also required to have a claim for an alkalizing agent or have a diagnosis of other disorders resulting from impaired renal tubular function (ICD-10-CM: N25.89). MarketScan Commercial Insurance Weights were then applied to project the sample to the total US ESI population.

Results: 89% of SS and 92% of SLE patients with ICD-10-CM diagnosis code of SS, SLE, or acidosis were identified. Of these, 1,125 were prescribed an alkalizing agent or had a diagnosis code of impaired renal tubular function. Applying the insurance weights to this sample, this projected to an estimated 6,716 secondary dRTA patients, which extrapolates to an unestimated 2°dRTA patient prevalence rate of 3.88 per 100,000 in the 2016 US ESI population.

Conclusions: The ability to unequivocally identify 2°dRTA patients based on a diagnostic code is limited. This approach used claims data to provisionally identify and estimate the prevalence of 2°dRTA patients in the US ESI population. According to the Kaiser Foundation, ESI represents 49% of the total US population. Further research is needed to validate this approach to effectively identify and characterize the treatment experiences of dRTA patients.

Funding: Commercial Support - Advicence

ACEI/ARB Use in Patients with CKD and at Risk for CKD in Two Large Health Systems

Susannah B. Nicholas,1 Ling Li,1 Kenn B. Daratha,2 Obidigwuru Duru,1 Carri R. Jones,3 Jenny I. Shen,3 Radica Z. Alicic,4 Sterling McPherson,2 Katherine R. Tuttle,2,4 Keith C. Norris,3 David Geffen School of Medicine, Los Angeles, CA;2 Providence St. Joseph Health, Spokane, WA;3LaBiomed at Harbor-UCLA, Torrance, CA;4Washington State University College of Medicine, Spokane, WA.

Background: Rates of ACEI/ARB use in patients with CKD and At-risk for CKD are unknown. We completed a retrospective analysis of ACEI/ARB use in CKD and At-risk for CKD patients from the UCLA-PSJH CKD Registry, populated from electronic health records.

Methods: The cohort: >2.6 million adults (2006-2017) based on labs and/or administrative codes for CKD, hypertension, diabetes mellitus, or pre-DM. We conducted analyses on patients with CKD (N=84,150) and At-risk for CKD (N=807,211) with administrative codes for CKD, hypertension, diabetes mellitus, or pre-DM. We conducted analyses of ACEI/ARB use in patients with CKD and At-risk for CKD. We selected as risks for adverse event including initiation of RRT.

Results: ACEI/ARB use in patients with CKD is associated with improved renal function over time. ACEI/ARB use in CKD patients is higher compared to At-risk CKD patients, and ACEI/ARB use with eGFR trajectories in decliners vs. non-decliners; p<0.001. While this effect was less pronounced in CKD3/4, deaths in association with HF increased in CKD3-5 pts with newly diagnosed HF than in pts wo HF or with newly diagnosed DM. This monocentric analysis of a large dataset demonstrated higher MO in CKD3-5 pts with newly diagnosed HF than in pts wo HF or with newly diagnosed DM. While this effect was less pronounced in CKD3/4, deaths in association with HF increased by 1/3 in CKD5 patients. A multicentric analysis approach should be used to generate more precise data on these associations in the German CKD cohort.

Conclusions: This monocentric analysis of a large dataset demonstrated higher MO in CKD3-5 pts with newly diagnosed HF than in pts wo HF or with newly diagnosed DM. While this effect was less pronounced in CKD3/4, deaths in association with HF increased by 1/3 in CKD5 patients. A multicentric analysis approach should be used to generate more precise data on these associations in the German CKD cohort.

Funding: Commercial Support - Advicence

Significant Predictor of Progression of Renal Dysfunction and Adverse Events for Non-Dialysis CKD Patients

Takahiro Kuragano, Internal Medicine Division of Kidney and Dialysis, Nishinomiya, Japan.

Background: It is well established that several factors such as anemia, hypertension, hyperuricemia, metabolic acidosis, and chronic kidney disease (CKD)-mineral and bone disorder (MBD) are associated with progression of CKD or adverse events of these patients. However, the significant factors which associated with progression of CKD or adverse events under the condition of appropriate control which according to guidelines have not been cleared.

Methods: The study was an observational study for a period of 3 years. In 88 patients with various stages of CKD (not on renal replacement therapy (RRT)) who were treated with ACEI/ARB for 1 year, we evaluated the association between time-varying parameters and renal adverse events, in addition to the hospitalization resulting in cardiovascular disease or infection by time-dependent Cox hazard model.

Results: Unexpectedly, under the condition of appropriate control by nephrologist, however, time-varying parameters such as CKD-MBD and inflammation were not selected as significant predictors of progression of renal dysfunction or adverse events. In multiple regression analysis, baseline blood level of lower Hb (β = 0.497, P = 0.001) and vitamin D 125 (β = 0.258, P = 0.006), and higher int-PTH (β = -0.334, P = 0.001), urinary phosphorus (β = 0.328, P = 0.001), urinary i2Mg (β = 0.225, P = 0.031) and urinary protein (β = 0.280, P = 0.02) levels were selected as significant predictors of decline of estimated glomerular filtration rate (eGFR) or urinary creatinine(UCr) at the end of the study. In the Cox hazard model, low calcium (HR: 0.37, P = 0.026), high phosphate (HR: 5.90, P = 0.001), low intact PTH (HR: 0.94, P = 0.013), high int-PTH (HR: 1.02, P < 0.001) level, use of a phosphate binder (HR: 4.95, P = 0.012), and use of vitamin D analogs (HR: 7.35, P = 0.014) are selected as risks for adverse event including initiation of RRT.

Conclusions: In this study, we found that among several factors, anemia and CKD-MBD factors were selected as significant predictors for the progression of renal dysfunction. Furthermore, although phosphate binder or vitamin D analogs were administered appropriately, CKD-MBD factors were associated with RRT initiation or adverse events of these patients. From these results, we presumed that the early intervention or strict control for CKD-MBD factors might attenuate the risk for adverse events of CKD patients.

Associations of Heart Failure and Diabetes with Mortality in CKD Patients: A Single-Center, Algorithm-Based Insight

Bernhard Hankestr.1, Eric Selbert,2, Olaf Hegerstr.1, Thomas Weinreich, Helmut Reichel. Nephrological Center Villingen-Schwenningen, Villingen-Schwenningen, Germany.

Background: Chronic kidney disease (CKD) shows a well-known stage-dependent increase in mortality. Heart failure (HF) and diabetes mellitus (DM) are two important factors potentially driving adverse outcomes (Kidney Int. 2018 June; 93(6): 1281–1292). Recent drug developments offer new therapeutic perspectives for HF and DM. However, there is a tremendous lack of reliable data from the German CKD population raising uncertainty about the relevance of such factors and subsequent interventions. We sought to improve the current situation with an initial monocentric approach.

Methods: A single-center analysis was performed using an Algorithm-based approach using the nephrologist Pro nephro software. We analyzed all patients (pts) out of a 5-year-period between April 1st, 2014 and March 31st, 2019. Diabetic pts were identified by ICD-10 codes E10, E11 and E14, CKD pts by ICD-10 N18.3-18.5 and HF pts by ICD-10 50.1, 50.9, 111, 113 and the terms “Kardiomyopathie” and “Herzinsuff”. Age ranges were chosen from 0-100 years and below 65 years. The diagnosis of HF or DM had to appear for the first time during the defined period. Mortality (MO) was calculated as % pts of the corresponding group that died during the time period and was analyzed for CKD with HF, CKD without HF and CKD with DM in CKD stages 3, 4 and 5.

Results: We analyzed 14.454 datasets. 5154 pts had a HbA1c ≤ 6% at least once, 3683 pts received the corresponding ICD diagnosis de novo. CKD3-5 was present in 7.530 pts, HF in 1838 pts out of which 49 received Saccubitil/Valsaltr. The combination of HF and DM was present in 840 pts. MO in 48 pts with DM and without (wo) CKD was 0%. MO was highest in CKD5 with HF (30.3%) and lowest in CKD3 wo HF (3.6%). Overall the MO was higher in HF groups compared to groups wo HF or with DM. Pts aged 65 or younger had a much lower MO in CKD3 or 4 which increased with CKD5 (table).

Conclusions: This monocentric analysis of a large dataset demonstrated higher MO in CKD3-5 pts with newly diagnosed HF than in pts wo HF or with newly diagnosed DM. While this effect was less pronounced in CKD3/4, deaths in association with HF increased by 1/3 in CKD5 patients. A multicentric analysis approach should be used to generate more precise data on these associations in the German CKD cohort.

Suggested Target Value for Serum Uric Acid in Advanced CKD Patients to Reduce the CKD Progression


Background: Recently, the role of uric acid (UA) as a factor that promotes progression of renal damage has been noticed. We retrospectively analyzed the factors affecting the rate of renal damage progression of non-diabetic CKD patients. We report
The results of the study, which suggested that serum uric acid level may have an impact on the progression of renal damage.

Methods: Patients who were newly received dialysis therapy in our facility between Jan 2015 and Dec 2018, and those whose results of a blood test six months prior to starting the dialysis were available were selected as study subjects. Patients with diabetic nephropathy as a primary diagnosis were excluded, and 144 patients were finally included in the study. The subjects were divided into two groups: a rapid progression group (R group, 35 cases), whose baseline eGFR was 15 mL/min or greater, and slow progression group (S group, 109 cases), whose eGFR was lower than 15 mL/min. We examined the difference between the groups in the baseline values (BL value) and those when dialysis was started (D value) of the following parameters: UA, proteinuria, Na, K, Mg, Ca, P, bicarbonate concentration as well as blood pressure (BP).

Results: Only UA-D value showed a significant difference between the R and S groups, and no difference was observed in UA-BL value or all other parameters such as BP, proteinuria and electrolytes (8.62±2.56 in R, 7.14±1.6 mg/dL, p<0.01). Next, we examined the correlation between the rate of eGFR decline and UA-D value using single regression analysis. No significant correlation was found in the S group, however, weak correlation was shown in the R group (R=0.503, R²=0.25, and p=0.0034). The ROC analysis showed the AUC value of UA-D value to be 0.822, by which the median value of eGFR decline showed 8.5 mg/dL as a UA-D cut-off value.

Conclusions: These results suggest that the control level of UA may affect the rate of progression of renal damage. At present, there are no established criteria for the controlling of serum UA concentration in advanced CKD patients. Present study may suggest that the UA value lower than 8.5 mg/dL contributes to reduce the renal damage progression.

PUB379
Annual Change of Estimated Glomerular Filtration Rate as an Alternative Surrogate Marker for ESRD
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Background: Doubling of serum creatinine or 57% declining of eGFR as standard surrogate marker for ESRD requires long-term follow-up which made profound obstacles for research in nephrology. It has been suggested that eGFR decline of 30% to 40% over 2 to 3 years may be acceptable for alternative markers for renal outcome, in which it is unclear whether estimation methods of eGFR affect diagnostic accuracy and annual rate of eGFR change (eGFR slope) can also be used as a surrogate marker for ESRD.

Methods: Laboratory data including serum creatinine acquired in baseline and 12 months follow-up periods with 3947 CKD stage 3-5 patients' cohort from three tertiary referral hospitals in South Korea, prospectively. The data of incidents to become ESRD was extracted from the ESRD registry of Korea additionally for more than 3 years after cohort observation. The eGFR was calculated by eGFRm equation (MDRD equation) and CKD-EPI 2009 creatinine equation (eGFRc) using IDMS-traceable creatinine value. We compared the effectiveness of each parameter to estimate the risk of ESRD using diagnostic accuracy indices.

Results: There were 11.8% (41/348) of ESRD patients during 38-month of follow-up period. The accuracy to estimate ESRD was more effective with eGFRc percent change than eGFR slope using both eGFRc. AUCs to predict ESRD were 0.804 (0.721-0.887) for eGFRm change, 0.802 (0.718-0.886) for eGFRc change while 0.705 (0.624-0.785) for eGFRc slope, and 0.692 (0.610-0.774) for eGFRc change (p<0.003). The findings of diagnostic accuracy of eGFRm showed similar patterns as those of eGFRc criteria. The criterion of eGFRc decrease of a 30% and a 40% shows similarly high accuracy compared to eGFRc decrease of a 57%, the standard surrogate marker. The sensitivity and specificity to estimate incident ESRD were 55.8% and 92.2% with the criterion of eGFRc 30% decline, 41.5% and 94.8% with the criterion of eGFRc 40% decline, and 9.8% and 97.7% with the criterion of eGFRc 57% decline, respectively.

Conclusions: There were no differences of AUC to estimate ESRD between eGFRc calculated by CKD-EPI equation and modified MDRD equation. The percent change of eGFR provided more diagnostic accuracy for renal outcome than the parameter of eGFR slope. The annual percent change of eGFR ≥30% can be suggested to alternate surrogate marker for ESRD.

PUB380
Association of Overweight with Glomerular Density and Glomerular Swelling in CKD Patients
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Background: Although glomerular hypertension suggested to be associated with progression of obesity-related glomerulopathy, its contribution is not known in chronic kidney disease (CKD) patients. On administrative data in a Tuscan city in 2011-2013, we show the results of the association between glomerular density, which reflects the total glomerular number, glomerular swelling, which reflects glomerular hypertension, and obesity in overweight CKD patients.

Methods: We recruited 76 CKD patients who underwent renal biopsy from January 1, 2000 to December 31, 2017. We excluded cases with endstage renal disease index (BMI) ≥40 kg/m², or with hypertension. We examined the association between glomerular density, which reflects the total glomerular number, glomerular swelling, which reflects glomerular hypertension, and obesity in overweight CKD patients.

Results: The median age, blood pressure, BMI and creatinine clearance (CCr) of the subjects were 51, 121/75 mmHg, 25.1 kg/m² and 63.1 ml/min, respectively. The prevalence of overweight group was comparable to that of non-overweight group (70% vs. 66%, p = 0.171). We observed lower glomerular density (2.2/µm² vs. 2.8/µm², p = 0.027) and larger maximum glomerular diameter (251 µm vs. 250 µm, p = 0.019) in the overweight group. Multiple logistic regression analysis revealed that BMI was significantly associated with maximum glomerular diameter, independently of age, sex, systolic blood pressure, diabetes mellitus, CCr, and use of renin-angiotensin-aldosterone inhibitors.

Conclusions: In CKD patients, obesity suggested to be associated with glomerular hypertension accompanied with decreased absolute glomerular number. Therefore, glomerular number may be potentially reduced in overweight group even if their CCr was comparable to those of non-overweight group.
The Risk of Socioeconomic Inequality in the Control of Diabetes Mellitus (DM), Hypertension (HA), and CKD in the Context of the Unified Health System (UHS)

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Background: There is evidence that correlates socioeconomic factors with a higher prevalence and risk factors for HA, DM, and CKD. OBJECTIVES: To evaluate the impact of social risk factors in patients with HA, DM, and CKD.

Methods: Retrospective cohort from August / 2010 to December / 2014. Inclusion criteria: Patients over 18 years of age who have undergone at least 2 visits at the Hipertensia Center in Juiz de Fora, which are referred for primary health care. Variables analyzed: socio-demographic data were collected at admission and the other variables (clinical and laboratorial) were collected in care. Clinical control goals related to hypertension, DM and CKD were evaluated, considering the markers at the beginning of follow-up and at the end of the study.

Results: A total of 6,369 patients were evaluated, of which 2,036 of the hypertension clinic, 2,336 from the DM and 1,997 from the clinic of CKD. We can observe the effectiveness of the treatment through the increase of the patients who managed to reach the goal of blood pressure control, from 2.5% at the beginning of follow-up to 32.1% in the target, at the end of the study. The percentage of patients with uncontrolled blood pressure was higher in the CKD group with family income up to minimum wage, OR1,155 (CI 1,042 - 1,281 p=0.006).

Conclusions: The color, income and education had a low impact on the progression of hypertension, DM and CKD. Only income impacted on the progression of DM, possibly due to the fact that access to medications by the population with the lowest income was restricted to the classes available in the UHS.

Association of Serum Phosphorus with Long-Term Hemoglobin Variability in Chinese Patients with CKD

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Background: Cross-sectional studies have revealed that there are independent correlations between serum phosphorus and anemia in patients with wide spectrums of chronic kidney disease. In this study, we intended to evaluate the impact of serum phosphorus level on the measurements of hemoglobin variability in appropriate.

Methods: There were 850 participants who were followed up for at least 2 years, and the measurements from baseline, year 1 and year 2, were selected for the analysis. Mechanisms of phosphorus are compared among serum phosphorus quartiles. Anemia was defined according to WHO criterion. Hemoglobin variability was defined by within-patient SD, range, coefficient of variance. Hemoglobin fluctuation was defined as never anemia (NA), constantly anemia (CA), normal HGB exhibited anemia (AA) according to WHO criterion. Hemoglobin variability was defined by within-patient SD, range, coefficient of variance. Hemoglobin fluctuation was defined as never anemia (NA), constantly anemia (CA), normal HGB exhibited anemia (AA) respectively in multinomial logistic regression analysis.

Results: A total of 6,369 patients were evaluated, of which 2,036 of the hypertension clinic, 2,336 from the DM and 1,997 from the clinic of CKD. A total of 6,369 patients were evaluated, of which 2,036 of the hypertension clinic, 2,336 from the DM and 1,997 from the clinic of CKD. Regression or multinomial logistic regression were applied to evaluate the association of serum phosphorus with anemia in the cohort of C-SRTIDE.

Conclusions: Serum phosphorus was independently associated with long-term hemoglobin variability in Chinese patients with CKD.

Perpetual Risk of Oxalate Nephropathy After Gastric Bypass Surgery

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Introduction: Oxalate nephropathy, a known complication of bariatric surgery, is characterized by deposition of calcium oxalate crystals in renal parenchyma and is often recognized only in advanced stages, thus, increasing risk of ESRD. We report a case of a patient with more than 15 years of near-normal renal function following bariatric surgery who was subsequently developed oxalate nephropathy.

Case Description: A 70-yr-old male was referred to renal clinic for AKI. History notable for hypertension, morbid obesity 85 kg, and history of nephrolithiasis. He underwent Roux-en-Y gastric bypass 18 years ago, CAD, hypothyroidism, h/o panniculectomy 3 years ago complicated by infection requiring multiple hospitalizations with prolonged courses of antibiotics. Serum creatinine (Cr) increased to 2.8 mg/dL from usual 1.21-1.5 mg/dL for several years, thought to be in the setting of relative hypotension. No urine sediment or proteinuria noted, no obstruction. AKI improved after adjusting medications (ACEI, thiazide) but Cr stabilized at 2mg/dL. Few months later Cr again increased to 4.8 mg/dL. A kidney biopsy was performed yielding oxalate nephropathy. Microscopy did not reveal any etiology, and showed severe tubular accumulation of calcium oxalate crystals, severe tubular atrophy and interstitial fibrosis. Immunofluorescence and electron microscopy were non-contributory. 24-hr urine showed elevated oxalate excretion. Patient was then started on low fat, low oxalate diet and calcium supplements following which Cr improved to 3mg/dL and has remained stable since then.

Discussion: Enteric hyperoxaluria, a complication of bariatric surgery, increases risk of nephrolithiasis and oxalate nephropathy. The underlying pathophysiology is complex and yet to be fully defined but the pivotal role of inflammasome recruitment and activation (especially NALP3) has recently been described in animal models. Inflammasomes can be activated by acute kidney injury thus potentiating crystal deposition and propagation of inflammation leading to fibrosis if unchecked, as is evidenced in the above case.
Patient Referrals: A 6-Month Retrospective Review
Celso a Multidisciplinary Outpatient Clinic: Minimizing Costs

Background: The advancement of chronic kidney disease (CKD) in Brazil does not seem to be a reason for alert for fiscal austerity policies on health in the Brazilian context.

Methods: Retrospective cohort of patients followed in a clinic center specialized in pre-dialysis care. The center focused on preventive care for Diabetes Mellitus (DM), Systemic Arterial Hypertension (SAH) and CKD. Data from 537 patients were evaluated in the period from 2011 to 2014. Sociodemographic data, stage of CKD, comorbidities and referral to dialysis therapy (DT) were analyzed. On the CKD evolution data, we calculated the transition probability between stages of the disease, following the parameters derived by Kidney Disease Improving Global Outcomes (Figure 1). The costs of pre-dialysis outpatient care were based on micro-costing (bottom-up) and performed according to the 2011/2012 Brazilian Unified Health System (USH) rates with the support of the public provider throughout the evolution of CKD in pre-dialysis care, comparing with the costs of USH to dialysis service providers.

Results: In general, a pre-dialysis program can generate an average reduction of R $ 33,023.12 (a R $ 1,676.80) for each year avoided in DT, already paying its operations, thus being cost-minimizers.

Conclusions: These results indicate that in the medium term (4 years) the real possibility of obtaining results visible to a budget that in the last 10 years has disbursed R $ 24 billion for DT.

Figure 1 - Changes of transition of the stages of evolution of Chronic Renal Disease between 2011 and 2014 (in %)

PUB389

Physical Activity Improves Kidney Function in CKD Patients; Improved Kidney Function Shortens Hospital Stays
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Background: Patients with chronic kidney disease (CKD) suffer diverse health complications. Participation in regular physical activity predicts improved outcomes in many clinical populations. Limited data support the effectiveness of physical activity as an adjunct intervention for CKD patients. However, isolated effects on estimated glomerular filtration rate (GFR), serum albumin, and length of hospital stay (LOS) remain undefined.

Methods: We analyzed 43 consecutively-admitted patients at a Midwestern hospital in 2018; all patients had a comprehensive physical activity biomarker panel, reported physical activity behavior, and had a diagnosis of CKD or end-stage renal disease (ESRD). Descriptive statistics characterized the study sample (means, standard deviations, categorical percentages). Independent-samples t-tests assessed differences between active and sedentary patients.

Results: The effect of daily physical activity on GFR and serum albumin, using linear regressions, holding constant liver function, use of dialysis, dyslipidemia, and kidney transplant status. We estimated the effect of GFR and serum albumin on hospital LOS using a negative binomial regression.

Conclusions: These results indicate that in the medium term (4 years) the real possibility of obtaining results visible to a budget that in the last 10 years has disbursed R $ 24 billion for DT.

PUB390

Changes in FGF-23, Neutrophil/Platelet Activation Markers, and Angiogenin in Advanced CKD and Effect on Arterial Stiffness
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Background: The aim of this study was to measure changes in fibroblast growth factor-23 (FGF-23), activation markers of neutrophil (elastase, lactoferrin) and of platelet (mean platelet volume per platelet count ratio, MPR), and angiogenin according to the chronic kidney disease (CKD) stages, and evaluate the association between these markers with arterial stiffness using brachial-ankle pulse wave velocity (ba-PWV).

Methods: According to the estimated glomerular filtration rate (eGFR) calculated by the CKD-epidemiology collaboration equation, patients were allocated to five groups: control (eGFR > 90 ml/min/1.73m²), stage 2 (eGFR 60-89, n=17), stage 3 (eGFR 30-59, n=22), stage 4 (eGFR 15-29, n=17), and stage 5 (eGFR ≤ 15 ml/min/1.73m², n=3). The serum FGF-23, elastase, lactoferrin, MPR, and angiogenin concentrations were measured to verify the association between the parameters with clinical (age, sex, presence of diabetes mellitus, blood pressure), biochemical (calcium, phosphorus, uric acid, intact parathyroid hormone (PTH), low-density lipoprotein cholesterol, high sensitivity C-reactive protein) variables, and ba-PWV levels in the CKD patients.

Results: The mean ba-PWV(cm’s) values were 1497.2±206.4 in the control, 1649.0±247.9 in stage 2, 1655.8±260.3 in stage 3, 1823.0±402.4 in stage 4, and 1905.2±74.1 in stage 5. As CKD stages progress, the mean log (FGF-23) concentrations were 0.7±0.07, 0.7±0.06, 1.10±0.03**, 1.35±0.48**, and 2.12±0.82***, the mean angiogenin(pg/ml) levels were 230.6±70.5, 283.0±53.5, 347.3±76.9**, 445.8±96.6**, and 370.9±142.6*** (p<0.05 vs control; **p<0.05 vs control stage 2; ***p<0.05 vs control stage 3; ****p<0.05 vs control stage 4; 1.50±0.05 vs control, stage 2, 3, 4). The mean elastase to neutrophil ratio to lactoferrin to neutrophil ratio in CKD stage 3-5 were significantly lower than the control and CKD stage 2. Multivariate linear regression analyses showed that age, pulse pressure, mean arterial pressure, IPHT, and FGF-23 were independently associated with ba-PWV values.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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Conclusions: Circulating FGF-23 and angiogenin concentration gradually increased as CKD advanced whereas neutrophil activation markers in CKD stage 3-5 were significantly lower than the control and stage 2 CKD. FGF-23 were weakly associated with ba-PWV in patients with CKD and no previous cardiovascular disease.

**PUB391**

CINAC Lesions in Kidneys of European Dairy Cows

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**Background:** CINAC is a form of chronic kidney disease of unknown etiology observed in Sri Lanka, Central America and several other tropical countries. Electron microscopically this disease is characterized by enlarged dysmorphic lysosomes in the proximal convoluted tubular cells of the kidney. This can be seen histologically on Jones silver stain as intracytoplasmic large irregular argyrophilic granules. Etiology is unclear but toxic exposure to agrochemicals is one of the possible causes. Cattle are at increased risk for uptake of agrochemicals through feeding and drinking water.

**Methods:** We investigate if these lesions seen in CINAC patients on Jones stain are also present in European cattle and if so there is any correlation with signs of chronic interstitial nephritis (CIN). At the slaughterhouse a kidney sample of 48 dairy cows older then 5 years and 11 beef cattle type bulls younger then 2 years were collected and histologically evaluated on H&E and Jones silver stain.

**Results:** In 44 of 59 kidney samples, a varying degree of intracytoplasmic accumulations of brown granular pigment was present in tubules in the outer medulla on H&E, visible on Jones stain as argyrophilic granules. In 41 kidney samples a varying degree of interstitial lympho-plasmacytotic inflammation and fibrosis with multifocal tubulointerstitial atrophy was present. Transmission electron microscopy (TEM) was performed on 12 kidneys with 4 of them having lesions on Jones stain. In 2 out of 12, both of them having lesions on Jones stain, CINAC-like lysosomes were present. Interestingly in any of the 11 beef cattle type bulls argyrophilic granules or signs of CIN were present.

**Conclusions:** The lesions as described above could point at a CINAC-like disease, at an early stage. Though CKD is not a common disease in cattle, it is possible these animals never reach further stages of the disease because of early death (often at 1/3th of life expectancy). Origin and significance of the argyrophilic granules is unclear. No histological lesions were present in the younger beef type bulls. This could indicate lesions did not develop because of a shorter toxic exposure time. Further toxicological, electron microscopic and epidemiologic investigation is needed to further clarify the significance of these findings.

**PUB392**

Patients with Kidney Stone of Uric Acid or Calcium Oxalate Are at Higher Risk of Lower Bone Mineral Density

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**Background:** Kidney stone disease prevalence and recurrence rates are increasing in recent decades. Kidney stones have not only been associated with an increased risk of CKD and USRD but also to lower bone mineral density (BMD). Diagnosis of osteoporosis and osteoporosis by routine CT abdominal scans has been evaluated to be clinically practical and reliable in Chinese population. Hounsfield unit (HU)<-175 was a good cut-off value for diagnosis of lower BMD.

**Methods:** Kidney stone formers and non-stone CKD patients hospitalized in our kidney disease center from Jan 2015 to May 2019 were included for study. Demographic and clinical data were documented. Chemical composition of stones were detected by Fourier transform infrared spectrometer. BMD score was expressed as the mean value of HU of L1-L5 vertebra. Mean values were compared by independent T test or one-way ANOVA. Correlation was performed using the Pearson correlation coefficient. Categorical data were analyzed using Chi square test. Multi-factor linear and logistic regression were applied to find the independent risk factor.

**Results:** 107 cases of kidney stone formers and 43 cases of non-stone CKD patients were eligible for analysis and *stone group’s CKD group* were named for comparison. The percentage of lower BMD in stone group were higher than that in CKD group (64.5% vs 44.2%, p<0.05). Stone group were divided into three subgroups according the chemical composition of the stone, as uric acid, calcium oxalate (n=35), and calcium oxalate group (n=43). BMD scores in uric acid group and calcium oxalate group were lower than that in CKD group (156a±37.6, 153a±44.7 vs 153a±44.7: p<0.01, p<0.05). While in apatite group the BMD score was comparable to that in CKD group (173±61.0 vs 181±85.5: p>0.05). Male percentage was lower in apatite group compared with that in uric acid group and calcium oxalate group (20% vs 88% 83%, p<0.001) while the BMD score in apatite group was the highest among the three stone subgroups. Although there were no difference in age among the four groups (the three stone subgroups and CKD group), the age was the unique and independent risk factor related to lower BMD in the multi-factor regression analysis.

**Conclusions:** Kidney stone formers are at higher risk of lower BMD, especially those with stone of uric acid or calcium oxalate composition. Aging is an independent risk factor for osteopenia.

**PUB393**

Factors Associated with Kidney Disease in Colombian Indigenous Communities

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**Background:** In the world there are 45 million indigenous people, Colombia there are 8 indigenous groups, being the 2nd with the largest number of ethnic groups. According to the Colombian High Cost Account, 11.685 were affiliated with an indigenous service company and the rest to other entities, 99.4% are affiliated in the subsidized regime and 0.57% contributory. The objective was to describe the sociodemographic, clinical, exposure factors and health regimen in some indigenous communities in Colombia, to characterize their risk of kidney disease.

**Methods:** Cross-sectional observational study, was collect date sociodemographic, clinical, exposure factors and health regimen after signing informed of respondents consent and physical examination with measurement was performed anthropometric data, proteinuria blood pressure, glucose measurement, hematuria and strip. At this stage no mass screening creatinine was performed.

**Results:** A total of 1774 persons over 17 ethnic groups, were surveyed. The most frequent age range was between adults (27-59y) with a representation of 59.6%. The sample was mainly composed of women (61.8%), which mainly dealt home. Economic activity was most important agriculture (32.6%). 78% said be covered by the state health system. 16.6% had a presumption diagnosed prediabetes, diabetes mellitus 5.8% of 4.3% and antecedent. It was found that 14.5% of women were diagnosed presumption of hypertension with sistrodiastolic blood pressure, 13.1% and 6.5% diastolic hypertension. 18% of men had presumed diagnosis of hypertension with sistrodiastolic Commitment-Diastolic. 20.8% systolic hypertension and diastolic hypertension 5.3%. 12.5% of individuals had a history of hypertension confirmed. 12.3% had a history of urinary tract infection and 5.2% bacterial vaginosis. 28.3% were overweight and 11.4% obese. 1.4% had hematuria and proteinuria 13.8%. Regarding risk behaviors 14.4% and 39.1% smoked they reported having a regular consumption of alcohol. As discovery, one case of nephritis Class IV and nephrolithiasis (n=2) were diagnosed. 1% reported a regular consumption of alcohol.

**Conclusions:** This population is vulnerable, being necessary to assess distal determinants of their own habitat and implement longitudinal studies studying the behavior of kidney disease to promote transdisciplinary design and implementation of programs to control.

**PUB394**

Heat Stress as the Main Cause of CKD in Agricultural Communities: Seven Arguments Against the Hypothesis

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**Background:** There are two main hypothesis on the uncertain etiology of the global epidemic of chronic interstitial nephritis of agricultural communities (CINAC): the toxic hypothesis implicating an environmental/occupational toxin and the heat stress/ dehydration hypothesis (HSIH) suggesting recurrent heat stress induced acute kidney injury to cause chronic kidney disease. Our aim is to demonstrate that heat stress is unlikely to be the main cause of CINAC.

**Methods:** The following data sets are used to refute the HSIH as the driver of CINAC: Ethnographical, 1. Epidemiological, 2. Ecological. 3. Epidemiological. 4. Ecological. 5. Physiopathological, 6. Biochemical and 7. Agrarian.

**Results:** 1. Geographical: Absence of CINAC in many hot agricultural regions of the world is a stronger anti-correlation than the correlation assumed by presence of CINAC in a few such regions. The mosaic pattern of case distribution in Sri Lanka contradicts the HSIH. 2. Climatological: It is doubtful that the small temperature increases in the latter twentieth century even with extreme temperature fluctuations caused devastating renal effects. 3. Epidemiological: CINAC is seen in people not exposed to hot working conditions, while it is not seen in many occupations with higher temperature exposure. Detection of pathologically proven CINAC in vineyards of France and absence in sugar cane plantations in Cuba argues against HSIH. 4. Ecological: Individuals drinking spring water are not affected in contrast to those drinking from shallow wells in Sri Lanka. 5. Physiopathological: It is doubtful that the degree of community-acquired pre-renal AKI seen in field studies of agricultural workers is adequate to cause CINAC. 6. Biochemical: Biochemical changes postulated to perpetuate CKD have not been proven. 7. Agrarian: In Sri Lanka, mechanization of paddy farming has reduced farmers' heat exposure since the late 20th century but CINAC epidemic has continued. Workers in high altitude sugar cane plantations in El Salvador are also exposed to heat stress but the prevalence is low.

**Conclusions:** It is plausile that heat stress is an important contributor to perpetuation of CINAC, but is unlikely to be the main driving force. An environmental/occupational toxic exposure is more credible as a main drive of this epidemic.
**PUB395**

New Findings Support Toxicological Origin of Chronic Intestinal Nephritis in Agricultural Communities

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**Background:** Two main hypotheses; the toxic hypothesis and the heat stress/dehydration hypothesis put forward to explain the etiology of chronic intestinal nephritis in agricultural communities (CINAC). Recent findings suggest calcineurin inhibition could be a possible pathway leading to proximal tubular damage in CINAC. Analysis of drinking water for organic substances revealed it is contaminated with several pesticide residues. Interestingly some of them show calcineurin inhibition properties.

**Methods:** 50 water samples (1 L each) collected from drinking water sources of CINAC endemic area: Anuradhapura district in Sri Lanka. Water extracted on a C-18 SPE cartridge, blown down to 1ml and analyzed by GC/MS. ELISA method was used to detect glyphosate.

**Results:** Glyphosate (3.20 ppb), Propachlor (40-900 ppb), Diazinon- organophosphates (200-650ppb), Propanil (86-1850 ppb) were detected in drinking water sources. Detection frequency was as follows: Propachlor (42/50), Diazinon 37/50), Propanil (32/50) and glyphosate 28/50).

**Conclusions:** Our previous findings revealed drinking water in CINAC endemic regions contain high amount of calcium, magnesium, fluoride and silica. However, inorganic substances couldn’t directly correlate to the etiology of disease. Further, in an epidemiologic study, we found that usage of glyphosate, parquat, bipyridic, mancozeb, MCPA and organophosphate are associated with CINAC. The present study confirms the presence of pesticide residues in drinking water sources. Pesticides with calcineurin inhibitory properties in drinking water could be the nephrotoxic agents behind the CINAC.

**PUB396**

Associations Between Nephrologists’ Cognitive Load and Practice Setting Characteristics

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**Background:** Among specialists, nephrologists are particularly at risk of burnout, and satisfaction with the profession is declining. Burnout, time pressures, stress, and poor work-life balance are associated with cognitive load, which can negatively affect clinical decision making, and may be greater in some practice settings. We will examine how cognitive load varies across care settings for nephrologists.

**Methods:** We are administering a new and innovative survey—the Transplant and Home Dialysis Recommendations Survey of Nephrologists, or THRoNe—in a nationally representative sample of n=120 nephrologists (non-pediatric). The THRoNe, which we have pre-tested and validated using a modified Delphi approach with 12 nephrologists and subject experts, collects data on nephrologists’ cognitive load and other practice and physician characteristics. Nephrologists are asked to characterize their cognitive load through 12 survey items related to workload, time pressures, stress, distractions, and workplace satisfaction. We will construct an index to support classifying nephrologists’ cognitive load as high, moderate, or low. Key practice characteristics included in the principal type setting (dialysis facility, CKD clinic, hospital, or other), perceived competence of non-physician clinical staff (e.g., nurses, dialysis technicians), average patient case complexity (e.g., % with CKD stage IV/V/ESRD, % with low health literacy), patient insurance mix (% Medicaid, % uninsured), and patient race/ethnicity mix (% black/African American, % Hispanic). We will describe the distributions of nephrologists’ cognitive load overall and for each related survey item, and we will use linear regression models to test for associations between cognitive load and key practice characteristics, adjusting for physician factors (e.g., years in practice, sex, race/ethnicity).

**Results:** Data collection is ongoing. We anticipate obtaining a response rate of about 70%, in line with response rates achieved in other difficult-to-reach clinician samples using our evidence-based recruitment protocol.

**Conclusions:** We will determine how U.S. nephrologists’ cognitive load varies across practices. Follow-on work will need to examine implications for variation in CKD patients’ quality of care across settings and opportunities to reduce cognitive load to improve CKD care quality.

**Funding:** Other NIH Support - Health Innovation Program of the Georgia Clinical & Translational Science Alliance (CTSA), supported by NIH (UL1-TR002378, Taylor)

**PUB397**

Kidney Check: Identifying Kidney Disease and Diabetes in British Columbia First Nations Communities


**Background:** Kidney disease has a strong impact on the health and wellness of Indigenous peoples in Canada. Therefore, a national strategy to improve kidney health must include meaningful, culturally appropriate engagement with Indigenous peoples. The Can-SOLVE CKD Network is a pan-Canadian patient-oriented kidney research initiative that is working to improve the health of all Canadians and bring Indigenous ways of knowing into health research.

**Methods:** The Can-SOLVE CKD Network is working with British Columbia Renal and the First Nations Health Authority to develop and implement a new program that will bring kidney, diabetes, and blood pressure checks to First Nations communities. Kidney Check is a screening, triage, and treatment program using point-of-care testing and trained health care teams. Each participating community has the opportunity to design and work with the Can-SOLVE CKD team to develop a locally acceptable program, which helps to identify healthy kidneys as well as those with mild, moderate or severe kidney problems. The results will be shared with participants in real time. Each person tested will also participate in building their own kidney health plan, including follow-up goals for maintaining kidney health.

**Results:** Ten BC communities have been chosen through a transparent process to be part of phase 1 of the program, which is launching in Spring 2019. The ultimate aim is to roll out Kidney Check to all Indigenous communities in BC. Kidney Check programs are also under development in Alberta and Manitoba.

**Conclusions:** The Kidney Check program aims to help keep kidneys healthy and is working in partnership with First Nations communities to do so.

**Funding:** Government Support - Non-U.S.
PUB399

Does the Incidence of Dementia Increase After General Anesthesia in Patients with CKD? A Nationwide Population-Based Cohort Study

Kyung Don Yu,1 Kyung sun Park,1 Jongha Park,1 Jong Soo Lee,1 Clara T. Kim.2
1Ulsan University Hospital, Ulsan, Seoul, Republic of Korea; 2Hallym University, Gangwon-do, Republic of Korea.

Background: Patients with chronic kidney disease (CKD) were regarded as increasing the risk of cognitive dysfunction according to kidney function. However, little is known about the relationship from the aspect of general anesthesia.

Methods: A population-based prospective cohort study was conducted using the Korean National Health Insurance Service-National Sample Cohort database over 50 years, including CKD from 2003 and 2013. The primary outcome was the incidence of dementia using Korean Classification of Diseases codes, and receipt of medication such as donepezil, rivastigmine, galantamine, and memantine. Time-varying Cox regression analysis was applied for risk analysis of dementia.

Results: The 84 of the 1,676 participants of general anesthesia groups had developed newly dementia after surgery (5.6%). Of the 3,821 controls that had CKD but did not have general anesthesia, 283 participants had presented incident dementia (Figure 1). In time-varying Cox regression analyses revealed that general anesthesia group did not increase the development of dementia in CKD patients, compare to control group (HR 1.053, 95% CI 0.819-1.353) after adjustment of age, sex, health security certification, history of depression, diabetes, hypertension, cerebrovascular disease, ischemic heart disease, quintile group for health care visit frequency and Charlson comorbidities score. Male sex, old age, history of depression and cerebrovascular disease were an independent risk factor of incident dementia in CKD patients, irrespective of anesthetic methods.

Conclusions: In CKD patients, general anesthesia operation did not increase the risk of incident dementia. Subgroup analysis was warranted, especially in patients with advanced CKD, including dialysis.

PUB400

Prognostic Investigation of CKD Patients in Japan by a Large Multi-center Retrospective Observational Study

Yuki Yamauchi,1 Daiki Yamada,1 Tomoyuki Aomura,1 Masatsugu Aida,2 Shitotomo Yamauchi.2 Nagano Kidney Evaluation Association: NKEA
1Department of Nephrology, Shinshu University School of Medicine, Matsumoto, Japan; 2Ethic Co., Ltd., Chiyoda, Japan.

Background: Since the background and medical interventions for CKD have changed in recent years, its prognosis and the contribution of known risk factors may have shifted as well. To clarify this possibility, we conducted a prognostic investigation of CKD patients in Japan by means of a large multicenter retrospective observational study. We also examined for surrogate markers to predict the hard endpoints of death and ESKD requiring renal replacement therapy.

Methods: Patients seen among 15 general hospitals in Japan between January and March 2014 were surveyed using medical records. The selection criteria were age >20 years, eGFR <60 mL/min/1.73 m², and medical treatment for CKD. Baseline patient characteristics, eGFR changes, and hard outcomes during observation were investigated.

Results: A total of 11233 CKD patients (60% male; mean age: 72 years, CKD G3a: 50%, G3b: 28%, G4: 15%, G5: 7%), mean eGFR: 41.5 mL/min/1.73 m², urine protein positive: 45%, diabetes: 46%, use of RAS inhibitors: 55% were analyzed. During the mean observation period of 2.34 years, hard endpoints (eGFR reduction during 2 years, death and ESKD, death and ESKD, death and ESKD) were seen in patients with higher CKD stage at baseline, and the occurrence of hard endpoints increased with the degree of eGFR decrease during 2 years. Statistically analysis of the relationship between eGFR changes and hard endpoints indicated that various indices, including hazard ratio, population attributable risk, number needed to treat, and number needed to harm, were significant in patients displaying over 30% eGFR reduction during 2 years. Kaplan-Meier testing and multivariate Cox regression analysis demonstrated that CKD stage and proteinuria at baseline were significant risk factors for composite outcomes (30% eGFR reduction during 2 years and ESKD, death, and ESKD death), whereas diabetes, sex, age, and use of RAS inhibitors, exerts little effect.

Conclusions: ESKD and death occurred at a high rate in real-world Japanese CKD patients. A 30% eGFR reduction during 2 years might represent a surrogate marker predicting hard endpoints. CKD stage and proteinuria remained the major risk factors of an unfavorable prognosis, whereas diabetes had only weak detectable association. Kidney disease prevention strategies should be targeted not only for diabetes but for all CKD patients.

Funding: Commercial Support - Kyowa Hakko Kirin Co., Ltd.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

1176

PUB401

Investigation of TMAP as a Novel Biomarker of Kidney Function

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Background: Although kidney function is critical for determining drug dosing and diagnosing chronic kidney disease (CKD), there is a lack of sensitive biomarkers for detecting early changes in kidney function. While the current gold standard is creatinine, serum levels of creatinine do not change until approximately 50% of kidney function has been lost. We previously used metabolomics to discover new biomarkers and identified N,N,N-trimethyl-L-alanyl-L-proline betaine (TMAP) as a novel biomarker of kidney function.

Methods: A liquid chromatography coupled to mass spectrometry (LCMS) method was developed for the quantitation of TMAP in CKD patient and control plasma samples, and evaluate changes in plasma concentration as CKD progresses. Plasma samples were spiked with varying concentrations of TMAP to generate a standard curve. Liquid chromatography coupled to quadrupole – time of flight (QToF) mass spectrometry was used to determine the concentration of TMAP in plasma of healthy controls and patients with CKD.

Results: Preliminary analysis of chromatogram response (areas under the peaks) of healthy control, CKD, HD and PD patient plasma samples (n= 3 for each) does not show significance by one way ANOVA (p= 0.2225). However, with a 6-fold, 7-fold and 3.5-fold increase in relative areas for CKD, HD and PD respectively when comparing TMAP levels in controls to controls, analysis of further samples shows promise.

Conclusions: TMAP has previously been shown to be a more sensitive indicator of decreased renal function than serum creatinine, the current standard for renal function evaluation. Quantitation of absolute levels of TMAP in plasma shows that as CKD progresses, TMAP plasma concentration increases.

Funding: Government Support - Non-U.S.

PUB402

Mortality Rates and Geographic Distribution of CKD in Peru

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Background: The prevalence of chronic kidney disease (CKD) is alarmingly high in Latin America. Importantly, mortality rates in these patients have not been comprehensively explored. We aimed to examine the case of Peru.

Methods: Secondary analysis from the Deceased Registry of the Peruvian Ministry of Health (2011-2016) database. Data pertaining to 24 provinces across the coast, highlands, and rainforest were obtained from 2015-2016. Code 585.9 was used to identify CKD deaths based on ICD 9. The PMH registry classifies deaths based on the birthplace of the patient. Calculations were made assuming an underreporting rate of 40% (PMH). We computed age-standardized mortality rates (ASMR) per 100,000 person-year. Cluster map was used to visualize data across regions.

Results: Overall, a total of 3607 deaths were identified in CKD individuals; being male predominantly affected(M:F ratio:1.18). ASMR (per 100,000 individuals) decreased among men from 7.48 to 5.02 (2015-2016). Similarly, ASMR decreased in women from 6.27 to 4.22 within the same period. In a sub-analysis by regions, ASMR among men/women decreased in the coast and in the highlands. However, ASMR (per 100,000 individuals) increased in the rainforest, from 2.87 to 2.97 in men, and from 2.41 to 2.42 in women. Such mortality rate increment corresponded to two rainforest provinces: Madre de Dios and Loreto.

Conclusions: Mortality rates in individuals with CKD in Peru are higher in male than females. While mortality rates among both gender groups decreased within the study period, there are marked regional differences. In the rainforest (mainly Madre de Dios and Loreto), mortality rates exhibited increment in both gender groups. These findings warrant special attention to identify specific epidemiological risk factors and guide intervention and policy.
Patient and Care Partner CKD Self-Efficacy

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1 Geisinger Medical Center, Danville, PA; 2 Geisinger Health System, Danville, PA; 4 Johns Hopkins School of Medicine, Baltimore, MD.

Background: Self-efficacy is an essential skill for chronic disease self-management; however, many nephrology patients rely on the assistance of a loved-one to help manage their care. We sought to better understand the self-efficacy skills of patients and their care partners.

Methods: We surveyed patients and care partners enrolled in a pilot study of a problem-solving intervention to support kidney disease self-management. We administered 6 questions from the chronic kidney disease self-efficacy (CKD-SE) instrument problem solving subscale. Responses were scored on a 10-point Likert scale from 1 (not at all confident) to 10 (totally confident). Paired t-tests were used to compare differences between patients and care partners.

Results: 11 patient-care partner dyads were surveyed. Dyad pairs were spouses (n=8), parent/child (n=2), and friend (n=1). Mean age was 68 for patients and 62 for care partners. The majority of patients were male (63%) and care partners were female (72%). Result of parent/child (n=2), and friend (n=1). Mean age was 68 for patients and 62 for care partners.

Conclusions: Care providers report significantly higher CKD self-efficacy than patients. Involvement of care partners may help to improve the CKD management of patients.

Funding: Private Foundation Support

Table 1

<table>
<thead>
<tr>
<th>Question</th>
<th>Patients</th>
<th>Care Partners</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I can understand the meaning of relevant laboratory data</td>
<td>3.9</td>
<td>7.6</td>
<td>0.002</td>
</tr>
<tr>
<td>I can seek out information that explains CKD related signs and symptoms</td>
<td>4.5</td>
<td>8.5</td>
<td>0.001</td>
</tr>
<tr>
<td>I can find information about kidney disease from a variety of sources</td>
<td>4.5</td>
<td>8.4</td>
<td>0.002</td>
</tr>
<tr>
<td>I can effectively deal with the risk factors associated with CKD</td>
<td>3.1</td>
<td>7.8</td>
<td>0.027</td>
</tr>
<tr>
<td>I can find resources needed to better control my (or my loved one’s) CKD</td>
<td>5.1</td>
<td>7.3</td>
<td>0.035</td>
</tr>
<tr>
<td>I can actively seek out necessary precautions to prevent my (or my loved one’s) CKD from worsening</td>
<td>4.9</td>
<td>7.9</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Mortality and Renal Risk Factors in a Cohort of Toba Aborigines, Chaco, Argentina

Eduardo N. Rodriguez,4 Ana M. Cusumano.5 School of Medicine. Northeast National University, Resistencia, Chaco, Argentina; CEMIC, CABA, Argentina; Facultad de Medicina Universidad Nacional del Nordeste, Corrientes, Argentina; School of Medicine. Northeast National University, Corrientes, Argentina.

Background: The Province of Chaco, at the northeast of Argentina, concentrates a high proportion of toba aboriginal people (4% of the population). Originally gatherers and hunters, during last century they have been forced to migrate from rural areas to the outskirts of the cities, in particular to Resistencia (Province capital city). A cohort of 385 suburban toba people has been followed since 2003, in order to identify cardiovascular and renal risk factors. The objective is to describe mortality rate, survival curves and hazard ratios for death causes during the period 2013-2018.

Methods: Medical records were revised. 25 individuals were lost of follow up. Weight, height, waist circumference (WC), urine and serum creatinine, fasting glucose, uP/urCr ratio were measured. GFR by MDRD-4 formula and renal risk (RR by KDIGO classification: no risk, moderate, high and very high risk) were calculated. Hypertension was defined as either a diastolic blood pressure ≥ 90 mmHg or a systolic blood pressure ≥ 140 mmHg, diabetes as fasting glucose ≥ 126 mg/dL, BMI was classified according to WHO, being obesity >30; central obesity (CO) was defined as WC >102 in men and >90 cm in women. Proteinuria was estimated as uP/urCr ratio mg/g ≥ 1.50, stage 1, 150 ≥ stage II and a 300 stage III. Renal risk (RR) defined as KDIGO. Kaplan Meir curves and Cox proportional hazards regression models were applied.

Results: 358 medical records were revised. 45 (12.5%) individuals had died, 6.2% females, mean age 53.87 yrs old, 24% hypertensive, 34% with CO, 2% DBT, 34,6% proteinuria, 5,3% with GFR < 60 mL/min. About RR, 63 % had no RR, 2,5% classified as Moderate, 12% as high and 2 % as very high RR. Causes of mortality were: CVD 20 (5,6%), Ca 12 (3,4%), TBC 9 (2,5%) and Miscelaneas 4 (1,1%). Mortality rate was 12.6.

Conclusions: This cohort of Toba people living in the outskirts of Resistencia city, has a high mortality rate, being causes of death similar to the observed in general population in the Province. RR was a predictive factor for mortality.

Funding: Private Foundation Support
Low Flow Colonic Ischemia (LFCI) Associated with Renoprotective Use of Renin-Angiotensin inhibitor Therapy (RASIT) 

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Introduction: Renin-Angiotensin inhibitors are commonly utilized renoprotective agents in multiple nephrological conditions. Some recipients may even be normotensive. Multiple Hemodynamic Adverse effects may be encountered. We present 6 episodes of LFCI in 3 patients in association with RASIT found retrospectively in a single practice over 15 years. LFCI may represent a form of uncommon Ischemic adverse event of RASIT.

Discussion: 1. 41 year old WM with morbid obesity, recurrent macrohematuria, mild proteinuria, lipohypertension, with Renal biopsy: Thin Basement Membrane Disease. On RASIT he developed two episodes of severe abdominal pain, lower Gi bleeding(LGBl) with colonicoscopic Ischemic Colitis(CI). RASIT was reduced with no subsequent recurrence. 2. 37 yo WM with recurrent macrohematuria, proteinuria hypertension with Renal biopsy: IgA Nephropathy. On RASIT he developed acute abdominal pain LGBl and Colonicoscopic CI. RASIT was reduced with no subsequent recurrence. 3. 69 yo WF with Stage 3 chronic kidney disease, hypertension and mild proteinuria. On RASIT she developed acute abdominal pain LGBl with Colonicoscopic IC. RASIT was reduced with no subsequent recurrence. Although these are anecdotal cases possibility of Ischemic Colitis as a possible adverse effect of RASIT may warrant further study.

Discussion: RASIT commonly utilized renoprotective therapy in multiple nephrological conditions including: IgA nephropathy, Proteinic states, Diabetic Nephropathy, and Chronic Kidney Disease. Hemodynamic adverse effects including hypotension, syncope and orthostatic symptoms may be encountered. Ischemic Involvement of colonic watershed area most likely due to hypotensive episodes, may be another ischemic manifestation. Exact mechanism is unclear, likely related to reduced blood flow in colonic watershed area. Direct effects of RASIT on: G1 tract, microvasculature, thrombotic, Immunologic and Inflammatory pathways may be speculative. Olmesartan associated Chronic Enteropathy, RASIT associated Bowel angioedema, worsening Inflammatory Bowel disease have been described. Acute LFCI seen in our patients seems phenotypically different. Patience on RASIT presented with acute intestinal syndrome. LFCI should be considered in the differential diagnosis. Dose reduction may prevent recurrent episodes. Although these are anecdotal cases possibility of Ischemic Colitis is a possible adverse effect of RASIT may warrant further study.

Exploring Cardiorenal Interactions During Therapy of Chronic Heart Failure with Preserved Ejection Fraction

Harrin Bejananda, Gajapathiraju Chanathri, Amir Kazory, University of Florida, Gainesville, FL.

Background: The complexity of cardiorenal interactions in heart failure (HF) has been increasingly recognized. Rise in serum creatinine (RSC), once considered a universally ominous sign, is now known to portend mixed prognostic values depending on the clinical setting. While heart failure with preserved ejection fraction (HFpEF) is common and includes half of the cases with HF, no established beneficial therapy exists for it. As such, aggressive management of comorbidities remains the key in the care of these patients. We sought to evaluate currently available data on the renal impact of therapies for HFpEF.

Methods: Articles cited in PubMed database using keyword “heart failure with preserved ejection fraction” were searched. Available data from contemporary randomized controlled trials (RCTs) of chronic HFpEF therapy performed between January 2008 and December 2018 were included in the analysis. These studies evaluated the role of renin-angiotensin-aldosterone system suppression in the setting of HFpEF and included data on renal function.

Results: A total of 408 citations were reviewed and 7 RCTs with 9039 participants were included. The mean age was 71.3 years and 56.9% were men. Mean baseline serum creatinine and eGFR were 1.3 mg/dl and 67 ml/min respectively. There was substantial variation across studies in the reporting of the renal parameters post-intervention as well as recording of the RSC. Whether the primary cardiovascular endpoint was achieved or not (+6.6min walk test, cardiovascular death, or unplanned hospitalization), RSC consistently developed more frequently in the intervention (6-36.2%) than the control group (4-20.6%) in those studies that reported it (mean 16.1±11.8% vs. 8.9±6.8% respectively).

Conclusions: To our knowledge, this is the first report focusing on the cardiorenal interactions and HFpEF therapy. Available evidence from contemporary studies suggests that HFpEF therapy may not per se portend untoward impact on the outcomes. While these results challenge our conventional thinking, they are in line with emerging data in other settings such as acute HF. Future studies need to explore whether this observation reflects development of RSC in the absence of true kidney injury, or it is related to other factors such as competing effect of therapies on the kidney and the heart.

National Survey of Patients’ Attitudes Toward Gout

Josie Peterson,1 Michelle Winokur,2 Amanda Conshofer,3 1Alliance for Gout Awareness, Washington, DC; 2Alliance for Patient Access, Washington, DC.

Background: Gout, a form of arthritis, affects more than 8 million Americans with painful attacks that come on suddenly. Many people don’t realize the relationship between gout and chronic kidney disease. And gout, left untreated, can lead to other serious health problems, include kidney stones.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Increase of 1,25-Dihydroxyvitamin D Levels in Sarcoideal Patients with Renal Dysfunction
Naoya Torii,1,2 Keichi Sumida,3 Yoichi Oshima,4 Hiroki Mizuno,2 Masayuki Yamanouchi,3 Junichi Hoshio,5 Yoshihumi Ubara,2 Kyoto University, Kyoto, Japan; Toranomon Hospital, Tokyo, Japan; 3University of Tennessee Health Science Center, Memphis, TN; 4Shizuoka Municipal Shizuwa Hospital, Shizuoka, Japan; 5Okinaka Memorial Institute for Medical Research, Tokyo, Japan.

Background: In sarcoidosis, renal involvement includes hypercalcemia-related nephrocalcinosis and granulomatous tubulointerstitial nephritis. Hypercalcemia is thought to be due to increased production of 1, 25 dihydroxyvitamin D (1-25D), but 1-25D levels have not been evaluated in sarcoidosis patients with renal dysfunction.

Methods: We enrolled 9 sarcoidosis patients who underwent renal biopsy, and compared the serum 1-25D concentration and eGFR with those in 428 non-sarcoidosis patients who had renal dysfunction (stage 2 or higher CKD with an estimated glomerular filtration rate <90).

Results: Serum calcium and 1-25D levels were significantly higher in the sarcoidosis patients than in the non-sarcoidosis patients (p <0.01 and p = 0.01, respectively). There was a positive correlation between 1-25D and eGFR in the patients without sarcoidosis (r = 0.693; p < 0.01). As the renal function of sarcoidosis patients was improved by steroid therapy, the serum 1-25D and adjusted serum calcium levels decreased to near the median values in non-sarcoidosis patients. On renal biopsy, CD68 staining was positive for tissue macrophages in all 8 patients who had tubulointerstitial nephritis (with or without typical granulomas), while Von Kossa staining showed calcification of tubules near or inside granulomas in 6 of these 8 patients.

Conclusions: While tissue macrophages promote development of tubulointerstitial nephritis and 1-25D overproduction in renal sarcoidosis, hypercalcemia secondary to elevation of 1-25D may be related to renal calcification and granuloma formation.

Association Between Insulin Resistance and Glomerular Filtration Rate in Patients with Non-Diabetic Pre-Dialysis CKD
Ardiyo R. Ardhan,3 Rendi R. Bramantya,3 Soebagijo A. Soelistijo,2 Chandra I. Mohani,3 Wido Wido,3 Airlangga University Indonesia, Surabaya, Indonesia.

Background: Metabolic syndrome is one of the recognized cause of kidney disease. Insulin resistance, as one of the component in metabolic syndrome, is known to be one of the condition occurs in patients with chronic kidney disease (CKD), even in those who doesn’t diagnosed with diabetes. The relationship between insulin resistance and the decline of glomerular filtration rate (GFR) in non diabetic patients is remain to be studied.

Methods: This is a cross sectional observational analytic study involved 35 subjects of CKD patients with non-diabetic predialysis who were diagnosed based on KDIGO criteria. The study population was CKD patients in the Outpatient Clinic of a tertiary referral hospital, Dr. Soetomo Hospital Surabaya. Insulin resistance is determined by calculation using the HOMA-IR formula, and GFR is estimated using Cockcroft-Gault formula.

Results: There were 35 subjects, 25 male and 10 female. The average age is 52.5 years, the lowest age is 31 years and the highest age is 60 years. Patients with stage 3 CKD were 11 people, stage 4 were 6 people and stage 5 were 18 people with mean for overall GFR 21.38 ± 16.69 ml/min/1.73 m2. HOMA-IR levels were 1.61 ± 1.13, with a median of 1.15 (IQR 3.2-4.59). There was a significant negative relationship between GFR and insulin resistance (p = 0.00, r = -0.828).

Conclusions: Insulin resistance and GFR have significant negative relationship in non diabetic predialysis CKD patients.
Methods: Retrospective evaluation was carried out for CKD patients under follow-up in outpatient nephrology clinics from January 1st 2001 till December 31st 2016. All patients diagnosed as CKD with different stages were included. Patients were screened for: Demographic data, Cause of kidney disease, Date at diagnosis of CKD, eGFR at time of diagnosis of CKD and at last follow up, degree of Albuminuria/proteinuria, Comorbid conditions, Use of ACEI/ARBs, Renal outcome as well as Patient outcome. 

Results: 969 patients were included. Mean follow up period was 10.14 years. 8.24% reached endpoint outcome as follows: expired 1.44% and ESRD 6.8%. Hazard risk to reach end point was dependent on cause of CKD, being highest with combined DM and HTN followed by HTN alone, DM alone and finally other causes (figure 1). Univariate analysis revealed that risk factors showing statistical significance to reach endpoint included older age, associated cardiovascular disease in addition to higher proteinuria, body mass index (BMI) and PTH levels at time of diagnosis of CKD. Multivariate analysis revealed that use of ARBs/ACEI was associated with significant less incidence of death and ESRD. 

Conclusions: Cause of CKD should be considered together with eGFR and degree of albuminuria during evaluation for risk of progression of CKD patients. Special formulas including CGA together with other risk factors (age, BMI, CVD,) might be invented to help predict prognosis of such patients.

Funding: Government Support - Non-U.S.

Figure 1

PUB415

Effect of Simulated In-Bed Training of Urination on Reducing Rate of Postoperative Dysuria in Patients After Renal Biopsy
Hong-li Shang, Hui-qun Li, Yan-ru Chen. The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

Background: Postoperative dysuria is one of the most common complications after renal biopsy. This study aimed to investigate whether the simulated in-bed training of urination is able to relieve the symptoms of postoperative dysuria in patients undergoing renal biopsy.

Methods: Patients who underwent renal biopsies between Jan 2017 and Dec 2018 were recruited. We reported the proportion and characteristics of patients underwent the simulated training of postoperative in-bed urination before the procedure, and compared with that of patients did not receive the training. The training refers to the simulation of postoperative conditions before the renal puncture procedure, during which the patient lay on the bad and finished an urination episode facing a chamber pot. The training was carried out within 30 minutes before the renal biopsy.

Results: A total of 531 patients underwent renal biopsies and 509 (95.9%) of them underwent the training. After renal biopsies, 439 patients had voluntary urination on the bed, accounting for 86.2% of the total number of trainees, and 28 patients who had induced urination, while 42 patients needed urethra catheters. There were 300 (58.9%) patients completed self-urination on the bed within 3 hours after the renal procedure, and the number of patients who completed self-urination on the bed within 6 hours was 396, accounting for 77.8% of the total number of trainees. For the 22 patients who did not receive the training, 11 (50.0%) of them were able to voluntary urinated, while the other 11 patients needed assisted urination care.

Conclusions: Simulated training of in-bed urination is able to reduce occurrence of dysuria associated with renal biopsy.

PUB416

Conservatively Managed Patients with Advanced CKD: What Medications Can Be Deprescribed?
Sadia Jahan, Michelle L. Rice, Carla E. Scuderi, Louise Purtell, Cassandra Rawlings, Ann Bonner, Helen G. Healy. 1Metro North Hospital and Health Service, South Brisbane, QLD, Australia; 2School of Pharmacy, University of Queensland, Brisbane, QLD, Australia; 3Queensland University of Technology, Brisbane, NSW, Australia; 4NHMRC Chronic Kidney Disease Centre of Research Excellence, Brisbane, QLD, Australia.

Background: Patients entering a Conservative Management Pathway (CMP) from advanced chronic kidney disease (CKD) have a legacy of high pill burden. An important component of CMP is judicious deprescribing, noting that tools described in the literature including the Beers or STOPP/START criteria do not take into consideration the patient’s symptoms and trajectory which is the focus of Kidney Supportive Care (KSC). The referral criteria to the KSC program includes patients on the non-dialysis CMP, on kidney replacement therapy (KRT) with high symptom burden and those who are pre-decision making. We aim to examine the number and type of prescribed medications of patients on CMP and identify medications that potentially may be deprescribed due to limited benefit.

Methods: Retrospective analysis of patients on a non-dialysis CMP referred to KSC Feb 2016 – Feb 2019. Only patients that were conservatively managed and not on a KRT care pathway were included. Patient demographics and clinical profile were extracted from the medical record. Medication lists were compiled by a renal pharmacist and assessed at last/ most recent KSC attendance. Medications that were highlighted as suitable to be deprescribed were grouped; with key groups including statins, proton pump inhibitors (PPIs) and supplementary vitamins.

Results: 47 patients met the inclusion criteria for these analyses, median age 83 years (range 29-92) and 53% were female. 74% had CKD 5 with the remainder having CKD 4. Total number of prescribed individual medications ranged from 5-31 (median = 13). Statins were prescribed for 36% patients, PPI for 55% and vitamins for 49%. 38/47 (81%) patients had at least 1 identified medication that could be deprescribed and 8/47 (17%) were on all three (statin, PPI and supplementary vitamins).

Conclusions: Deprescribing medications has the virtue of reducing medication burden, financial cost and side effects, contributing to important quality of life. Many patients continue to receive medicines with limited therapeutic benefit whilst on CMP despite the scope for de-prescribing these medications. More research is required to develop a deprescribing tool in this unique population.

PUB417

Prevalence of CKD in the National Hospitalization Database in Ecuador as a Pointer to CKD of Undetermined Etiology Prevalence
Ramya Bhargava, Siriram Narsipur, Anna M. Stewart iBarra. 1Nephrology, Upstate Medical University, Syracuse, NY; 2Upstate Medical University, Syracuse, NY.

Background: Chronic Kidney Disease of uncertain etiology (CKDu) is a emerging healthcare crisis in South America, primarily affects young males with no pre-disposon factors such as diabetes or hypertension, and has been reported extensively from Nicaragua and Guatemala. CKDu results in increased mortality in working age males, often pushing entire families into poverty. Though it has been reported in Ecuador, the extent of the problem is not known. There is no renal registry and access to primary care is variable depending on the geographical area and the patient’s socio-economic status.

Methods: As part of a mixed-methods scoping study, we analysed the national hospitalization database for the years 2010 to 2015 for ICD10 codes N18 (CKD) and N19 (Unspecified kidney failure) for prevalence amongst men and women, and across different ages. Since there is no separate ICD10 code for CKDu, N18 and N19 were used.

Results: Image Table

Conclusions: There is a clear increase in the prevalence of CKD in hospitalized males < 40 years of age from 2010 to 2015 in Ecuador. This study is limited by insufficient data on outpatient community CKD. While there is an increase across all ages, likely because of better reporting, there is a striking doubling of cases in working age men < 40 years of age. It is not possible to opine from the data if this is all CKDu, but this pattern of CKD is similar to the pattern of CKDu incidence in other countries. Our data supports the need for well-designed prevalence studies to define the scope of CKDu contributing to the observed rise in CKD in Ecuador, in a vulnerable population with potential global health implications.

Funding: Commercial Support - DCl Inc - Non-profit organization

Table 2: Age-wise incidence of CKD in men

<table>
<thead>
<tr>
<th>Years</th>
<th>31 - 60 years</th>
<th>41 - 50 years</th>
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</thead>
<tbody>
<tr>
<td>2010</td>
<td>0.41</td>
<td>0.95</td>
</tr>
<tr>
<td>2011</td>
<td>0.56</td>
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<td>2015</td>
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**PUB418**

**Diagnostic Value of NT ProBNP in CKD Patients with Acute Decompensated Heart Failure**

Syeda H. Zarrash,1 Sidra Saleem,1 Zain Rasool,1 Nimra N. Zaman,1 Shahbaz Sarwar,2 Shahmeer M. Nawaz,2 Shahyara A. Sheik,2 Shamila Ashfan,2 Abeera Mansur.1 1Doctors Hospital and Medical Centre, Lahore, Pakistan; 2Punjab Institute of Cardiology, Lahore, Lahore, Pakistan.

**Background:** NT pro-BNP is a promising marker of integrated cardiorenal function in the setting of volume overload. However, diagnosis of volume overload in CKD patients is complicated by NT-proBNP levels that are higher than in the non CKD patients. The aim of this study is to establish a cut off value for NT Pro BNP in CKD patients for Acute decompensated Heart Failure (ADHF).

**Methods:** From 1st May, 2018 through 30th April, 2019, 450 patients who presented in the Emergency Department of Doctors Hospital, Lahore with acute dyspnea and potential fluid overload were assessed. Out of these, 85 patients who had simultaneous echocardiography and NT Pro BNP measurement were included in the study. Both CKD (<60ml/min GFR) and non CKD patients with reduced ejection fraction (LV EF<40%) and preserved ejection fraction (LV EFa50%) were included. eGFR was measured using the CKD-EPI equation and all data was analysed using SPSS version 25.

**Results:** Mean value of NT Pro- BNP in patients with eGFR < 60 ml/min with Volume Overload and Pulmonary Capillary Wedge Pressure(PCWP) >15mmHg as determined by 2D echo (Group A) and in patients with eGFR > 60 ml/min with volume overload and PCWP >15(Group B) is 1905.7±10.57 and 550.66±7.42(pmol/L) respectively, as shown in Image 1. In Group A patients, NT pro BNP cut off value of 1900 resulted in sensitivity and specificity of 63% and 71.21% respectively with a Negative predictive value (NPV) of 87.04% and accuracy of 69.41%(p value 0.003), as shown in Image2.

**Conclusions:** The cutoff value of NT Pro BNP for diagnosis of ADHF in CKD progressively increases as the stage of CKD increases. To obtain optimal results, cut off concentrations have to be adjusted for renal function.

**PUB419**

**Effect of Educational Program on Lowering Blood Pressure and Urinary Protein in Japanese CKD Patients**

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**Background:** Educating patients by interprofessional collaboration with doctors, nurses, pharmacists and nutritionists is effective in controlling chronic kidney disease (CKD) progression. We have been conducted an inpatient CKD educational program by multiple occupations and compared the effects of the program on various kidney diseases.

**Methods:** We retrospectively reviewed 31 Japanese patients who participated in our one-week CKD educational program from April 2014 to April 2019. All patients took low-salt diet (6 g/day) and were carried out 24-hour urine testing twice during the program. In addition, we examined clinical features of 18 patients (10 in diabetes mellitus (DM) group and 8 in non-DM group) whose antihypertensive drugs were not changed during the program.

**Results:** The mean age of patients was 72.8 ± 11.7 years, and 68% were male. Nephrosclerosis was the most common diagnosis (63% [19 of 31]), followed by diabetic kidney disease (55% [11 of 31]), IgA nephropathy (10% [3 of 31]) and so on. The average body weight decreased from 67.3 kg to 64.8 kg (3.7% reduction), the systolic blood pressure (BP) decreased from 140.3 mmHg to 131.6 mmHg (6.2% reduction), and the mean protein excretion decreased from 1.84 g/day to 1.37 g/day (25.5% reduction), and the 24-hour urinary sodium excretion decreased from 107.4 mEq/day to 77.8 mEq/day (27.6% reduction) during the one-week program. In a study of 18 patients whose antihypertensive drugs were not changed, the BP and the urinary protein level on the first day of program were DM group: 138.2 mmHg vs non-DM group: 132.8 mmHg, DM group: 2.31 g/day vs non-DM group: 1.29 g/day, respectively. In DM group, the percentage of BP reduction was higher (DM group: 9.3% vs non-DM group: 1.8%), while the percentages of proteinuria and body weight reduction were lower during this one week program (DM group: 16.0% vs non-DM group: 29.5%, DM group: 3.4% vs non-DM group: 3.7%, respectively).

**Conclusions:** Our educational program was effective on lowering BP and urinary protein of CKD patients. Furthermore, the BP-lowering effect was obvious especially in DM patients probably due to the promotion of sodium sensitivity as previously reported.

**PUB420**

**The Efficacy and Safety of Endothelin Receptor Antagonist on Renal Outcomes: An Updated Systematic Review of Randomized Trials**

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**Background:** Preclinical studies suggest that blockade of the endothelin receptor reduces proteinuria and may confer renal protection. With the recent publication of the SONAR trial, this systematic review and meta-analysis aims to summarize evidence from randomized controlled trials (RCT) regarding the benefits and risks of ERA on renal outcomes.

**Methods:** MEDLINE, Embase and Cochrane Central Register of Controlled Trials were searched for RCTs evaluating ERAs in adults with this reported renal outcomes. The primary outcome was kidney failure (end-stage kidney disease, renal failure, or doubling of creatinine, or as reported by the authors). The secondary outcomes were change in kidney function (estimated glomerular filtration rate or creatinine clearance), albuminuria and systolic blood pressure from baseline to last measurement, all-cause mortality, cardiovascular mortality and adverse events. Treatment effects were summarized using random-effects meta-analysis.

**Results:** Seven RCTs (7612 participants, median sample size 379, median follow-up 7.4 years) satisfied eligibility criteria. The risk of kidney failure (3 trials, risk ratio [RR] 0.76, 95% CI 0.65, 0.89) and albuminuria (3 trials, SMD -0.30, 95% CI -1.49, -0.40) ERA had uncertain effect on all-cause mortality (5 trials, RR 1.48, 95% CI 0.95, 2.34). There was substantial heterogeneity in baseline kidney function and study population. Compared to placebo, ERA significantly reduced the risk of kidney failure (3 trials, risk ratio [RR] 0.76, 95% CI 0.65, 0.89) and albuminuria (3 trials, SMD -0.30, 95% CI -1.49, -0.40). ERA had uncertain effect on all-cause mortality (5 trials, RR 0.99, 95% CI 0.84, 1.17), cardiovascular mortality (2 trials, RR 1.11, 95% CI 0.67, 1.83), kidney failure (6 trials, standardized mean difference [SMD] -0.06, 95% CI -0.21, 0.11) and pulmonary edema (2 trials, RR 1.37, 95% CI 0.91, 2.07), but increased the risk of systemic edema (7 trials, RR 1.19, 95% CI 1.03, 1.39) and hospitalization for heart failure (5 trials, RR 1.32, 95% CI 0.87, 2.01).

**Conclusions:** Short-term trials suggest that ERA treatment may reduce the risk of kidney failure and albuminuria. Adequately powered RCTs with long-term follow-up are required to evaluate whether ERA treatment improves renal outcomes.
Myco phenolate Sodium in Primary Membranous Nephropathy: A Retrospective Analysis
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Background: We studied the efficacy and safety of myco phenolate sodium (MMs) in primary membranous nephropathy (MN).

Methods: A Retrospective observational study of 58 cases of treatment naïve MN. Patients received a prednisolone (20mg/day for 2 days) along with MMs (2 tablets of 360mg twice-a-day) and changes in eGFR and proteinuria from baseline to the end of one year were noted. Results: A total 44 cases were included in analysis. There is no significant worsening of eGFR (0.85±0.17 mg/dl v/s 0.95±0.30 mg/dl, p=0.23) or eGFR (105.97±19.10 vs 97.18±0.20±35 ml/min/1.73 m2, p=0.33). There is an improvement in s. albumin levels (2.17±0.62 v/s 2.7±0.49 g/dL, p<0.001) and urine protein levels (681.36±1654.50 v/s 330.34±2270.54 g/day, p<0.001). At 12 months, partial response (PR) was seen in 29.54%, complete response (CR) in 20.45% and no response in 50%. The mean time to attain PR was 9.47±1.8 mon and for CR, 10.33±1.5 mon. PLAR 2 positive cases had significantly earlier PR. The common complications were hypertension (18%) and diarrhoea (11%).

Conclusions: A 12-month course of MMS decreased proteinuria and improved renal function in patients with MN with less side effects.

PUB222
Renal Sarcoidosis: Clinical Presentations and Outcomes

Background: Renal sarcoid is one of the silent clinical manifestations of sarcoidosis. It typically causes gradual impairment in kidney function due to chronic tubulointerstitial disease with or without granuloma formation. In addition, it also affects calcium and phosphate metabolism.

Methods: Ten patients with renal sarcoidosis diagnosed between 2002 and 2017 were included in this study. All patients had biopsy proven renal sarcoidosis or sarcoidosis diagnosed by biopsy of other organs in addition to decline in kidney function with or without hypercalcemia, nephrocalcinosis or nephrolithiasis.

Results: All patients had renal involvement at the time of diagnosis 90%(Lung, 90%; Liver, 20%;Skin). One patient had neurosarcoidosis with pan peripheral neuropathy, another had Heerfordt syndrome. In all patients with renal biopsy, pathology showed granulomatus interstitial nephritis. Of the three who did not have renal biopsy, two had granulomatous dermatitis on skin biopsy and one had granulomatous hepatitis. Three patients had nephrotic range proteinuria. All patients were treated with oral steroids (Prednisolone 60mg for 4 weeks tapered to 15-20mg daily over 2 months). No patient had nephrolithiasis or nephrocalcinosis on imaging. Renal function improved significantly at 6 months in all patients except one patient who had an eGFR of 5ml/min/1.73m2 at presentation. Hypercalcemia resolved in all but one patient who had a mean serum calcium of 11.6±1.4 mmol/L at 6 months.

Conclusions: Renal involvement with sarcoid is a rare cause of CKD/AKI but responds well to steroid treatment even in patients with severe impairment of kidney function at presentation.

PUB223
Renoprotective Role of Metformin in a Mouse Model of Adenine-Induced CKD
Hao Yi, Chunling Huang, 2Qinghua Cao, 1Ying Shi, 2Xinning Chen, 2Carol A. Pollock. 2Kolling Institute, Sydney; NSW, Australia; 1University of Sydney; Sydney, NSW, Australia; 3Kolling institute, the University of Sydney, St. Leonards, NSW, Australia; 4The University of Sydney, St. Leonards, NSW, Australia.

Background: Chronic kidney disease (CKD) is a worldwide public health problem and current best clinical practice only slows the progress of renal fibrosis in CKD. Inflammatory and fibrotic signaling pathways play important roles in the progression of CKD. Thus, it may be beneficial to limit renal fibrosis through inhibiting target inflammatory and fibrotic responses. Metformin is a widely used glucose-lowering medicine for type 2 diabetes mellitus. Recent studies have explored its potential for many other clinical conditions including renal fibrosis. However, the exact mechanisms of metformin in limiting renal injury is not fully understood.

Methods: To examine the role of metformin in the development of CKD, C57BL/6 mice were delivered adenine (40mg/20ul water) through gavage to induce CKD for 21 days. Mice given water only served as control. Coincident with adenine treatment, mice were administered with metformin (0.4 mg/ml) in drinking water or water only (control) for 21 days, at which time animal experiments were terminated, blood, urine and kidney were collected. Urinary albumin to creatinine ratio (UACR) was assessed. Inflammatory and fibrotic markers and their signaling molecules were analyzed by immunohistochemistry (IHC), qRT-PCR and Western blotting.

Results: Adenine induced increase in UACR was attenuated by metformin treatment (p<0.01). Adenine increased expression of inflammatory markers MCP-1, F4/80, fibrotic markers types IV collagen, fibronectin and TGF-β1, and phosphorylation of Smad3, ERK1/2, and P38 in kidneys compared to control groups, which were partially reversed by metformin treatment (p=6, p=0.01).

Conclusions: Metformin attenuates adenine-induced renal interstitial fibrogenesis through both Smad and non-Smad signaling pathways.

PUB242
Smac4 regulates Vascular Smooth Muscle Cell Calcification Through Inhibiting Autophagy
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Background: Vascular calcification (VC) is one of the most common clinical manifestations for patients with end stage renal disease (ESRD). However, the pathological mechanism of VC is not fully understood and there is no reliable early biomarker to predict the risk of VC.

Methods: In order to elucidate the mechanism of VC, we performed a detailed molecular characterization of high phosphorus induced VC model both in vitro and in vivo. The label free proteomics screening results of high phosphorus induced aortic vascular smooth muscle cells (ASMCs), pathological assessment, cellular characterization and molecular signaling detection upon target gene elucidated a comprehensive profile about VC.

Results: Label free proteomics analysis and pathological studies highlighted Smac4, also known as BRG1, significantly related to osteoblastoid differentiation from ASMCs during the development of VS. Smac4 showed to regulates high phosphorus induced-VC by its anti-autophagy role associated with suppression of autophagyosome formation and autophagy pathway.

Conclusions: Smac4 regulates high phosphorus induced-calcification of ASMCs at an early stage involving its anti-autophagy role. Yi Li and Li Wang should be addressed as corresponding authors and these two authors contributed equally to this study.

Funding: Government Support: Non-U.S. 

PUB245
Lnc-Gm44981 Induces Renal Aging by Regulating the p53/p21/RB Pathway
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Background: Aging is a natural and gradual process of aging in the process of degenerative changes in tissues and organs of the body over time. The kidney, which is a metabolically active organ, is extremely susceptible to aging, but the mechanism of kidney aging is unclear. Long-chain non-coding RNA (lncRNA) is a non-coding RNA consisting of 200 nucleotides. It is generally considered that they do not encode proteins, but are expressed in various forms in the RNA level.

Methods: The expression of Inc-Gm44981 was detected using qRT-PCR. SA-β-gal staining and immunohistochemistry were operated for the detection of the p53, p16 and p21 expression in different ages. Transfer Inc-Gm44981 siRNA to measure aging-associated protein expression levels in TCMK-1 cell.

Results: We found that the expression of Inc-Gm44981 decreased during aging. And we found that SA-β-gal expression gradually increased with age, and p53, p16 and p21 expression gradually increased. Then the transfection of Inc-Gm44981 siRNA has an effect on the expression of aging-related proteins.

Conclusions: Inc-Gm44981 plays an important role in kidney aging by acting on the p53 signaling pathway.
Evidence of Urate Deposition in the Kidneys in Gout Patients
Brad A. Marder, Puja Khanna, Brian LaMoreaux, Ada Kumar.
1Horizon Pharma, PLC, Lake Forest, IL; 2Horizon Therapeutics, Lake Forest, IL;
1University of Michigan, Ann Arbor, MI; 2Colorado Kidney Care, Denver, CO.

Background: The common inflammatory arthropathy in U.S. adults. Although tophi in the extremities are well known, urate deposition in the renal parenchyma is not as well recognized. Patients with gout commonly have concomitant renal disease, however, a casual role between these entities has not yet been established. Direct urate deposition in the renal parenchyma may be of significant interest since it could explain ongoing subclinical renal tissue damage and its potential role in the propagation of chronic kidney disease in gout patients.

Methods: PubMed (from 1940 to 2019) was searched to identify reports of autopsy, pathology and radiology imaging demonstrating urate deposition within the native renal parenchyma in patients with gout. Key words included: gout nephropathy, chronic urate nephropathy, renal tophi, gouty kidney, autopsy findings in gout, and renal imaging in gout. The reference lists from these publications were also used to identify additional articles. Literature referencing urate nephrolithiasis and renal transplants were excluded from the study.

Results: There were 25 articles documenting renal parenchymal urate deposition in gout patients confirmed by autopsy, biopsy and/or radiology imaging in native kidneys. Among the 19 articles examining urate deposition by autopsy or tissue sampling, 100% found renal urate deposition in the tubules and interstitium of the medulla. 68% found urate deposition in the renal cortex and/or cortical scarring. 74% reported renal vascular pathology including arteriole fibrous thickening of the intima, hyaline degeneration and occlusions. In addition, 89% found inflammatory cells and fibrosis surrounding the parenchymal “microtophi”. There were 6 imaging articles that all reported abnormal renal ultrasound findings in the medulla that were attributed to urate deposition.

Conclusions: Several case reports document renal parenchymal deposition of urate in patients with gout based on autopsy, pathology and imaging evidence. Renal urate vasculopathy was also commonly noted. Given the strong association of gout with renal disease, this demonstrates a need for further research to determine the clinical significance of urate deposition with respect to potential renal parenchymal injury and ongoing subclinical inflammation.

Funding: Commercial Support - Horizon Therapeutics

Modulation of Inflammatory and Fibrotic Processes by Histone Lysine Demethylase
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Background: Histone lysine methylation and demethylation has been suggested to have a modulating effect on inflammation and fibrosis.

Methods: In this study, we analyzed the effect of JIB-04, a pan inhibitor of Jumonji histone demethylase on inflammatory process in murine macrophage cell line, RAW264.3, and rat renal proximal epithelial cell line, NRK-49F.

Results: JIB-04 pretreatment prevented LPS-induced expression of inflammatory cytokines in RAW264.3 cells and TGF-β-induced expression of profibrotic cytokines and EMT markers in NRK-49F cells, respectively. In addition, JIB-04 pretreatment inhibited both NF-κB activation and increase of snail1.

Conclusions: Taken together, these results suggest that histone lysine demethylation may play a contributing role to the induction of fibrosis as well as inflammation in the kidney by modulating activation of key transcription factors. In the future, JIB-04 could be developed as a new anti-fibrotic agent.
Cigarette Smoking Cessation Resulted in a Decline in Kidney Function: Paradox Explained

Khaled Boobes, Rashia Alawihe, Lee A. Hebert. Ohio State University Medical Center, Columbus, OH.

Introduction: Smoking tobacco is a well-known risk factor for cardiovascular disease and chronic kidney disease (CKD). Smoking cessation is always encouraged, but limited data is available regarding the short-term effects of smoking cessation on serum creatinine (Cr) and the actual and estimated glomerular filtration rate (eGFR).

Case Description: We present a case of a 59 years old patient who underwent a living donor kidney transplant in 1975. His serum Cr remained stable within the normal range at about 1.0-1.5mg/dL up until 2013 when he quit smoking. His serum Cr started to gradually increase afterwards until it stabilized around 1.8mg/dL. Notably, his weight also gradually increased from about 105lbs to 130lbs. His serum Cr has since been stable at 1.8mg/dL.

Discussion: Smoking cessation is well-linked to an increase in appetite and weight. Increased consumption of cooked meat is also known to increase serum Cr levels. Our patient did report an increase in appetite, meat consumption along with activity level after smoking cessation. We speculate that the low initial muscle mass in our patient coupled with the baseline decreased renal function made the increase in serum Cr more noticeable. His weight also increased from about 105lbs to 130lbs. His serum Cr has since been stable at 1.8mg/dL.

Results: Smoking cessation is well-linked to an increase in appetite and weight. Increased consumption of cooked meat is also known to increase serum Cr levels. Our patient did report an increase in appetite, meat consumption along with activity level after smoking cessation. We speculate that the low initial muscle mass in our patient coupled with the baseline decreased renal function made the increase in serum Cr more noticeable. His weight also increased from about 105lbs to 130lbs. His serum Cr has since been stable at 1.8mg/dL.

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Conclusions: Smoking cessation could be linked to an increase in serum creatinine, that is related to increased creatinine production, not a decrease in GFR. This increase would be more evident especially in patients with low muscle mass and/or chronic kidney disease to begin with. Further studies need to be conducted to better characterize this phenomenon.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PUB432

Graphene Quantum Dots Attenuate CKD Progression

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Background: Graphene Quantum Dots (GQDs) have drawn much attention for its biomedical applications, such as biotaging, drug delivery and tissue engineering. Also, the substances themselves have antioxidant, anti-inflammatory and immune regulatory effects. However, the role of GQDs in fibrotic diseases remains unclear. In this study, the effect of GQDs in kidney fibrogenesis was investigated.

Methods: Unilateral ureteral obstruction (UUO) was induced in 7- to 8-wk-old male wild-type C57BL6 mice. GQDs were injected in kidney fibrosis models through the tail vein. As in vitro model, rhTGF-β1 was used to induce epithelial to mesenchymal transition of kidney primary tubule epithelial cells. After treatment of GQDs, the pattern of change of fibrotic and mesenchymal markers and the activity of the TGF-β/Smads pathway and PI3K/Akt/mTOR pathway were evaluated. In addition, tubular apoptotic cell deaths were assessed.

Results: UUO induced renal fibrosis and morphological changes in the obstructed kidney, whereas administration of GQDs reduces fibrosis and improves kidney structural changes. At the mRNA and protein levels, GQDs significantly reduced the expression of fibrotic markers such as collagen 1α1, fibronectin and α-SMA and increased E-cadherin expression. GQDs significantly decreased TGF-β1 expression, as well as affected Smad-dependent signaling pathways and the PI3K/Akt/mTOR pathway. In addition, TUNEL staining and Bax/Bcl12 ratio were increased in the untreated group compared with GQDs-treated group.

Conclusions: This study revealed the role of GQDs in renal fibrosis, and its effectively attenuated fibrogenesis in 2 ways as follows: via the inhibition of Smad-dependent TGF-β1 signaling pathway and the anti-apoptotic pathway. Thus, GQDs may be a therapeutic option for the chronic kidney disease progression.

PUB433

DDAH1 Inhibitor PD 404182 Increases Serum Asymmetric Dimethylarginine but Does Not Promote Renal Fibrosis

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Background: Plasma asymmetric dimethylarginine (ADMA) is a risk factor for chronic kidney disease, however we recently showed that renal ADMA is anti-fibrotic. ADMA is metabolized by dimethylarginine dimethylaminohydrolase isofrom 1 (DDAH1). PD 404182 is a novel inhibitor of DDAH1 exhibiting anti-tumor and anti-HIV activities. We aimed to determine the effect of PD 404182 on renal fibrosis and explore its underlying working mechanisms.

Methods: After sham or unilateral ureteral obstruction (UUO) operation, 20-25g male C57 mice were treated with vehicle or PD 404182 for 13 days. Moreover, human kidney (HK) cells were treated with various concentrations of PD 404182 in the presence of 2.5 nm TGF-β1. Protein samples from in vivo and in vitro experiments were collected to assess renal fibrosis.

Results: Treatment with PD 404182 enhanced serum ADMA levels in UUO mice, however it did not change the deposition of extracellular matrix proteins, the expression of α-smooth muscle actin (α-SMA) and connective tissue growth factor (CTGF) in UUO induced fibroblastic kidneys. We further showed that PD 404182 reduced the expression of DDAH1 in UUO kidneys which was correlated with increased production of ADMA. In TGF-β1 stimulated HK2 cells, PD 404182 dose-dependently increased ADMA production, and inhibited the expression of pro-fibrotic proteins. Exogenous addition of ADMA inhibited the expression of profibrotic proteins and attenuated the anti-fibrotic effect of PD 404182.

Conclusions: PD 404182 enhances serum ADMA levels but does promote renal fibrosis in obstructed kidneys, which is possibly due to a balance between serum and renal ADMA.
**Changes of Pericyte in Aging Kidney**

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**Background:** Our previous study has shown the changes of pericytes in aging mice kidney. However, its mechanism was unclear. And no such studies have been undertaken in human aging kidneys. In this study, we investigated the pericytes changes in human aging kidneys and mechanism of aging-related pericyte changes.

**Methods:** Renal biopsy from KT donors were analyzed. Donors under age 25 were assigned to young group and donors over age 60 to old group. 2, 24-months-old mice and aging kidneys and mechanism of aging-related pericyte changes.

**Results:** Changes of pericytes in human renal tissues were consistent with those in the aging mice model. In the old age group, pericytes were decreased and interstitial fibrosis blot.

**Conclusions:** In aging human kidney, pericytes have been shown to exhibit numerical reduction and loss of perivascular location as in the aging mice model. These changes in pericytes are thought to be induced by angiotensin 2.
Methods: Using cell-based functional assay for KIM-1 mediated uptake of ox-LDL, we screened 3,414 unique small molecule compounds. After setting up a score for each compound, we selected and cherry-picked the 240 potential hits from the primary screening. We performed reconfirmation and dose dependency studies on two KIM-1 expressing cells (769-P cells and LLC-PK1 cells) expressing human KIM-1. A total of 32 compounds were selected based on reconfirmation and dose dependency studies as potential hits.

Results: We selected JB1 for secondary and tertiary assays as it was top scored. JB1 is not toxic to cells up to 11.11 μM. JB1 does not cleave KIM-1 indicating that JB1 inhibits the uptake of ox-LDL. JB1 doesn’t quench DCFH-DA. JB1 significantly inhibits the uptake of BODIPY-labeled palmitic acid. Additionally, JB1 does not inhibit uptake by inhibiting Bcl-2 pathways.

Conclusions: We have developed a high throughput cell-based functional assay for screening compounds that can inhibit the uptake of ox-LDL by KIM-1. The small molecule inhibitors that we found can be of therapeutic importance for treating kidney disease.

Funding: Private Foundation Support

PUB437

Evaluation of Biomarkers of Interest in Nephrectomized Animals


Background: Chronic kidney disease (CKD) is a worldwide health problem associated with morbidity and mortality, and its development and progression is related to various conditions such as hypertension, diabetes and dyslipidemia. Experimental models of CKD includes the 5/6 nephrectomy rat model, which shares multiple features observed in humans and therefore has been proven clinically relevant.

Methods: We investigated the effect of 5/6 nephrectomy on serum biochemistry and urinary kidney biomarkers, and bone markers as well as histopathological changes. For this purpose, blood and urine samples were collected from 6 control and 12 nephrectomized rats once monthly.

Results: Increases in serum urea nitrogen, creatinine, cholesterol and osteocalcin were consistently observed throughout the evaluation period. Increases in serum alpha2 macroglobulin, urine total protein, and urine biomarkers: osteopontin, neutrophil gelatinase-associated lipoclin (NGAL), kidney injury molecule (KIM-1), cystatin C and β2-microglobulin, and decreases in serum albumin were observed over the course of the evaluation period. Lesions in the kidneys of nephrectomized rats were mild to moderate tubular hypertrophy and hyperplasia with dilatation and cast, resulting in an overall enlargement of the kidney; minimal to moderate tubular degeneration and regeneration; mild to marked glomerulomorphy and minimal to mild chronic inflammation. Mineralized foci were also identified in the kidneys of nephrectomized rats by image analysis. Vascular changes were noted in small to medium size ventricular arteries and consisted of minimal mural degeneration and minimal to mild pemiurval inflammatory cell infiltrates and fibrosis.

Conclusions: These changes observed in serum and urine samples, as well as histopathologically, are indicative of chronic kidney disease. Therefore the model is considered suitable for the investigation of new treatments for CKD.

PUB438

Cordyceps Militaris Extract Attenuates the Pathological Fibrotic Changes in Unilateral Ureteral Obstruction Mice Model

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Background: Cordyceps militaris (CM) is a kind of functional mushroom. This study aimed to evaluate the effect of CM in kidney fibrosis induced by unilateral ureteral obstruction (UUO) mice model.

Methods: Study mice were divided into five groups: Sham surgery, UUO, UUO + solvent (saline), UUO + CM 150mg/kg (CM low dose) and UUO + CM 300mg/kg (CM high dose). Study agents were fed orally daily after UUO induction until animals were sacrificed on day 7. Kidney samples were collected for H&E stain and Masson’s Trichrome stain. Severity of kidney damage was graded from one to five depending on severity: 1 = (< 1%); 2 = (1-25%); 3 = (26-50%); 4 = (51-75%); 5 = (76-100%). The value of p <0.05 was considered statistically significant.

Results: All groups except sham surgery had obvious kidney damage range from 2-4. The interstitial fibrosis on H&E stain and Masson’s Trichrome stain were both significantly less severe in CM low dose group compared to it was in UUO + solvent group. The CM high dose group had significantly higher scores in interstitial fibrosis both on H&E stain and Masson’s Trichrome stain and ECM accumulation compared to CM low dose group. Besides, CM high dose group also had significantly higher scores on ECM accumulation and fibrosis on Masson’s Trichrome stain compared to UUO + solvent group (Figure 1).

Conclusions: According to our findings, a adequate dosage of CM might have an anti-fibrosis effect in kidney but a high dose CM might have a negative effect. Further studies on protein and mRNA expression to support this finding and investigate the molecular mechanisms are needed.

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PUB439

Extrarenal Pelvis Mimicking Parapelvic Cysts: Contrast Is the Key

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Introduction: Extrarenal pelvis refers to the presence of the renal pelvis outside the confines of the renal hilum. It is a normal anatomical variant that is found in ~10% of the population. An extrarenal pelvis appears as a hypoechoic mass just outside the renal sinus and can mimic a dilated pelviccalyceal system giving a false impression of hydronephrosis. In addition, it can also be confused with a parapelvic cyst. With renewed interest in point-of-care ultrasoundography (POCUS), nephrologists must be aware of this finding and herein, we report a case where POCUS was not able to differentiate between these entities.

Case Description: A 62-year-old man with a history of nephro lithiasis and recurrent urinary tract Infections presented to the outpatient clinic for the management of chronic kidney disease stage 3A. The renal sonogram showed the presence of a relatively well-defined anechoic lesion near the left renal pelvis, which could be a parapelvic cyst or mild hydronephrosis or an extrarenal pelvis. Because of the presence of microscopic hematuria, a computed tomography (CT) evaluation of the abdomen with contrast was obtained, which showed a left extrarenal pelvis [Figure] and multiple radiodense foci within the left pelvis, likely phleboliths. Subsequently, cystoscopy revealed a bladder tumor, for which he underwent resection with the resolution of hematuria.

Discussion: Renal sonogram might not be able to demonstrate the ‘extrarenal’ location of the extrarenal pelvis unless it is significantly dilated. Therefore, it can be easily confused with mild hydronephrosis or a parapelvic cyst. It is important to note that hydronephrosis appears as an anechoic ‘branching’ structure extending into the kidney instead of a ‘well-defined’ mass. In our case, CT Urogram has clearly demonstrated the extrarenal location of the pelvis without intrarenal extension. Parapelvic cyst was excluded because a cyst would not communicate with the collecting system and therefore, should not be filled with contrast.
to have significant leukocytosis (180 K/uL) and a new intra-abdominal mass concerning for metastatic disease. Broad-spectrum antibiotics were initiated without significant improvement. A peripheral smear showed increased leucocyte count with bands but no blasts or schistocytes, favoring a leukemoid reaction from advanced neoplasmic disease. His hospital course was complicated by oliguric AKI (creatinine of 2.0 mg/dL, up from 0.8 mg/dL), CRP peaked at ≥200 K/uL in 2 days followed by ≤20 K/uL. The serum uric acid level was found to be 21 mg/dL. Urinalysis revealed pyuria, hematuria, bacturia, casts, and uric acid crystals. The patient was continued on intravenous fluids and received one dose of rasburicase. Within 24 hours, the creatinine improved to 1.66 mg/dL. Due to the patient's poor overall prognosis, the family elected to pursue comfort care.

Discussion: Uric acid has pro-inflammatory and vasoconstrictive properties and it has recently been described as a potential nephrotoxic agent. Crystal deposition and tubular toxic damage are the main mechanisms of injury, though recent studies have also implicated their role in severe afferent vasoconstriction. While our patient had severe traditional risk factors for AKI, his kidney function deteriorated only after the WBC reached a level ≥200 K/uL, and his uric acid peaked above 20 mg/dL. Leukemoid reactions are not associated with lysis syndrome. However, it might pose a potential complication in patients with an acute and rapid increase in WBC. Early consideration of this complication and timely rasburicase administration can salvage kidney function.

PUB441

A Solvent Drag: Traditional Medics Mixed with Ethylene Glycol in a Nigerian Patient on Dialysis
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Introduction: Unregulated traditional medications and their solvents are nephrotoxic. A Nigerian patient presented with a rapid progression of kidney disease following daily ingestion of an aphrodisiac dissolved in ethylene glycol. The diagnosis was confirmed with kidney biopsy and elevated serum uric acid levels. The epidemic of kidney disease in rural communities may in part be explained by this solvent.

Case Description: The patient is a 49-year-old Nigerian male with a 10-year history of diabetes mellitus and hypertension. One year prior to presentation, the serum creatinine was 1.6 mg/dL with 0.8 gram/day proteinuria. The patient began ingesting a traditional aphrodisiac known as Water Fruits. This is a customary practice in his village, outside Abuja, Nigeria. His serum creatinine increased to 8.9 mg/dL and the patient commenced thrice weekly hemodialysis. His local physician was concerned and the patient was sent to Houston, TX for a second opinion. Home medications included calcium carbonate, proton pump inhibitor (PPI), multivitamin, and a DPP-4 inhibitor. A full laboratory evaluation for immunologic or infectious causes of kidney failure was unremarkable. Kidneys were 12 cm bilaterally, with one non-obstructing calculi (7mm) in left kidney. A kidney biopsy revealed protracted tubular injury with isometric vacuolization and numerous calcium oxalate crystals. There was minimal glomerulosclerosis, and severe interstitial fibrosis / tubular atrophy. A serum uric acid level was subsequently checked, and elevated at 25 mmol/L (Range 1.8-3.2). There was no evidence of primary hyperuricemia. His local physician later ascertained that ethylene glycol was used as a solvent for the traditional aphrodisiac. Kidney damage was irreversible and the patient returned to Nigeria.

Discussion: Worldwide, the increasing use of traditional, unregulated, herbal supplements has the potential to cause epidemics of kidney disease in rural communities. In Africa, attention has focused on nephrotoxic herbs (e.g. aloe vera and cymbopogon citratus) that are better-recognized as the role of the herbal alkaloid solvent. Chronic use of ethylene glycol results in oxalate nephropathy. A thorough history and work-up should be pursued in all patients with a rapid decline in kidney function, even in the presence of known risk factors for CKD.

PUB442

Fibrotic renal cortex with an artery occluded by cholesterol clefts (arrow)

Two Cases of Rhabdomyolysis with Near Normal Creatine Kinase
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Introduction: Rhabdomyolysis (RM) is a well-known cause of acute kidney injury (AKI). Elevation of creatine kinase (CK) is considered essential for the diagnosis of severe AKI from RM. We present 2 cases of severe AKI from non-traumatic, non-exertional RM with mildly elevated CK.

Case Description: Case 1 A 55-year-old Caucasian male with history of DM and HTN was admitted with 1-week history of dyspnea and found to have AKI. There was no history of trauma or IV drug use. Exam showed BP of 150/80 and no edema. Serum creatinine was 1.4 mg/dL 2 months prior, 3.1 mg/dL on admission and rose to 12.6 mg/dL. Renal ultrasound was normal, day 2), LDH 552 IU/L (day 2) and plasma myoglobin 263 ng/dl (day 5). Urine myoglobin was undetectable when checked on day 6. Serum sodium was 128 mmol/L and plasma osmolality 291mOsm/Kg. Evaluation for rapidly progressive glomerulonephritis (RPGN) was negative. A renal biopsy on day 4 showed severe acute tubular injury with many myoglobin casts. Renal function slowly returned to normal with conservative treatment. Case 2 A 48-year-old Native American male with history of DM, HTN, CAD and alcohol use. Exam showed BP of 150/80 and no edema. Serum creatinine was 1.4 mg/dL 2 months prior, 3.1 mg/dL on admission and rose to 12.6 mg/dL. Renal ultrasound was normal, day 2), LDH 552 IU/L (day 2) and plasma myoglobin 263 ng/dl (day 5). Urine myoglobin was undetectable when checked on day 6. Serum sodium was 128 mmol/L and plasma osmolality 291mOsm/Kg. Evaluation for rapidly progressive glomerulonephritis (RPGN) was negative. A renal biopsy on day 4 showed severe acute tubular necrosis. He required dialysis for 6 days. Renal function continued to improve after stopping dialysis.

Discussion: Case 1 was negative. A renal biopsy on day 5 showed severe acute tubular necrosis. He required dialysis for 6 days. Renal function continued to improve after stopping dialysis. Both patients had severe AKI with biopsy proven acute tubular necrosis.

Discussion: Both patients had severe AKI with biopsy proven acute tubular necrosis. In both, CK was only mildly elevated and plasma myoglobin was more definitely elevated. Both had non-specific hematuria and proteinuria prompting evaluation for RPGN. Both patients had low plasma sodium with normal plasma osmolality consistent with pseudohyponatremia. The cause of pseudohyponatremia was not clear and would be an interesting subject for further study. Rhabdomyolysis should not be excluded as a cause of severe AKI based on near normal CK.

PUB444

Patient with AKI of Uncommon Etiology
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Introduction: Acute kidney injury is a common complication of congestive heart failure. Here we present a case report of a patient with acute kidney injury complicating congestive heart failure but of unexpected etiology.

Case Description: 70-year-old man with history of hypertension, hyperlipidemia and Chronic Obstructive Pulmonary Disease (COPD) who has seen a physician for several years presented with acute respiratory distress requiring mechanical ventilation. He was treated for new onset heart failure and acute pulmonary edema. Echocardiogram reported left ventricular ejection fraction of 30% and global hypokinesis. He was extubated after 24 hours, but his creatinine increased rapidly from 1.9 mg/dL at the time of initial presentation to 9.5 mg/dL within 4 days post extubation. Anti-Neutrophil Cytoplasmic Antibodies and Anti-Nuclear Antibodies were negative; C3 and C4 were within normal limits. Renal biopsy was performed which surprisingly showed Cholesterol embolization along with interstitial fibrosis, tubular atrophy as well as mild acute tubular necrosis. CT angiogram showed Bilateral renal artery stenosis, occluded right main renal artery and severe near occlusive single left renal artery. Percutaneous transiluminal angioplasty and stenting of the left renal artery was performed and placed on Clopidogrel. Patient’s blood pressure remained well controlled with no further acute pulmonary edema.

Discussion: Cholesterol embolization on biopsy prompted further workup. There was no preceding vascular intervention suggesting the cholesterol embol with syntax of the endothelium. Mortality is likely to be high in these patients especially in elderly males, most commonly due to cardiac and renal etiologies as per previous reports (1). 1. Am J Nephrol. 1993;13(6):489-93.

PUB444

Anticoagulant-Related Nephropathy in IgA Nephropathy
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Introduction: Anticoagulant-related nephropathy (ARN) is a potential complication of warfarin use. This is the case of an ARN in a patient with IgA nephropathy (IgAN).

Case Description: A 68-year-old man with hypertension, CKD stage 3, and atrial fibrillation on warfarin was admitted with edema, acute kidney injury (AKI), and gross hematuria. His creatinine was 2.9 mg/dL (baseline 1.4-1.6 mg/dL); INR was 2.5. Renal ultrasound was normal, urine-protein creatinine ratio (UPCR) was 19.9 g/rolic work-up was negative, and complement levels were normal. Renal function worsened. A kidney biopsy revealed mild mesangial hypercellularity with tubules containing red blood cell (RBC) casts, and mesangial IgA and C3 granular deposits. His anticoagulation was held, and renal function improved. On follow-up, his creatinine was 1.1 mg/dL and UPCR improved to 0.6 g/g.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Discussion: ARN causes RBC casts in the tubules leading to obstruction and AKI. Patients with IgAN may be at higher risk for ARN because of their propensity for hematuria. In the original description of ARN, underlying IgAN was present in 1/3rd of patients, and supertherapeutic INR was present in the majority of cases. Other risk factors include age, diabetes, hypertension, and cardiovascular disease. The risk of AKI in warfarin-treated patients with supertherapeutic INR is higher in those with CKD (13%) as compared to those without CKD (16.5%). Given the widespread use of warfarin and other anticoagulants, it is important to recognize the risk of ARN, and avoid excessive anticoagulation, particularly in patients with CKD and IgAN.

AKI in a Patient with History of Recurrent Hemoptysis

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Introduction: Presentation of patients with pulmonary-renal syndrome may vary. Here we present a patient with acute kidney injury after several episodes of hemoptysis.

Case Description: 65-year-old female patient with a history of recurrent episodes of shortness of breath and hemoptysis follows as idiopathic Pulmonary Fibrosis (PF) presented with creatinine of 5.5mg/dl. Her baseline creatinine was 1.2mg/dl 4 months ago, with no prior history of kidney disease. Patient had a family history of PF with no kidney abnormalities. Urinalysis positive for moderate blood and proteinuria of 1.7mg/dl. Renal ultrasound was negative for hydronephrosis. Complement levels were within normal limits. Antinuclear antibodies, Anti GBS antibodies and rheumatoid factor were negative. Cytoplasmic and perinuclear anti-nuclear cytoplasmic antibodies (ANCA) positive at 1:640, proteinase3 (PR 3) elevated at 4.3U/ml. Renal biopsy which showed Focal Necrotizing and crescentic Glomerulonephritis, MPO- ANCA associated with advanced chronic changes characterized by IgG- and LRP2-containing immune complexes in the TBM. This case suggests the existence of any IgG-containing TBM immune deposits without proliferative glomerular lesions should aware us about the possibility of this disorder.

Discussion: Here we present a patient with acute kidney injury after several episodes of hemoptysis. In Retrospect recurrent episodes of hemoptysis despite prednisone alone probably indicative of vasculitis. Higher mortality rate of ANCA-associated vasculitis possibly can be lowered with serological testing in every patient with recurrent hemoptysis probably indicative of vasculitis. Higher mortality rate of ANCA-associated vasculitis possibly can be lowered with serological testing in every patient with recurrent hemoptysis probably indicative of vasculitis. Higher mortality rate of ANCA-associated vasculitis possibly can be lowered with serological testing in every patient with recurrent hemoptysis probably indicative of vasculitis. Higher mortality rate of ANCA-associated vasculitis possibly can be lowered with serological testing in every patient with recurrent hemoptysis probably indicative of vasculitis. 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Introduction: Acute kidney injury (AKI) has been related to drugs, infectious and multiples autoimmune diseases against glomerular antigens. We present an under-reported case of AKI secondary to kidney anti-brush border antibodies LR2(ABBA disease). Our case is remarkable due to the atypical presentation of nephrotic range proteinuria 7.3g in compare to sub nephrotic range proteinuria of previous cases reported. ABBA can present as an AKI, progress to ESRD or recur in a kidney transplant. This case alerts the clinicians about the diagnosis of tubular injury which is not part of the usual initial assessment. The existence of any IgG-containing TBM immune deposits without proliferative glomerular lesions should aware us about to the possibility of this disorder.

Case Description: A 72 y/o M with pmhx of HTN presents with acute kidney injury. Family, social and medication history were unremarkable. He presents with creatinine 1.5mg/dl, albumin 2.1 and 7.3 g of proteinuria. Glomerular work up resulted negative, urinalysis with proteinuria >300mg and blood positive. Physical examination remarkable for Bp 143/82, general weakness and bilateral leg edema. Kidney ultrasound was within normal limits. Kidney biopsy resulted with Anti Brush Border Ab disease/ LR2( Megalin Related Nephropathy). Patient was treated with IV steroids for 3 days and then started with prednisone 80 mg daily, MMF 750 mg BD, Bactrim SS 3 times a week.

Discussion: We present an underreported cause of AKI LR2 associated with circulating autoantibodies to the tubular brush border protein LR2/megalin and characterized by IgG- and LR2-containing immune complexes in the TBM. This case should alert clinicians of other causes of AKI.

Magnesium Toxicity: A Perfect Storm

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Introduction: Hypermagnesemia is a rare condition in the absence of renal failure since the kidneys are effective in maintaining the normal plasma magnesium concentration. 50 to 70 % of the filtered magnesium is passively reabsorbed in the cortical aspect of the thick ascending limb of Henle. Loop reabsorption is appropriately diminished with magnesium loading, thereby allowing the excess magnesium to be excreted in the urine. Here we present a case of a patient with preeclampsia treated with IV magnesium that led to magnesium toxicity.

Case Description: 29 years old G1P0 admitted for preeclampsia and started on IV Mg Sulfate. After she received Nifedipine and IV labetalol post-partum, she developed shortness of breath, dizziness, abdominal pain and distention, decrease urine output. Hyponatremia caused flushing, delayed deep tendon reflexes (DTR), muscle weakness, lethargy, decrease respirations, bradycardia, and hypotension. Urinalysis showed pyuria, Leukocyte esterase, urine protein 10 mg/dl. Creatinine was 0.92 mg/dl and normal LFT. Due to worsening abdominal pain, milk of magnesium and miralax were given. She later became anuric with decreased DTR with Mg level at 11.3mg/dl, creatinine elevated to 4.3mg/dl and EKG showed sinus tachycardia[A1]. IV Calcium gluconate and Foley catheter placed at which point she had 1 Liter of urine. She was maintained on IVF and magnesium levels continued to decrease and normalization of her creatinine.

Discussion: Use of calcium channel blockers can potentiate neuromuscular blockade action of Mg SO4. Abdominal pain, urinary retention due to muscle relaxation, and milk of magnesia further potentiated her renal failure and cardiac toxicity. It is critical to recognize the hypermagnesemia early since loss of DTRs common in Mg >7 mg/dl and cardiac conduction defects and arrest common in Mg >12mg/dl.
PUB448

Rare Case of Anti-GBM Antibody Disease with Thrombotic Microangiopathy Caused by Hypertensive Emergency
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Introduction: Anti-Thromlateral Basement Membrane (GBM) Antibody Disease is one of the most aggressive form of glomerulonephritis resulting in renal insufficiency and more than 95% of patients have crescents at the time of biopsy. It can be lethal limited or in combination with pulmonary hemorrhage (Goodpasture’s syndrome). In rare case, glomerulonephritis can be seen concurrently with thrombotic microangiopathy (TMA), a disease involving endothelial injury that results in thrombosis in capillaries and arterioles and can lead to thrombocytopenia, anemia, purpura, and kidney failure. Here we present a rare case of anti-GBM with concurrent TMA.

Case Description: We present a case of a 57-year-old female with history of COPD who presents with headache, fever and blood pressures in the 200s/100. Labs notable for a creatinine of 13.02 from 4.2 a week ago (baseline 8.53 years ago). Other labs are notable for Hemoglobin 7.9, platelet 104, LDH 551 and haptoglobin <10 with schistocytes. Kidney biopsy showed necrotizing cellular crescents and focal segmental necrotizing lesions. Immunofluorescence showed linear capillary loop staining of the glomeruli, with antisera to IgG, C3, kappa, and lambda light chains suggestive of Anti-GBM antibody disease. Follow up laboratory testing confirmed the diagnosis as Anti-GBM antibody disease as the measurement of anti GBM IgG antibodies was 7.9.

Discussion: Anti-GBM disease is a rare disorder and a literature review revealed just 10 published accounts of concurrent anti-GBM and TMA in a total of 15 patients. Of those, 3 cases were attributed to TTP and abnormalities in ADAMTS13, 3 were attributed to complement-mediated TMA (aHUS), 1 was attributed to mechanical destruction due to hemodialysis, 1 was attributed to Heparin-induced thrombocytopenia, and 6 were not otherwise specified. No cases attribute the TMA to hypertensive emergency as we report here. In the setting of TMA, empiclasmapheresis is generally initiated, however, many causes of secondary TMA including hypertensive emergency have not been shown to respond to treatment. This was consistent with our patient's presentation as the thrombocytopenia and MAHA failed to improve despite the plasma exchange. Our patient continued to have a decline in kidney function and eventually required hemodialysis.

PUB449

An Uncommon Case of Drug-Induced Acute Interstitial Nephritis
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Introduction: Drug-induced acute interstitial nephritis (DI-AIN) is a common cause of acute kidney injury (AKI) and often presents as an unexplained rise in serum creatinine level (SCr). Despite the frequency of acute interstitial nephritis (AIN), there remain cases underreported and undiagnosed.

Case Description: We report a 54-year-old male, presented with fatigue for a week and had increased SCr from baseline 2.0 mg/dl to 21 mg/dl with a BUN of 125 mg/dl. He denied recent changes in his medications or recent use of the counter or herbal agent. He had a history of hypertension and was on losartan with worsening renal function, therefore requiring hemodialysis. Patient’s kidney biopsy revealed moderate interstitial inflammatory infiltrate associated with interstitial edema consistent with AIN. Reported potential causes of the patient’s AIN included amlodipine and allopurinol which he was taking for almost 4 years and both were held. Given rapidly progressive nature of this patient’s presentation, steroid therapy was started. His urine output increased within 24 hours of initiation of steroid therapy. Hemodialysis was stopped one week later. At the time of discontinuation of dialysis, SCr was 2.5 mg/dl and following one month of steroid therapy, it was 1.8 mg/dl.

Discussion: Our case highlights the inherent difficulty in recognition of acute DI-AIN, which would result in difficulty in decision making regarding proper management. After withdrawal of the offending drugs and initiation of steroid, a rapid improvement of kidney function was noticed. The diagnosis of DI-AIN is typically made with classic triad of rash, fever and eosinophilia within a few days of initiation of a culprit drug. However, these findings appear in a small number of patients, and the onset may be delayed by weeks or months after initiation of medication. Diagnosis relies on maintaining a high index of suspicion in those at risk and obtaining a kidney biopsy. The hallmark pathologic features are interstitial edema, interstitial inflammation with a predominance of lymphocytes and mononuclear cells, with variable numbers of eosinophils. The mainstay of treatment is discontinuation of the offending drug. Multiple studies have evaluated the benefit of steroid therapy to facilitate the recovery of renal function, with inconclusive results. This patient’s timely recovery from dialysis could support the use of steroid in dialysis dependent AIN.

PUB450

Amphotericin-Induced Myoglobinuric Kidney Injury: A Classic Yet Intriguing Tale
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Introduction: Rhabdomyolysis, characterized by necrosis of muscle cells and release of intracellular contents into the blood constitutes 7-15% of all cases of acute kidney injury (AKI) and often presents as an unexplained rise in serum creatinine level (SCr). According to National Center for Health statistics, the prevalence of obesity in the USA exceeds 30% and 228,000 bariatric surgeries were done in 2017. Electronic database for case reports and series with biopsy proven oxalate nephropathy in native or transplanted kidneys from 1950-01/2018 showed fat malabsorption (88%) and excessive dietary oxalate consumption (20%) as causes of oxalate nephropathy. According to a review, patients presented diagnosed with oxalate nephropathy between 1969-2018 with a follow-up to 8 years after bariatric surgery. Diagnosis of oxalate nephropathy includes 24 hours urine collection for oxalate excretion and kidney biopsy. Treatment includes low-fat, low oxalate diet and high fluid intake. Secondary oxalate nephropathy is a rare cause of renal failure and can present after many years of bariatric surgery. Renal replacement therapy is required in >50% of patients, and most patients remain dialysis-dependent. Oxalate nephropathy should be suspected in a patient with remote history of bariatric surgery who presents with sub-acute renal failure.

PUB451

Calcium Oxalate Nephropathy: A Rare Etiology of ESRD
Richa Handa, Muhammad A. Farooq, Jian Li, Sandeep S. Soman. Henry Ford Hospital, Dearborn, MI.

Introduction: Oxalate nephropathy is a rare cause of renal failure. It is characterized by tubular crystalline deposits of calcium oxalate leading to acute and chronic tubular interstitial fibrosis and resulting in renal insufficiency. Our patient presented with oxalate nephropathy, primary and secondary. Secondary hyperoxaluria is more common and is the result of increased dietary oxalate intake, decreased intestinal oxalate degradation, increased colonic permeability to oxalate. We present a case in which a patient with history of bariatric surgery (40 years ago) diagnosed with oxalate nephropathy and developed ESRD.

Case Description: A 74 y female with past medical history of gastric bypass surgery, renal function was normal 1 year prior to hospital admission, NASH cirrhosis presented with abdominal pain, vomiting and melena. On presentation, the patient had creatinine of 12 mg/dl, bicarbonate of 7 mg/dl and hemoglobin of 5.8 gm/dl. Endoscopic evaluation showed two large varices. Due to minimal recovery of renal function, she was started on intermittent hemodialysis. Further workup showed positive ANA with titer of 1:840, positive deDNA and low complement levels. Patient’s urinalysis showed RBC=182/HPF and proteinuria 100 mg/dl. Kidney biopsy showed acute tubular injury changes with tubular crystals consistent with calcium oxalate.

Discussion: According to National Center for Health statistics, the prevalence of obesity in the USA exceeds 30% and 228,000 bariatric surgeries were done in 2017. Electronic database for case reports and series with biopsy proven oxalate nephropathy in native or transplanted kidneys from 1950-01/2018 showed fat malabsorption (88%) and excessive dietary oxalate consumption (20%) as causes of oxalate nephropathy. According to a review, patients presented diagnosed with oxalate nephropathy between 1969-2018 with a follow-up to 8 years after bariatric surgery. Diagnosis of oxalate nephropathy includes 24 hours urine collection for oxalate excretion and kidney biopsy. Treatment includes low-fat, low oxalate diet and high fluid intake. Secondary oxalate nephropathy is a rare cause of renal failure and can present after many years of bariatric surgery. Renal replacement therapy is required in >50% of patients, and most patients remain dialysis-dependent. Oxalate nephropathy should be suspected in a patient with remote history of bariatric surgery who presents with sub-acute renal failure.
Natalia
A Case of Acute Renal Infarction Associated with Hyperhomocysteinemia
Publication-Only

The patient was a 61-year-old male with a history of radiculopathy who presented to the hospital with worsening signs of lower extremity weakness. On admission, physical exam revealed right flank tenderness. Labs showed a creatinine (cr) of 1.38 mg/dl (baseline, 1.05 mg/dl), leukocytosis (17 x 10^3/mm3), and transaminitis (ALT 57 IU/L, AST 71 IU/L). LDH was 915 IU/L, CRP 261 mg/L. CT abdomen/pelvis with IV contrast suggested right ARI from a thrombus in the right renal artery. Acute management included anticoagulation with unfractionated heparin. Thrombolyis was not performed, given the patient’s development of fever, stabilization of creatinine, and lack of high-quality evidence for benefits vs. risks of the procedure. Given the patient’s recent viscus disturbance (potentially, amanous fusions) a percutaneou exam was performed and was normal. No evidence of a cardioembolic source was identified. An extensive vasculitits panel was negative. Drug screen and blood/urine cultures, negative. Thrombophilia evaluation was negative, except an elevated serum homocysteine (Hcy) level of 46.6 mcmol/L. On day 5 renal doppler visualized flow within main renal arteries with normal resistive indices. Cr at discharge was 1.27 mg/dl.

Discussion: Despite a lack of definitive evidence, the best treatment for ARI is timely anticoagulation. Our case is a rare example of an ARI in the absence of a cardioembolic source. The patient responded well to heparinisation, which likely due to the presence of a non-cardioembolic source. A follow-up renal biopsy is recommended to rule out other causes of renal failure.

PUB454
A Case of Acute Renal Infarction Associated with Hyperhomocysteinemia
Publication-Only

Introduction: The patient was a 61-year-old male with a history of radiculopathy who presented to the hospital with worsening signs of lower extremity weakness. On admission, physical exam revealed right flank tenderness. Labs showed a creatinine (cr) of 1.38 mg/dl (baseline, 1.05 mg/dl), leukocytosis (17 x 10^3/mm3), and transaminitis (ALT 57 IU/L, AST 71 IU/L). LDH was 915 IU/L, CRP 261 mg/L. CT abdomen/pelvis with IV contrast suggested right ARI from a thrombus in the right renal artery. Acute management included anticoagulation with unfractionated heparin. Thrombolyis was not performed, given the patient’s development of fever, stabilization of creatinine, and lack of high-quality evidence for benefits vs. risks of the procedure. Given the patient’s recent viscus disturbance (potentially, amanous fusions) a percutaneou exam was performed and was normal. No evidence of a cardioembolic source was identified. An extensive vasculitits panel was negative. Drug screen and blood/urine cultures, negative. Thrombophilia evaluation was negative, except an elevated serum homocysteine (Hcy) level of 46.6 mcmol/L. On day 5 renal doppler visualized flow within main renal arteries with normal resistive indices. Cr at discharge was 1.27 mg/dl.

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Cocaine-Induced ANCA Negative Vasculitis: A Diagnostic Dilemma
Kunal Bhuta, Kriti Devkota, Haris M obeen, William DiFilippo. SUNY Upstate Medical University, Syracuse, NY.

Introduction: Cocaine is an addictive stimulant drug. In 2014, 913,000 Americans met the criteria for dependence or abuse of cocaine. Almost 69% of Cocaine is contaminated with Levamisole which has been found to be immunogenic with anti-neutrophil cytoplasmic antibody (ANCA) associated cutaneous vasculitis in 88-100% patients.

Case Description: 24-year old male with a history of substance abuse presented with bilateral lower limb weakness associated with burning pain and numbness in the right leg for 10 hours. He used cocaine one week prior to admission. Vitals were normal. See Table 1 for full lab results. He was treated with empiric therapy of 1351 L U, SGPT 460 U/L, elevated WBC. Urine analysis - pH 6.0, Hb 3+, RBC 14 and Protein 100. Renal ultrasound and Urine toxicology were negative. CPE levels (17,000 U/L) tended downwards. Urine microscopy showed muddy brown cast. Histopathology, Immunology including ANCA, C3, C4 were normal. Renal biopsy was performed and showed normal renal architecture along with focal collections of interstitial eosinophils. It was treated with hemodialysis and steroids.

Discussion: Cocaine can cause AKI by Rhabdomyolysis, Vasculitis, Platelet activation. Biopsy showed some focal vasculitis. Vasculitis in Cocaine abusers can be due to drug induced toxicity or, an anti-helminthic agent withdrawn due to multiple side effects. Levamisole is added to cocaine to enhance its euphoric effects. Levamisole induced ANCA positive vasculitis is well known. Our case is one of the few ANCA negative renal vasculitis responding to steroids. Levamisole is detectable in urine for only 5-6 hours making diagnosis challenging. The role of steroids in the treatment of this condition has not been established. This patient responded well to steroids likely due to presence of interstitial inflammation. Research is required to understand effective ways to treating this condition. Until then, primary treatment continues to be cessation of drug use and renal replacement therapy if needed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

PUB455
Two Variants of Mickey Mouse Sign on Urinary Bladder Point-of-Care Ultrasound: One with the Tail and One Without
Manzar Hussain,1 Harini Bejanki,1 Abhilash Koratala.2,1 University of Florida, Gainesville, FL; University of Texas Health Science Center, San Antonio, TX.

Introduction: For nephrologists, ‘Mickey Mouse’ by default reminds of dysmorphic red blood cells in the urine. With the increasing use of point-of-care ultrasonography (POCUS), we discuss the Mickey Mouse sign in the context of urinary bladder ultrasound. This case also illustrates the common POCUS aphorism, “one view is no view.”

Case Description: A 72-year-old gentleman with a history of chronic kidney disease stage 5 secondary to autosomal dominant polycystic kidney disease, hypertension, and benign prostatic hyperplasia presented to the hospital with worsening signs of hyperpernia. He was also found to have worsening renal function compared to prior baseline, and nephrology was consulted for possible initiation of renal replacement therapy. On POCUS, the medical student reported that the patient had bilateral hydroureter. However, on a careful review of images and longitudinal scanning, the anechoic sac-like structures posterior to the bladder were found to be diverticula in the setting of chronic bladder outlet obstruction and not hydroureter [Figure: left panel is diverticula and right hydroureter]. Moreover, there was no nephropenia on either side.

Discussion: A bladder diverticulum is a sac or pouch that protrudes out of the bladder wall. Diverticulae may be congenital (primary) or acquired (secondary), and acquired diverticula from chronic bladder outlet obstruction are commonly encountered in the adult population. They appear as Mickey Mouse ears on bladder ultrasound, with the bladder representing the head. Hydroureter (s) can mimic diverticula in the transverse plane, but on the longitudinal scan plane, it usually appears as an anechoic tubular structure resembling the tail of the Mickey Mouse. Moreover, hydroureter is more likely to be associated with hydronephrosis than diverticula. Also, normal ureteric jets, that is a visualization of the normal physiological peristaltic efflux of urine on color Doppler will be seen with diverticula, while they are expected to be weak or absent in the case of a hydroureter. Copyright © 2023 Wolters Kluwer Health, Inc. All rights reserved.
Case Description: A 65 year old female with past history of protein S deficiency, hypertension and CKD stage 3 presented with blood in urine. She was found to have oliguric AKI with a supratherapeutic INR of 7.8 and Creatinine of 14.1 mg/dL while on warfarin therapy for multiple deep venous thrombosis in the past. Home medications included warfarin and lisinopril. Review of systems was otherwise negative with no recent contrast administration. The disease is significant only for hematuria. Coagulation profile showed PT of 46.9 seconds and PT of 82.5 seconds. All other labs were within normal limits. Several RBCs with RBC casts were seen on urinalysis. Urine protein creatinine ratio was 0.9. Ultrasound disclosed echogenic kidneys with no nephrocalcinosis. All medications including warfarin were held immediately on admission and despite volume resuscitation, BUN and Cr did not show any improvement. After 5 days of hospitalization her INR improved from 7.8 to 2.6 and Cr came down to 4.17 mg/dL. Renal biopsy revealed severe occlusion of renal tubules by red blood cells and casts with tubular cell damage consistent with acute tubular necrosis proving warfarin induced renal injury.

Discussion: There is growing evidence that ARN is a potentially serious complication of anticoagulation therapy. In addition to warfarin, there are several recent case reports that ARN can develop in patients on dabigatran or on apixaban. The recent retrospective analysis of RE-LY shed light on it as well. The higher prescription volume of anticoagulants, that ARN can develop in patients on dabigatran or on apixaban. The recent retrospective analysis of RE-LY shed light on it as well.

Acute tubular necrosis (ATN) is one of the most common causes of acute kidney injury (AKI) in hospitalized patients. Chronic pathophysiological changes in renal hemodynamic from an underlying cardiac disease named cardio-renal syndrome (CRS) is one of the risk factors of AKI. Nephrotic ATN can occur in patients who are at risk even in those with normal renal function. Close monitoring for renal function should prevent and early diagnose for AKI. We report a case of a middle-aged African American woman with chronic congestive heart failure (CHF) who received multiple nephrotic agents without judicious renal function monitoring and subsequently had a delay in diagnosis for non-oliguric AKI.

Introduction: The symptoms in the present case were mild and improved spontaneously without specific therapy including plasma exchange or ecollulubn. Japanese patients with C3 p.I1157T mutation, which was identified in this case are reported to show a favorable prognosis, and spontaneous recovery of an AHS patient with MCP mutation triggered by influenza B has been documented. The data suggest that a mild defect of complement regulation including C3 p.I1157T resulted in the present patient’s mild AKI symptoms.

Cardio-Renal Syndrome: Clinical Predictor of AKI
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Introduction: Acute tubular necrosis (ATN) is one of the most common causes of acute kidney injury (AKI) in hospitalized patients. Chronic pathophysiological changes in renal hemodynamic from an underlying cardiac disease named cardio-renal syndrome (CRS) is one of the risk factors of AKI. Nephrotic ATN can occur in patients who are at risk even in those with normal renal function. Close monitoring for renal function should prevent and early diagnose for AKI. We report a case of a middle-aged African American woman with chronic congestive heart failure (CHF) who received multiple nephrotic agents without judicious renal function monitoring and subsequently had a delay in diagnosis for non-oliguric AKI.

Discussion: A 43-year-old African American woman with a past medical history of advanced systolic heart failure secondary to mitral valve (MV) regurgitation status post prosthetic MV replacement and automatic intracardiac device (AICD) presented with fever. She developed acute compensated heart failure and was found to have prosthetic AC MV endocarditis. Rifampicin, gentamycin, and cefazolin were initiated and the AICD was removed. She was diuresed with IV bumetanide. Her baseline serum creatinine (SCr) was 0.9-1.1 mg/dL, which had been stable until hospital day (HD) 15 when renal function was no longer checked. On HD 18, she had head and carotid CT angiography for pre-heart transplant work-up. Four days later, urine output (UOP) decreased to 460 mL/day and SCr increased to 5.44 mg/dL. She did not have hypotensive episode and sign of dehydration. A renal ultrasound showed bilateral cortical echechogenicity without sign of obstruction. Unianals revealed protein of 30 mg/dL and 1 RBC/HFP. FeV1, was 69.9%. Gentamicin was discontinued given its supratherapeutic level of 2.3 µg/mL. IV bumetanide was held. Follow-up daily renal function showed a gradually decreased SCr and an increased UOP.

Discussion: Our patient presented with AKI which is secondary to nephrotic ATN from gentamycin and IV contrast exposure. Although she had normal baseline SCr, her underlying CHF can contribute to renal hemodynamic impairment from type 2 CRS. The renal ultrasound supports underlying chronic kidney disease (CKD). Therefore, renal function should be closely monitored in such a high risk patient who has underlying CRS especially while receiving nephrotic agents in order to prevent and early diagnose for AKI.
Discussion: Oselamivir (Tamiflu) is a neuraminidase inhibitors recommended for influenza A and B, as well as for prophylaxis. Dose is adjusted renally to avoid renal injury since is excreted renally. Most common side effects include nausea, vomit and abdominal discomfort, but renal failure is rarely seen. In our case, patient ended with chronic renal replacement therapy after taking medication and no other causes were found. Caution should be taken when taking it as prophylaxis. No report has been found related as renal failure due to oseltamivir given as prophylaxis.

Lihido Enhancing Herbal Supplementation-Induced Acute Interstitial Nephritis
Tina Motazed, Anita Shah, Samaya J. Anumadu. Baylor College of Medicine, Houston, TX.

Introduction: Acute interstitial nephritis (AIN) results from kidney injury characterized by inflammation in the kidney interstitium, often in the setting of exposure to offending medications. We report a case of AIN in a healthy male after routine colonoscopy with exposure to multiple non-prescribed herbal medications.

Case Description: A 52-year-old previously healthy male on multiple herbal supplements including black maca, Tongkat Ali extract, Mucauna extract, and saw palmetto increased libido presented to the hospital with acute kidney injury (AKI) approximately one month after a routine screening colonoscopy. The patient had no known kidney disease prior to his procedure. Post colonoscopy, he developed right sided flank pain followed by weight loss and anorexia. Labs were notable for creatinine of 4.06 mg/dL. Urinalysis with glucosuria, proteinuria and moderate leukocytes, with rare eosinophils in the urine. Renal ultrasound showed normal kidney sizes. Kidney biopsy was consistent with acute allergic interstitial nephritis, with mild interstitial fibrosis or tubular atrophy. Kidney function improved with cessation of all herbal supplements and treatment with prednisone.

Discussion: This case illustrates a rare case of acute interstitial nephritis induced from herbal supplements and to the best of our knowledge has not been well reported in the literature. There is little known about the safety profile of these medications and the mechanism in which they induce such injury. Thorough history taking is imperative on part of clinicians to be able to identify these medications (that are often not reported initially), especially by nephrologists in settings where kidney injury cannot be explained by other processes. This allows for early diagnosis, kidney biopsy if possible, avoidance of further use of the medications, and prompt initiation of treatment in hopes to prevent long-term kidney damage.

Mycohenolate Mofetil in an Atypical Granulomatous Pattern of Tubulointerstitial Nephritis and Uveitis Syndrome
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Introduction: Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disease in which the underlying physiopathology is to date poorly understood though some hypothesize that infection, drugs and autoimmunity are involved. Diagnosis criteria exists and categorizes TINU as definite when uveitis with several granulomas are present 2 months before or 12 months after tubulointerstitial nephritis (TIN), in the absence of other systemic disorder. Pathologically tubulointerstitial nephritis is always found as a constant. Granulomas are rare.

Case Description: We report a 31-years-old woman who came for fatigue, headache, fever, ophthalmic pain, weight loss and acute kidney injury (AKI) (plasma creatinine (PCr) 2 mg/dL). She had no medical condition except for a recent history of hypertension treated by nifedipin. Renal biopsy showed TIN and several, small non-necrotizing granulomas. Concomitantly, bilateral anterior uveitis with several, small granulomas was found. Laboratory tests showed high levels of C-reactive protein. Infectious serology and autoimmune screening were negative, Nifedipin was discontinued for more than 2 weeks regarding the possibility of drug-induced interstitial nephritis without, however, improvement of the renal function. Patient was therefore diagnosed with TINU syndrome after excluding other differential diagnosis such as tuberculosis, sarcoidosis and drug-induced TIN. As renal function declined (PCr 3.7 mg/dL), we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started, we started steroid pulses (3 mg/dL) started. Ophthalmologic relapse and creatinine increase motivated introduction of mycophenolate mofetil and resulted in rapid clinical improvement of pan-uveitis and renal function.

Discussion: There is no evidence-based guidelines regarding TINU treatment, however systemic steroids are widely used and renal outcome is usually good. Granulomatous pattern of TINU syndrome has been only rarely reported. It differential diagnosis can be very challenging because both TINU and sarcoidosis are diagnosis of exclusion. Here we suggest that Nifedipine can be a trigger for TINU syndrome. Also we report the potential benefit of MMF.
PUB464

Physiology or Pathology? An Interesting Case of Rise in Serum Creatinine in a Female-to-Male Transgender Patient
Pulkit Gandhi, Ankur Shah, Edward G. Medeiros. Brown University, Providence, RI.

Introduction: Transgender hormone therapy is a mainstay in the management of gender incongruence. Female to Male (FTM) transgender individuals are typically maintained on testosterone to induce a phenotype that matches their identity. Testosterone is known to have multiple adverse effects including tubular injury and FSGS. We present an interesting case of FTM transgender with a benign creatinine elevation while on testosterone and discuss the interpretation of serum creatinine (sCr) in transgenders undergoing hormone therapy.

Case Description: A 35yo FTM transgender patient with past medical history of TIA secondary to PFO on clopidogrel was referred to our Nephrology clinic for consultation for an elevation in sCr. A review of records shows that his sCr has fluctuated between 1.1 and 1.3 mg/dl over the preceding 8 years. He denied any acute changes in health, recent or remote NSAID use, no LUTS. His only medications are clopidogrel, dexamethasone, and testosterone. Urinary microscopy was negative for cellular elements or casts. Urinary microalbumin/creatinine ratio was 3.8 mg/g. The most recent sCr was 1.3, estimating a GFR of 33 ml/min via the CKD-eGFR equation. A 24 hour urine collection was performed and the 24 hr urinary creatinine clearance was found to be 92 ml/min.

Discussion: Creatinine elevations in the setting of testosterone therapy can represent physiology or pathology. Acute kidney injury due to testosterone has a differential diagnosis including ATN, FSGS while a physiologic increase in skeletal muscle mass may result in increased creatinine generation. A careful examination of the urine and measurement of urinary protein excretion can help differentiate pathology and physiology. A 24 hour urine creatinine to estimate creatinine clearance was diagnostic in our patient of a state of altered physiology, not pathology. Interestingly, the creatinine clearance more closely approximated the CKD-Epi estimation of the male gender, not female gender in our patient. This experience was also seen in two case series of metabolic parameters during transgender hormone therapy, in which sCr was shown to rise 19-42% after initiation of therapy. In estimating eGFR in FTM patients on transgender hormone therapy, we recommend the male gender in calculations.

PUB465

NSAID Use Associated with Bilateral Renal Infarction: A Case Report
Jonathan B. Lis, Yejoo Jeon, William G. Chang. Yale University School of Medicine, New Haven, CT.

Introduction: Renal infarctions are caused by interruptions in renal arterial blood flow, and are relatively rare. We present the case of a 37 year old woman whose renal infarction was likely due to the vasocostrictive effects of non-steroidal anti-inflammatory drugs (NSAIDs). Although high-dose NSAIDs are known to cause a decrease in renal perfusion, they are generally not implicated in renal infarction.

Case Description: A 37-year-old woman with a history of cholestasis during pregnancy presented to the emergency department with acute on chronic abdominal pain. She was given 60 mg of intravenous ketorolac, and discharged on ibuprofen 600 mg every 6 hours as needed. Her pain persisted and she returned 7 days later. Her vital signs were normal with mild hypertension. Physical examination was notable only for diffuse abdominal pain. Initial labs showed new acute kidney injury (AKI) and bland urinalysis. ESR and CRP were elevated; LDH was normal. Cardiac and hypercoagulability workups were normal. Computed Tomography (CT) scan revealed bilateral renal infarction, corroborated on renal ultrasound with doppler. The patient was treated with volume resuscitation. She was discharged 3 days after admission with moderate improvement in creatinine. Follow-up 14 days after discharge showed normalization of creatinine.

Discussion: Despite imaging studies qualifying a diagnosis of renal infarction, LDH was normal, suggesting that the extent of renal tubular damage was not as profound as the imaging suggested. This is also supported by the improvement in renal function with only fluid resuscitation and no anticoagulation. Furthermore, workup for infectious, cardiogenic, autoimmune, renovascular, or hypercoagulable etiologies was negative. NSAID medication taken prior to presentation was thus the most likely causative factor. Mechanistically, hypovolemia prior to presentation may have caused a prostaglandin-dependent state, thus causing renal hypoperfusion when NSAIDs were introduced. To our knowledge, only one other similar case report exists in the literature, and this phenomenon may be more common than previously thought.

PUB466

Toxic RBC Casts as the Culprit of Irreversible AKI in IgA Nephropathy
Bhushan Suyal,1 Leal Leal,2 Lis, Yejoo2, Chang. Yale University School of Medicine, New Haven, CT.

Introduction: Acute tubular necrosis (ATN) driven by RBC casts occurs in 20% cases of IgA nephropathy (IgAN). Similar mechanism of AKI is observed in Henoch-Schönlein nephritis, thin basement membrane disease and anticoagulation related nephropathy. Eventhough, glomerular hematuria in the absence of proteinuria is considered a benign entity without long term renal impact, up to 25% of patients with macrohematuria related AKI have incomplete renal recovery. Poor prognostic factors include increased age, prolonged duration of hematuria, severity of ATN and degree of interstitial fibrosis.

Case Description: A 50 year old male with cryptogenic cirrhosis presented with AKI. He had the like symptoms 2 weeks before presentation. Workup revealed elevated creatinine of 3.4mg/dl from a baseline of 1mg/dl. Urinalysis showed ~25 RBC and protein:Cr ratio of 1.1g. On urine microscopy, dysmorphic RBCs and RBC casts were seen. Serological workup showed low C3 (77mg/dl), normal C4 and elevated ASO(476 IU/ml). Renal biopsy showed RBC casts and tubular vaculolization. IgA and C3 deposits were seen on immunofluorescence consistent with mesangio proliferative IgAN. Crescents were absent and there was minimal interstitial fibrosis. Scant subendothelial deposits were present on electron microscopy. Immunosuppression use was deferred in the absence of glomerular involvement and history of spontaneous bacterial peritonitis. Low dose linsiprol was initiated. After 3 months Cr had declined to 2.3.

Discussion: The ability of toxic RBC casts to independently cause AKI in the absence of glomerular involvement tends to be overlooked, but is now being increasingly recognized in cases of anticoagulant nephropathy. Intra tubular obstruction by RBCs, direct tubular toxicity by hemoglobin(Hb) byproducts and intra renal vasoconstriction play a role. Data on specific therapy is scarce and the role of renal heme oxygenase and Hb scavenging by CD163 receptors on tissue macrophages may provide a potential avenue for future therapeutic ventures.

PUB467

Subclinical Urea Cycle Defect Discovered in Pregnancy
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Introduction: We report a subclinical urea cycle defect (UCD) which manifested clinically in pregnancy. Mild variants of UCDs, often (-) by genetic analysis, can occur via a second hit leading to a high morbidity and mortality if not recognized.

Case Description: 33 YO G1P0 with no known PMHx presented at 35 weeks gestation with new onset hypertension & decreased fetal movement: BP 174/90, lehagy, 1+ proteinuria. Labs: WBC 14, Hgb 5.4, Hct 15.3, platelets 33 (periph smear mod schistocytes), LDH 1359, haptoglobin-4, UN 36, SCr 3.89, Alb 1.9, AST 348, ALT 182, Thbii 9.6 (con 8.1), Lactate 8.0, NH3 61, INR 3.9. ADAMS13 42%, UA 1+ prot +1 bld 3-5 rbc. UOP 410 mg/g. US confirmed fetal demise. She developed seizures & was emergently taken to C-section. She was listed for liver transplant & started on CVVH. She developed bowel ischemia requiring emergent colectomy. Within 1 week, her encephalopathy, kidney & liver failure resolved. CVVH was held, & her LFTs, NH3 and INR normalized w/out liver transplant. She began rehab w/ nutritional support via TPN & became outbundled with an NH3 of 375. Emergent HD was performed for NH3 clearance with improvement in her mental status. She was rechallenged with TPN & again developed encephalopathy with isolated hyperammonemia despite normal liver U/S, LFTs, INR and CRB. This eventually resolved by limiting protein in her TPN. Genetic analysis for Ornithine Transcarbamylase Gene (OTC) was (-).

Discussion: Our patient presented with acute fatty liver of pregnancy with hepatic encephalopathy & HELLP syndrome with eclamptic features. After delivery & supportive care, she improved. As isolated hyperammonemia with encephalopathy occurred after TPN, a subclinical UCD was suspected but testing was (-) for OTC. This test is only positive in 80% of cases and other enzymes in the urea cycle such as Carbamyl phosphate synthetase I, argininosuccinate lyase, or argininosuccinate synthetase could have been normal. Most UCDs present in the neonatal period from complete absence of these enzymes. When there is only partial deficiency; the symptoms often arise in adulthood after a second hit such as pregnancy. Genetic testing, especially with partial deficiency, can be (-), but the disease should be considered when there is isolated hyperammonemia & encephalopathy, especially after a protein load, in the absence of liver disease.
Dabigatran-Associated Acute Interstitial Nephritis

Kevin Fu,1 Mariam P. Alexander,2 Samih H. Nasr,2 Scott D. Cohen,1 1George Washington University, Washington, DC; 2Mayo Clinic, Rochester, MN.

Introduction: There are few case reports of acute interstitial nephritis (AIN) in the setting of novel oral anticoagulants (NOACs). One described a patient on dabigatran who developed biopsy-proven AIN; another described a case of apixaban-related AIN. The mechanism of NOAC-associated AIN is unclear.

Case Description: A 79-year-old male with history of right RCC s/p nephrectomy in 2014, atrial fibrillation, and hypertension presented with 3 days of hematuria. He became anuric 24 hours prior to admission. His home medications were atorvastatin, dabigatran, and metoprolol; dabigatran was held on admission. Labs were significant for serum creatinine 11.7 mg/dL, BUN 107 mg/dL, potassium 7.2 meq/L, INR 2.9, PTT 75 seconds; prior serum creatinine was 1.2 mg/dL. EKG showed peaked T-waves and hyperkalemia was treated medically. CT abdomen w/o contrast showed no hydronephrosis. Urinalysis showed specific gravity 1.020, pH 6.0, 4+ protein, moderate blood, >100 RBC/hpf, 5-10 WBC/hpf, and no cellular casts. Serologic studies were negative. Renal biopsy was recommended but due to coagulopathy and a solitary kidney, biopsy was postponed. The patient was initiated on hemodialysis (HD) for hyperkalemia and discharged. Two months later, he remained HD dependent, coagulopathy corrected, and he was readmitted for kidney biopsy. Biopsy showed acute and chronic interstitial nephritis. There was acute tubular injury with 4 out of 15 glomeruli globally sclerotic. The etiology of his tubular damage may have been secondary to anticoagulant-related nephropathy (ARN) although classic biopsy features of glomerular hemorrhage and renal tubules filled with RBC casts were not seen.

Discussion: This case expands the differential of AKI in the setting of anticoagulation to include not only ARN with associated acute renal tubular injury but also AIN. Despite stopping dabigatran and treatment with steroids for the past 12 weeks, there has been no renal recovery to date.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Leukocyturia: Not Always a Urinary Infection

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Introduction: The increased presence of white blood cells in the urine, leukocyturia, can be interpreted as a urinary infection; however, the absence of a typical clinical picture accompanied by acute kidney injury and other findings in the urine may be the key to reach the actual diagnosis.

Case Description: A 32-year-old woman with no known pathology went to the ER with constitutional symptoms, no fever. She was evaluated repeatedly before admission and prescribed with antibiotics for suspected urinary infection. It is hospitalized when the condition was accompanied by anasarca and increase in creatinine from 1.7 to 6.44 mg/dl. The diagnosis of acute kidney was made. Urinalysis 2+ albuminuria. Urinary sediment: leukocyturia and red blood cell cylinders. Renal ultrasound, normal size with increased echogenicity. A renal biopsy was performed, finding kappa light chain cylinders in the tubules as well as tubulointerstitial atrophy without glomerular involvement. The diagnosis of cast nephropathy was made and serum protein electrophoresis was performed, finding a monoclonal peak by free kappa chains. Bone marrow biopsy with 20% of mature plasma cells. The definitive diagnosis of Multiple IgG kappa myeloma with associated cylinder nephropathy (myeloma kidney) is made. Currently with clinical improvement, creatinine at 1.78 mg/dl after chemotherapy and awaiting for autologous bone marrow transplantation.

Discussion: The approach of leukocyturia without a typical clinical picture of urinary infection must include other renal diseases in the differential diagnosis. Renal disease is a common complication of monoclonal gammapathies secondary to the deposition of light chains in different compartments of the kidney in this case a “myeloma kidney”.

AKI Transurethral Resection of the Prostate Secondary to Pigment Nephropathy

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Introduction: AKI post TURP can be caused by intratubular precipitation of hemoglobin pigment secondary to hemolysis after the use of hypotonic solutions for irrigation during TURP.

Case Description: 78 year old male with history of atrial fibrillation and BPH presented to ER on same day after being discharged post TURP with generalized fatigue. Labs were relevant for serum Cr of 2.2 mg/dl (baseline 1.1 mg/dl prior to surgery). Physical exam unremarkable with clear lungs, benign abdomen and no lower extremity edema. Foley catheter in place with bloody urine. There was initial concern for obstruction post TURP. However, CT scan revealed diffuse urinary bladder wall thickening and no evidence of hydronephrosis. Hospital course relevant for progressive renal failure with creatinine peak 12.0 mg/dl at day 8. Relevant labs showed drop of hemoglobin from 15.4 gm/dl (pre-TURP) to 12 gm/dl (POD2) and LDH of 702 units/L. Haptoglobin 9 mg/dl (low). There was concern for hemolysis leading to pigment nephropathy. Patient underwent kidney biopsy on day 3: Acute tubular injury with intratubular hemoglobin casts. Mild interstitial inflammation (figure 1&2). Renal function improved with conservative management and creatinine began to improve by day 9. He did not require renal replacement therapy and latest creatinine is 1.6 mg/dl.

Discussion: Pigment nephropathy should be considered in any patient who presents with AKI post TURP procedure who develops renal failure and no evidence of obstruction is found on imaging studies. The use of hypotonic fluids for irrigation during the procedure and the presence of hemolysis on lab workup will help in diagnosis. The prostatic plexus can reabsorb significant amount of fluid during TURP. If hypotonic solutions are used then there can be significant hemolysis leading to pigment nephropathy. Treatment is usually supportive and includes monitoring for diuresis needs.
**Discussion:** Post inflammatory syndrome is a systemic inflammatory response immediately following EVAR is seen in 14 to 60 % of the patients. Our patient had inflammatory process following EVAR, which worsened with embolization procedure and was aggressive enough to cause bilateral ureteral obstruction and acute renal failure.

**PUB476**

**Oxalate Nephropathy After Antibiotic Use in a Gastric Bypass Patient**

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**Introduction:** This is a case of oxalate nephropathy secondary to antibiotic use for osteomyelitis in the setting of post gastric bypass surgery.

**Case Description:** A 73-year-old Caucasian female with history of gastric bypass surgery, history of recent right foot osteomyelitis treated with Vancomycin, Ampicillin and Sulbactam for proteus mirabilis presented with worsening renal function. She finished her antibiotic course for osteomyelitis prior to admission and was found to have Creatinine of 3.1 post antibiotic treatment. Kidney biopsy revealed ATN with many calcium oxalate crystals and tubular atrophy and interstitial fibrosis. Subsequently she required dialysis.

**Discussion:** Antibiotic use and gastric bypass anatomy could be related to oxalate nephropathy. Antibiotic use in this patient might have caused decreased gut microbial Oxalobacter Formigenes, resulting in increased colonic oxalate absorption and the development of calcium oxalate crystals in the kidney. Research in administration of oxalobacter probiotic may help identify a potential prevention of this condition.

**PUB477**

**A Case of Secondary Hyperparathyroidism in a Patient on Hemodialysis with Parathormone Levels Within the Targets and High Total Alkaline Phosphatase**

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**Introduction:** Levels of parathormone (PTH) in dialysis patients are not always accurately correlated to the degree of bone remodeling. International guidelines suggest the use of other bone markers, such as serum total alkaline phosphatase (TALP). Although the measures of PTH and TALP are often considered as complementary, these two markers can evolve in opposite directions.

**Case Description:** Our patient was a 61-year-old Haitian woman on hemodialysis due to diabetic nephropathy. In 2011, she developed secondary hyperparathyroidism while on alphacalcidol. Cinacalcet 30 mg once a day was started since her phosphocalcic product was 4.81. She seemed to respond well to treatment, with her PTH reaching the targets set by guidelines. In 2012, she accused bone pain. Her laboratory results indicated high TALP (1772 U/L) with PTH within the targets (26.2 pmol/L) and low vitamin D (22.2 nmol/L). Her alphacalcidol was switched to calcitriol 0.5 mcg orally three times per week with vitamin D 10 000 IU orally once per week. In 2013, her bone pain was not relieved, with her TALP still high (1917 U/L) and her PTH within targets. An electrophoresis of TALP was done which showed that 97% was of bone origin. Multiple radiographs were also performed, which were suggestive of poorly controlled hyperparathyroidism. Her calcitriol and her cinacalcet were thus increased, and surprisingly, her PTH peaked significantly after this treatment adjustment as her TALP was lowering (cf. image), revealing her hyperparathyroidism.

**Discussion:** This case shows us that some patients on hemodialysis may suffer from secondary hyperparathyroidism despite having PTH levels within the targets set by KDIGO and emphasizes the importance of taking into consideration other bone markers such as TALP.
A Case Illustrating Similarities and Differences Between Calcific Uremic Arteriolopathy (CUA) and Non-Uremic Calciphylaxis (NUC)

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Introduction: CUA is a rare vasculopathy described in those with end-stage renal disease. NUC is an even less well-described clinical entity; one literature review identified 36 cases. The infrequency with which it is encountered renders NUC a diagnostic challenge.

Case Description: A 57 year-old female with diabetes and peripheral vascular disease was admitted for suspected above-the-knee amputation stump infection and subsequently underwent right hip disarticulation. Post-operatively, she developed a left thigh ulcer. A bedside skin biopsy was non-diagnostic. Due to clinical suspicion, the patient was taken to the operating room for a wedge biopsy that was diagnostic of NUC. The patient had no prior diagnosis of CKD and the GFR was only mildly low when adjusted for obesity and amputation. The patient was started on sodium thiosulfate (STS) and discharged. The patient was re-admitted a week later due to pain and lesion progression despite STS. Goals of care were revisited and she was ultimately discharged to hospice.

Discussion: NUC occurs in patients who have no or mild renal dysfunction. Risk factors include diabetes among others. This patient had no associated conditions except for uncontrolled diabetes since 2012. CUA and NUC both present with non-healing wounds, though CUA affects the trunk and NUC affects the extremities. One review of NUC cases demonstrated most patients had normal serum calcium (sCa) and serum phosphorus (sP). Pathophysiology is thought to be related to hyperphosphatemia, hypercalcemia, and hyperparathyroidism. This patient had no metabolic derangements besides mildly elevated sPhos, suggesting pathogenesis is more complex than current understanding.

Diagnosis of CUA primarily clinical, but in atypical scenarios a biopsy is necessary. This patient had classic features on biopsy including intramural calcification as well as positive Von Kossa. Sensitivity of biopsy can be low, related to limited specimen depth or the non-specific histologic findings of early disease, as in this case. Treatment is limited though one review demonstrated STS was associated with improved healing and mortality, though in this case lesions progressed despite STS. Physicians must maintain a degree of suspicion for calciphylaxis if characteristic lesions develop, even in the absence of renal impairment.

Too Much of a Good Thing: A Case of Hypercalcemia and Acute Renal Failure from Incorrect Dosing of Vitamin D Supplement

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Introduction: Hypercalcemia is known to cause acute renal failure through several mechanisms including renal vasoconstriction and volume depletion from nephrogenic diabetes insipidus. Here we describe a case of hypercalcemia and acute renal failure from incorrect ergocalciferol dosing that was treated effectively with IV fluids alone.

Case Description: A 55 year-old female with history of hypertension and type 2 diabetes presented to the emergency room with a week of progressive leg swelling, leg pain, and mild memory loss. Exam notable for mild hypertension and trace lower extremity edema. She was found to have a creatinine of 5.0 mg/dL (baseline <1 mg/dL), total calcium 12.5 mg/dL, and ionized calcium 6.76 mg/dL. On review of home medications, the patient noted being prescribed hydroxyvitamin D supplement by her primary care physician several months prior to admission. A family member brought her pill bottle from home, which confirmed a prescription for ergocalciferol 50,000 units daily. Subsequent hypercalcemia and AKI workup notable for vitamin D 25-OH level above assay at >96 ng/mL, vitamin D 1,25(OH)2 vitamin D 4 pg/mL, and PTH 4 pg/mL, as well as normal SSTR/UPP, CK, TSH, uric acid, and UA. The patient received 3 days of aggressive IV fluid resuscitation with gradual improvement in renal function and calcium level. Labs one month after discharge showed creatinine 1.29 mg/dL and total calcium 9.9 mg/dL.

Discussion: Vitamin D intoxication has been well described in children, but is being increasingly recognized as a cause of hypercalcemia in adults as well. As more attention is drawn to the significance of vitamin D deficiency, and with the cultural shift toward naturalistic therapies, patients are more likely to seek out and be prescribed vitamin supplements. This case describes a unique cause of hypervitaminosis D due to medication error and highlights the need for detailed medication reconciliation that includes vitamin supplements and over the counter medications, particularly given the multiple formulations of many of these drugs. Ergocalciferol has a half-life of around 2 weeks, and there is evidence to support the addition of bisphosphonates in the treatment of hypercalcemia from vitamin D intoxication. Effective strategies for the prevention to cause hypocalcemia, and this case is an example of effective therapy with IV fluids alone.

Calcific Uremic Arteriolopathy in a Patient with ESRD: A Case Report

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Introduction: Calcific uremic arteriolopathy (CUA), also known as calciphylaxis, is a rare but life-threatening condition that is characterized by progressive cutaneous ulceration associated with small- and medium-sized vessel calcification, occurring in patients with end-stage renal disease (ESRD) on renal replacement therapy. It is a rare condition, described in 1% to 4% of patients on dialysis, mainly in those with a history of diabetes mellitus, liver disease, and hyperparathyroidism. This patient had no metabolic derangements besides mildly elevated sPhos, suggesting pathogenesis is more complex than current understanding.

Case Description: We describe a case of a 42-year-old male, Filippo, known hypertensive, diabetic, a diagnosed case of chronic kidney disease secondary to diabetic nephropathy on hemodialysis three times a week for two years, who came in with severe progressive calciphylaxis in the form of a chronic painful non-healing necrotic wound on the glans penis. He was initially managed as a case of herpes zoster balanitis when he was seen in the emergency department for outpatient consult, but did not improve with oral acyclovir and oral antibiotics. Also noted in the second and third digit of his right hand, were non-healing ulcers and necrotic plaques. Calciphylaxis of Chronic Kidney Disease was considered based on clinical, laboratory and radiologic data. Goals of care and progression were discussed with the patient. He opted to be managed medically. His hemodialysis sessions were continued and intensified to four times a week, and he was started on sodium thiosulfate for IV x 1 hour starting the last hour of hemodialysis for three months. Other modalities utilized in the management of this case include hyperbaric oxygen therapy, and topical sodium thiosulfate. On follow-up, patient improved and is currently doing well on hemodialysis despite high mortality and morbidity seen in high patients with CUA.

Discussion: The pathogenesis of CUA is not well understood, but is thought to be due to vascular calcification leading to soft tissue necrosis that is usually described in patients with end-stage kidney disease on dialysis. Our patient had several predisposing factors for calciphylaxis, one of which had been present for a long time. Nonetheless, the immediate trigger for the acute worsening of calciphylaxis is unknown. Clinical diagnosis of CUA requires a high degree of suspicion.

Calcific Uremic Arteriolopathy (CUA)

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Introduction: CUA carries an extremely poor prognosis, mortality rate of at least 50%, and if coinciding with ulcerations, mortality may exceed 80%. Comorbid conditions increasing the risk of CUA include chronic kidney disease, time on dialysis, diabetes, obesity, secondary hyperparathyroidism and the use of calcium based phosphate binders, warfarin, iron and steroids. The disease usually presents as skin necrosis which can quickly become infected leading to multiorgan dysfunction, septic shock and death.

Case Description: This is a 57 y/o man with ESRD receiving thrice weekly hemodialysis/HD for five years, diabetes mellitus 2, atrial fibrillation receiving warfarin, chronic hyperphosphatemia with normal calcium and secondary hyperparathyroidism at goal for his stage CKD who presented with painful skin lesions compatible with CUA. Use of warfarin precluded obtaining a skin biopsy. Patient was treated with intensification of HD and sodium thiosulfate for nearly one year. Symptoms and skin lesions healed after one year of continuous therapy. After four years of follow up, there has been no evidence of recurrence.

Discussion: It is imperative for nephrologists to maintain a low threshold of suspicion for CUA and, for when to begin treatment. When possible, the diagnosis should be confirmed with tissue biopsy. There is no clearly defined treatment, but it is generally accepted to treat with sodium thiosulfate for at least three months which can be extended depending on the patients’ response. Any medications that can contribute to CUA should be stopped. Other therapies with variable rates of success include use of hyperbaric oxygen, parathyroidectomy, paradoxical use of steroids and bisphosphonates.
Severe Eryglycemic Diabetic Ketoacidosis Secondary to Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor: A Diagnostic Challenge

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Introduction: SGLT2 inhibitors are a relatively new class of antihyperglycemic agents that inhibit glucose reuptake in the kidney. These agents have been increasing in use likely due to favorable effects on glucose variability, weight loss and reduction of insulin doses as well as recent trials supporting their benefit in cardiac and renal disease patients. Of note, prior studies have shown very low risk of eryglycemic diabetic ketoacidosis (eDKA) associated with use of SGLT2 inhibitors. Rarity of this presentation makes it a diagnostic challenge. We report a case of severe eDKA in a hospitalized surgical patient in order to raise awareness.

Case Description: A 46 year old woman with type 2 diabetes was admitted for nectroizing soft tissue infection of the buttocks. Home medications included metformin, empagliflozin 25mg daily, and insulin glargine. Initial evaluation showed blood glucose of 329 mg/dL, creatinine 0.90 mg/dL increased from baseline 0.43 mg/dL, bicarbonate 25 mg/dL, and lactate 1.55 mmol/L. She was taken to debridement on admission and again two days later, while remaining primarily NPO and receiving minimal insulin. Post-operatively she was noted to have encephalopathy and worsening respiratory status found to have pH 7.22 and pCO2 <12 mmHg on arterial blood gas, bicarbonate <5 mmol/L, lactate 1.0 mmol/L, beta-hydroxybutyrate (BHB) 9.42 mmol/L (normal range 0.02-0.27 mmol/L), with blood glucose 115 mg/dL. Alcohol screen, salicylate, and acetaminophen levels were negative. She was diagnosed with eDKA and initiated on continuous intravenous insulin and lactated ringer’s with dextrose. Her acidosis resolved over the following 12 hours and bicarbonate returned to normal levels in 24 hours with BHB of 1.39 mmol/L. She did not receive empagliflozin during admission.

Discussion: Eryglycemic DKA is a serious medical condition. The rarity and atypical nature of this form of DKA makes it a diagnostic challenge. Risk factors associated with development of eDKA include infection, surgery, or decreased oral carbohydrate intake. SGLT2 inhibitors are gaining popularity, and a high index of suspicion is needed in caring for surgical patients on these agents. Monitoring anion gap and serum bicarbonate levels might be a better method of evaluating for DKA in such patients given eryglycemic state.

Recurrent Dialysis Disequilibrium in a Patient Receiving Inconsistent Hemodialysis

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Introduction: Dialysis disequilibrium syndrome (DDS) is characterized by transient neurologic symptoms during or immediately following a dialysis treatment. While nephrologists modify hemodialysis parameters in at-risk patients, the prevalence of DDS today is unknown, and peri-dialytic management of at-risk patients individually varies.

Case Description: A 68-year old patient presented to the emergency-room with her usual pre-dialysis symptoms of nausea and muscle cramps. She had received hemodialysis via right internal jugular tunneled dialysis catheter every 7-10 days since 2014, and was unable to obtain a dialysis home due to undocumented immigration status. Her pre-dialysis blood urea nitrogen level was 65 mg/dL. Upon completion of a 3-hour hemodialysis treatment with an ultrafiltration rate of 10 cGKg/hr, the patient became obtunded and non-responsive to name. She had had 4 prior episodes of obtundation post-dialysis without identifiable cause. Other past medical history was significant for hypertension, diabetes, hypothyroidism, coronary artery disease, and remote cerebrovascular accident. Her post-dialytic mental status represented a significant deviation from her baseline cognitive impairment per her family. On admission, the patient was afibrile and hemodynamically stable, with no acute changes in EKG, chest X-ray, and CT head. The serum lactate, WBC count, glucose, sodium, B12, TSH, and folate were normal. Her post-dialysis BUN was 23 mg/dL, representing a 65% reduction. Without further treatment, the patient’s mental status returned to baseline within 12 hours. In the absence of other explanation for her recurrent episodes of cognitive impairment after hemodialysis, the diagnosis of dialysis disequilibrium syndrome was applied.

Discussion: There are 47 published case reports of DDS. Amongst the 47 identified case reports, altered mental status/restlessness were most commonly reported (28/47). A 2012 survey of 232 practicing nephrologists found that over 50% had encountered at least one case of DDS within the preceding year, with 2% encountering more than 20 cases. DDS is likely under-reported and may be more common among patients receiving inconsistent hemodialysis. Therapy should always be tailored for high risk patients, and further investigations should explore if subclinical, recurrent DDS results in cognitive decline.
The “Double-Line” Sign to Identify Perirenal Fat Pad: A Must-Know

**Introduction:** Perirenal fat is a fat pad located in the retroperitoneal space surrounding the kidney. As nephrologists performed point-of-care ultrasonography (POCUS) is on the rise, it’s important to be aware of this structure for two reasons: 1. It can mimic free fluid in the Morrison’s pouch and also subcapsular hematoma, which is particularly important when performing POCUS after a kidney biopsy 2. Recent epidemiological studies have shown that perirenal fat is a risk predictor for Cardiovascular disease, and it may turn out to be a promising target in the management of these patients. The ‘double-line’ sign we describe here can aid in the identification of this structure.

**Case Description:** A 52-year-old gentleman on maintenance hemodialysis was noted to have elevated hemoglobin (15 mg/dL) in the absence of erythropoietin stimulating agent therapy. A renal sonogram was performed to screen for renal mass/renal cell carcinoma as the potential etiology for elevated hemoglobin, which demonstrated hypoechoic, sharply demarcated area in the perirenal area bilaterally mimicking intraperitoneal free fluid in addition to small kidneys with thin parenchyma. However, no intervention was undertaken because of the striking ‘double-line’ sign suggestive of perirenal fat pad bilaterally.

**Discussion:** Cardiac-renal ascites formation may represent a challenge to remove in those with coexisting severe heart failure and ESRD. Ascites fluid accumulation represents the hemodynamic “sinkhole” for patient with cardiac ascites and may be difficult to mobilize these during conventional HD. Plastic catheters in the blood stream are more likely to cause bacteremia than those placed in visceral surfaces (pleura, abdominal cavity). In those ESRD patients with cardiac and cirrhotic ascites, who cannot perform dialysis at home, with more frequent hemodialysis (HD; x4/week) but he experienced recalcitrant ascites (developed abdominal distension that plaques into the abdominal cavity (PleurX drainage system), originally designed for repeated evacuation of pleural fluid accumulation), 4 months after HD initiation. Tolerability of HD improved and peripheral edemas well-controlled thereafter. Home health monitors his care and performs dialysis at least x3/week. Exit site infection completed with local gentamycin cream and no interval peritonitis was observed so far (9 months).

**Conclusion:** Perirenal anechoic to hypoechoic structure surrounded by two hyperechoic bright lines (Figure-inset) constitutes this sign, where these echogenic lines are caused by fascial planes surrounding the kidney. Moreover, the fat pads typically contain low-level echoes within the hypoechoic region, unlike fluid and move with the kidney as it changes position during respiration. It may be difficult to distinguish this structure from post kidney biopsy subcapsular hematoma, but visualization of bilateral double-line sign favors fat pads.

PUB487

The Utility of Renal Replacement Therapy in Hepatic Encephalopathy

**Introduction:** Severe liver failure may cause the brain to swell, leading to significantly altered sensorium. In the treatment of these patients, we utilize the ability of the gastrointestinal system to clear ammonia. However, we often come across patients who do not respond to this regimen. In this case, our patient was somnolent requiring intubation because of the striking ‘double-line’ sign suggestive of perirenal fat pad bilaterally.

**Case Description:** A 58-year-old male who has a history of cirrhosis with portal HTN who presented with shortness of breath and cough for 2 weeks. He was initially admitted for COPD exacerbation. He developed further worsening respiratory failure requiring intubation and antibiotic therapy. CT chest revealed left upper lobe pneumonia and respiratory viral panel came back positive for H1N1 so he was started on Tamiflu. His physical examination off sedation included no purposeful movements and not following commands so he continued to be intubated. Ammonia level returned at 229. He received lactulose enema, lactulose 20mg QID, and rifaximin 500mg BID through orogastric tube. Given his minimal response and rising ammonia levels, CRRT was started.

**Discussion:** Post-renal dialysis, his abdomen became increasingly distended and rigid. Abdominal X-rays revealed subcapsular coilous. Retching was placed for colonic decompression. Lactulose was switched to Miralax QID and he received another CRRT session. The following day, he had increasing output from his rectal tube. Serial abdominal X-rays revealed decreasing colonic distention. He was extubated and started to communicate, eat by mouth and eventually transferred to the floor.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Ammonia Clearance in Acute Liver Failure with Continuous Venovenous Hemodialfiltration
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Introduction: Hyperammonemia in acute liver failure and inborn errors of metabolism can cause life-threatening cerebral edema. While intermittent hemodialysis clears ammonia more rapidly, continuous renal replacement therapy (CRRT) is often used in acute liver failure due to hemodynamic instability and rebound of ammonia levels. We present the first case of severe ammonia clearance measured using the Cordoba equation in continuous venovenous hemodialfiltration (CVVHDF). In a patient with acute liver injury and hyperammonemia.

Case Description: A 27-year old previously healthy Hispanic man with alcohol overdose presented with one week of malaise, abdominal pain, and confusion after taking acetaminophen overdosage. Physical exam was notable for tachycardia, hypotension, asterixis, scleral icterus, and laboratory studies were remarkable AST and ALT > 6000U/L; total bilirubin 9.1mg/dl; INR 6.3; ammonia 107µmol/L; and serum creatinine 4.7mg/dl. Urine microscopy revealed multiple tubular epithelial casts and head CT showed diffuse sulcal narrowing. Diagnosis of grade 3 hepatic encephalopathy due to intracranial edema from hyperammonemia due to acute liver failure complicated by oliguric acute tubular necrosis was established, and the patient was listed for liver transplantation with a MELD of 40. CVVHDF was initiated on hospital day 1 with a total effluent of 33mL/kg/hr was delivered (12mL/kg/hr dialysis and 21mL/kg/hr ultrafiltration). On hospital day 3, after 36 hours of continuous hemodiafiltration, serum ammonia was 77µmol/L, effluent ammonia was 19µmol/L, and hourly effluent was 2700mL. Using the Cordoba equation, we calculated ammonia clearance of 11mL/min. The patient’s acute liver failure resolved without need for transplantation from hyperammonemia. He was transitioned to intermittent hemodialysis on hospital day 4, and achieved renal recovery becoming free from renal replacement therapy on hospital day 13. His most recent serum creatinine is 0.8mg/dl.

Discussion: In this case of hyperammonemia, ammonia clearance was modest despite delivering an effluent volume that exceeded KDIGO practice guidelines. Given the increased attention that CRRT is receiving for treatment of hyperammonemia, the need for improved work is needed to determine the optimal dose and method of CRRT in such instances.

Utility of Procalcitonin (PCT) and Brain Natriuretic Peptide (BNP) in a Patient on Hemodiafiltration (HD)
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Introduction: In the general population, PCT and BNP are used to assess likelihood of bacterial infection and volume overload based on absolute values above 100µg/mL and 0.08ng/mL respectively. Baseline values are elevated to a variable degree and both markers are cleared by high-flux dialysis membranes commonly used in the acute care setting resulting in ambiguity interpreting the meaning of PCT and BNP levels. We present a case showing their utility in resolving diagnostic uncertainty.

Case Description: An 84-year-old man was hospitalized for four weeks of worsening ascites, cough, and dyspnea. His initial BNP level was 1211pg/mL and PCT was 0.40ng/mL. Chest x-ray (CXR) showed pulmonary vascular congestion, bilateral pleural effusions and lower lung opacities. With large-volume paracentesis and ultrafiltration via hemodialfiltration, his symptoms improved. On day 6, dyspnea worsened and mental status declined. CXRs were unchanged from baseline. Ultrafiltration was increased with minimal improvement. A repeat PCT level on day 8 was 0.73µg/mL, and he developed fever; chest CT revealed multifocal consolidation, and his respiratory and mental status improved with antibiotics.

Discussion: Interpretation of PCT and BNP can be challenging in patients with CKD treated by hemodialfiltration in the acute setting. The numerous potential causes of dyspnea in our patient created diagnostic uncertainty. Trends in the levels of PCT and BNP helped narrow our differential diagnosis improving our ability to successfully manage our patient.

Carbamazepine Intoxication and Role of Dialysis
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Introduction: Carbamazepine (CMZ) at therapeutic levels is highly albumin bound. Acute liver failure due to hemodynamic instability and rebound of ammonia levels. We present the first case to our knowledge measuring the clearance of ammonia using arterial ammonia concentrations (CVVHDF) in a patient with acute liver injury and hyperammonemia.

Case Description: A 26-year-old female with 12 weeks of gestation was admitted with intentional carbamazepine overdose. She was severely encephalopathic with GCS of 6 on arrival. She was having seizures refractory to treatment and required intubation for airway protection. She was hemodynamically unstable needing vasopressor support. CMZ levels were found to be above the assay limit (40.3µg/microgram/ml) on serial measurements at our lab. Normal reference range of 4.0-10 microgram/ml. After evaluation and literature review we started her on sustained low efficiency dialysis (SLED). After 10 hours of SLED, CMZ levels were lowered to a measureable levels. Levels for CMZ and its active metabolite were sent from the dialysis effluent. She continued to show clinical improvement and normalization of hemodynamic stability and improved neurological status. She was extubated. Clearances of CMZ and its metabolite CMZ-E were found significant supporting the available limited data for use of extracorporeal therapy including SLED.

Discussion: Despite the scarce clinical evidence for high protein bound drugs like carbamazepine our experience supports use of extracorporeal removal in severe poisonings. Our case adds to the limited literature available for role of extracorporeal therapy for severe CMZ poisoning. It essentially means that non-protein-bound drug was eliminated which helped in eventually decreasing the toxic levels of CMZ.

First Report of Short Bowel Syndrome Complicated with Uremia
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Introduction: Patients with short bowel syndrome (SBS) often suffer from water-electrolyte disturbance, nutritional malabsorption, doing to shortened intestine. Some of the patients subsist largely on parenteral nutrition. Hemodialysis is main treatment of uremia, during which the excess water and electrolytes of the body are removed together with uremic toxins. SBS complicated with uremia is very rare. The treatments of the two diseases always conflicting. There is no relevant literature for reference.

Case Description: The patient was a 36-year-old woman with a 20-year history of Crohn disease who had undergone nine times intestinal resections and less than fifty centimeters residual intestinal, subsisted largely on parenteral nutrition now. Long-term chemotherapy and radiation treatment, she got the chronic renal failure half year ago, when she had no choice but to start the hemodialysis treatment. With low body weight(38kg),low blood pressure(85/43mmHg), hypo-albuminemia (30.4g/L), plenty of parenteral nutrition solutions, it was hard to evaluate the ultrafiltration volume. With very low serum phosphorus(0.04mmol/L), calcium(1.89mmol/L), PTH(3.98pg/ml), and active VD3(4.8ng/ml), she suffered with severe bone pain always. Meanwhile, long-term use of peripherally inserted central catheter (PICC), there was no conditions to establish conventional dialysis access. A specialized physician team established for the patient. The patient was treated on hemodialysis to achieve hemodynamic stability and necessary guidance of chronic kidney disease, to provide right dosage of energy, protein, liquid, and electrolytes intake of HD status. Real-time monitoring of blood gas analysis during hemodialysis, timely replenishing glucose and electrolytes, maintaining the balance of acid-base, water and electrolyte. Supplemented erythropoietin, trace elements, and intravenous active vitamin D3 to improve uremia metabolism. At the same time, we take the vein cuffed venous catheter was use for transition, we created the left forearm ulnar side arteriovenous fistula (AVF) as permanent vascular access. Now the nutritional status, uremia complications, and life quality of the patient improved significantly.

Discussion: Short bowel syndrome complicated with uremia is very rare. It is not only necessary to prevent the complications of continuous use of parenteral nutrition support, but also to intervene the complications related to maintenance hemodialysis.

Using Intermittent and Continuous Venovenous Hemodialfiltration to Treat Hyperammonemia in Acute Liver Failure
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Introduction: Hyperammonemia with levels >200µmol/L is usually associated with poor neurologic outcomes and death. The primary goal of renal replacement therapy (RRT) is to reduce blood ammonia concentration and achieve resolution of neurological symptoms. Although RRT has been used to treat hyperammonemia in neonates with inborn errors of metabolism, its use in adults is poorly studied. We present a case of severe hyperammonemia due to acute liver failure secondary to hepatitis A.

Case Description: A 70-year-old male with history of CAD and HTN was transferred from another hospital with jaundice and altered mental status secondary to acute liver failure. Labs were significant for creatinine of 3.26mg/dl, INR 8.20, Bilirubin 11.8mg/dl; AST/ALT of 7167/9544U/L. Ammonia level was 540µmol/L. Serology showed positive Hepatitis A IgM. CT head was negative for cerebral edema. He was started on intermittent hemodialysis (IHD) emergently started by CVVHDF. Ammonia levels dropped post IHD from 540 to 320 and <100 within 72 hours. His mental status initially worsened but improved after 2 days. Unfortunately, his hospital course was complicated by septic shock.
and ischemic colitis. He went into cardiac arrest after subtotal colectomy and was made comfortable. He passed away on day 9 with a potassium level <10 mmol/L on CVVHD.

Discussion: Ammonia is similar to urea in terms of its clearance; hence both IHD and CRRT are effective in removing it. The longer ammonia remains elevated, the higher the chance of mental impairment. IHD is considered a preferred modality as it decreases ammonia concentrations rapidly. CRRT has been used successfully with this condition to prevent ammonia rebound. Our patient presented with very high ammonia levels, hence we started IHD to decrease the ammonia level rapidly followed by CRRT. He responded well within 48 hours with this method. His ammonia level remained less than 100 mmol/L subsequently. Currently, there is limited data regarding which modality to use in adult patients with hyperammonemia. More studies are needed to assess the efficacy of hemodialysis in these patients.

PUB495

Hypertension on Dialysis: It’s Not Always Hypovolemia

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Introduction: Hypersensitivity reactions (HSR) to dialysis filters are rare and can be challenging to diagnose. Here, we describe a case of Type A HSR secondary to a polysulfone (PS) filter on continuous renal replacement therapy (CRRT).

Case Description: A 66-year-old male with NYHA IV heart failure and stage III chronic kidney disease presented for elective placement of a left ventricular assist device (LVAD). Initial creatinine was 1.69 mg/dL. Post-operatively, he developed sustained ventricular tachycardia leading to anuric AKI & hyperkalemia. CRRT with ultrafiltration (UF) was initiated. He tolerated it for 30 minutes and then the circuit clotted. Within 2 minutes of restarting, mean arterial pressure (MAP) dropped to 30 mmHg from 65 mmHg with hypoxemia, needing intubation. It was stopped and the MAP improved spontaneously. A third attempt of CRRT with no UF again resulted in hypotension and cyanosis within 30 seconds despite pre-emptively increasing vasopressors and giving crystalloids. Relevant labs include a low C3, normal C4 & tryptase, and no eosinophilia. CRRT was immediately stopped and extracorporeal blood not returned. We switched to a cellulose based filter with concerns for HSR to the PS filter. Our CRRT machines were incompatible with other filters, so intermittent hemodialysis (IHD) with blood & dialysate flows of 200ml/min & 400ml/min respectively with a cellulose filter was done successfully. Further HD sessions with cellulose filters had no issues.

Discussion: Our case describes a Type A HSR to PS dialysis filters with resolution after switching to a cellulose filter. HSR on dialysis was reported in 4/1000 sessions of dialysis per year for synthetic membranes and can be associated with dyspnea and hypotension. Type A reaction is immediate and takes place within 5 minutes to 2 hours. It’s often linked to a sterilizing agent ethylene oxide and AN-69 dialysis membranes in patients on ACE-Inhibitor which he wasn’t on. Recent reports highlight other substrates, like PS membrane, as an important but under recognized cause of HSR. Hypersensitivity can be mediated by Immunoglobulin E or complement activation. Management includes; not returning blood and dialysate flows of 200ml/min & 400ml/min respectively with a cellulose filter was done successfully. Further HD sessions with cellulose filters had no issues.

PUB496

Nephrology Team Leading Molecular Adsorbent Recirculation Therapy (MARS) Therapy: Case Reports

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Introduction: Acute liver failure (ALF) from any cause has an extremely high mortality and sometimes liver transplantation is the only final treatment. Molecular Adsorbent Recirculation System (MARS) lead by Nephrology has been successfully used in two patients as a bridge to full recovery and liver transplantation respectively.

Case Description: 1) 34 Year old Female presented with nausea, vomiting, with labs significant for AST 15,785 U/L, ALT 10,888 U/L, Total Bilirubin 17.4 mg/dL, INR 2.32. Diagnosed with ALF due to Acute Hepatitis B, was started on N-Acetylcysteine, Lactulose, Rifaximin and Tensilon 24 hrs into admission her mental status worsened requiring intubation. CT showed cerebral edema. Decision was made to start MARS to remove toxins and help liver in regeneration by improving microenvironment. Received 56 hrs total of MARS therapy for four days. Bilirubin improved from 25.27 mg/dL to 9.5 mg/dL, mental improvement and was eventually discharged. 2) 28 yr old Male admitted for ALF secondary to alcohol intoxication. Labs were significant for AST >7000 U/L, ALT >7000 U/L, Bilirubin 8.41 mg/dL, Lactate >15 mmol/L. Due to lack of spontaneous recovery and worsening clinical condition he has been started on MARS therapy and listed for Liver transplantation with a wait time of 48 of MARS therapy. During his stay, several issues complicated his postoperative course. He is currently waiting long term re hab placement for continued recovery.

Discussion: MARS is a potential lifesaving therapy in selected patients. A multidisciplinary team is required to provide this extracorporeal therapy and nephrology should take the lead.

PUB497

Dialysis Disequilibrium Syndrome Despite Standard Preventive Measures

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Introduction: There have been very limited cases of dialysis disequilibrium syndrome (DDS) reported in recent literature. Compared to the 1970s and 1980s, our patients are admitted with a lower Blood Urea Nitrogen (BUN) concentration. Standard preventive recommendations for the first dialysis sessions have limited the incidence of DDS significantly. As a result, cerebral edema and brain herniation have become rare entities.

Case Description: Our patient is a 54-year-old female with hypertension, CKD stage 4 who presented with 2 weeks of fever, generalized weakness and shortness of her breath. Blood pressure (BP) was 194/137. She was lethargic with asthenia. Lung exam revealed crackles. Her sodium was 131 mEq/L, potassium 4.5 mEq/L, bicarbonate 21 mEq/L, BUN 191 mg/dl, creatinine 16.6 mg/dl. Chest computed tomography (CT) had multifocal pneumonia with pulmonary edema. Dialysis was started for 2 hours with F16 dialyzer, blood flow of 250ml/min and dialysate flow of 500 ml/min. Within 5 minutes of dialysis, she became unresponsive and her systolic BP dropped to 98. The session was stopped immediately. Her mental status and her blood pressure improved in the afternoon but worsens in the evening. Dialysis was started overnight with the same prescription. She tolerated the procedure well until her blood pressure rose to the 200’s and she became unresponsive. She was disconnected 90 minutes later. Head CT showed cerebellar edema and tonsillar herniation. Calculated serum osmolality change pre and post dialysis was 27 mmol/L. Neurology diagnosed her with Posterior Reversible Encephalopathy Syndrome.

Discussion: DDS is a very rare complication of dialysis. Established protocols usually provide preventive outcomes. This case is an important reminder that standard preventive recommendations may not be sufficient. Our patient had a complex presentation and did not benefit from the recommended measures. This syndrome has also been reported with continuous renal replacement therapy. Female patients were preexisting neurological conditions and HSR are more than 175 mg/dl are more prone to this condition. In this high-risk population, the use of one of the smallest dialyzers such as F3 with a lower than the recommended blood flow and dialysate flow rate might have a more desirable outcome.

PUB498

Addressing Social Determinants of Health in Haitian-American Patients with ESRD

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Introduction: African Americans with ESRD have higher rates of morbidity and mortality compared to their white counterparts. Additionally, social determinants of health (SDOH) such as race, class, and income are often associated with health outcomes. Therefore, it is crucial to address SDOH to improve patient outcomes. Our study aimed to understand how addressing the SDOH affect morbidity and mortality.

Case Description: African Americans with ESRD have higher rates of morbidity and mortality. Social determinants of health (SDOH) are contributory as these create obstacles to attaining healthcare, legal assistance, appropriate nutrition, financial stability, employment, education. We compare interventions for patients with ESRD on hemodialysis in the setting of an interdisciplinary Neighborhood outreach program (NHELP). We aim to understand how addressing the SDOH affect morbidity and mortality.

Discussion: African Americans with ESRD have higher rates of morbidity and mortality. Social determinants of health (SDOH) are contributory as they create obstacles to attaining healthcare, legal assistance, appropriate nutrition, financial stability, employment, education. We compare interventions for patients with ESRD on hemodialysis in the setting of NHELP. We aim to understand how addressing the SDOH affect morbidity and mortality.
Cefepime-Induced Neurotoxicity in a Peritoneal Dialysis Patient: An Increasingly Common Scenario
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Introduction: Cefepime is a generally well-tolerated antibiotic used for a variety of infections. Neurotoxic effects, including nonconvulsive status epilepticus (NCSE), have been described and are typically seen in patients with renal dysfunction or end-stage renal disease (ESRD) receiving high doses. While up to 70% of a given cefepime dose is removed with hemodialysis (HD), the clearance is reduced to only 25% with peritoneal dialysis (PD). We present a case of cefepime-induced neurotoxicity in a PD patient requiring treatment with temporary HD.

Case Description: An 80-year-old man with multiple system atrophy and ESRD on PD presented to our hospital with a decreased level of consciousness (LOC), found to have urinary retention. Empiric treatment for a complicated urinary tract infection was started with cefepime 1 g every 24 hours. On day 3, the patient developed aphasia and myoclonic jerks with further decline in alertness. An electroencephalogram (EEG) was performed demonstrating triphasic discharges suggestive of toxic encephalopathy. Despite 2 days of continuous peritoneal dialysis, his mental status remained poor. Cefepime was deemed the most likely culprit and on day 6, HD was pursued for increased drug clearance. HD was performed for 3 consecutive days with improvement in mental status after the first session and return to baseline after the third.

Discussion: The neurotoxic effects of beta-lactams have been attributed to gamma-aminobutyric acid antagonism leading to diminished LOC, myoclonus, and NCSE. The cefepime dosage error seen in this case was likely a preventable event because many providers are not aware of the poorer drug clearance this diazylia modality may provide. Further, even when pharmacy oversight measures are in place, cefepime is not typically included in the list of monitored medications. Our institution has approved alternate broad-spectrum antibiotics (e.g., piperacillin-tazobactam) for use in the intensive care unit for patients with ESRD in hopes of reducing the incidence of cefepime-induced neurotoxicity. Meanwhile, HD remains the modality of choice for recognized cases.

Hernia Repair and Peritoneal Dialysis: A Case Report of Successful Perioperative Management in Peritoneal Dialysis at a Veterans Hospital by an Interdisciplinary Team
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Introduction: Inguinal hernia is a common complication of peritoneal dialysis (PD). It is a usual practice in the United States to transition PD to hemodialysis (HD) for hernia repair due to concern for dialysate leak and hernia recurrence, despite recommended protocols to continue PD without this transition in appropriate patients. There are few reports of successful use. We report the first case of elective inguinal hernia repair in a continuous cycling PD (CCPD) patient using a personalized protocol at the Veterans Hospital.

Case Description: The patient is a 62-year-old African American man with a past history of hypertension, congestive heart failure, and end-stage renal disease (ESRD) on PD since 1 year. He was diagnosed with right inguinal hernia and planned for elective mesh repair. The patient expressed his wish of not wanting to switch to HD unless absolutely required. Multidisciplinary liaisons including the primary nephrologist, surgery team, renal dietician, PD nurse, and the patient’s family worked out a modified, personalized version of the published protocols. The patient agreed that if there were any issues needing the transition during this period he would be switched to HD. The patient had right inguinal repair with large prolene hernia system mesh early March and discharged the same day. Labs were done every 3 days to assess the need for dialysis. The PD nurse closely followed the patient with daily phone calls to assess functional status. We were able to implement the above protocol successfully without requiring to switch the patient to HD and without extending the hospital stay. His post-op course was complicated by hyperkalemia (potassium ranging from 5.2-6.0) due to poor diet compliance. The renal dietician revisited the prior advised diet modifications. Potassium returned to normal with medical management and diet control.

Discussion: Though there is literature on successful maintenance of PD during perioperative management, there are few published reports. The use of recommended protocols is not robust. From our knowledge, this is the first case report at a Veterans hospital in the USA; our case demonstrates a successful modification of protocols for the US population with an interdisciplinary team approach, with no increase in the hospital stay.

Severe Polymicrobial Peritonitis with a Successful Outcome
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Introduction: Polymicrobial peritonitis involving gram negative organisms is considered a serious complication of peritoneal dialysis and catheter removal might be warranted in refractory cases. We present a unique case with recent initiation of peritoneal dialysis who developed severe polymicrobial peritonitis.
Case Description: A 53-year-old female was recently diagnosed with end-stage renal disease and started on continuous cycling peritoneal dialysis (CCPD) one month ago. She presented with severe abdominal pain, vomiting, and constipation. Pertinent clinical findings included tachycardia and diffuse abdominal tenderness. Initial peritoneal fluid analysis showed leukocyte count 86,325 cells/μL with 92% segmented cells. On first day, intraperitoneal fluid (IP) ceptefine and linezolid were administered, but IP 350 mOsm/kg and calculated osmolality was 222 mOsm/kg, both too low to cepetphone. CCPD using tidal setting, intraperitoneal (IP) ceftipime (both daily loading and maintenance doses), and IP heparin 500 units/L in all PD bags were undertaken. Over the next five days, the patient demonstrated clinical improvement and peritoneal fluid leukocyte count decreased to 5748 on day five and 387 on day seven. The patient was discharged home on CCPD and daily IP ceftipime in long dwells. Admission of four weeks of intraperitoneal antibiotic the patient is free of symptoms and tolerating CCPD well.

Discussion: This case was unique because of the complexity of peritonitis in terms of severe abdominal discomfort, unusually high leukocyte count, and identification of two gram-negative bacteria. Following initial intravenous antibiotic administration, PD fluid WBC count markedly rose but IP antibiotics using both daily loading and maintenance doses in this patient who is new to dialysis with significant residual renal function was successful. Tidal CCPD facilitated management of patient’s discomfort and continue PD. It was critical to thoroughly evaluate the patient for surgical indications and prudently manage peritonitis.

PUB504
Hemodialysis Catheter-Induced Air Embolism
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Introduction: Air embolism is one of the fatal complication associated with central line. In a dialysis patient it is less common but if it occurs it can be life threatening. Air can enter blood vessel through the dialysis catheter or through the blood pump due to a negative pressure in circuit. This complication is relevant to field of nephrology as it is a complication of use of central venous catheters with dialysis (1). We hereby report a case of paradoxical air embolism due to air entry from hemodialysis catheter.

Case Description: 72-year-old female with a history of end stage renal disease on home hemodialysis, was found unresponsive while on dialysis with a detached catheter. Work up showed, pneumocephalus, air embolism leading to acute stroke and cerebral edema. Echocardiogram showed intracardiac shunt. Finally, the patient died.

Discussion: This case illustrates the dreadful complication associated with dialysis catheter. Recognition of this complication is important to prevent air embolism by taking appropriate preventive measures while handling dialysis catheter and also to provide education to health care provider, patient about this complication. With improvements in dialysis technology the risk is reduced but sporadic cases are reported (2). There is paucity of data on management of air embolism, and preventive measures along the recognition of the complications are essential. Reference Sherman RA; Douglas JS. Handbook of dialysis 5th edn. Hysell MK: ‘Cerebral air embolism after hemodialysis’ J Emerg med 2015; 49

PUB505
Hyperglycemia-Induced Hyponatremia: A New World Record?
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Introduction: We present a case of hyperglycemia-induced hyponatremia, with a serum glucose value greater than the upper limit of laboratory detection. This poses a unique management challenge. When is this approach to hyponatremia without a definitive measurement of serum glucose? The Guiness World Record for the highest serum glucose is 2,656 mg/dL—does our patient hold a new world record or is this a laboratory error?

Case Description: A 39-year-old male with IV HAART and Diffuse B-Cell lymphoma on R-EPOCH chemotherapy was admitted to the ED for intractable nausea and vomiting of one week’s duration with accompanying significant weight loss. History revealed he had had a recent PET scan at an outside facility showing a gastric mass surrounding the pylorus and he was thus determined to have metastatic GOO. ABG revealed severe metabolic acidosis 7.68/49/66 with a bicarbonate of 46 with an acute kidney injury. Infranormal normal saline with potassium replacement and pantoprazole was given and his alkalemia was measured.

Discussion: When opting for medical management in patients with true arterial volume depletion treatment typically begins with intravenous normal saline. Sodium, Chloride, and Potassium (replenishments) should correct hypokalemia and increase intravascular volume (3). Meanwhile, H2 blockers or proton pump inhibitors help curb nausea and decrease the quantity of HCL lost in the vomits.1 In select patients with poor kidney function and in whom increasing urinary bicarbonate output with acetazolamide is not feasible, acid infusions (ex: hydrochloric acid) can be cautiously considered. If the aforementioned measures fail and if there is no way to excrete acid in the urine, then dialysis is the best option. Beyond a certain point alkalemia (pH >7.65) becomes a medical emergency and carries a high risk of complications.2 Despite the severity, a cutoff of when to choose to dialyze remains elusive. A survey of 25 Yale-affiliated nephrologists revealed that only 4 of 25 elected to use dialysis for patients with severe metabolic acidosis.3 When choosing a dialysis duration—bicarbonate dilution is performed as it rapidly impacts alkalemia. In our patients’ case, correcting the underlying cause is the best approach to permanently reverse his alkalemia.

PUB506
Management of Severe Metabolic Alkalosis in a Patient with Intractable Vomiting
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Introduction: Gastric secretion of hydrogen chloride is normally neutralized by bicarbonate secreted by the pancreas, liver, and intestine. Gastric output dilution (GOD) may cause intractable vomiting with potentially life-threatening metabolic derangements including hypochloremic, hypokalemia, metabolic alkalosis. Prompt recognition and management is critical, however the decision if-when to dialyze a patient remains somewhat controversial.

Case Description: A 39-year-old male with HIV on HAART and Diffuse B-Cell lymphoma on R-EPOCH chemotherapy was admitted to the ED for intractable nausea and vomiting of one week’s duration with accompanying significant weight loss. History revealed he had had a recent PET scan at an outside facility showing a gastric mass surrounding the pylorus and he was thus determined to have metastatic GOO. ABG revealed severe metabolic acidosis 7.68/49/66 with a bicarbonate of 46 with an acute kidney injury. Infranormal normal saline with potassium replacement and pantoprazole was given and his alkalemia was measured.

Discussion: When opting for medical management in patients with true arterial volume depletion treatment typically begins with intravenous normal saline. Sodium, Chloride, and Potassium (replenishments) should correct hypokalemia and increase intravascular volume (3). Meanwhile, H2 blockers or proton pump inhibitors help curb nausea and decrease the quantity of HCL lost in the vomits.1 In select patients with poor kidney function and in whom increasing urinary bicarbonate output with acetazolamide is not feasible, acid infusions (ex: hydrochloric acid) can be cautiously considered. If the aforementioned measures fail and if there is no way to excrete acid in the urine, then dialysis is the best option. Beyond a certain point alkalemia (pH >7.65) becomes a medical emergency and carries a high risk of complications.2 Despite the severity, a cutoff of when to choose to dialyze remains elusive. A survey of 25 Yale-affiliated nephrologists revealed that only 4 of 25 elected to use dialysis for patients with severe metabolic acidosis.3 When choosing a dialysis duration—bicarbonate dilution is performed as it rapidly impacts alkalemia. In our patients’ case, correcting the underlying cause is the best approach to permanently reverse his alkalemia.
Fanconi Syndrome and Hypomagnesemia: An Overlooked Association or Diagnostic Entity?
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Introduction: Fanconi’s Syndrome is associated with hypophosphatemia, aminouiciduria, and renal glycosuria. However, there is significant variability in the phenotypical presentation of this disease process. Time to diagnosis and length of underlying etiologies such as multiple myeloma or medications can play a role in the presentation, specifically between acquired and congenital Fanconi’s Syndrome. Though typically not considered a classic association with Fanconi’s Syndrome, hypomagnesemia is occasionally noted in the literature in association with this disease and seems to be an underrecognized feature of this entity.

Case Description: A 65 year old female with history of recently diagnosed multiple myeloma (2 months prior), hypertension, and previously treated hypercalcemia now hypocalcemic presented with carpo-pedal spams. One month prior she was treated with cyclophosphamide, bortezomib, dexamethasone, and denosumab. Corrected calcium was 6.2 mg/dL, bicarbonate 16 mEq/L, potassium 2.4 mEq/L, chloride 112 mEq/L, magnesium 1.3 mEq/L, phosphorus 1.3 mg/dL, anion gap 15, and creatinine 1.42 mg/dL with AKI with a baseline of 0.6 mg/dL. Urine bicarbonate was 8 in the setting of acidosis. Fractional excretion of magnesium was 28% in the setting of hypomagnesemia. Urine anion gap was 20, pH of the urine 8.0. No glucosuria. TTKG was 4.75 indicating potassium losses in the setting of hypokalemia. Aminouiciduria was present. With these findinds, the diagnosis of Fanconi’s Syndrome Renal Tubular Acidosis Type II in association with Multiple Myeloma was made. Oral replacements of electrolytes and Amiloride were started, with stabilization of electrolytes.

Discussion: Though hypomagnesemia is not classically noted as an association with Fanconi’s Syndrome, such as glucosuria, aminouiciduria, and hypophosphatemia, it appears to be an under-recognized feature of this disease process. As stated in the limited literature with this association, there is cellular injury at the neuron primarily at the proximal tubular cells impairing passive reabsorption of magnesium in Fanconi’s Syndrome. Underestimating this electrolyte disorder in this syndrome may better allow future clinicians to recognize hypomagnesemia in the setting of a non-anion gap metabolic acidosis and perhaps be considered as a diagnostic entity.

Hypokalemic Periodic Paralysis in Sjogren Syndrome
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Introduction: Renal involvement in Primary Sjogren’s syndrome is a rare event usually occurs in less than 10% of the patient and usually has a favorable prognosis. Renal involvement may include isolated electrolyte disorders, nephrolithiasis, nephrocalcinosis, hypokalemic periodic paralysis, proximal tubular nephropathy, tubulointerstitial nephritis. We report a case of periodic paralysis due to severe hypokalemia secondary to Distal Renal tubular acidosis (dRTA), with primary disease as Sjogren’s syndrome.

Case Description: A 50 year old hypertensive male, presented with complaints of general body weakness for the past 4 weeks, with complaints of intermittent left flank pain. There was no history of any Urinary abnormalities, Gastrointestinal, Respiratory, or any history of autoimmune features. The only medicine, which the patient was taking, was allopurinol for his HTN. On examination the only significant findings were decreased peripheral pulses, hypertension, normal reflexes and normal sensory system. Basic metabolic panel revealed Normal complete blood count (CBC), with normal renal function tests and liver function tests. Serum electrolytes revealed potassium of 1.9 mEq/dL, Sodium 136 mEq/dL, Chloride 116 mEq/dL, Bicarb levels 10 mEq/L, Calcium 9.7 m/g/dL, Magnesium 2.1 mg/dL, normal serum anion gap, urinalysis revealed pH of 8, with no proteinuria or active urinary sediment. Extractable Nuclear Antigen Antibodies (ENA) profile revealed Anti nuclear antibodies titer of 1:320, ANIT SS-B (La) and ANIT Ro-52 antibodies were strongly positive. Complement levels were normal. 24 Hrs Urinary potassium levels were 32.34 mmol/24 Hrs and the urinary anion gap of 40 mEq/L. Ultrasonogram reveals 2 calculi in the lower pole, with mild hydronephrosis. Laboratory investigations were consistent with diagnosis of Primary Sjogren’s syndrome with dRTA. We replated the patient with intravenous potassium chloride and bicarbonate, with subsequent shift to oral potassium citrate which markedly improved the patients symptoms. The patient was referred to Rheumatologist for further management.

Discussion: Primary Sjogren’s syndrome as with most rheumatologic diseases is more common in females, male presenting with renal involvement is scarcely reported to the best of our knowledge. Further diagnosing primary Sjogren’s without any clinical symptoms (i.e. xerostomia, or xerophthalmia) is a rare entity.

Normal Saline Mitigates Refractory Alkalosis in Continuous Renal Replacement Therapy
Anu Rajasekaran, Ashita J. Tolwani. University of Alabama at Birmingham, Birmingham, AL.

Introduction: Respiratory alkalosis is typically a sign of an underlying pulmonary or central nervous system disease. Emergent treatment is warranted when pH levels are above 7.5. Treatment is usually correction of the underlying cause. We describe a patient with refractory respiratory alkalosis on continuous renal replacement therapy (CRRT) which was offset by the use of normal saline (NS) in the pre and post-CRRT filter replacement fluids.

Case Description: A 68 year old lady on peritoneal dialysis (PD) presented with septic shock secondary to peritonitis. Hospitalization course was complicated by hypoxic respiratory failure necessitating mechanical ventilation, subsegmental pulmonary thromboembolism (PTE), and subacute ischemic white matter infarcts with no evidence of increased intracranial pressure or cerebral hemorrhage. She was on broad spectrum antimicrobials, stress dose steroids and vasopressors. PD catheter was removed; and she was started on Continuous Venovenous Hemodiafiltration modality of CRRT. The prefill, dialysate, and postfilter replacement fluids were at 700 cc/hr, 700 cc/hr and 200 cc/hr respectively. Each of these solutions contained 35 mEq/L of bicarbonate given septic shock, severe lactic acidosis and fulminant hepatic failure. No fluid was actively removed through CRRT. Efluent dose was 26 ml/kg/hr. ABG was consistent with an acute uncompensated primary respiratory alkalosis (pH 7.7 and serum bicarbonate level of 23 mEq/L) which did not improve despite optimal sedation, pain control and varied ventilator setting adjustments. The etiology was thought to be due to central neurogenic hyperventilation secondary to cerebral infarction and peripheral pulmonary receptor stimulation caused by PTE. The pre and postfilter solutions were replaced by normal saline at 500 cc/hr each; with the dialysate and fluid removal rate remaining unchanged at 700 cc/hr and 0 cc/hr respectively. The total bicarbonate amount for this combination was 14 mEq/L. Efluent dose was 27 mg/kg/hr. Within 12 hours, serum bicarbonate levels decreased to 14 mEq/L and pH improved to 7.48. Despite this, she had worsening hypoxia and hypercarbia, and subsequently died.

Discussion: NS is acidic with a pH of 5.5-6.6, and its use in CRRT can help mitigate refractory alkalosis. Furthermore, dialysis against NS results in loss of bicarb down a concentration gradient since NS does not contain any alkali.

Use of Gastric Anion Gap (GAG) in Acute Metabolic Alkalosis

Introduction: Metabolic Alkalosis(MA) is a common electrolyte disorder seen in hospitalized patients. It is due to loss of acid or gain of alkali. MA is routinely seen in hospitalized patients with vomiting, use of diuretics, and Naso-Gastric(NG) suction.
Blood glucose of 152, Na+ 120, K+ 2.5, Cl− <60, Mg 1.4 mmol/L, bicarbonate 46, BUN creatinine was 1.6, 2 months prior to presentation. On physical examination, the blood pressure was 116/59 mm Hg, pulse of 105, respiration of 20 and BUN 7.7. The patient was alert and oriented with respirations regular and unlabored. Labs were significant for blood glucose of 152, Na+ 120, K+ 2.5, Cl− <60, Mg 1.4 mmol/L, bicarbonate 46, BUN 113, Cr 5.7, ABG 7.88/56/84/43. Urimalys showed large leukocytes, small blood, RBC 5, and urine culture Na 10, Cl+ 10, Cr 115. He was treated with 2 L normal saline and continued normal saline with potassium 40 meq at 150 ml/hr and Pantoprazole 40 mg IV. Oral potassium initiated after he was able to tolerate oral intake.

Discussion: Severe metabolic alkalosis is a medical emergency due to electrolytes imbalance, especially, Na+. History is key to narrow diagnosis and diagnosis of underlying cause. In his case, the patient had multiple electrolyte imbalance, severe hypernatremia, hypokalemia alone with renal insufficiency in setting of hyperperfusion. We approached conservative management since our patient did not have chronic illnesses along with renal impairment and he underwent surgical resection with improvement of AKI. Post operatively patient developed ileus and had significant drainage from NG suction. During this time, he had recurrence of AKI with severe MA with Venous pH of 7.63. Serum electrolytes revealed Potassium(K) of 3.1meq/dl and CO2 50meq/dl with Creatinine of 7mg/dl. He was discharged after 5 days with no recurrence of AKI and improvement of renal function.

Prognosis: We concluded that careful selection, monitoring, and counseling of patients who receive pre-biopsy DDAVP are necessary. In our case, severe hyponatremia may have been avoided by careful patient understanding of potential decreased urinary output, avoiding excess free water intake, and transplant team notification. This case demonstrates the importance of careful selection, monitoring, and counseling of patients who receive pre-biopsy DDAVP.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
course of stay, the patient required CBI for removal of clots within the bladder and to prevent further injury; Lack of drainage from the catheter was noted multiple times and between 8-10 L of fluid were drained providing symptomatic relief. On day 8, HCO3 was 11 mmol/L and Cl was 122 mmol/L. Acidosis began to improve by hospital day 9 after patient was started on 650 mg of sodium bicarbonate, with the patient’s bicarbonate levels returning to normal within several days on bicarbonate.

Discussion: CIB with 0.9 percent normal saline (NS) is the standard of care for clot evacuation. Elliot et al., studied exfoliation rates of urothelial cells in patients with chronic urinary tract infections and in patients with long-term indwelling catheters. They observed bladder irritability in patients with an increased urine flow rate and increased disruption of urothelial cell layer in turn predisposes the bladder to recurrent infections. In 2014 Paolo et al., reported acute severe pulmonary edema in an 85-yr-old male who underwent CBI. In this case, bladder irrigation led to systemic absorption of fluid from bladder urothelium that manifested as NAGMA. As the serum chloride level started to increase, it decreased serum HCO3 causing H-NAGMA. Once we held bladder irrigation, the chloride levels decreased followed by improvement of HCO3 and resolution of acidosis. The patient was not on IV fluids suggesting that systemic absorption occurred from bladder urothelium leading to pulmonary edema and acidosis.

PUB517 Metformin-Associated Lactic Acidosis: Treatment With Different Types of Renal Replacement Therapy Raul Mellado,1 Patricia C. Ruiz Palacios.1 1Soporte Renal Integral, Mexico, Mexico; 2Hospital Ángeles del Pedregal, Mexico, Mexico.

Introduction: A potential complication of metformin is the development of type B (non-hypoxic) lactic acidosis. We present the case report of two patients who were receiving treatment with metformin and developed severe metformin-associated lactic acidosis. Both whom received different types of renal replacement therapy for the management of lactic acidosis and renal failure.

Case Description: CASE 1: A 70-year-old woman with type 2 diabetes treated with metformin, developed bacteriological, hemodynamically unstable and hyperlactatemia metabolic acidosis with serum lactate of 17 mmol/L, creatinine 5.04 mg/dL. We rule out different causes of severe lactic acidosis. Metformin serum levels were obtained with a total of 41 mcg/mL. The patient received treatment with 23 hours of continuous hemodialysis. At the end the patient, recover her renal function to normal standards. CASE 2: A 63-year-old man treated with metformin, presented with a history of abdominal pain accompanied by nausea and vomit. At his arrival to the ER we found him hemodynamically unstable and bradycardic, which, developed to asystolia soon after. He required advanced cardiorespiratory lift support and he was found with a hyperlactatemia metabolic acidosis with a serum lactate of 15mmol/L and creatinine 14.54 mg/dL; we ran serum metformin levels with a result of 14 mcg/mL. We started renal replacement therapy with conventional hemodialysis for 8 hours. It was interesting to watch a rebound and raise of metabolic acidosis 6 hours after we finish the first hemodialysis session. We then decided to reinitiate another 8-hour of hemodialysis; the patient did not require any other maneuver for acidosis with progressive improvement to his evolution. After he was discharged from the hospital he required once-weekly hemodialysis session only for one month.

Discussion: In our experience, both cases presented in the context of an acute kidney injury; another thing to highlight is that we found a rebound of lactic acidosis after the first hemodialysis session in a period of 6-6 hours. The different types of dialysis in both cases were adequate, but an osmotic diuresis allows a faster clearance of serum metformin. We report two cases with levels less with time and cost, it should always be considered as first choice in all patients who have immediate access to it.

PUB518 Excessive Water Intake Causing Severe Metabolic Alkalosis Julien Sanon,1 Eric J. Bloom,2 Darance Chewprong,1 Imara Dissanayake.1 1Einstein Healthcare Network, Cheltenham, Pa; 2Albert Einstein Medical Center, Bervyn, Pa; 3Einstein Medical Center Philadelphia, Bryn Mawr, Pa.

Introduction: Severe metabolic alkalosis is one of the most dreaded acid-base disorders. It is defined as a pH of more than 7.60 with serum bicarbonate levels over 40 mmol/L. Clinical features include confusion, seizures, and cardiac arrhythmias. Mortality rates range from 50% to 100% and can reach up to 87% with a pH of more than 7.60. We present a case of severe metabolic alkalosis with a pH up to 7.70 in a patient with a jejunostomy and a gastronomy tube.

Case Description: The patient is an 82-year-old female with diabetes mellitus, cardiac arrhythmias and carcinoid syndrome. The severity of the disease can reach up to 87% with a pH of more than 7.60. We present a case of severe metabolic alkalosis with a pH up to 7.70 in a patient with a jejunostomy and a gastronomy tube. Formal instructions were to only take occasional sips of water. The day prior to admission, she had increased thirst and started to drink a large amount of water. She then noticed large drainage into her gastrostomy bag. Admission arterial gas showed a pH of 7.70, PaCO2 of 70 mmHg. Blood work had sodium of 137 mEq/L, potassium of 2.5 mEq/L, chloride of 60 mEq/L, bicarbonate more than 50 mEq/Liter and glucose of 466 mg/dL. Urometry showed a pH of more than 9. ERK had arterial pH 7.63 with 35% respiratory alkalosis. We diagnosed severe hypernatremia (sodium levels >190 mEq/L) of uncertain cause that progressed over a period of 3 months. Case Description: An 82-year-old woman was admitted to our hospital with impaired consciousness and a 3-day history of progressive weakness. One month prior to admission, she had been started on a regimen of furosemide that was thought to be responsible for the development of hypernatremia. She was found to be in severe hypernatremia (sodium levels >190 mEq/L) of uncertain cause that progressed over a period of 3 months. Case Description: An 82-year-old woman was admitted to our hospital with impaired consciousness and a 3-day history of progressive weakness. One month prior to admission, she had been started on a regimen of furosemide that was thought to be responsible for the development of hypernatremia. She was found to be in severe hypernatremia (sodium levels >190 mEq/L) of uncertain cause that progressed over a period of 3 months.
Prophylactic Dose of Posaconazole Causing Syndrome of Apparent Mineralocorticoid Excess

Nwabundo Anusim, Naushaba Mohiuddin, Ishmael Jaiyesimi, Neera; Beaumont Hospital, Royal Oak, MI; St. Clair Specialty Physicians, Bloomfield hills, MI.

Introduction: Acute myeloid leukemia (AML) is typically treated with induction chemotherapy and prophylactic antifungal, antiviral and antibiotics. Posaconazole (PCZ) is an extended-spectrum antifungal agent used during induction chemotherapy for AML. We report a case of acquired syndrome of apparent mineralocorticoid excess (AME) from prophylactic dose of PCZ. AME syndrome is characterized by hypertension, metabolic alkalosis and hypokalemia.

Case Description: A 62-year-old female with newly diagnosed AML was treated with idarubicin, cytarabine, prophylactic PCZ, levamisole and acyclovir. She was normotensive, normokalemic with normal serum bicarbonate [HCO3-] on admission. She developed hypokalemia and metabolic alkalosis on day 5 of treatment, initially attributed to diarrhea. Over 100 meq of potassium (K) supplementation per day was given with no improvement in hypokalemia, despite resolution of her diarrhea. Serum K nadir was 2.3 meq/l, serum HCO3- levels peaked to 33 meq/l. She was hypertensive despite feltride norvexine, poor oral intake and start of losartan. Further investigation revealed Urine K/creat (potassium to creatinine) ratio of 3.8meq/mmol (abnormally high for serum K of 2.3 meq/l). Serum aldosterone of <30 ng/dl and renin of <21 pg/dl. PCZ was discontinued. Serum K, serum HCO3-, Urine K/creat ratio were followed at 1, 2 and 3 weeks. K supplementation was gradually decreased, and was completely discontinued at 3 weeks. Serum HCO3- and systolic blood pressure normalized to 24 meq/l and 110mmhg respectively.

Discussion: Resolution of AME, with discontinuation of PCZ is suggestive that the AME is attributable to PCZ. The mechanism of action is thought to be due to inhibition of the 11β-hydroxylase enzyme resulting in AME activity. There are a few case reports with similar presentation on therapeutic dose of PCZ. Prompt recognition of this adverse effect, even on prophylactic dose of PCZ, by oncologist and consulting nephrologist is necessary to avoid complications of severe refractory hypokalemia. Testing of urine K/creat ratio, aldosterone and renin levels should be undertaken to screen for AME. Discontinuation of PCZ and starting an alternative antifungal becomes imperative, if AME screening is positive.

PUB524

FGF-23-Mediated Severe Hypophosphatemia: A Rare Manifestation of Malignancy

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Introduction: Hypophosphatemia is not an uncommon electrolyte disorder. It can be secondary to renal or non-renal etiologies. Identifying the underlying cause is essential for proper management.

Case Description: We present a case of a 61-year-old man with hypertension and diabetes who was admitted to our hospital for abdominal pain, and was eventually diagnosed with diffusely metastatic esophageal squamous cell cancer. His phosphate level was in the 1-2 mg/dl (2.2-4.6), reaching <1 mg/dl on multiple occasions. His hypophosphatemia was difficult to correct, despite IV and oral supplementation. Extensive workup showed elevated urinary fractional excretion of phosphate (55%) which reflects renal wasting. The serum calcium was high (11.8 mg/dL) and the PTH was low (12 pg/mL). Inactive Vitamin D (47 ng/mL) and active Vitamin D (25 pg/mL) were normal. The PTHrP level was mildly elevated (2.9 pmol/L). There was no evidence of Fanconi’s syndrome. Further evaluation revealed an elevated FGF23 level of 2330 relative units (RU)/ml (Reference < 180) suggestive of an oncogenic osteomalacia-induced phosphate wasting. Unfortunately, the patient had advanced stage malignancy and passed away in less than a month after presentation.

Discussion: This case illustrates the importance of a thorough diagnostic workup of hypophosphatemia. Oncogenic osteomalacia is a rare paraneoplastic syndrome with many clinical and laboratory manifestations, usually seen in benign mesenchymal tumors. The mechanism of hypophosphatemia is secretion of FGF23 by tumor cells, which illustrates the important role of FGF23 in the bone-kidney axis. The management includes tumor localization and resection if possible, which is curative. The unusual aspects of this case are the presence of hypercalcemia, and the nature of the tumor being a metastatic squamous cell cancer.
Potassium levels. This dysregulation can lead to low-level hyperkalemia, causing undue
with the binding of extracellular potassium to Na-K ATPase, causing an increase in serum
rapid changes in serum lactate without a significant change in the anion gap may be helpful
poisoning should always be considered. The presence of osmolar gap, urine crystals and
may be misread by certain laboratory analyzers as lactic acid. On patients with unclear
lead to life threatening complications. Glycolic acid, a metabolite of ethylene glycol,
later (2/14/19), showed improvement of serum potassium to 5.2.
unremarkable. Patient was asked to stop the use of turmeric (active compound: curcumin)
medical problem is hyperlipidemia for which he was recently started on a statin. Vitals:
standing hyperkalemia. Patient is active and uses a lot of supplements in order to preserve
by our patients. We also need to be aware of the possible side effects associated with their
Diagnosis of Ethylene Glycol Toxicity from the Presence of a Lactate Gap
Babak S. Jazayeri-Moghadass, Joshua D. King, Bhuvan Kayastha, Parichi V. Buch, Simran Dhillon. University of Maryland Medical Center; Baltimore, MD.
Introduction: Ethylene glycol poisoning is life threatening and needs rapid
decision of high risk fatalities. If the patient is unresponsive, the anion gap was maintained at
and hypocalcemia were absent in our patient. Intravenous hydration and agents like
new tumor cells and calcium binding of excess phosphorus is absent. Hyperphosphatemia
results from tubule precipitation of uric acid (urate nephropathy), calcium phosphate or
hypoxanthine. In STLS, the released phosphorus is immediately utilized to regenerate
Factors like significant tumor burden, dehydration and renal failure, along with dramatic lab abnormalities can assist in early validation of the
even in the absence of a pathological confirmation or chemotherapy exposure. It is imperative to maintain a high level of suspicion because STLS can be fatal if left untreated.
An Interesting Case of Turmeric-Associated Hyperkalemia
Introduction: Advancements and understandings of modern medicine includes the
for its possible health benefits.
Case Description: 67 yo M with history of HLD presenting for evaluation of long-
and rasburicase remain the mainstay of therapy, but renal replacement therapy
and hypocalcemia were absent in our patient. Intravenous hydration and agents like
allopurinol and rasburicase. His labs showed improvement and he was eventually discharged on
metastatic disease involving multiple lymph nodes, hepatic, gastroesophageal junction,
the data remains limited to case reports.
Introduction: Tumor lysis syndrome (TLS) is an oncological emergency frequently
associated with highly-proliferative hematological malignancies, usually after the
initiation of chemotherapy. It is uncommon in solid tumors with some reports in uterine,
urinary, hepatoceleular and pancreatic cancer. Spontaneous TLS (STLS) in a
chemotherapy naïve patient is very rare. Exact incidence is difficult to ascertain because the
data remains limited to case reports.
Case Description: A 53-year-old male was recently diagnosed with extensive
metastatic disease involving multiple lymph nodes, hepatic, gastroesophageal junction,
and an isolated rib mass. Lymph node biopsy was consistent with poorly differentiated
adenocarcinoma and no apparent primary lesion was identified. Prior to initiation of
chemotherapy, he was admitted for significant laboratory abnormalities including
hyperuricemia (7.1 mmol/L), acidosis (pH 7.36), hypercalciuria (2.1mmol/dl),
hypercalcemia (13.9mg/dl), elevated LDH (4090 UI/L) and liver enzymes. A diagnosis of STLS was made and treatment started with intravenous hydration and
rasburicase. His labs showed improvement and he was eventually discharged on
allopurinol.
Discussion: TLS is a constellation of metabolic abnormalities (hyperkalemia,
hyperuricemia, hyperphosphatemia and hypocalcemia) described by the revised Cairo-
Bishop Criteria. It results from rapid destruction of cancer cells during chemotherapy
but may occur spontaneously. Risk factors for STLS in our patient were high LDH
levels and extensive metastatic involvement (particularly hepatic). Acute renal failure
results from tubule precipitation of uric acid (urate nephropathy), calcium phosphate or
hypoxanthine. In STLS, the released phosphorus is immediately utilized to regenerate
new tumor cells and calcium binding of excess phosphorus is absent. Hyperphosphatemia
and hypocalcemia were absent in our patient. Intravenous hydration and agents like
allopurinol and rasburicase remain the mainstay of therapy, but renal replacement therapy
may be required for severe cases. Factors like significant tumor burden, dehydration and renal failure, along with dramatic lab abnormalities can assist in early validation of the
diagnosis even in the absence of a pathological confirmation or chemotherapy exposure. It is imperative to maintain a high level of suspicion because STLS can be fatal if left untreated.

**PUB526**

Severe Acidemia in Pregnancy with De Novo Acute Myeloid Leukemia
KEYSHA LOPEZ VEGA, ILEANA ECOSIO MENELZEN, FATIMA CINTON-ROSAS, STEPHANIE COLON LOPEZ, CARLOS G. RIVERA-BERMUDEZ. Nephrology, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico.
Introduction: Starvation ketoacidosis is an important cause of acidosis in pregnancy,
specifically after the second trimester. A day of severe vomiting is enough to trigger this
serious disorder and its presence should prompt physician to face exaggerating causes.
We present a case of severe metabolic acidosis in a pregnant woman with underlying acute
myeloid leukemia (AML).

**PUB527**

Metastatic Adenocarcinoma Causing Spontaneous Tumor Lysis Syndrome
AIMEN LIQAT, HAMEEDA KHAN, HARSH MEHTA, SAAD AAMIN. SAINT BARNABAS Medical Center, West Orange, NJ; RWJBarnabas health, West Orange, NJ.
Introduction: Tumor lysis syndrome (TLS) is an oncological emergency frequently
associated with highly-proliferative hematological malignancies, usually after the
initiation of chemotherapy. It is uncommon in solid tumors with some reports in uterine,
urinary, hepatoceleular and pancreatic cancer. Spontaneous TLS (STLS) in a
chemotherapy naïve patient is very rare. Exact incidence is difficult to ascertain because the
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Case Description: A 53-year-old male was recently diagnosed with extensive
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allopurinol and rasburicase remain the mainstay of therapy, but renal replacement therapy
may be required for severe cases. Factors like significant tumor burden, dehydration and renal failure, along with dramatic lab abnormalities can assist in early validation of the
diagnosis even in the absence of a pathological confirmation or chemotherapy exposure. It is imperative to maintain a high level of suspicion because STLS can be fatal if left untreated.
explained by poor oral intake concomitantly with immunosuppressed state and infectious process leading to preterm labor. RTA was considered but in the setting of high urine unmeasured anions due to ketoacidosis, urine AG was not reliable. Identification of acidemia etiology and rapid treatment was paramount to avoid further fetal and maternal complications including fetal demise.

PUB529
Management of Hyponatremia Overcorrection with 2.5% Dextrose in Water Solution in Diabetic Patient
Mariam Charkviani,1 Natia Murvelashvili,1 Mariam Aebesham.1 Internal Medicine, Amtia Saint Francis Hospital, Evanston, IL; 2Amtia Saint Francis Hospital, Evanston, IL.

Introduction: Overcorrection of hyponatremia is a medical emergency and associated with disastrous neuropathologic condition, osmotic demyelination syndrome. To minimize the risk of overcorrection, sodium correction rate should not exceed 6 to 8 mEq/L in any 24-hour period. We will present a case diabetic patient whose hyponatremia overcorrection was managed with 2.5% dextrose in water (D5W) solution.

Case Description: 63-year-old male presents to our hospital for concern of possible bladder rupture. Patient had anuria and constipation for three days, associated with generalized abdominal pain and episodes of disorientation. At the emergency department, his initial labs at 8 pm showed severe hyponatremia with Na 116 mEq/L and acute kidney injury with creatinine 3.3. Foley was placed to relieve urinary tract obstruction and infusion of normal saline was started. CT abdomen was concerning for colonic impaction with possible bladder rupture and he was transferred to our hospital. Patient developed post-obstructive diuresis and by the time of arrival, repeated sodium was 130 mEq/L. Sodium overcorrection with 14 mEq occurred in less than 10-hour period. Normal saline was stopped, DSW with 250 ml/hr was started and desmopressin was administered. Next sodium level 3 hours later was even higher 133 mEq/L. As the patient had history of Diabetes Mellitus and was requiring excessive and rapid administration of fluids, use of D5W was decided. The goal was to decrease the sodium to <125 mEq in 24 hours period. Patient received desmopressin treatment and by 8 pm of the next day, sodium was 124 mEq/L. After that regular management of hyponatremia was started with appropriate correction rate and the patient was discharged home with sodium 134 mEq/L and no neurologic deficit.

Discussion: One of the strategies to avoid ODS after rapid overcorrection of hyponatremia is slow lowering of the sodium. Most commonly used re-lowering agents are DSW and Desmopressin. Our patient developed nephrogenic diabetes insipidus due to post-obstructive diuresis, didn’t respond to desmopressin and was requiring high infusion rate of DSW. DSW is safe at low infusion rates but in rapid and excessive administration, especially in diabetic patients, serious adverse effects, hyperglycemia, hyperosmolar syndrome, and even intracerebral hemorrhage may occur. Usage of D5W instead is very rare and this case was exceptional.

PUB530
A Six-Pack of Paralysis in a Healthy 27-Year-Old
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Introduction: Hypokalemic periodic paralysis is a rare disorder with autosomal dominant inheritance. A mutation in skeletal muscle Ca channels is the most common genetic abnormality. Attacks generally begin in 1st or 2nd decades of life and present as sudden-onset painless weakness/paralysis. Symptoms may be precipitated by heavy exercise, fasting, or high-carbohydrate meal. If hypokalemic periodic paralysis is suspected, workup should be focused on ruling out secondary causes of hypokalemia and weakness. Herein we present a case that demonstrates the importance of this workup in a somewhat atypical presentation of this rare condition.

Case Description: A previously healthy 27-year-old male presented due to severe weakness. Symptoms started two days prior to arrival with mild pain of the arms and legs and subjective weakness. No changes in physical activity. No changes in eating habits. The morning of admission, patient was unable to get out of bed. On admission, exam was notable for profound extremity weakness. Initial workup demonstrated K 1.7, Mg 2.1, phos 1.0, creatinine 0.95, CR 506, TSH 0.41, and QTc 622. Muscle weakness improved with potassium replacement. Subsequent urine studies did not demonstrate excess renal potassium loss and patient had no history of extra renal losses. Serum renin and aldosterone levels were normal. Urinary potassium levels were unremarkable. Upon further questioning, patient reported drinking a six-pack of soda the day prior to admission (equivocal carbohydrate load to 8 pieces of a large pizza).

Discussion: Despite an atypical presentation of hypokalemic periodic paralysis (first episode in third decade of life, no family bx, and the presence of pain), the workup did not reveal an alternative diagnosis. There was no identifiable secondary cause of hypokalemia. No primary neurologic phenomenon identified, and despite muscle pain only mild elevation in CK and no myogloburinaemia. QT was prolonged; however patient lacked the symptoms associated with Anderson Syndrome. This case demonstrates the importance of having a high suspicion for hyperkalemic periodic paralysis in the setting of hypokalemia and weakness, even if some aspects of the presentation are not typical for the diagnosis. Also, the systematic approach for evaluating alternative diagnoses enabled prompt treatment and education regarding preventative measures.

PUB531
D-Lactic Acidosis: Uncommon and Often Forgotten
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Introduction: Lactate (DL) is undetectable by standard analyzers and differs from L-lactate as it crosses the blood brain barrier which leads to neurotoxicity when D-Lactic Acidosis (DLA) ensues. DLA is a rare but known complication of short bowel syndrome (SBS) following a carbohydrate load. Due to a low index of suspicion DLA is often misdiagnosed and recurred.

Case Description: A 65 year-old woman was brought to the ED unconscious soaked in loose clothes. She was unresponsive and withdrew on the right only concerning for stroke SBS. She had a metabolic acidosis (MA) pH 7.17, pCO2 17 mmHG on BVH, HCO3 36 mEq/L, AG 17 mEq/L, Cl 120 mEq/L, lactate 0.8 mmol/L. Urine toxicoology, serum osmolar gap and CT head were not diagnostic. Lactated Ringers (LR) was started. Nephropathy was consulted for worsening MA. A laparotomy scar was noted. Family who was not previously available for collateral, confirmed the patient had bowel surgery four years ago. Since then she had SBS with chronic diarrhea, developed new onset neurological symptoms requiring medications and had two suicide attempts. The family also noted she ate almost a whole cake in honor of her birthday a day before. We suspected DLA. Urine AG and osmolar gap was positive at 78 mEq/L and 420 mmOsm/kg, respectively. LR was immediately stopped; IV sodium bicarbonate, IV thiamine and PO clidamycin were started. DL levels were not available. Within a few hours the neurological symptoms and MA resolved and she returned to her baseline.

Discussion: Our patient presented with classic DLA after a large carbohydrate load in the setting of altered gut microbiome in SBS. DL reduces intracellular pH and interferes with pyruvate metabolism by inhibiting pyruvate dehydrogenase complex (PDHC). The severity of symptoms may depend on the preexisting intracellular reserves of cofactors (such as lipoic acid or coenzyme A) that are necessary for PDHC that are usually compromised in SBS which leads to a wide range of neurological symptoms. Commonly these patients have lower “AG” as anticipated by DL levels due to hyperchloremia and are wrongly treated with LR which contains DL and worsens symptoms, as seen in our patient, or are misdiagnosed as RTA and symptoms recur. Fortunately, measuring DL is not practical and awareness is needed. Management consists of avoiding large carbohydrate meals, altering the gut flora with antibiotics and restoring cofactors.

PUB532
Double Trouble: A Case of Hyperkalemia from the Combination of Fluconazole and Heparin, and Its Treatment with Fludrocortisone
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Introduction: Medication-induced hyperkalemia is common and can be dangerous. Treatment options may be limited if a precipitating medication cannot be discontinued. We present a case of hyperkalemia from co-administration of fluconazole and heparin that improved with fludrocortisone.

Case Description: A 39 yo man with CML and recent MSSA endocarditis requiring mechanical MVR was admitted for concern of possible Candida parapsilosis fungemia, and fluconazole was started. One week later he developed Candida parapsilosis fungemia, and fluconazole was started. The following day he developed acute hyperkalemia up to 8.0 mmol/L without EKG changes. Whole blood potassium (WBPot) was checked with a point of care analyzer with a similar result. WBC, uric acid, LDH, haptoglobin, CK, and lactate levels were normal, serum bicarbonate 24 mEq/L, and SCR 1.3 mg/dL. He began fludrocortisone 0.1 mg daily for medication-induced hyperkalemia, as well as furosemide and oral bicarbonate. Heparin was discontinued the following day. WBPlt improved with fludrocortisone but remained elevated at 5-6 mEq/L. Fluconazole was then discontinued, and WBPlt stabilized at <5 mEq/L, at which time fludrocortisone was stopped.

Discussion: Heparin and azole antifungal agents, particularly ketoconazole, can lead to hyperkalemia by decreased aldosterone production. Fluconazole has been shown to have the same effect, though weaker, and only a few cases of fluconazole-induced hyperkalemia have been reported. This case provides further evidence of the potential for severe hyperkalemia from fluconazole, particularly when given with heparin, and highlights the importance of considering medicine-related drug interactions. There are also reports of fludrocortisone use in heparin-induced hyperkalemia, and though fludrocortisone did not normalize this patient’s potassium, it helped reduce it to a safer level while decisions were made regarding alternative therapies to heparin and fluconazole. This suggests that fludrocortisone can be used as a bridge to help prevent dialysis until safer medications are chosen.

PUB533
Hypercalcemia Secondary to Silicone-Induced Granuloma Treated with Ketoconazole
Bianca Madrid. University of Miami, Miami, FL.

Introduction: Hypercalcemia mediated via extra-renal 1, alpha-hydroxylation activity has been described. We present a patient who developed hypercalcemia from silicone-induced granulomas.
Tuberculous Lymphadenitis Presenting as Symptomatic Hypercalcemia and AKI: A Case Report

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Introduction: Incidence of Tuberculosis associated hypercalcemia has been variably reported to be as low as 2% and as high as 28% depending upon the studied population. However, severe or symptomatic tuberculous hypercalcemia is very rare entities. AKI is another very rare presentation of granulomatous hypercalcemia. We are presenting a case of moderate hypercalcemia secondary to tuberculous lymphadenitis that presented with symptomatic hypercalcemia and AKI.

Discussion: Case 40 years old male presented to various doctors with increased urinary frequency and occasional constipation. His repeated urine examination was bland with negative cultures but renal function tests were mildly deranged consistently for past one month. When he presented to our center, he was afibrile but had enlarged inguinal and few cervical lymph nodes. Workup showed normal hemoglobin, urea of 143 mg/dl, creatinine of 4.1 mg/dl, serum calcium of 13 mg/dl and Phosphorous of 4 mg/dl. ESR was 60 and LDH was 160 IU/L. PTH was suppressed to 59 pg/ml (15-65 pg/ml). Right inguinal lymph node biopsy showed multiple granulomas comprising of epithelioid cells with Langhans type giant cells, central cascaating necrosis and no atypical cells. Patient was managed with aggressive hydration and Anti tuberculous therapy (ATT) along with steroids for 1 month. Patient showed marked improvement in RFT (Urea 24 mg/dl, creatinine 1.1) on discharge and calcium improved to 9.8 mg/ dl subsequently. After two months, his urea was 18mg/dl, creatinine 0.9 and calcium 9.2 with increased appetite, normal urinary frequency and bowel movements. On completion of ATT patient has normal RFTs and calcium levels.

Discussion: To our knowledge, no established relationship between severity of hypercalcemia and various forms of tuberculosis. As in our case, short course of steroid along with ATT has been used with success in treating granulomatous hypercalcemia.

Thiamine Deficiency as a Cause for Persistent Hyperlactatemia

SHEETAL KOUL, SOURAB DHUNGE, AVRUM GILLESPIE, TEMPLE UNIVERSITY HOSPITAL, PHILADELPHIA, PA.

Introduction: Hyperlactatemia is often associated with tissue hypoxia also known as Type A lactic acidosis. However, it can result from less common mechanisms like thiamine deficiency as described in our patient. Effective treatment of persistent hyperlactatemia requires correct identification of the precipitating cause.

Case Discussion: A 47-year-old female with past medical history of schizophrenia presented to the ED with altered mental status. She was tachycardic without tachypnea and had hyponatremia. Laboratory data was significant for a bicarbonate of 13 mmol/L, sodium of 115 mmol/L, potassium of 3.0 mmol/L, chloride of 89 mmol/L, anion gap of 24 mmol/L and lactate of 3.6 mmol/L. The patient had a serum osmol gap of 23 mOsm/kg. Her urine output was adequate but her mental status did not improve with intravenous saline administration. She was offered to start corticosteroids as treatment of the hypercalcemia, but the patient refused due to concern for the aesthetic adverse effects of steroids. Therefore, she was started on ketoconazole. Within 4 weeks of treatment, her serum calcium had decreased from 12.8 to 11.0mg/dl.

Discussion: The main treatment is surgical resection of the surgical implants or resection of the granulomatous tissue. Corticosteroids remain the primary therapeutic option for hypercalcemia produced by excessive production of 1.25-(OH)2 vitamin D3 by the macrophages present in the sarcoid granulomas. Ketoconazole is an imidazole antifungal that inhibits the 1-alpha-hydroxylase from the macrophage and has been used to treat hypercalcemia associated to primary hyperparathyroidism, tumors, sarcoidosis and tuberculosis. The patient presented is the first case of ketoconazole use for the treatment of hypercalcemia due to silicone-induced granuloma after injection for cosmetic purpose.

Parapelvic Cyst: A “Must Know” Differential Diagnosis for Hydronephrosis on Point-of-Care Ultrasound


Introduction: Point of care ultrasonography (POCUS) performed by the nephrologist is a valuable bedside tool that enhances patient care. Detection of obstructive uropathy is one of the most common indications for POCUS and hydronephrosis is relatively easy to recognize appearing as ‘anechoic’ or ‘black’ branching, interconnected areas in the renal collecting system. However, caution needs to be exercised in calling an anechoic structure hydronephrosis if the renal pelvis and collecting system are normal. We present a case of a 47 y/o caucasian female with recently diagnosed small cell carcinoma of the cervix presented to the hospital with worsening confusion and lethargy after her 3rd dose of Chemotherapy. Serum sodium was 115 mmol/L, compared to serum sodium of 142 mmol/L measured 3 days prior to start of chemotherapy. Serum osm was 240 mOsm/kg H2O. Her blood pressure was low-normal with exam notable for dry skin. Urine Na was 75 mmol/L, urine creatinine was 22 mg/dl, and FeNa was 1.4%. Urine Osm was 606 mOsm/kg and Urine specific gravity was 1.019. An initial diagnosis of SIADH vs Renal Salting Was made and given the patient’s mentation, she was treated with iv hypertonic saline with improvement in serum sodium. Over the next day, urine sodium values rapidly decreased to under 30 mmol/L with FeNa <1, making SIADH unlikely. Serum sodium continued to improve with isotonic saline along with oral salt tablets while urine osmolality decreased to 335 mOsm/kg. The patient’s mentation and serum sodium normalized within a week.

Discussion: Our patient’s presentation fits with the hypothesis that she developed transient renal salt wasting that resolved spontaneously with appropriate urinary concentration returning 4 days after her last dose of chemotherapy. Cisplatin may cause hyponatremia by inducing SIADH or renal salt wasting. This may initially be difficult to distinguish but a careful assessment for volume depletion and distinction between the two conditions is warranted for correct management. It is notable that renal salt wasting in our patient was only transient and occurred in isolation without any other manifestations of tubular epithelial cell toxicity that are more common with Cisplatin use. It must also be pointed out that this effect did not recur with continued chemotherapy when combined with preventive saline infusions.
antibiotic therapy. She underwent revision hip surgery, suffered from myocardial infarction post-operatively and subsequently developed AKI stage III. Renal POCUS was suggestive of right moderate hydronephrosis. However, on careful review of the trainee-performed images [Figure, top panel], the anechoic area in the renal pelvis area was found to be a simple cyst mimicking hydronephrosis. The patient’s renal failure was diagnosed to be secondary to acute tubular injury and she later required renal replacement therapy. A formal sonogram obtained a few days later confirmed the interpolar cyst.

Discussion: Parapelvic cysts can mimic hydronephrosis because of their anechoic nature and close proximity to the renal collecting system. Hydronephrosis appears as branching ‘interconnected’ anechoic area [Figure, bottom panel] as mentioned above, while parapelvic cysts are seen as well-circumscribed ‘noncommunicating’ renal sinus cystic masses. Moreover, a parapelvic cyst is more spherical as opposed to irregular contour of hydronephrosis and is not connected to hydroureter distally.

**Fig. 1**

**Discussion:** MTP is involved in fatty acid oxidation and is essential for energy homeostasis, especially in times of fasting. MTP is encoded by two genes: HADHA and HADHB. Variants in these genes can cause MTP deficiency, presenting with early onset hypoketotic hypoglycemia and cardiomyopathy or later onset myopathy, rhabdomyolysis, and polyneuropathy. This is the first reported case of MTP deficiency presenting with SRNS. WES and IF of patient kidney tissue suggest that mutations in HADHB gene, consistent with autosomal recessive MTP deficiency. Biochemical analysis of cultured fibroblasts confirmed the diagnosis. Despite a trial of CoQ10, carnitine, and other vitamins, he continued to deteriorate and died at age 21 months. Immunofluorescence (IF) was performed on patient kidney tissue to delineate the role of HADHB in nephrotic syndrome. IF of an age-matched control displayed HADHB throughout the renal tubules. In contrast, patient tissue revealed complete absence of HADHB throughout the kidney (Fig 1).

**Discussion:** Our case is a rare and unique presentation of renal AML as the patient not only presented with spontaneous retroperitoneal hematoma due to rupture of a renal AML but the size of AML was 3 cm. Moreover, the patient’s hypertension was caused by renal parenchymal compression from the subcapsular and perinephric hematoma, a phenomenon known as Page kidney. In patients with life-threatening hemorrhage, selective renal artery embolization is recommended. All patients with AMLs should be screened for TSC, however, it is not necessary to screen for LAM. Surveillance for AML is dependant on size: for < 2 cm, ultrasound every 3-4 years, for 2-4 cm, annual renal ultrasounds, and > 4 cm tumors, surgical resection is recommended.
hypertension, mild proteinuria (0.58 g/gCr/day), microscopic hematuria (50-99 HPF) normal, whereas ATS typically results in end-stage renal disease (ESRD). Therefore, (ATS) are familial nephropathy characterized by structural abnormalities in the glomerular

Shinichi
Takashi

Novel Heterozygous COL4A3 Mutation of the Type IV Collagen Alpha3.

Hypertension from Apparent Mineralocorticoid Excess in a Cushing
Publication-Only

PUB541

Two Pearls in an Oyster: Thrombotic Microangiopathy due to Malignant Hypertension from Apparent Mineralocorticoid Excess in a Cushing Syndrome Patient with Primary Bilateral Macronodular Adrenal Hyperplasia

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Introduction: Malignant hypertension (HTN) is characterized by severe HTN and target organ damage and can rarely cause thrombotic microangiopathy (TMA). Primary bilateral macronodular adrenal hyperplasia(PBMAH) causes Cushing’s syndrome in less than 2% of the cases, leading to difficult to control HTN. We report this unique case of a patient with malignant HTN and TMA due to apparent mineralocorticoid excess from PBMAH.

Case Description: 47-year-old male, with malignant HTN for two years, uncontrolled on four antihypertensives (including diuretics) presented with fatigue, muscle weakness and unintentional weight gain (45 lbs). Physical exam remarkable for BP:160/100; weight 172lbs, moon face, central face, obesity with buffalo hump, supraclavicular and dorsocervical fat pads and purple abdominal striaes, proximal muscle weakness and thin/scaly skin. Primary Cushing’s syndrome was suspected and confirmed with high free AM cortisol at 37mg/dL, low ACTH at <5 pg/mL. CT abdomen revealed bilateral adrenal adenomas. Further work up: microscopic hematuria and sub-nephrotic proteinuria (1.8g/24hrs), Cr 1.2mg/dL. Kidney biopsy: intracapillary thrombi; marked podocyte hypertrophy, consistent with TMA. An extensive workup ruled out the most common causes of TMA like TTP, HUS and complement deficiency. On further tests, he was diagnosed with apparent mineralocorticoid excess through the high 24 hr urine free cortisol/ free cortisone ratio. A bilateral adrenalectomy was performed to treat the disease and at 12-month follow up visit, BP was controlled (110/70) only on Lisinopril 10mg/day and he had lost 48lbs. Proteinuria: 203 mg/dL.

Discussion: PBMAH causes Cushing’s syndrome in less than 2% of cases. This patient also had TMA present, likely from two pathways: 1. Cushing’s syndrome as a hypercoagulable state (high factor VIII levels, decreased fibrinolysis, and abnormal Von Willebrand factor). 2. Malignant HTN causing endothelial dysfunction and thrombosis formation. Malignant HTN was secondary to the apparent mineralocorticoid excess from PBMAH. Both HTN and Cushing’s syndrome resolved after bilateral adrenalectomy. PBMAH is a rare cause of Cushing’s syndrome and, to the best of our knowledge, this is the first case of this condition causing apparent mineralocorticoid excess leading to HTN and TMA.

PUB542

Novel Heterozygous COL4A3 Mutation of the Type IV Collagen Alpha3 Gene in a Family with Thin Basement Membrane Nephropathy

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Introduction: Thin basement membrane nephropathy (TBMN) and Alport syndrome (ATS) are familial nephropathy characterized by structural abnormalities in the glomerular basement membrane (GBM). Gene mutations in the type IV collagen genes COL4A3 and COL4A4 genes are reported to cause both ATS and TBMN with the autosomal recessive and autosomal dominant form, respectively. The renal function of TBMN is usually kept normal, whereas ATS typically results in end-stage renal disease (ESRD). Therefore, differentiation between TBMN and ATS is mandatory for correct prediction of prognosis and gene counseling.

Case Description: A 39-year-old woman presented with recent diagnosis of hypertension, mild proteinuria (0.58 g/gCr/day), microscopic hematuria (50-99 HPF) and mild decrease in eGFR at 59.5 mL/min/1.73m². She experienced asymptomatic hematuria since childhood, and a family history of microscopic hematuria. She received a renal biopsy at the age of 29 years, light and electron microscopic findings revealed thinning of GBM and effacement of the podocyte foot processes. Blood pressure was 137/92 mmHg with the prescription of amlopidine (10mg per day). The renopreservation was unremarkable with no lower extremity edema. The next-generation sequencing and Sanger Sequencing were performed on DNA samples of the patient and her family (father, elder sister, younger sister, nephew, daughter), and heterozygous COL4A4G155 mutation [COL4A4NM_000093] xG43A:p.G315S was identified in the mother with persistent hematuria, except her nephew who never experienced hematuria. She was diagnosed of TBMN, and antihypertensive treatment by angiotensin receptor blocker decreased proteinuria to about 0.2gCr/day, increased eGFR, while microscopic hematuria persisted.

Discussion: Clinical diagnosis of this case was TBMN on the following basis; autosomal dominant hereditary form, no ESRD patients in the family, no irregular thickening and multilamination of the GBM in the kidney, and no type IV collagen c5 defect. Mild proteinuria and decrease in eGFR at admission were considered not associated with TBMN but with untreated hypertension. This is the first case of TBMN with the novel COL4A3 hetero mutation of type IV collagen c3 which is responsible for the microscopic hematuria in this family.

PUB543

Severe Microangiopathic Anemia in an ESRD Patient Unmasks Complement-Mediated Atypical Hemolytic-Uremic Syndrome (aHUS) and Successful Management with Treatment of aHUS

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Introduction: Anemia amongst ESRD patients is mostly due to erythropoietin deficiency and disordered iron metabolism. We present an ESRD patient with severe complement-mediated hemolytic anemia due to aHUS. Eculizumab, a therapeutic candidate, has been shown to correct complement dysregulation in complement regulatory proteins and use of complement inhibitors lead to successful resolution of near-fatal anemia. We posit that the underlying cause for ESRD might be related to anHUS presenting as ANCA-negative vasculitis.

Case Description: A 39-year old African-American female patient with ESRD was admitted for severe symptomatic anemia and need for red-blood cell transfusion despite erythropoietin-stimulating agents (ESA). She was evaluated a year prior for chronic kidney disease with a nephritic presentation. Serological evaluation was negative. Kidney biopsy reported as pauci-immune ANCA-negative glomerulonephritis with significant chronicity. Given renal-limited vasculitides and chronicity, she didn’t receive immunosuppressives. Hemoglobin & renal function remained stable. Blood pressure was controlled with ACE-I, eGFR dropped in 4 months with a decline in hemoglobin and proteinuria. Hemoglobin improved within 2 weeks and eventually normalized while on Eculizumab. Genetic testing for aHUS showed multiple, heterozygous, missense variants of complement factor H (CFH). Prior renal biopsy showed changes of arteriolar intima that cemented concerns for aHUS. She remains transfusion-independent and on Eculizumab.

Discussion: CFH mutations are the commonest amongst genetic causes for aHUS. In African-American patients, CFH variants might be just as impactful in causing CFH-related GN and ESRD. Our patient had hemolytic anemia due to complement-mediated aHUS with brisk response to Eculizumab. Testing reveals her genetic predisposition to aHUS with multiple CFH variants, common amongst ESRD patients of African-American origin. CFH deficiency is a rare cause for anemia in ESRD patients, use of complemet-mediated aHUS might have been the original cause for ESRD in this patient.

PUB544

Fabry Disease: Management in Carriers for Enzyme Alpha-Galactosi- dase A (a-GAL-A)

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Introduction: Fabry disease is an X-linked recessive deficiency of the enzyme alpha-galactosidase A (α-GAL-A), resulting in the accumulation of globotriaosylceramide (Gb3) within lysosomes in a variety of cells. It is the second most common lysosomal storage disease with clinical manifestations ranging from asymptomatic to very severe cardiac manifestations and end-stage renal disease. We report a case of Fabry disease in a young female who was asymptomatic initially and slowly started showing renal manifestations of the disease.

Case Description: The patient is a 26-year-old female referred to our office by her primary care physician for evaluation of proteinuria and hematuria with CKD stage 1 with a significant history of renal disease in the family. She had complaints of tingling/pain in her hands and feet along with episodes of excessive sweating. On exam, she was found to have angiokeratomas in the periumbilical regions. Her baseline serum creatinine was 0.5 – 0.8. On genetic testing and she was noted to be a heterozygous carrier for the Fabry Disease. We suggested Enzyme Replacement Therapy (ERT) along with a focus on the control of blood pressure, metabolic derangements, lipids, blood sugars and avoidance of nephrotoxic drugs. We emphasized the importance of scheduled follow-up visits with specific focus on every 2-3 months to monitor disease progression.

Discussion: Fabry disease can be diagnosed in males by detecting low a-GAL A activity in leukocytes or in the plasma. In women, a-GAL A activity level is unreliable for diagnosis and therefore it is necessary to perform mutation analysis of the a-GAL A gene. Carriers may be completely asymptomatic but with advancing age may develop left ventricular hypertrophy, valvular disease, cardiomyopathy, myocardial ischemia, infarction,
Hypokalemic Periodic Paralysis
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Introduction: Hypokalemic periodic paralysis is a condition that causes muscle weakness beginning in childhood and adolescence. Mutations in the CACNA1S or SCN4A can cause HPP, those genes codify for proteins that control the flow of positive ions in muscle cells. We reported a case of HPP that carries a lot of frustration since patients usually have multiple ER and clinic visits before the right diagnosis.

Case Description: Patient is a 40 y.o white female who began having symptoms at the age of 12, initially with pain in legs that eventually progressed to her neck, shoulders, and hips. At age 20, her K+ was detected around 3.5 mg/dL, and due to her symptoms, she was initially placed on steroids, which resulted in muscle weakness. At age 32, she developed a profound paralysis and her K+ was found to be around 3.1 mg/dL. Since then, K+ supplementation has been increased to 100 mg daily, with additional K+ administered PRN for acute paralytic episodes. She is also taking acetazolamide, amiloride, and eplerenone, a combination which has resulted in improvement.

Discussion: The initial hypokalemic start with the separation of K losses (renal and extrarenal) and transcellular shifting. Unfortunately, there is no appropriate test to differentiate the potential mechanism. The total urine K+/Creatinine and transtubular K+ gradient (TTKG) are not completely accurate test due to renal physiologic mechanisms. Therefore after ruling out common etiologies, the approach should approximate unusual renal K+ wasting conditions and transcellular shifting in parallel. (HPP) can be divided in to: (familial, associated with thyrotoxicosis and associated with cardiac dysrhythmias- Andersen Tawil syndrome). Genetic testing should be part of the armamentarium to get closer to the final diagnosis. A periodic paralysis genetic panel includes analysis of the following four most common associated genes: SCN4A, CACNA1S, KCN2 and RYR1. Unfortunately, genetic testing is not definitive since a proportion of patients lack abnormalities in the mentioned genes. Finally, the treatment will imply K+ replacement with the adjuvant of K+ sparing diuretics such as amiloride, triamterene and spironolactone. Close monitoring is required since other electrolyte abnormalities and acid base disorders may ensue. Our case report intent to raise the awareness of this rare condition and establish that multidisciplinary approach needed to delineate the diagnostic approximation of HPP.

Overlapping Features of Membranous Glomerulonephritis and Focal Segmental Glomerulosclerosis in a Patient with Nephrotic Syndrome
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Introduction: Nephrotic syndrome may be classified into different histopathologic patterns, including membranous glomerulonephritis (MGN) and focal segmental glomerulosclerosis (FSGS). While MGN may be secondary to drug exposure, FSGS is more commonly seen due to obesity, uncontrolled hypertension, and HIV. Overlap between these two conditions is rare and, when coexisting, tends to clinically resemble primary MGN. We present a case with overlapping features of NSAID-induced MGN and FSGS.

Case Description: A 37-year old Caucasian male with chronic daily headaches on ibuprofen daily presented for elevated creatinine (2.4 mg/dL, compared to 0.8 mg/dL 3 years prior). Vital signs were notable for hypertension (219/107 mmHg), and physical examination was notable for 2+ pedal edema. Urinalysis showed 3+ protein and no blood. His UPC was 7.5. C3 and C4 levels, hepatitis B and C, HIV, ANA, dsDNA, RNP, Smith, SSA, SSB, and Histone serologies were within normal limits. Renal biopsy demonstrated MGN with negative PLAR and THSD7A staining, global sclerosis in 3/23 glomeruli, segmental sclerosis in 3/23 glomeruli, and moderate tubular atrophy and interstitial fibrosis. He was advised to stop all NSAID use and was started on amiodarone, carvedilol, lisinopril, and spironolactone. At 2-week followup, his blood pressure was 110/72 mmHg, creatinine was 2.3 mg/dL, and UPC was 2.5.

Discussion: The coexistence of MGN and FSGS is a rare phenomenon, but may occur in patients who share risk factors like chronic NSAID use, uncontrolled hypertension, and obesity. Although the pathogenesis is unclear, MGN injury may contribute to FSGS since subepithelial deposits may hinder podocyte adhesion, and FSGS-mediated podocyte damage may lead to local antigen exposure and subepithelial immune complex formation.

An Aggressive Form of Nephrotic Syndrome Secondary to IgA Nephropathy
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Introduction: Patients with IgA Nephropathy (IgAN) often present with nephritic syndrome, but nephrotic syndrome (NS) is less common. Several features of IgAN have been associated with poor prognosis, including hypertension, glomerular range proteinuria and fibrosis on histopathology. Here we discuss a patient with IgAN presenting with NS and malignant hypertension.

Case Description: A 33 year-old Asian female with history of hypertension presented with one week of headache, nausea and vomiting. Physical examination remarkable for elevated blood pressure of 205/131 mmHg, peripheral swelling and lower extremity pitting edema. Laboratory findings showed elevated serum creatinine (2.9 mg/dL) and LDL (172 mg/dL). Urinalysis was negative for hematuria, showed 3+ proteinuria and microalbumin. creatinine ratio of 3881 mcg/mg consistent with nephrotic range proteinuria. When hypertension was controlled, work up for proteinuric kidney disease was initiated. Results were unrevealing, including autoimmune antibodies and complements, except for a positive hepatitis B surface antigen. Renal biopsy revealed severe interstitial fibrosis and global glomerulosclerosis. Patient was diagnosed with IgAN nephropathy due to the presence of mesangial IgA deposits on immunofluorescence (Oxford classification: M1 E0 S1 T2 C0). This patient presented with intravascular fluid overload and severe hypertension. His symptoms improved with blood pressure control. Immunosuppressive therapy was not considered due to chronicity of renal scarring.

Discussion: IgAN is the most common cause of glomerulonephritis, more frequent in Asians than Caucasians. IgAN typically has slow progression to end stage renal disease (ESRD) with ~50% of patients developing ESRD over ~20 years. Severity of disease is described using the Oxford classification. Our patient’s Oxford score of 29 indicates five-year incidence of ESRD is likely greater than 50%. Significant morbidity and poor outcomes are reported in IgAN associated with NS, which is poorly understood. The occurrence of malignant hypertension and coexistent hepatitis B infection potentially increases risk of ESRD. Limited data is available on use of steroids for treatment of proteinuria in IgAN. Use of Renin-Angiotensin-System blockade for blood pressure control is recommended in proteinuric disease. Early identification, exclusion of other etiologies and management of high risk features can delay progression to ESRD.
a serum albumin (sAlb) of 1.7 g/dL, and a serum creatinine (sCr) 1.2 mg/dL. Kidney biopsy shows APOL1 associated nephropathy (collapsing FSGS with 60-70% IFTA and microcystic tubular dilatation). She was initially treated with high dose steroids with UC only improving to 16 g/day after 6 months. Prednisone was decreased and cyclosporine added with varying compliance. Edema improved and hospitalizations from volume overload decreased. 18 months later patient presented with sclerotic crisis and severe anemia with hemoglobin nadir of 2.8 g/dL, sCr peaked at 3.2 mg/dL, sAlb 1.5 g/dL, and UPC of 23.5 g/g. Rituximab was given for autoimmune hemolytic anemia. Around 6 weeks later sCr improved to 2.3 mg/dL, sAlb 2.2 g/dL, and UPC remains 20 g/g, however patient still has edema and signs of volume overload.

Discussion: Historically glomerular hypertension in SCD has been seen as a secondary cause of FSGS. This case is unique in being APO1 positive and her severe presentation is more likely primary FSGS. We will continue follow-up closely and if continued improvement consider continuing low dose prednisone and additional rituximab.

PUB549

A Rare Case of Fibrillary Glomerulonephritis and Advanced Diabetic Glomerulosclerosis Class IIb in a Patient with Newly Diagnosed Nephrotic Syndrome

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Introduction: Fibrillary glomerulonephritis is a rare and underdiagnosed glomerular disorder. It was first described by Rosenmann and Eliaim in 1977. It is defined by the ultrastructural finding of haphazardly arranged, straight fibrils measuring 10 to 30 nm in thickness. According to literature, it coexists in about 20% of Type 2 diabetic patients but the connection between these is a topic of debate. We present a case of fibrillary glomerulonephritis coexisting with diabetic nephropathy in a type 2 diabetic with newly diagnosed Nephrotic syndrome.

Case Description: A 48 years old female with past medical history of CHF, polysubstance use, CKD and hypertension, who presented for follow up at renal clinic following diagnosis of glomerulonephritis in hospital. She had presented to the emergency room with uncontrolled blood pressure (245/112mmHg), acute kidney injury and nephrotic syndrome, physical examination generated 2+ pitting edema. Creatinine level was 4.1 mg/dL, eGFR of 14, urinary protein excretion was 3.1/g/day, total cholesterol of 159 mg/dL, LDL was 125mg/dL and albumin of 3.1g/dL. Kappa/Lambda ratio of 2.56, SPEP had positive polyclonal gammopathy. The patient’s kidney biopsy showed fibrillary glomerulonephritis and diabetic nephropathy, moderately advanced, diffused diabetic glomerulosclerosis, interstitial fibrosis and tubular atrophy, severe arteriolar sclerosis and moderate arteriolar sclerosis. She was offered treatment for high blood pressure with lisinopril, amloclpine, labetalol, clonidine and statins.

Discussion: Reports have shown that fibrillary glomerulonephritis can coexist with diabetic nephropathy, but a true connection has not been proven. Accelerated glycosylation of proteins in diabetics and advanced glycosylation end products capable with diabetic nephropathy, but a true connection has not been proven. Accelerated diabetic glomerulosclerosis, interstitial fibrosis and tubular atrophy, severe arteriolar sclerosis and moderate arteriolar sclerosis. It has been postulated that smoking promotes formation of advanced glycosylation end products (AGE), induction of oxidative stress, angiogenesis (increased PDGF, TGF B AND IGF-R) altering intrarenal hemodynamics. Our patient has chronic hypoxia from persistent asthma along with resistant hypertension which could be the likely culprit nephropathy in ING (he is not a smoker and never had diabetes). Further studies are needed to unravel the complex pathogenicity of ING resulting from chronic hypoxia.

PUB551

A Rare Case of Nephrotic Syndrome Precipitated by Pre-Eclampsia and Bevacizumab in a Patient with Underlying Diabetic Nephropathy

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Introduction: Nephrotic syndrome is characterized by nephrotic range proteinuria (urinary protein excretion of over 3.5 grams a day), hyperalbuminemia, edema and hyperlipidemia.

Case Description: A 27-year-old female with hypertension, chronic kidney disease, uncontrolled type 1 diabetes mellitus complicated by proliferative diabetic retinopathy (treated with intravitreal bevacizumab) and nephropathy presented to the hospital in August 2018 complaining of dyspnea on exertion, 35-lbs weight gain and lower extremity edema after being discharged from volume overload.

She was afebrile, HR 94/min and BP 158/88 mm Hg. Labs included serum creatinine 1.4 mg/dL, albumin 2.7 g/dL and nephrotic range proteinuria with a spot urine protein-creatinine ratio of 13.6 g/g. Hepatitis serologies, HIV, ANA, complement profile, ANCA and serum anti-PLA2R antibody were normal. A kidney biopsy was performed which showed a background of advanced diabetic glomerulosclerosis with severe glomerular and podocyte injury prompting a diagnosis of collapsing glomerulopathy (CG). She was started on a diuretic regimen with improvement in her symptoms and was subsequently discharged home with close follow-up with her nephrologist.

Discussion: Pre-eclampsia has been associated with kidney injury causing thrombotic microangiopathy and collapsing glomerulopathy secondary to endothelial injury following inhibition of vascular endothelial growth factor (VEGF) by the soluble fms-like tyrosine kinase 1 (sFlt 1) produced by placenta. Intravitreal bevacizumab, an inhibitor of vascular growth factor (VEGF), which is used in the management of proliferative diabetic retinopathy has similarly been associated with acute kidney injury and proteinuria/nephrotic syndrome with a wide spectrum of histological changes, including collapsing or proliferative glomerulonephritis, interstitial nephritis, and thrombotic microangiopathy. The precise mechanism of glomerular injury induced by VEGF-inhibitors is unknown and merits further studies.

PUB552

Diffuse Alveolar Hemorrhage: A Rare Manifestation of IgA Nephropathy

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Introduction: Pulmonary Renal Syndrome (PRS) describes combined renal and respiratory failure, often in the setting of glomerulonephritis (GN) with diffuse alveolar hemorrhage (DAH). IgA Nephropathy (IgAN) is the most common GN worldwide, but rarely causes DAH, and can be overlooked as a cause of PRS. We describe a case of PRS from IgAN successfully treated with plasmapheresis and glucocorticoids.

Case Description: A 71-year-old woman with hypertension and diabetes developed proteinuria and hematuria and her creatinine rose from 1.0 to 2.0 mg/dL over 9 months. Renal biopsy showed IgA nephropathy with 40-50% tubulointerstitial fibrosis and 15/33 glomeruli globally sclerosed. MEST-C score was M1, E1, S1, T1, C0. She was treated with maximum dose lisinopril. She had no findings to suggest an IgA vasculitis at the time of biopsy. Three months later she presented with dyspnea, cough, and fevers. Chest x-ray showed multifocal infiltrates concerning for pneumonia. Despite antibiotics and diuresis, she developed worsening hypoxic respiratory failure and acute kidney injury. Renal replacement therapy was started for volume removal with no improvement in respiratory failure. A bronchoscopy was diagnostic for DAH. Other vasculitic workup was negative, leaving IgAN as the etiology. With high dose steroids and 7 sessions of plasmapheresis, renal replacement therapy was stopped, proteinuria resolved, lung infiltrates cleared, and breathing returned to normal.

Discussion: Proposed mechanisms for DAH in IgAN include nonspecific mucosal hemorrhage, immune complex-mediated damage of the GBM (Type III hypersensitivity), or IgA-mediated capillaritis against GBM antigens (Type II hypersensitivity). Type II hypersensitivity is most likely given elevated IgA levels, deposition of IgA in lung tissue, and case reports of IgA deposits on the skin and circulating IgA1 immune complexes. The prognosis of PRS due to IgAN is variable. It is fatal in a quarter of patients and leads to end-stage kidney disease in half of patients. Recurrence of disease has also been documented, given its rarity. Given its rareness, we do not treat IgAN with DAH. Patients are usually given glucocorticoids and sometimes methotrexate, cyclophosphamide, or azathioprine. Plasmapheresis has also been used in treatment.
Hepatitis C-Associated Membranous Nephropathy: Key to Unlocking Publication-Only

A Case of ANCA Glomerulonephritis with Anti-GBM Double Positivity

AMERICAN SOCIETY OF NEPHROLOGY
Boston, MA, USA

Hematological malignancies have been associated with a number of secondary glomerulopathies; however, the association of Hepatitis C virus (HCV) with membranous nephropathy (MN) has not been well defined. In this report, we present a case of MN associated with HCV and review the current literature on HCV and MN.

A 52-year-old male presented with several weeks of increasing shortness of breath, orthopnea, lower extremity edema, weight gain, and one week of hemoptysis one month prior, blood urea nitrogen of 72 mg/dL, and urinalysis with 3+ protein and 3+ blood. On arrival, he was hypertensive and hypoxic. Physical exam revealed 3+ lower extremity edema, and bilateral pulmonary crackles. Labs revealed a creatinine (Cr) of 6.60 mg/dL (was 1.9 mg/dL one month prior), blood urea nitrogen of 72 mg/dL, and urinalysis with 3+ protein and 3+ blood. Urine microscopy revealed red blood cell (RBC) and muddy brown casts. Computed tomography of the chest revealed diffuse multi-focal airspace opacities. Pulmonary function tests revealed severe restrictive lung disease. The patient was hypoxic and subsequently started on non-invasive ventilation with oxygen saturation of 96%. A computed tomography of the chest and abdomen revealed diffuse ground glass opacities. The patient was evaluated for autoimmune disease and malignancy with no significant findings. A comprehensive work-up for secondary causes of renal disease was performed but was unremarkable. A renal biopsy was performed and showed diffuse mesangial hypercellularity with predominance of mononuclear cells. No diastase-resistant PAS-positive material was present. Immunofluorescence showed weak granular capillary wall staining for C3, weak linear staining for IgM, and focally granular staining for IgA. electron microscopy revealed diffuse foot process effacement with a mild increase in non-specific mesangial matrix. A diagnosis of ANCA vasculitis with anti-GBM double positivity was made. Further testing revealed elevated serum anti-GBM antibodies with normal anti-PLA2R antibodies.

Case Description: A 54 year old white male with history of hypertension, pulmonary embolism, smoking and newly diagnosed HCV presented with maculae and shortness of breath. Proteinuria was present without hematuria. Serum albumin was 1.8 with 22 grams of proteinuria on 24 hour collection. Directs were started. Creatinine was 1.42 mg/dL on admission. 4 months prior, there were 9 grams of proteinuria and creatinine was 0.98 mg/dL. Lupus panel, cryoglobulin and HJV was negative. Not hepatitis C. Renal biopsy was performed and diagnosed with Grade II Membranous Nephropathy with negative PLA2R staining. Given these findings, a diagnosis of MN associated with HCV was made. Statin, Vitamin D replacement, and an ACE inhibitor weber started. He was very morbid and had a short hospitalization and required severe immunosuppression for treatment of Hepatitis C for hopeful resolving of the membranous nephropathy.

Discussion: Apparently 3% of the world population is infected with HCV. Membranoproliferative glomerulonephritis is most common pattern associated with HCV. Though still disputed as a direct cause, growing number of cases indicate strong association and further research must be emphasized on the mechanism of this virus at the glomeruli to which it causes this degree of proteinuria. Around 8.3 % of MN patients were HCV positive. The pathogenesis of MN may be related to the deposition of immune complexes containing HCV proteins in glomeruli. It is unknown how exactly Hepatitis C initiates at the glomeruli whether glomerulonephritis or podocytopathy. If future research can determine why certain processes only allow red blood cells as opposed to only albumin, these entities, through study of Hepatitis C, can provide the key to that question.

Hepatitis C-Associated Membranous Nephropathy: Key to Unlocking Podocytopathy

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Introduction: Membranous Nephropathy is typically associated with malignancy, infections, and idiopathic. The association with Hepatitis C and MN has been debated, there is growing amount of case reports in the medical literature to suggest this connection.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Membranous Nephropathy Associated with Sjögren Syndrome, Primary Biliary Cirrhosis, and Autoimmune Hepatitis

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Introduction: Membranous nephropathy (MN) is an autoimmune glomerular disease with ~75% of cases being due to phospholipase A2 receptor antibody (PLA2R). MN may also be secondary to conditions such as autoimmune diseases, chronic infections, malignancy, and drug side effects.

Case Description: 63-year-old African-American female patient with a past history of Sjögren Syndrome (SS), primary biliary cirrhosis (PBC), and autoimmune hepatitis, was referred to nephrology clinic for proteinuria. She was receiving azathioprine, hydroxychloroquine, and a tapering dose of prednisone. Most recent serum creatinine was 0.6 mg/dL and urinalysis demonstrated proteinuria of 2+ (-), negative for erythrocytes and leukocytes. She had non-nephrotic range proteinuria of 685 mg/dL. Serologic studies were strongly positive for SS-A antibodies and also positive for anti-nuclear, anti-mitochondrial, and anti-smooth muscle antibodies. Histology of needle-core needle liver biopsy revealed predominantly periportal lymphocytic infiltration and mild cholestasis. Kidney biopsy revealed normal appearing glomeruli by LM. IF was for 3+ positive for granular deposits of IgG and IgA along capillary loops and mesangial regions and 2+ for C3 and 1+ for C1q. PLA2RB staining was negative. EM showed numerous small subepithelial and rare mesangial electron dense deposits, features consistent with secondary MN.

Discussion: MN accounts for up to one-third of biopsied cases of nephrotic syndrome. Most cases of primary MN are due to PLA2RB. Secondary causes of MN include autoimmune diseases, infection, drugs, and malignancy. Our patient developed secondary MN in association with multiple autoimmune related conditions, including SS, autoimmune hepatitis, and PBC. The combination of SS with kidney and liver involvement in one entity is extremely rare. Patients with SS can present with renal involvement of diverse etiology with chronic tubulointerstitial nephritis (TN) with mild proteinuria and tubulointerstitial fibrosis being the most common finding, followed by acute TN. However, glomerular disease due to immune complex deposition, has been rarely described in SS and PBC. Renal involvement often goes unrecognized until significant renal dysfunction occurs. The renal lesions in SS can improve significantly with treatment, emphasizing the importance of early diagnosis with renal biopsy and aggressive treatment.

Fibrillar Glomerulonephritis and Hashimoto Thyroiditis

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Introduction: FGN, a rare primary glomerular disease. Most previously reported cases of FGN were idiopathic. Underlying malignancy, dysproteinemia, or autoimmune diseases are not uncommon in patients with FGN. No fibrillary CN case report was found in association with Hashimoto thyroiditis.

Case Description: 41 y/o F of Micronesian descent. Recent U/L, gestational DM and pre-eclampsia w/ SOB, found to have an acute onset grade III AKI & nephrotic syndrome requiring dialysis. Family hx- nephw w/ ESRD of unknown etiology; currently on dialysis. U/A 3+ protein, no RBC, no granular casts. ER3-101, CRP- 2.1, mildly elevated LDH. Negative strep antibody, Cryoglobulins, HIV screening, ANCA panel, glomerular basement membrane antibody, Hepatitis panel and Double stranded DNA antibody. Monoclonal workup negative. ERA panel positive for SmNPRAb. Abnormal C normal, mildly elevated C4 levels. Normal renal U/S. Biopsy- 75 glomeruli, 90% of the glomeruli globally sclerotic. Mesangial hypercellularity, expanded matrix and thickened capillary basement membranes. A single focal and decreased by 20% mesangial deposits within capillary loops by LM, and mesangium. Interstitium with inflammatory infiltrate (3+), of lymphocytes, plasma cells and neutrophils. Medium and large-sized vessels with marked myointimal sclerosis. Cellular Changes- non-specific deposits of IgM, C3, and C1q (2+). Electron microscopy- Thickened capillary basement membranes, focal los of foot processes, isolated intramembranous deposits and large sub-endothelial mesangial fibrillary deposits. Fibrillary deposits with thickness of 20.0 nm. CT chest- Multiple right thyroid nodules. No malignancy on Abd/pelvis CT and mammogram. FNA thyroid- Cellular Changes Consistent With Lymphocytic (Hashimoto’s) Thyroiditis. Therapeutic Intervention- Considering observation of an active crescent, initially was given 3 doses of 1g Methyl prednisone and was discharged on prednisone taper. Now dialysis dependent.

Discussion: Association with autoimmune disorders and exact pathogenesis of the disorder is unclear. Further case series of such cases might indicate an association between autoimmune disorders and Fibrillar GN.

Clinicopathological Features of Hypocomplementemic Urticarial Vasculitis

Valiollah Vaziri,1 Rajan A. Subramaniam,1 Raluca Leparau,1 Marina F. Paraschiv,1 Bogdan Obruscia,1 Bogdan M. Sorohan,1,2 Sonia Balanici,1 Roxana A. Jurubita,1 Andrea A. G. Andronesi,1,2 Geni Ismail,1,2 *Nephrology, Fandeni Clinical Institute, Bucharest, Romania; 2Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

Introduction: Hypocomplementemic urticarial vasculitis (HUV) is an unusual cause of nephrotic syndrome in adults. Our patient’s flu-like symptoms, CD4 count of 604, and high viral load were consistent with a recently seroconverted HIV infection. During seroconversion, the virus replicates in tubular and glomerular epithelial cells causing the biopsy characteristics seen in HIVAN: interstitial inflammation, microcystic tubular dilation, and sclerosing multiplication of glomerular cells. Rapid development of heavy proteinuria in early HIV, as seen in our patient, should prompt high-suspicion of HIV AN. Early renal biopsy should be performed as to not delay initiation of appropriate suggested therapies. Evidence for or against these therapies were not available for our patient and a typical course of therapy is recommended for all individuals found to be HIV positive as prompt initiation has been found to be associated with longer mean renal survival. ACE/ARBs are currently recommended for proteinuric patients. Steroids have been associated with improvements in renal function but have been shown to have minimal effect on disease activity with rapid decline while on HAART. In this case, HAART was initiated and biopsy obtained within seven days of last known normal renal function. A trial of steroids was begun, and renin-angiotensin inhibition was not added.

Acute Tubulointerstitial Nephritis and Minimal Change Disease in a Patient with Allogeneic Hematopoietic Stem Cell Transplant Complicated by Chronic Graft vs. Host Disease

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Introduction: We present a case of a de novo acute nephrotic syndrome (NS) due to membranous change disease (MCD) and acute tubulo-interstitial nephritis (ATIN) following allogeneic hematopoietic stem cell transplantation (allo-HSCT) and chronic graft versus host disease (GVHD).
malignant etiologies. Light microscopy evaluation of a renal biopsy showed mild increase in glomerular mesangial cellularity and matrix deposition without endocapillary hypercellularity, segmental sclerosis, or cellular focalons. Focal interstitial inflammation was seen with an increased number of eosinophils. Immunofluorescence staining showed no specific pattern of antibody deposition. Electron microscopy showed uniform basement membrane thickening and 80% podocyte foot process effacement.

Discussion: NS is a rare complication following allo-HSCT associated with GVHD. Pathological etiologies include membranous nephropathy, thrombotic microangiopathy, and MCD, consistent with our findings. Our patient had a course of daily ibuprofen use for one month prior to presentation, which could account for his pathological findings of ATIN and MCD. Our case proposes the possibility of ATIN as an additional manifestation of renal GVHD. He was placed on oral prednisone with improvement of protein to creatinine ratio to 2.5 mg/g. Further studies will be required to identify the association between ATIN and renal GVHD.

PUB562 Membranoproliferative Glomerulonephritis Presenting with Overwhelming Cryoglobulin Deposition Masked by Acute Tubular Necrosis

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Introduction: This case highlights the importance of a thorough work up for acute renal failure, which includes determination of baseline renal function, temporality of renal insults with clinical history, urine sediment microscopy, and protein quantification. A low threshold for biopsy in the setting of active sediment, lymphopenopahy, and serologic markers can change management.

Case Description: The patient is a 46-year-old female with intellectual disability who presented with altered mental status and shock physiology, requiring resuscitation and pressor support. Her exam was pertinent for tachypnea, hypovolemia, bulky cervical lymphadenopathy, and a right knee effusion. She had anuric acute renal failure (BUN 677, serum creatinine 4.08, with normal renal function on outpatient labs 10-days prior). A urinalysis reported 4+ protein, 2+ blood. We obtained a spot urine total protein and creatinine, with a ratio of 38.17. Urine sediment by microscopy had florid coarse granular casts, tubular epithelial cells, and few non-dysmorphic RBCs. Retropertioneal ultrasound was unremarkable. Renal replacement therapy was initiated for her presumed ATN. However, her lymphadenopathy, joint effusion, and severe proteinuria did not fit simple ATN. Serologies showed EBV IgM positivity with quantification log 2.96. She was otherwise Parvovirus, CMV, HIV, Hepatitis B&C negative. QuantiFeron Gold, SPEP, IF and SELLC were also negative. Core biopsy of cervical node showed necrotizing and granulomatous lymphadenitis without malignancy. The patient underwent renal biopsy revealing lobular deposits in the mesangium, capillary loops, afferent arterioles, tubules, and Bowman’s space. Small vessels contained fragmented RBCs and deposits with karyorhexis. IF revealed 3+ C3, IgG and IgM. Supportive serologies included positive ANA, La, Ro, dsDNA, reduced C4 and normal C3.

Discussion: The patient’s shock state could have distracted from the more ominous cause of renal failure. Anuric AKI due to ATN requiring RRT is not uncommon in critical insults with clinical history, urine sediment microscopy, and protein quantification. A low threshold for biopsy in the setting of active sediment, lymphopenopahy, and serologic markers can change management.

PUB563 Scleroderma Renal Crisis with Subtle Clinical Signs in a Young Male

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Introduction: A young man with unassuaging scleroderma renal crisis with very subtle clinical signs. The reason this case is important from a renal prespective is atypical presentation of scleroderma renal crisis, it’s a diagnosis not to be missed.

Case Description: A 43 year old man presented with history of headache and neck ache with nausea and vomiting for 6 weeks. Found to have high blood pressure with renal insufficiency. Systemic inquiry no history of oral ulcers, joint pain, rash, weight loss or features of Raynaud’s phenomenon. Examination showed BP 180/100mmHg with 1+ edema over his hands. Differential diagnosis was hypertension leading to chronic renal failure, haemolytic uraic syndrome and scleroderma renal crisis. Initial investigations showed deranged renal function with features of thrombotic microangiopathy. Ultrasound kidneys-normal. ANA speckled patterns with 1:640 titres and rheumatoid factor profile was normal. Renal biopsy - Consistent with features of thrombotic microangiopathy. Initially treated as HUS with 900mg of Eculizumab. His ANA, La, Ro, dsDNA, and rest of the autoimmune profile was normal. Renal biopsy : Consistent with features of thrombotic microangiopathy. Onion ring appearance of a blood vessel.

Discussion: The patient is a 46-year-old female with intellectual disability who presented with altered mental status and shock physiology, requiring resuscitation and pressor support. Her exam was pertinent for tachypnea, hypovolemia, bulky cervical lymphadenopathy, and a right knee effusion. She had anuric acute renal failure (BUN 677, serum creatinine 4.08, with normal renal function on outpatient labs 10-days prior). A urinalysis reported 4+ protein, 2+ blood. We obtained a spot urine total protein and creatinine, with a ratio of 38.17. Urine sediment by microscopy had florid coarse granular casts, tubular epithelial cells, and few non-dysmorphic RBCs. Retropertioneal ultrasound was unremarkable. Renal replacement therapy was initiated for her presumed ATN. However, her lymphadenopathy, joint effusion, and severe proteinuria did not fit simple ATN. Serologies showed EBV IgM positivity with quantification log 2.96. She was otherwise Parvovirus, CMV, HIV, Hepatitis B&C negative. QuantiFeron Gold, SPEP, IF and SELLC were also negative. Core biopsy of cervical node showed necrotizing and granulomatous lymphadenitis without malignancy. The patient underwent renal biopsy revealing lobular deposits in the mesangium, capillary loops, afferent arterioles, tubules, and Bowman’s space. Small vessels contained fragmented RBCs and deposits with karyorhexis. IF revealed 3+ C3, IgG and IgM. Supportive serologies included positive ANA, La, Ro, dsDNA, reduced C4 and normal C3.

Discussion: The patient’s shock state could have distracted from the more ominous cause of renal failure. Anuric AKI due to ATN requiring RRT is not uncommon in critical insults with clinical history, urine sediment microscopy, and protein quantification. A low threshold for biopsy in the setting of active sediment, lymphopenopahy, and serologic markers can change management.

PUB564 A Case of Lupus Nephritis with Acute Tubulointerstitial Nephritis Presenting Multiple Low-Density Lesions on Contrast-Enhanced CT

Kakihiko Yanoano, Hirokiyuki Kawahara, Shinya Hirono, Ryo Nishioaka, Takeshi Zoshima, Satoshi Harabi, Kiyoko Ito, Ichiro Mizushima, Hiroshi Fujii, Mitsuhiro Kawano. Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan.

Introduction: Lupus nephritis (LN) usually involves glomeruli but sometimes involves the tubulointerstitium and contributes to renal dysfunction. However, there have been no case reports of the radiological abnormalities of tubulointerstitial lesions in LN.

Case Description: A 27-year-old Japanese woman was admitted to our hospital due to a suspected flare-up of systemic lupus erythematosus(SLE). She had been diagnosed 2 years previously with SLE based on malar rash and positivity for anti-nuclear, anti-ds-DNA, and anti-Sm antibodies, and treatment with prednisolone (PSL) 5 mg/day was initiated. She was transferred to our hospital 4 months ago because of fever, fatigue, left small malar rash, and renal dysfunction. Bilateral renal multiple low-density lesions were detected on contrast-enhanced CT. Her symptoms recovered spontaneously, so she was discharged under continued treatment with PSL at 20 mg/day. Three weeks ago, after tapering the PSL to 16 mg/day, joint pain, palmar and nail erythema, and fever appeared gradually, and she was re-hospitalized. A blood test showed a creatinine level of 0.91 mg/dl with no reduction in complement and no elevation of the anti-ds-DNA antibody level. Urinalysis showed a urinary protein level of 0.10 g/gcr, no microscopic hematuria, and no granular or erythrocyte casts. Contrast-enhanced CT revealed remaining bilateral renal multiple low-density lesions. Renal biopsy showed diffuse lymphoplasmacytic infiltration in the tubulointerstitium, indicating acute TIN. In the glomerular, mesangial cell proliferative phase and endo and subendothelial cellularity were observed with IgG- and C3- predominant deposition, leading to a diagnosis of LN ISN/RPS class III (A). The fever and joint pain were alleviated, and bilateral renal multiple low-density lesions disappeared when the PSL dose was increased to 30 mg/day.

Discussion: LN with acute TIN can present with bilateral renal multiple low-density lesions on contrast-enhanced CT. Tubulointerstitial lesions of LN should be considered as a differential diagnosis of renal multiple low-density lesions.

PUB565 C3-Dominant Post-Infectious Glomerulonephritis Occurring in a Patient with Meticillin-Susceptible Staphylococcus aureus Bacteremia

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Introduction: C3 glomerulopathies are a group of renal disorders characterized by complement dysregulation, and may represent a disease continuum. We present a case of C3-dominant post-infectious glomerulonephritis (PIGN) occurring in a patient with MSSA bacteremia who presented with AKI and nephritic range proteinuria.

Case Description: This is a 48 year old man with history of poorly controlled type 2 DM and osteomyelitis of right great toe, s/p digital amputation, presenting with right foot swelling, pain, and erythema. Right foot exam notable for ulcers but intact distal pulses. Admission sCr was 1.1. Admission blood cultures isolated MSSA in both sets, so patient was started on nafcillin. Echocardiogram did not show valvular vegetations. Podiatry was consulted and performed bone biopsies, which showed acute osteomyelitis. On hospital day 12, patient developed AKI with sCr 1.38 mg/dl, the following day trending up to 1.6 mg/dl. Urinalysis revealed 10-20 RBC, 5-10 WBC, and protein of 600 mg/dl, with 24 hour urine collection 10.4 g. Nephrology was consulted and autoimmune workup was negative with the exception of low serum C3 level. Renal biopsy revealed onion ring appearance of a blood vessel.
glomerulopathy is warranted.

Waqas
Microscopic Polyangiitis Presenting with Acute Abdominal Pain
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Background: Microscopic Polyangiitis (MPA) is an autoimmune systemic vasculitis that is associated with positive anti-neutrophil cytoplasmic antibodies (ANCA). MPA is divided into two categories, Proteinase 3 (pANCA)-positive and Myeloperoxidase (MPO)-positive.

Case Description: A 40-year-old woman presented with CD flare and abdominal pain, nausea, vomiting, poor oral intake, an intermittent pruritic rash and gross hematuria. She was treated with a steroid taper and re-initiation of adalimumab. On initial evaluation she was hypertensive with diffuse abdominal pain. Laboratory evaluation was notable for a serum creatinine for 3.6 mg/dL up from a baseline for 0.8 mg/dL, hematuria and proteinuria of 6.6 g/dL. Serologic studies including ANA, MPO, PR3, hepatitis B and C and anti-GBM were negative. Complement C3 and C4 were normal. Imaging showed perinephric stranding and a small non-obstructing stone. Patient was treated with steroids, adalimumab, and IV fluids. Serum creatinine peaked at 5.8 mg/dL and then trended down and patient was discharged home with close renal follow up. She was readmitted with acute kidney injury.

Discussion: The complication of SLE with AIH and PBC is very rare. A previous study demonstrated that autoimmune disease accounts for only 4.7% of cases of liver enzyme elevations in SLE patients. On the other hand, liver enzyme elevations are often accompanied by SLE; 50% of SLE patients have liver enzyme elevations. Therefore, it is very important to differentiate causes of liver enzyme elevations in SLE patients. The complications of SLE and AIH or SLE and PBC are relatively rare; however, AIH, PBC, or complications of AIH and PBC should be considered if liver disease is found in SLE patients.

PUB569
Paucci-Immune Crescent Glomerulonephritis with Re-Initiation of Adalimumab for Crohn Disease

Introduction: Inflammatory bowel disease (IBD) is associated with a number of renal disease processes most commonly nephrolithiasis, IgA nephropathy and interstitial nephritis. Certain tumor necrosis factor alpha (TNFa) inhibitors, which are commonly used for treatment of IBD, have been rarely associated with pauci immune crescent glomerulonephritis (PICG). We present a unique case of PICG in the setting of re-initiation of adalimumab (TNFa inhibitor) in a patient with Crohn’s disease (CD)

Case Description: A 40-year-old woman presented with CD flare and abdominal pain, nausea, vomiting, poor oral intake, an intermittent pruritic rash and gross hematuria. She was treated with a steroid taper and re-initiation of adalimumab. On initial evaluation she was hypertensive with diffuse abdominal pain. Laboratory evaluation was notable for a serum creatinine for 3.6 mg/dL up from a baseline for 0.8 mg/dL, hematuria and proteinuria of 6.6 g/dL. Serologic studies including ANA, MPO, PR3, hepatitis B and C and anti-GBM were negative. Complement C3 and C4 were normal. Imaging showed perinephric stranding and a small non-obstructing stone. Patient was treated with steroids, adalimumab, and IV fluids. Serum creatinine peaked at 5.8 mg/dL and then trended down and patient was discharged home with close renal follow up. She was readmitted with acute kidney injury.

Discussion: The TNFa inhibitors infliximab and etanercept have a rare association with IBD. PICG. At last follow up her serum creatinine was down trending but had not returned to normal.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.

1218
Immunotactoid Glomerulopathy in a Patient with Monoclonal B-Cell Lymphocytosis: A Rare Finding

Hitesh Glomerulopathy? Publication-Only
Rhyan Publication-Only
J Am Soc Nephrol 30: 2019
peripheral paraproteinemia. An early target-directed therapy towards B-cell or plasma-cell studies, peripheral flow cytometry and bone marrow biopsy even in the absence of a of evaluation for an underlying lymphoproliferative disorder with appropriate imaging early diagnosis and treatment. Our case in a patient with MBL highlights the importance developing end stage renal disease within few years of diagnosis, underscoring the need for
and/or mesangial organized deposits with a microtubular substructure. 40-50% of patients with reduction in proteinuria to 1.6gm, normalization of serum albumin and preserved
repeat bone marrow biopsy showed 0.01% involvement and clinical symptoms improved with a reaction in proteinuria to 1.6gm, normalization of serum albumin and preserved renal function.
Discussion: Immunotactoid glomerulopathy is characterized by glomerular capillary and/or mesangial organized deposits with a microtubular substructure. 40-50% of patients develop end stage renal disease within few years of diagnosis, underscoring the need for early diagnosis and treatment. Our case in a patient with MBL highlights the importance of evaluation for an underlying lymphoproliferative disorder with appropriate imaging studies, peripheral flow cytometry and bone marrow biopsy even in the absence of a peripheral paraproteinemia. An early target-directed therapy towards B-cell or plasma-cell clone may result in preservation of renal function.

Membranous-Like Glomerulopathy with Masked IgG Kappa Deposits

Rhyvan Madrigal,1,2 Jonathan J. Taliercio,1,2 Cleveland Clinic, Cleveland, OH; 1Glickman Urological and Kidney Institute, Cleveland, OH.
Introduction: Glomerulonephritis is pathologically diagnosed by examining changes using light, immunofluorescence, and electron microscopy of the renal biopsy. Routine direct immunofluorescence on fresh tissue is considered the gold standard for the detection and characterization of immune deposits. An additional antigen retrieval step has recently been developed that enhances the visualization of immune deposits. A recent study evaluated this technique in correlation with renal biopsy findings.
Case Description: 33-year-old female with a past medical history of three pregnancies presented to nephrology clinic for evaluation of proteinuria. During her second and third pregnancies she developed proteinuria. During her second pregnancy, a 24-hour urine collection revealed 0.53 grams of protein. During her third pregnancy, a 24-hour urine collection revealed 1.99 grams of protein. She never experienced hypertension or proteinuria.
Discussion: Routine immunofluorescence is considered the gold standard for detection of protein in kidney biopsies. Light-chain proximal tubulopathy crystalline inclusions in the proximal tubule occasionally do not react with immunofluorescence. Without marking of the immunoglobulin with pronase, many patients may be incorrectly labeled as C3 glomerulonephritis, a disease with C3-restricted deposits that can show predominance of subepithelial deposits by electron microscopy. Membranous-like glomerulopathy should be considered in all patient with unexplained proteinuria in the setting of autoimmune disease.

Lupus-Mediated Kidney Damage: Lupus Nephritis or Collapsing Glomerulopathy?

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Introduction: Lupus nephritis is a well-known entity and treatment options for it are clearly defined. However, Lupus nephritis with collapsing glomerulopathy (CG) is less common and pose special challenges in terms of management.

Case Description: 47-year-old Hispanic female presented with chills, epigastric discomfort and lower extremity edema for 10 days. 1-2+ bilateral lower extremity pitting edema found on examination. Labs revealed Normocytic anemia, hyperlipidemia, hypoproteinemia. Creatinine of 6.3 mg/dl Marked proteinuria. UPCR 17 g/g. Hypocomplementemia present. ANA titers 1:40. Anti-dsDNA, ANCA, anti SM and RNP negative. Renal biopsy: collapsing glomerulopathy superimposed on focal glomerulosclerosis, immune complex type, suggestive of lupus podocytopathy superimposed on lupus nephritis class III. Treatment: patient treated with IV pulse Methylprednisolone 1g for 5 days and Cyclophosphamide 500 mg IV, and then Prednisone tapering down to 80 mg daily. Creatinine levels decreased to 4.3 mg/dl (first creatinine levels reported, on July 4/2018) to 2.8 mg/dl (on August 25/2018).
Discussion: Reports of SLE-related CG with Lupus Nephritis are lacking. The patient described in this case report has both findings. In the largest series of cases with biopsy-proven CG in the setting of SLE or SLE-like disease, Salvatore et al. showed that only 7 patients (out of 19) had morphologic changes of lupus nephritis along with CG findings. To the best of our knowledge, fewer than 25 cases have been reported about this specific finding. For the treatment of Lupus Nephritis class III/IV, the immunosuppressive treatment consists on induction and maintenance phases. As per the guidelines of the American College of Rheumatology, induction therapy should consist of steroids combined with mycophenolate or cyclophosphamide, for about 6 months. Rationale to use cytotoxic drug like cyclophosphamide in such cases is because these variants have progressive and relentless course.
IgA Nephropathy Causing Rapidly Progressive Glomerulonephritis

NEIL RANGWANI, MANSUR ASSAAD, RUPESH RAINA. 

**Introduction:** Although IgA nephropathy (IgAN) is the most common cause of glomerulonephritis worldwide, this condition is seldom reported as a cause of rapidly progressive glomerulonephritis (RPGN). Furthermore, it is not commonly reported as a cause of glomerulonephritis in African Americans. IgAN can rarely present as a more aggressive RPGN, and patients may display different degrees of renal dysfunction, hypertension, edema, and proteinuria. Prompt renal biopsy is often needed in these patients, as management often differs depending on the underlying pathology.

**Case Description:** A 26-year-old African American male with no prior past medical history presented with acute-onset shortness of breath, cough, and musculoskeletal chest pain. Lab work was indicative of a new acute kidney injury with a creatinine of 4.02 mg/dL and notable proteinuria with a urine microalbumin-creatinine ratio of 7.5 mg/mg. The patient was admitted, and the nephrology team was consulted. Further lab work showed a negative ANA level, negative ANCA titer, normal C3 and C4 levels, negative HIV screen, negative hepatitis panel, normal plasma aldosterone-renin activity ratio, and normal plasma metanephrine level. Although urinary free kappa light changes and free lambda light chains were notably elevated, the free kappa-lambda light chain ratio was within normal limits. Renal biopsy revealed IgA-mediated immune-complex glomerulonephritis with marked arteriolar sclerosis and glomerulosclerosis. He received high-dose intravenous (IV) methylprednisolone and IV bumetanide. The patient improved significantly and was discharged on a prednisone prednisone taper. The patient later started immunomodulatory therapy with mycophenolate mofetil for his biopsy-proven rapidly progressive IgA crescentic glomerulonephritis.

**Discussion:** Rapidly progressive crescentic IgA nephropathy is rare, and there are few reported cases showing evidence of progression to end-stage renal disease (ESRD) with variable response to immunosuppression. Current data suggests that renal survival in cases of rapidly progressive crescentic IgAN is 50% at one year and 20% at five years. There is only recently published data supporting the use of high-dose corticosteroids and immunosuppressive therapies in patients with crescentic IgAN. Although a rare cause of RPGN, IgAN should be considered, and kidney biopsy should be pursued early so as to not delay appropriate renal-saving therapy.

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**ANCA-Associated Glomerulonephritis with Linear GBM Staining in the Absence of Anti-GBM Antibody: A Variant of Double-Positive MPO and Anti-GBM Antibody**

JANIS CHo, YASHPAL S. KANWAR, VIKRAM AGGARWAL. 

**Introduction:** Anti-glomerular basement membrane antibody disease (Anti-GBM) is a rare disease with severe renal-pulmonary manifestation. About 10-38% of patients with anti-GBM nephritis also has positive ANCA at the time of diagnosis, most often P-ANCA. They are termed double positive and has different prognosis and outcomes. Recently, there has been described patients with renal biopsies with linear GBM immunoglobulin staining without detectable anti-GBM antibodies. Such diagnosis is termed atypical anti-GBM disease with overlap with ANCA-associated vasculitits (AAV).

**Case Description:** A 70-year-old Indonesian male with past medical history of vitiligo, chronic kidney disease, hypertension, and prostate cancer with recent radiation treatment was hospitalized for management of overt hematuria and acute kidney injury. He had nephritic presentation and no evidence of obstructive nephropathy. Kidney biopsy showed 40% crescentic glomeruli, necrotizing glomerular lesions, 20% sclerosis and tubular atrophy, few small subendothelial deposits on electron microscopy, and linear GBM reactivity with anti-IgG on immunofluorescence. Serology showed negative Anti-GBM antibody, positive P-ANCA antibody 1:160 and MPO antibody elevated to 21.4. He had no pulmonary manifestations. He received high dose steroid, 6 doses of plasmapheresis and rituximab. He was discharged with tapering steroids and received repeat rituximab in 2 weeks. At 3 month, creatinine improved to nadir 2.08 mg/dl and started azathioprine for maintenance therapy.

**Discussion:** Our patient had linear IgG staining consistent with Anti-GBM disease without anti-GBM antibody (Atypical anti-GBM disease) overlap with P-ANCA positivity. While overlap of typical anti-GBM disease and AAV has been described, coexistence of atypical anti-GBM nephritis and AAV as a variant is rarely reported. The overlap syndromes with double positive antibodies (anti-MPO and anti-GBM) has a distinct clinical phenotype needing better understanding of pathogenesis, recognition of specific epitope, classification, prognostication and different treatment strategies. Recently, anti-peroxidasin antibodies disrupting collagen structure of GBM and cross-reacting with MPO have been identified and can help elucidate such overlap syndromes.
Parvovirus B19: Does It Cause Kidney Disease? A Case Presentation and Review of the Literature

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Introduction: Parvovirus B19 (HPVB19) is a DNA virus linked to multiple clinical syndromes and has been linked to glomerular disease. Here we present a rare case of acute HPV B19 infection and unexplained end stage kidney disease with literature review.

Case Description: A 20 year-old male presented to an Australian teaching hospital with 3 weeks of nausea and vomiting, confusion, headache, diarrhoea, fevers, abdominal rash and pleuritic chest pain. He was hypertensive at 190/135mmHg with sinus tachycardia of 118bpm. He had a pericardial rub and saddle ST-elevation on ECG. Echocardiogram confirmed a moderate-sized pericardial effusion. His creatinine was 1930 μmol/L with urea 61.4 mmol/L. Haemoglobin was 68g/L with platelets of 246 x 10^9/L and an MCV of 84fL. Blood film and haemolysis screen were unremarkable. ADAMTS-13 was normal and a glomerulonephritis screen was negative. Urine PCR was 642 g/mol creatinine with 60 leucocytes x 10^6/L and 40 erythrocytes x 10^6/L. The patient was commenced on haemodialysis. Renal biopsy showed a mesangial-proliferative pattern. There was severe tubular atrophy and interstitial fibrosis, moderately severe arteriosclerosis and arteriolosclerosis and a chronic inflammatory infiltrate. Arterioles showed features of acute thrombotic microangiopathy. Immunofluorescence was non-specific. Electron microscopy revealed foot process effacement and tubuloreticular inclusions. Parvovirus particles were not seen. Persistent anaemia prompted HPVB19 serology with an initial negative test. However, 3 weeks later the IgM and IgG titres were elevated. HPVB19 DNA was detected in renal biopsy tissue on PCR. After 3 months, he showed no evidence of renal recovery.

Discussion: 10 cases have been reported with an acute illness associated with HPVB19. Serum positivity for IgG and IgM, renal disease and renal tissue DNA PCR positivity. 2 patients had an FSGS lesion with the remaining 9 demonstrating endocapillary glomerulonephritis. A consistent correlation between PCR positivity for HPVB19 on renal tissue and renal disease has not been proven. This was a rare case of end stage kidney disease, fever, anaemia and pericarditis associated with acute HPV B19 infection. This work adds to the body of knowledge describing the potential for HPVB19 associated glomerulopathy in our patients.

Diabetic Ketoacidosis and Atypical Hemolytic Uremic Syndrome: An Unlikely Pairing

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is an extremely uncommon, life-threatening illness, characterized by the triad of microangiopathic haemolytic anaemia (MAHA), thrombocytopenia and acute renal failure. Diabetic ketoacidosis (DKA) as a result of new-onset Type II diabetes mellitus has never been described as an initial presentation of aHUS.

Case Description: A 31-year old African American male with no past medical history presented with altered mental status. Four days prior to admission, the patient returned from a trip to Belize, where he exhibited new-onset polyuria, polydipsia, polyphagia and severe nausea. Initial assessment was consistent with DKA. Patient was also found to have acute kidney injury secondary to pre-renal azotemia. Four days into admission, clinical course deteriorated: patient developed MAHA (hemoglobin-6.9 g/dL & lactate dehydrogenase-3452 units/L), a drop in platelet count with schistocytes (260 to 18 K/mm³) and worsening kidney function; evolving from pre-renal azotemia to acute tubular necrosis with anuria. Despite initiation of hemodialysis, kidney function did not markedly improve (BUN-111 mg/dL & serum creatinine-12.20 mg/dL). This prompted renal biopsy which revealed thrombotic microangiopathy (TMA), cortical infarct and collapsing glomerulopathy. The differential diagnosis of TMA can include thrombotic thrombocytopenic purpura, Shiga-toxin producing Escherichia coli hemolytic uremic syndrome and aHUS. As ADAMTS13 activity was normal (59%) and stool culture was negative for Shiga-toxin, a diagnosis of aHUS was made. Treatment was initiated with plasmapheresis in conjunction with IV eculizumab. Within five days of treatment, patient’s percentage of patients despite optimum known medical management (i.e. plasmapheresis). Even with eculizumab use, most aHUS patients develop end-stage renal disease and undergo chronic dialysis. Our patient due to early detection and initiation of the above, demonstrated normalization of kidney function and was able to come off hemodialysis 6-months post-discharge. This case highlights DKA as an atypical initial precipitant of aHUS and the importance of early eculizumab use for treatment in hospitalized patients over plasmapheresis alone.
A Rare Case of Isolated IGA Nephropathy Without Granulomas
Associated with Neurosarcoidosis

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Introduction: Systemic sarcoidosis associated with a variety of glomerular and interstitial lesions. We present an interesting case of neurosarcoidosis with concomitant IgA nephropathy without renal granulomas.

Case Description: 40 years old Hispanic male with past history of anemia, CKD stage 3 presented to hospital with, left sided facial droop and reduced visual acuity in the left eye. He reported, weight loss and night sweats few weeks prior. CT chest, abdomen and pelvis which showed diffuse nonspecific lymphadenopathy, head and neck imaging was unremarkable. Pertinent labs ACE level ~97 unit/L (normal range 14-82 units/L) Quatiferon negative,. Patient was started on oral steroids. Lymph node Biopsy - reactive changes with non-necrotizing granuloma. He was diagnosed as neurosarcoidosis. Patient presented a month later with progressive lower limbs edema and AKI. Patient admitted he had not been compliant with his medications (oral steroids). Creatinine on admission ~ 2.5 mg/dl (baseline 1.7mg/dl), Urine protein to creatinine ratio was 3.5 g/24hours. Renal biopsy was performed. Renal biopsy showed LM-hypertensive nephropathy, focal Nephrosclerosis and mesangial hypercellularity, IF was 3+ for IgA. EM showed mesangial and subendothelial electron dense deposits, diffuse foot process effacement (fig2). Patient was started on IV and oral diuretics, Oral Steroid treatment was restarted with improvement in creatinine to 2.0 mg/dl, edema and proteinuria.

Discussion: Sarcoidosis has been associated with a myriad of glomerular and interstitial lesions. The epidemiological and biological factors affecting the phenotype of renal involvement in sarcoidosis need larger studies including renal biopsy, proteomic, metabolomics and genomic profiling of such patients.

Immunosuppression was not initiated. HCV was treated with Mayvert, resulting in a sustained viral response. Six months after viral clearance, proteinuria improved to 2 gms/gm on spot ratio, ANA remained negative and creatinine was stable at 1.2 mg/dl.

Discussion: In HCV MPGN, IC deposits are typically restricted to the subendothelial and mesangial compartments and are of the IgG class. Full-house IF staining is a hallmark feature of LN, but was not observed in our case. We report a case of SLE. Reports of full-house nephropathy with negative serologies for SLE exist. Conditions with the potential for polyclonal B cell expansion, such as HCV and HIV, can result in IC formation and staining patterns mimicking a “lupus-like” IF. This is seen with sustained viral clearance, proteinuria improved to 2 gms/gm on spot ratio, ANA remained negative and creatinine was stable at 1.2 mg/dl.

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**PUB586**

Polyautoimmunity Syndrome with Renal Involvement: Kaleidoscopic Presentation of a Systemic Syndrome

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**Introduction:** Polyautoimmunity is defined as the presence of more than one autoimmune disease; few publications emphasize kidney damage and its treatment. We present the case of a patient with polyautoimmunity syndrome and renal affection by three autoimmune diseases.

**Case Description:** 40-year-old female with history of systemic lupus erythematosus diagnosed in February 2015, without renal involvement during follow-up. In May 2018 she complained of fatigue, generalized hyperpigmentation and thickening of the skin, Raynaud’s phenomenon, followed by sclerodactyly and gastric reflux. In December 2018 she consulted rheumatology service, who diagnosed Sjögren Syndrome (dry mouth/eye symptoms, salivary gland biopsies, positive Schirmer test and anti-Ro elevation) and systemic sclerodermma (thickening of skin on hands, telangectasias, Raynaud’s phenomenon, anti-topoisomerase II positive); after an arrangement to nephrology clinic because of serum creatinine of 2.24 and proteinuria in 24 hours of 1.2gr, a kidney biopsy was performed and revealed glomerulonephritis consistent with classII lupus, active tubulointerstitial nephritis with plasma cells and acute tubular injury, chronic glomerular hyperperfusion, grade II interstitial fibrosis, obliterative arteriopathy, changes attributable to Sjögren’s syndrome and scleroderma. Treatment was started on mycophenolate mofetil due to the risk of renal scleroderma crisis. Currently, the patient reports clinical improvement and proteinuria decreased to 0.7gr/gr.

**Discussion:** Our case reports the renal affection of three autoimmune pathologies with different temporality and therapeutic approach. The difficulty lies in the treatment of renal disease with contraindication to the use of steroids for the treatment of tubulointerstitial nephritis due to risk of renal scleroderma crisis. Likewise, the treatment of proteinuria with ACEI or ARB II is complex due to the probable masking of the aforementioned crises.

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**PUB587**

Efficacy and Safety of Sofosbuvir Plus Simeprevir as Therapy for HCV-Associated Glomerulonephritis: Report of Two Cases

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**Introduction:** HCV patients with glomerulopathies were treated, initially, peg-interferon (PEG-IFN) associated with ribavirin (RBV), but this therapy has been induced serious side effects and low sustained virologic response (SVR). The new direct-acting antivirals (DAAs) treatment are considered revolutionary antiviral therapy, leading to infection cure in more than 90% of patients. Since 2016 new reports have emerged using DAAs in HCV-associated glomerulopathies but there are still few reports.

**Case Description:** Patient 1 - male, 41-year-old, with diagnosis of chronic HCV infection associated with glomerulopathy admitted in 2016 with nephrotic syndrome with anti-HCV and HCV-RNA positive (viral load of 2,064,884 UI/mL and log 6). He was treated with SOF (400 mg/day) plus SIM (150 mg/day) for 12 weeks, evolving with normalization of aminotransferases normalizations and HCV-RNA negativity at the end of treatment and after 12 weeks (SVR), cryoglobulinemia negativity and significant proteinuria reduction. Patient 2 – male, 50-year-old, was diagnosed 24 years ago with HCV infection prior to blood donating. He lost outpatient follow-up and returned in 2005, when genotype 1b infection was identified. He had no response to PEG-IFN plus RBV and in 2014, he presented with thrombocytopenia, nephrotic syndrome, C3 and C4 consumption, cryoglobulinemia positive. In 2016, he was treated with SOF plus SIM for 12 weeks, evolving with transaminases normalization, HCV-RNA negativity at the end of treatment and after 12 weeks, cryoglobulinemia negativity and significant reduction of proteinuria. Baseline and after treatment exams are in Table.

**Discussion:** This report describes two cases of HCV related Glomerulopathy with cryoglobulinemia treated with SOF plus SIM therapy showing no significant side effects and improvement hepatic and renal diseases.

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**PUB588**

Collapsing Glomerulopathy Superimposed on Diabetic Nephropathy: A Case Series

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**Introduction:** Diabetic nephropathy is the leading cause of End Stage Renal Disease (ESRD) in many countries. 35-45% of both Type-I and Type-2 diabetic patients develop ESRD in 20-35 years. Some patients present with new onset nephrotic range proteinuria and deteriorating renal functions. Renal biopsy showed non-diabetic glomerular lesion in 10-12%. The development of collapsing glomerulopathy in the background of diabetic nephropathy is a very rare phenomenon. We present a case series of 6 cases of Collapsing Glomerulopathy superimposed on Diabetic nephropathy.

**Case Description:** The average age of our patients was 55 years. All 6 patients had history of long standing Type-2 Diabetics Mellitus - average of 15 years. Baseline serum creatinine in 3 of them was in the range of 1.8-3.5 mg/dL. The clinical presentation and indications for renal biopsy were: 2 patients had progressive renal failure, 2 patients had new onset nephrotic range proteinuria requiring ICU care, 3 patients had worsening oedema and uncontrolled blood pressures, 1 patient had new onset hypertension and pedal oedema. All patients had nephrotic range proteinuria. 4 patients had severe renal failure at presentation and were initiated on dialysis. 2 patients had a subclinical creatinine clearance of 4 ml/min and 1.8mg/dl. Renal biopsy showed collapsing glomerulopathy superimposed on diabetic nephropathy. 1 had class IIb, 1 had class III, and 4 had class IV diabetic nephropathy. 3 biopsies had Interstitial fibrosis and Tubular atrophy (IFTA) more than 50%. All biopsies showed arterial hyalinosis. 4 patients who presented with severe renal failure were listed as ESRD and were continued on hemodialysis. 2 patients were in CKD stage 3 at presentation, progressed to ESRD by next 2 years and later underwent renal transplant.

**Discussion:** Collapsing Glomerulopathy contributes to an increased level or a new onset proteinuria in Diabetic nephropathy. This is usually intractable and rapidly progresses to End Stage Renal Disease (ESRD). Collapsing Glomerulopathy in Diabetic nephropathy is presumably due to ischemic podocyte injury and is of prognostic significance.

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**PUB589**

From Membranous Nephropathy to Proliferative Glomerulonephritis with Monoclonal IgG1 Kappa Deposits: A Pediatric Case

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**Introduction:** Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a rare entity described mainly in adults with only 6 reported cases in 2016. It is characterized by monoclonal immunoglobulin deposits in the kidney which can mimic immune complex glomerulonephritis. Histologic patterns described are membranoproliferative or endocapillary proliferative with membranous features. If stains most commonly for IgG3 Kappa and EM reveals granular non-organized deposits. Dysproteinemia is detected in 50% of cases. This case illustrates the challenge of diagnosis of PGNMID in a young girl with primary membranous nephropathy (pMN).

**Case Description:** A 19-year-old woman with pMN was transferred from the pediatric to the adult nephrology clinic with anasarca. At 13 years of age she was found to have a monoclonic syndrome secondary to biopsy proven MN. The urine PCR was 4g/l. She received prednisone then a calcineurin inhibitor then rituximab without clinical response. A repeat biopsy three years later showed membranous like glomerulopathy with monoclonal IgG1 Kappa deposits. Prednase dosage was not done. She was maintained on conservative therapy with RAAS blockade. Repeat work-up was significant for 24h urine PCR 10g/l, serum albumin 2g/dl, Scr up to 1.5mg/dl, + speckled ANA (1:320), negative serum PLA2R antibody. A third kidney biopsy showed PGNMID IgG1 kapa (Figure 1).
Secondary Syphilis-Associated Crescentic Glomerulonephritis
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Introduction: Syphilis-associated nephropathies are uncommon. Membranous nephropathy (MN) is the most well-recognized while crescentic glomerulonephritis (CGN) is rare. We report the second case in the literature of secondary syphilis-associated CGN.

Case Description: A 71-year-old male was admitted with shock and oliguric acute kidney injury with a serum creatinine of 3.89 mg/dL (baseline 1 mg/dL). He reported having a skin rash preceded by a transient painless penile lesion. Urine sediment showed dysmorphic RBCs, abundant WBCs, muddy brown and coarse granular casts. Urine protein/creatinine ratio was 1300 mg/g. Laboratory investigations revealed a positive (1:256) rapid plasmin reagin. Syphilis infection was confirmed by a reactive Treponema pallidum passive particle agglutination test. Immune and serologic tests were all negative including ANCA. A renal biopsy showed diffuse necrotizing CGN with greater than 75% cellular crescents and MN. The patient was treated with penicillin G, pulse methylprednisolone for 3 days, oral prednisone, and hemodialysis. He was discharged 20 days after admission, with improved urine output but remained dialysis dependent. At follow-up weeks later, the patient still required hemodialysis. He refused re-biopsy and no other immunosuppression was tried given his poor compliance with close follow-up visits.

Discussion: Syphilis-associated kidney disease is uncommon with a reported incidence of 0.3% and is usually associated with secondary syphilis. Secondary syphilis-associated CGN is very rare with only one previously reported case in the literature. As in infectious GN, treatment is aimed at the underlying infection. The use of corticosteroids is recommended by some experts when crescents are present. There is no clear evidence that additional immunosuppression is beneficial. In the first reported case of secondary syphilis-associated CGN described by Walker et al (Am. J. Med. 76: 1106-1112, 1984), plasmapheresis was empirically used for suspected vasculitis followed by corticosteroids and the acute kidney injury improved but without returning kidney function to normal. The present case adds to the evidence that secondary syphilis can be associated with crescentic glomerulonephritis. The clinical course of this patient points to the need for better treatments for this rare, yet important, condition.

Fibrillar Glomerulonephritis Presenting as Hematuria
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Introduction: Fibrillar glomerulonephritis (FGN) is a glomerular disease with pathognomonic findings seen on EM revealing randomly arranged nonamylod as fibrils deposits that are 10 to 30nm. The disorder is found only in <1% of native kidney biopsies. New markers such as DNAJB9 has shown to identify FGN without the need of EM. Serum level of DNAJB9 has also been shown to predict diagnosis of FGN. This case is unique since patient did not have the classic signs of FGN. Currently there are no optimal treatments for idiopathic FGN and high as 40-50% of patients develop ESRD.

Discussion: While LP was initially thought to reflect a rare co-existence of LN with other glomerulopathies, the sparse data so far seem to denote it as an unclassified LN variant characterized by nephrotic-range proteinuria and diffuse foot process effacement in the absence of endocapillary proliferation. In order to avoid misclassification and management errors, clinicians should be aware of this variant; in the cases of a discrepancy between clinical presentation and histological findings a diagnosis of LP needs to be contemplated and the nephrologist should insist on electron microscopic examination of the glomeruli.
Atypical Hemolytic Uremic Syndrome in a Patient with Primary FSGS

Introduction: Atypical hemolytic uremic syndrome (aHUS) is an uncommon cause of acute kidney injury accompanied by hemolysis and thrombocytopenia. It can occur as a primary disorder or secondary to an underlying systemic disorder or drug. Case Description: The patient is a 33 year old female diagnosed with biopsy proven minimal change disease in 2013. Subsequent biopsy in 2015 performed due to persistent nephrotic range proteinuria despite treatment showed focal segmental glomerulosclerosis (FSGS). She was treated with mycophenolate mofetil and steroids. In April 2018, her creatinine was 1.3 mg/dl with UPCR of 1.7 g/mg. Mycophenolate and prednisone were stopped. She was given hormonal therapy for upcoming egg harvesting. In July she had UACR of 3.8 g/g and creatinine of 2.0 mg/dl and resumed her mycophenolate and prednisone. Her nephrotic syndrome worsened and she was admitted to the hospital in September. At that time, her creatinine was 3.4 mg/dl, UPCR 7.6 g/mg, hemoglobin 10.6 g/dl and platelets 238 k/µl. Her creatinine, hemoglobin, and platelets rapidly worsened over the next five days (5.2 mg/dl, 6.8 g/dl, and 50 k/µl respectively). ADAMTS13 was 70%, shiga-like toxin was negative, C3 was mildly low, and C4 was normal. A lesion in her axilla was positive for varicella zoster virus (VZV). Eculizumab was started due to concern for aHUS. Renal biopsy demonstrated focal segmental and global glomerulosclerosis as well as changes of thrombotic microangiopathy (TMA) and tubular injury. Immunofluorescence was negative. Electron microscopy examination showed thickening of the glomerular basement membrane, expansion of subendothelial space, mesangiosis, and nearly complete foot process effacement without electron dense deposits. Prior biopsies were reviewed with no evidence of TMA. Genetic testing was performed which was equivocal for aHUS genetic mutations. She was continued on eculizumab but progressed to ESRD.

Discussion: aHUS is a rare syndrome and this case is an exceptional presentation of disease. Though there have also been case reports of genetic aHUS developing in patients with pre-existing FSGS, this is not a common association. There have also been case reports of VZV infection triggering aHUS. U.S. Government.

Disclosure: The views expressed are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense (DoD), or the U.S. Government.

PUB595
Ruptured Intracranial Aneurysm as Presentation for Systemic Lupus Erythematosus (SLE) and Antineutrophil Cytoplasmic Antibody-Associated Vasculitis (AAV) Overlap Syndrome

Introduction: We present a rare case of intracranial aneurysm rupture as presentation of SLE AAV (Systemic Lupus Erythematosus ANCA Associated Vasculitides) overlap syndrome. Only one other case of overlap syndrome presenting with hemorrhagic stroke has been reported. Two other cases have been reported to present with cerebral ischemia.

Case Description: 53-year female with HTN, h/o hemorrhagic pontine stroke (at age 50), inflammatory arthritis and CKD presented with headache and altered mental status. Family history of early stroke or HTN or kidney disease. HTN had been well controlled on metoprolol 25 mg daily and hydralazine 50 mg bid. CT scan showed diffuse subarachnoid hemorrhages with slightly greater involvement of R Sylvian fissure and mild ventriculomegaly. EVD drain was placed and patient underwent urgent cerebral angiogram with coiling of ruptured R PCA aneurysm. No bleeding noted from L PCA aneurysm. Patients’ clinical condition did not improve after coiling of aneurysm and EVD drain placement. She continued to have significant EVD drainage and was scheduled for VP shunt placement. Patients’ baseline serum creatinine was ~15 mg/dl with no known proteinuria or hematuria. On admission, patients’ creatinine was 2.9. While frank hematuria after addition of antplatelet agent resolved, she continued to have microscopic hematuria. Quantitation in urine showed 6.2 g/g proteinuria. Necrotic workup revealed ANA (1:640), low complements, p-ANCA positive, MPO positive. Renal biopsy showed nephritis (generalized glomerulonephritis). After initiation of steroids, patients mental status improved and EVD drainage decreased. Patient also received Cyclophosphamide. Her creatinine improved to previous baseline of 1.5 and proteinuria below 1g/g on follow up.

Discussion: Rapid neurologic and renal recovery was seen in response to immunosuppressive therapy. While renal involvement is common in SLE-AAV, neurologic involvement is rare. To our knowledge, this is the second case described in the literature with overlap syndrome (∆ANA and ANCA) presenting with intracranial hemorrhage. Prompt diagnosis and treatment is crucial in management of such complicated case.

PUB596
Double Trouble: Combined ANCA Vasculitis Relapse and Antibody-Mediated Rejection in a Kidney Transplant Recipient

Introduction: A female kidney transplant recipient, presented with graft dysfunction associated with headache, polyarthralgia, sinustitis, epistaxis, fatigue and vomiting for 2 weeks. She had a history of PR3 positive anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), diagnosed 6 years prior, resulting in end-stage renal disease, despite treatment with the CYCLOPS protocol and plasma exchange. She received a standard immunologic risk deceased donor kidney transplant 3 years later. Maintenance immunosuppression (IS) included Prograf 7mg BD, Mycophenolate Mofetil 750mg BD and prednisolone 5mg OD. The patient denied medication non-adherence.

Case Description: Examination was unremarkable. Initial investigations revealed severe non-oliguric acute kidney injury (creatinine 685 µmol/L from 110 µmol/L baseline). Urinalysis showed many red cells and 1+ protein. Serum creatinine peaked at 2 mg/dl and at last follow-up was 1.6mg%. Myeloperoxidase (MPO) ANCA (>100 U/ml) and histone AB were positive, suggesting drug-induced SLE with ANCA positive pauci-immune glomerulonephritis, with hyaline casts as the offending agent.

Discussion: Hyaline casts are widely used, but may have rare, severe side effects, including lupus-like syndrome. In our patient, renal function stabilized after hyaline casts discontinuation, and appropriate treatment for ANCA-associated glomerulonephritis. ANCA vasculitis has been rarely reported in hyaline casts-associated lupus syndrome, and then in conjunction with MPO antibody, rather than Proteinase 3, as in our patient. Disclosure: The views expressed are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense (DoD), or the U.S. Government.

PUB597
Rare Presentation of Membranoproliferative Nephropathy in Pulmonary Alveolar Scleroderma

Introduction: Pulmonary alveolar proteinosis (PAP) is characterized by intra-alveolar accumulation of phospholipid and protein-surfactant material with minimal inflammation or fibrosis. Membranoproliferative nephropathy (MPN) has rarely been associated with PAP and to

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

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our knowledge has not been previously reported in minimal change disease (MCD). We describe a patient with MCD who subsequently developed MN in the setting of PAP.

**Case Description:** A 43-year-old female with low dose steroid-dependent MCD and idiopathic PAP associated with asthma and eosinophilia presented with acute dyspnea, fever, and malaise. She was found to have nephrotic range proteinuria, eosinophilia (18,000/mm³) and eosinophiluria. Secondary causes of eosinophilia were excluded. Bone marrow biopsy revealed hypocellular marrow with eosinophilia without fibrosis, myeloproliferative or clonal hematopoietic processes. Serum IgE levels were elevated (3556 IU/L). Bronchoscopy confirmed PAP and bronchoalveolar lavage showed >85% eosinophils. She developed non-oliguric AKI with serum creatinine increasing from 0.8 mg/dl to 2.8 mg/dl. Urinalysis showed 3+ protein and 4+ eosinophils. 24-hour urine collection demonstrated 10,428 mg of protein; serum albumin was 3.1 mg/dl.

Autoimmune and infectious serologies were unremarkable, as were complement levels and tests for immunohemolysis and rheumatoid factor. Renal biopsy showed subepithelial immune complex deposits with minimal basal membrane reaction, segmental thinning of GBM, and no eosinophilic infiltration. Serum PLA2R titers were negative and other autoantibodies and serum immunofixation electrophoresis results. Renal biopsy showed membranous nephropathy (n=3), crescentic GN, IgAN, ECPGN, and lupus nephritis. All patients were complicated with autoimmune antibody positivity. After treated by steroid (1mg/kg/d) and/or immunosuppressant, significant improvement in proteinuria and Scr were observed.

**Discussion:** Renal involvement of MN is rare, and the prognosis of UC associated glomerulonephritis is well.

### Table 1 Clinical data of 7 cases of UC associated glomerulonephritis

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>35</td>
<td>45</td>
<td>41</td>
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<td>Creatinine (mg/dl)</td>
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<td>1.3</td>
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<td>BUN (mg/dl)</td>
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| Triglyceride | 190/120. Initial labs were notable for a serum creatinine of 2.8mg/dl, albumin of 2.4g/dl, platelet count of 134,000, total cholesterol of 265mg/dl, and estimated 24 hour urine protein of 15g/day with no hematuria. Renal ultrasound revealed normal sized kidneys and was negative for renal vein thrombosis. Echocardiogram demonstrated an ejection fraction of 25% and left ventricular hypertrophy. Serologic work-up was positive for Hepatitis B surface antigen, envelope antigen, and HBV-DNA (>170,000,000 IU/ml) and otherwise negative including HIV, HCV ab, Parvovirus B19, CMV, hemoglobin A1c and urine drug screen. Renal biopsy demonstrated CGP, thickened glomerular basement membranes and moderate hyalination of arterioles. Immunofluorescence had nonspecific staining and there was no immune complex deposits on electron microscopy. There was 10% visceral epithelial cell foot process effacement. There were no viral cytopathic changes. Tenoforv was initiated and aggressive blood pressure control was achieved during hospitalization. Subsequently, proteinuria decreased to 3g per day with a gradual improvement in serum creatinine to 2.1mg/dl at discharge.

**Discussion:** CGP is a distinct pattern of proliferative parenchymal injury with a number of infectious causes previously identified. There are few reported cases of its association with hepatitis B infection. In our case, an adult African American male presented with acute hepatitis B associated CGP and subsequent malignant hypertension leading to severe ischemic injury, nephrotic range proteinuria, renal dysfunction, and cardiac dysfunction. Our patient had significant reduction in proteinuria and demonstrated stabilization of serum creatinine levels with initiation of antiviral treatment of hepatitis B infection and blood pressure control including the use of an angiotensin receptor inhibitor. This case suggests a causative role of hepatitis B in CGP.
Collapsing Glomerulopathy: Report of 10 Cases
Monica Sanchez cardenas,1 Virginia Soto,2 Karla B. Cano Escobar,2 1UNAM, Ciudad de Mexico, Mexico; 2INCA Ignacio Chavez, Mexico City, Mexico; 1Instituto Nacional Cardiologia Ignacio Chavez, Tlalpan, Mexico.

Introduction: Collapsing pathology represents one of the most aggressive forms of glomerulopathy described, representing 15% of the biopsies described as focal and segmental glomerulosclerosis. The knowledge of its characteristics in our population is crucial for its better understanding and management.

Case Description: Materials and methods: By reviewing the medical records, we proceeded to identify cases of collapsing glomerulopathy with complete clinical follow-up in our institute, registered from 2010 to date. Results: The age range at diagnosis was from 17 to 60 years, with 3 cases of the male gender and 7 registered women. The proteinuria recorded at diagnosis had an average of 10.01 g (4.2-12 grams). The creatinine at diagnosis had an average of 3.8 mg/dl (0.47-11 mg/dl) with a mean basal albumin of 2.15 g/dl (1.0-3.4 g/dl). Nine of the ten cases were hypertensive at diagnosis, with creatinine in eight of the cases. Similarly, 8 of the cases integrated complete diagnosis of nephrotic syndrome in the initial clinical presentation. Upon arrival at the institute, the average evolution time was 5.5 months (1-24 months) and the most common symptom of presentation was lower limb edema. One of the cases was linked to EBV, one to HIV and one was triggered after pregnancy. No specific etiology was identified in the rest of cases. Given the degree of progression of renal damage, it was necessary to start dialysis therapy during hospitalization in 5 of the 10 cases. In 4 of the cases, immunosuppressive therapy was given and in one more antiretroviral therapy at the beginning given the etiology of the therapy with rituximab 375 mg/week for 2 of the cases. In the last 6 months, methylprednisolone, plasmapheresis and monthly boluses of cyclophosphamide. One of presentation was lower limb edema. One of the cases was linked to EBV, one to HIV Immune Complex Kidney Disease (HIVICK), nonetheless the association of these two diseases is rarely described, since their pathophysiopathology are not alike.

Discussion: In our group of patients, despite the short time to diagnosis, the vast majority unfortunately were detected with advanced fibrosis without the possibility of treatment given the benefit risk ratio. In recent years, the trend is toward earlier diagnosis with the possibility of treatment and intentional etiology search. The prognosis regarding renal function continues to be discouraging.

Use of IVC Filter in the Management of Percutaneous Renal Biopsy (PRB) Complicated by Perinephric Hematoma (PNH) and Acute RLE DVT in a Patient with C-ANCA-Positive Crescentic Glomerulonephritis Aileen Wang,1 Anton Cabellon,1 Carrie L. Phillips,1 Ayman Hallab,1 Richard N. Hellman.2 Indiana University Department of Medicine, Division of Nephrology, Division of Hematology, and IUHP 1Indiana University School of Medicine, Indianapolis, IN; 2Indiana University Division of Nephrology, Indianapolis, IN.

Introduction: A 37 year old MWF with a prior history of morbid obesity, gastric bypass, hypertension, prior calcium oxalate nephrolithiasis presented to her local hospital with diarrhea, lower abdominal pain, arthralgia’s, sinus congestion. She was found to have micro hematuria, 2 g proteinuria, metabolic acidosis, hyperkalemia and AKI with a serum creatinine of 4.5 mg/dl with normal renal function. A CT of the abdomen revealed normal kidneys but thickening of the terminal ileum, a positive ANA (1:120) and a positive rheumatoid factor. Labs showed creatinine (CR) 0.4 mg/dL and proteinuria 30 mg/dL. Her proteinuria rapidly progressed to 2.6 g/L and a renal biopsy showed MN secondary to SLE (ISN-RPS Class V).

Discussion: Use of conventional therapy for MN with OC may result in increased carcinogenesis. As such, mass resection and chemotherapy (CTx) are prioritized. First line treatment with Bleomycin-Etoposide-Cisplatin (BEp) has known nephrotoxic effects. Its impact on proteinuria is unclear. Here, we report a case of a MN secondary to OC in the setting of BEp with partial remission of proteinuria with OC.

Partial Remission of Proteinuria with Bleomycin-Etoposide-Cisplatin (BEp) in Systemic Lupus Erythematosus-Related Membranous Nephropathy and Ovarian Cancer M. I. Villegas Kastner,1 Katherine Garcia De Jesus,1 Janice B. Desir,1,2 Nephrology/Internal Medicine, SBH Health System, New Rochelle, NY; 1Kidney Medical Associates, PLLC, Bronx, NY; 2Internal Medicine, SBH Health System, Bronx, NY.

Introduction: Systemic Lupus Erythematosus (SLE) and ovarian cancer (OC) are both associated with secondary causes of membranous nephropathy (MN). The incidence of OC with MN is rare and coexistence with SLE has not been documented in the literature.

Discussion: Although rare, HIV-positive patients, even with undetectable viral load, may develop immunological kidney disease (HIVICK) in combination with the non-immunological form (HIVAN). At our perspective, the kidney tissue could be seen as a viral reservoir, justifying a collapsing glomerulopathy even with long time of negative viral load.

BPE602
BPE603
BPE604

Discussion of the estimated prevalence of kidney disease in HIV-infected patients ranges from 2 to 17% and can be classified into HIV-associated Nephropathy (HIVAN) and HIV Immune Complex Kidney Disease (HIVICK), nonetheless the association of these two diseases is rarely described, since their pathophysiopathology are not alike.

Discussion: This case illustrates the first proposal of an anti proteinuric effect of BEP in SLE MN with OC. This is important to consider in the management of germ cell tumors with OC. It also has implications in other forms of MN not responsive to standard therapy. Further research is required to understand the full treatment of these agents in MN.
A Rare Case of Idiopathic Nodular Glomerulosclerosis in a Non-Diabetic and Non-Smoker with Untreated Hypertension

Yasolatha Chachichehmal, Nephrology Fellowship Program, DHMC Dartmouth Hitchcock Medical Center, Lebanon, NH.

**Introduction:** Nodular glomerulosclerosis is a classical finding in diabetic nephropathy. It can occur in the absence of diabetes, often in older men with long standing smoking, hypertension, Fibrillary GN, amyloidosis, Takayasu arteritis, light chain nephropathy, nodular variant of membranous proliferative glomerulonephritis. We are reporting a case of idiopathic nodular glomerulosclerosis leading to nephrotic syndrome needing dialysis.

**Case Description:** 67 y/o non-smoker with no prior medical care with untreated hypertension for long time, presented with sudden onset of AKI following fall at home and prior progressive lower extremity edema and exertional SOB. Found to have complete heart block, oliguria, nephrotic syndrome with serologies negative for hepatitis, HIV, paraproteinemia, ANA, C-ANCA, P-ANCA, PLA2R Antibody with normal complements and IBAIC of 5.4. Renal biopsy showed diffuse global, nodular glomerulosclerosis, severe arterial hyaline sclerosis, interstitial fibrosis(80-90%), no evidence of immune complex deposition.

**Discussion:** Though not commonly seen, idiopathic nodular glomerulosclerosis should be considered as one of the differentials for patients presenting with nephrotic syndrome like in our case with no history of diabetes in a non smoker.

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**Surprise on Renal Biopsy: Crescentic Glomerulonephritis**

Latoya N. Gayle, Marnie Aguasvivas, Alejandro Matos wells, Louis C. Jan, Englewood Hospital and Medical Centre, Englewood, NJ; Englewood, Englewood, NJ; Bergen Kidney Center, Cresskill, NJ.

**Introduction:** IgA Nephropathy(IgAN) is the most common glomerulonephritis, with variable presentation, prognosis and controversial treatment. Though less common in adults, there has to be a high index of suspicion in those with presentation of high-risk markers such as severe proteinuria and signs of systemic vasculitis. We present a 41-year-old female with leukocytoclastic vasculitis, proteinuria and normal renal function with focal crescentic glomerulonephritis.

**Case Description:** 41-year-old Asian female, no prior illness, presented with a purpuric lower extremity rash, knee and ankle pain. Skin biopsy revealed leukocytoclastic vasculitis. 4 months later, her random urine protein was 3099mg/gm creatinine, 2+ blood. Save for positive ANA and elevated CRP of 17.9(<10mg/L), her dsDNA, Heparitis, ANCA, cryoglobulin, ASO and serum protein electrophoresis were negative. Total cholesterol and triglycerides elevated at 203(<200mg/dL) and 321(<150mg/dL) respectively. Normal-sized kidneys and echogenicity on renal ultrasound. Background of cutaneous vasculitis in the presence of proteinuria, prompted renal biopsy. It revealed focal crescentic glomerulonephritis with scattered glomerular double contours, consistent with IgAN.

**Discussion:** Treatment was commended with Prednisone, Ramipril and Arotavastatin, resulting in complete resolution of her proteinuria, rash, normalization of her triglyceride and cholesterol levels. She has been in remission with normal BUN and CR.

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**Thrombectomy for Renal Vein Thrombosis in Membranous Nephropathy**

Elisa Park, Peyman Borghi, John Sy; Anna Jin; Joline L. Chen, University of California, Irvine, Irvine, CA; Long Beach VA Medical Center, Long Beach, CA.

**Introduction:** Bilateral renal vein thrombosis is a rare complication of nephrotic syndrome. We hereby report a case of extensive systemic thrombosis with successful percutaneous suction thrombectomy.

**Case Description:** A 45-year-old male with no past medical history presented with lower extremity edema, dyspnea, right flank pain and pleuritic chest pain for two days. A diagnostic computed thorography (CT) revealed a nonocclusive acute thrombus in the bilateral renal veins, extending into the suprarenal infrarenal inferior venacava (Figure 1A), and right lower lobe pulmonary emboli. Initial serum creatinine was 0.87mg/dL. A 24-hour urine collection revealed protein >4.5 g/day. Labs were also remarkable for a serum albumin of <1 g/dL and a positive Phospholipase A1 Receptor at 212 RU/mL. A renal biopsy showed membranous nephropathy. Due to significant flank pain and severe clot burden, patient underwent percutaneous image-directed catheter-directed suction thrombectomy of bilateral renal veins, IVC, and right lower lobe branch pulmonary artery using CAT-8 Penumra suction thrombectomy device with 500cc of clot removed. The patient’s pain improved significantly the next day (2-3/10). Patient underwent renal biopsy on post op day two. Patient was anticoagulated with heparin and transitioned to apixaban. He was treated with modified Pontiellci protocol. Renal function remained stable one month post procedure. Follow up CT scan showed resolution of the bilateral renal vein thrombus (Fig 1B).

**Discussion:** Acute bilateral renal vein thrombosis is a rare complication of nephrotic syndrome, and can be associated with renal function decline. Thrombectomy may be considered a safe therapy to prevent sequelae of long term clot burden.

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**Surprise on Renal Biopsy: Crescentic Glomerulonephritis**

Latoya N. Gayle, Marnie Aguasvivas, Alejandro Matos wells, Louis C. Jan, Englewood Hospital and Medical Centre, Englewood, NJ; Englewood, Englewood, NJ; Bergen Kidney Center, Cresskill, NJ.

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**Discussion:** Treatment was commended with Prednisone, Ramipril and Arotavastatin, resulting in complete resolution of her proteinuria, rash, normalization of her triglyceride and cholesterol levels. She has been in remission with normal BUN and CR.

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**Coagulopathy and Nephrotic Syndrome in a Patient with AL Kappa Amyloidosis**

Michael Bournia, Sophia L. Ambursou. University of Colorado, Denver, CO.

**Introduction:** We present a 64-year-old man with nephrotic-range proteinuria and coagulopathy from systemic kappa light chain (LC) amyloidosis and associated plasma cell dyscrasia.

**Case Description:** The patient presented with anasarca, hypotension and decreased oral intake. History was notable for chronic memory loss, cognitive decline and rapid deterioration preceding admission. On exam, he had BP of 76/59, HR 107, anasarca, lethargy, and confusion. Initial serum labs included creatinine of 3.0 (baseline 1.8), albumin of 1.1, and INR of 3.4 with normal liver function. Urinalysis had moderate blood and large protein, while direct microscopy revealed many non-dysmorphic RBCs and granular casts. Urine protein to creatinine ratio was 13g/g. Renal ultrasound showed normal sized kidneys. HIV, HCV, HBV, ANA, ANCA, C4, RF all normal. C3 mildly low at 75. SREP revealed kappa monoclonal LC. Serum free kappa LC were 408, serum free lambda LC were 21.4, and kappa/lambda ratio was 19. Fat pad biopsy was unremarkable, however, the bone marrow biopsy showed 13% plasma cells on the aspirate and apple-green birefringence of three vessels with congo red staining showing vascular mural amyloid deposition. Official diagnosis: systemic kappa LC amyloidosis associated with plasma cell dyscrasia. Renal biopsy was not performed due to patient’s coagulopathy. Hematology consulted due to the unusual finding of coagulopathy in a nephrotic patient. Coagulation factors V and X were found to be deficient (27% and 16%, respectively). Patient decided against chemotherapy and was discharged on hospice.

**Discussion:** A kappa-predominant AL amyloidosis is a less common cause of nephrotic proteinuria compared to the lambda LC variant, which occurs three times more often. It is suggested that AL Kappa Amyloidosis as a cause of nephrotic syndrome is more common with multiple myeloma, as seen in our patient. Interestingly, while nephrotic patients are generally thought to be hypercoagulable, our patient had an elevated and uncorrectable INR. Those with AL amyloidosis often have a bleeding diathesis which can be due to a coagulopathy, the presumed mechanism of which is factor X adsorption by
amylod fibrils causing factor X deficiency, as observed in our patient. In patients with nephrotic syndrome and bleeding diathesis and/or coagulopathy, a unifying diagnosis can be AL amyloidosis.

**PUB609**
Nephrotic Syndrome in a Patient with Diabetes: Things Are Not Always As They Seem
Harshal P. Shah, Ping Li, Samir S. Patel. 1 Georgetown University Hospital, Arlington, VA; 2 Washington Veterans Affairs Medical Center, Washington, DC; 3 Veterans Affairs Medical Center and George Washington University, Washington, DC.

**Introduction:** Diabetic patients with renal involvement with proteinuria were previously thought to have diabetic nephropathy in up to 70% of cases. A kidney biopsy is not always pursued in these patients due to this presumed diagnosis, especially in the presence of uncontrolled blood sugars, long duration of diabetes, and other markers of microvascular disease such as retinopathy and neuropathy. The mainstay of treatment for these patients is strict glycemic control, the use of diuretics for volume management and inhibition of the renin-angiotensin-aldosterone system (RAAS). Despite treatment, mortality remains high with a progression to end stage renal disease. More recent literature has suggested that diabetics with atypical features have a non-diabetic renal disease or mixed renal disease in up to 50% of cases.

**Case Description:** A 37-year-old man with an 8-year history of DM2 without retinopathy A1C of 18% presented with anosarca and nephrotic syndrome. Laboratory studies revealed serum creatinine 1.2 mg/dL, albumin 1.0 g/dL, hyperlipidemia and UPCR 8 g/g. Kidney biopsy showed early diabetic nephropathy and he was started on standard treatment. He continued to have diuretic resistance with multiple episodes of AKI. He required three inpatient admissions for intravenous diuresis over the next 7 months. Due to atypical presentation and persistence of symptoms, repeat kidney biopsy was performed. Biopsy showed a FSGS lesion in a single glomerulus. Due to his uncontrolled diabetes, second line therapy with a calcineurin inhibitor (CNI) was started. Within the next 6 months, he achieved complete remission with reduction in proteinuria to <300 mg/g. Normalization of albumin and resolution of edema.

**Discussion:** Diffuse foot process effacement on electron microscopy is a defining feature of diseases with proteinuria, and without an accompanying glomerular lesion on light microscopy, distinguishing FSGS from other proteinuric kidney diseases can be difficult. Current literature suggests glaucoctocoids as first line therapy in patients with primary FSGS with nephrotic syndrome. CNIs are reserved for steroid resistant or steroid dependent disease, and their use in early FSGS has not been extensively studied with RCT’s. This case not only illustrates the importance of a kidney biopsy in diabetic patients, but also the quick resolution of FSGS with second line therapy.

**PUB610**
Toxic Effects of Tonic Water, a Case of Quinidine-Induced Thrombotic Microangiopathy
Kishore Patcha, Josephine Abraham, Nirupama Ramkumar, Martin C. Gregory. University of Utah, Salt Lake City, UT.

**Introduction:** Quinine is one of the most common medications which can cause drug induced immune mediated Thrombotic microangiopathy. Here we present a case of thrombotic microangiopathy who exposed quinine in the form of tonic water. Diabetic patients with renal involvement with proteinuria were previously thought to have diabetic nephropathy in up to 70% of cases. A kidney biopsy was not always pursued in these patients due to this presumed diagnosis, especially in the presence of uncontrolled blood sugars, long duration of diabetes, and other markers of microvascular disease such as retinopathy and neuropathy. The mainstay of treatment for these patients is strict glycemic control, the use of diuretics for volume management and inhibition of the renin-angiotensin-aldosterone system (RAAS). Despite treatment, mortality remains high with a progression to end stage renal disease. More recent literature has suggested that diabetics with atypical features have a non-diabetic renal disease or mixed renal disease in up to 50% of cases.

**Case Description:** A 25-year-old female presented with flu-like symptoms including nausea, vomiting, diarrhea, malaise, and generalized abdominal pain. Diagnostic work-up showed elevated lapsedase (724U/L) mildly elevated liver enzymes and normal appearing liver and kidneys on CT abdomen/pelvis. Patient underwent cholecystectomy for presumed gall stone pancreatitis. Shortly after discharge, she noticed worsening swelling in her legs, abdomen, and weight gain to 300lbs. Urinalysis showed 3+ proteinuria, hematuria, urine protein/creatinine ratio of 2.7 g/g. Platelet count was 138 k/ul, Hgb=7.7g/dl, creatinine 1.58 mg/dL. Peripheral smear demonstrated sickocytes. Renal biopsy showed thrombotic microangiopathy consistent with TTP vs atypical HUS. While werologies were pending, she was treated with plasma exchange, Eculizumab 900mg, Rituximab 375mg/m2 and prednisone. ADAMTS13 was 51%. Complements C3 and C4 were normal. Anti-complement factor H, ANA, scleroderma antibodies and stool studies were all negative. On further review of history, she reported drinking tonic water intermittently as a restaurant server. Intermittent ingestion of quinine can cause TMA, quinine-dependent antiplatelet antibodies were tested and found to be negative.

**Discussion:** Quinine is a widely used remedy for leg cramp. Quinine was the first drug reported to cause TTP-HUS and it remains the most common cause of drug-induced TTP-HUS. Quinine is one of the most common medications which can cause drug induced immune mediated Thrombotic microangiopathy. Here we present a unique case of recurrent DIC and thrombotic microangiopathy in a patient who has been taking quinine supplements for leg cramps.

**Case Description:** A 81-year-old female with history of recurrent DIC was hospitalized with night sweats, fevers, chills, vomiting, acute kidney injury and recurrence of DIC. She underwent an extensive diagnostic work up to evaluate for occult malignancy and infection with negative results. Peripheral smear showed schistocytes and she had a WBC of 4.7 k/ul, Hgb 10.6 mg/dL and platelets 10 k/ul. Serum creatinine was 6.55mg/dL, total bilirubin 8.2mg/dL, AST 831 u/L, ALT 366 u/L, albumin 3.1mg, LDH 566u/L, D-dimer >20,000/ug/ml, haptoglobin <10mg/dL, fibrinogen 430mg/dL. PTT 52 and INR 1.2. She was noted to have normal ADAMS13 activity and stool studies were negative for Shiga toxin. Immunofixation electrophoresis and complements C3 and C4 were normal. Quinine-dependent antplatelet antibodies were positive for both IgG and IgM. After eliminating quinine, she continues to improve clinically and creatinine trended down to 3.8 at time of discharge.

**Discussion:** Quinine is a widely used remedy for leg cramps. Several over the counter therapies, nutrition products, and beverages such as tonic water and bitter lemon contain quinine. Allergic reactions to quinine can be severe and can affect multiple organs. Quinine is the only drug to be associated with acute thrombotic TTP, and it remains the second most commonly reported cause of drug-induced thromboticocytopenia. Quinine was the first drug reported to cause TTP-HUS, it remains the most common cause of drug-induced TTP-HUS. Development of quinine-dependent antibodies to antigens is thought to be the mechanism. Quinine can bind to surface molecules, altering their structure and exposing new parts of the cell membrane molecule to plasma; these revealed sequences are then recognized by the immune system as foreign antigens. Drug-dependent antibodies can be detected by flow cytometry. Exposure to quinine can cause multisorgan failure, TMA, severe hemolytic anemia and it is critical to recognize quinine-induced disorders for prevention of recurrent disease.

**PUB611**
Quinine-Induced Immune-Mediated Recurrent Disseminated Intravascular Coagulation and Thrombotic Microangiopathy
Kishore Patcha, Martin C. Gregory, Nirupama Ramkumar. University of Utah, Salt Lake City, UT.

**Introduction:** Quinine is one of the most common medications which can cause drug induced immune mediated Thrombotic microangiopathy. Here we present a unique case of recurrent DIC and thrombotic microangiopathy in a patient who has been taking quinine supplements for leg cramps.

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PUB613

Primary Amyloidosis with Rapidly Progressive Pattern: Case Report

Lionel C. Vargas,1 Virgilia Soto,1 L. M. Perez-Navarro,2 Rafael Valdez-Ortiz,1 Juan C. Trímino,1 Maribel Merino,1,3 Hospital General de México, Mexico City, Mexico; 3Hospital General de México Dr. Eduardo Liceaga, Mexico City, Mexico, Instituto Nacional de Cardiología, Mexico City, Mexico.

Introduction: Primary systemic amyloidosis (AL) is a plasma cells disorder characterized by fibrils deposition (8-15 nm) of monoclonal Ig light chains. The incidence is 0.9 cases per 100,000 persons.

Case Description: 68 years old female, resident of Mexico. History of DM2 and hypertension, both newly diagnosed. She began in July 2017 with asthenia, adynamia, headache, abdominal pain and nausea; she presented in the hospital with blood pressure of 180/100 mmHg, kidney function test: creatinine 5.9 mg/dL, urea 202 mg/dL. (in November 2016, creatinine was 1.3 mg/dL). The patient was evaluated because rapidly progressive kidney failure pattern. She began with hemodialysis. On the work up, we found proteinuria of 0.26 g/g, erythrocyturia was not found. Renal ultrasound: normal kidneys; renal biopsy was performed. Glomerular-Interstitial and vascular Amyloidosis, Positive Lambda (immune amyloid). IgG: (3+) in the amyloid material, IgA, IgM and C3C: (1+) positive in the amyloid material, C1q, C4C and fibrinogen: negative, Kappa: negative, Lambda: (2+) positive in the amyloid material, red congo positive. (Figure 1) Clinical Diagnosis: Primary systemic amyloidosis.

Discussion: The mean age of presentation is 65 years. Less than 20% of patients show progressive renal failure (creatinine >2 mg/dL). This patient had an unusual presentation of amyloidosis with a rapidly progressive loss of renal function. Cases of multiple myeloma (MM) with amyloidosis have been described. Both conditions are plasma cell proliferation and between them, there are minimum differences. A patient with clinical manifestations of AL, with no MM symptoms, would have AL diagnosis; however; if the patient has MM symptoms (anemia, bone pain, osteolytic lesions) the diagnosis would be MM with associated AL.

Figure 1. Kidney Biopsy

PUB614

Transient Nephrotic Range Proteinuria After Acute HIV Infection

Andrew Vissing, Sara E. Jandeksa. Rush Children’s Hospital, Chicago, IL.

Introduction: Nephrotic syndrome is common among patients living with HIV. Although the majority of cases are diagnosed with HIV-associated nephropathy, a collapsing FSGS variant, immune-mediated etiologies and minimal change disease have also been described. There is an absence of literature describing acute HIV infection and its immediate renal sequelae. We describe a case of transient nephrotic range proteinuria without features of minimal change disease.

Case Description: A 17-year-old African-American male presented with pharyngitis, abdominal pain, fever, and lymphadenopathy. HIV antibody was undetectable but viral load measured 1.3 million copies/mL (CD4 count 304 cells/ml) suggestive of acute HIV infection. He was discharged with darunavir, emtricitabine-tenofovir, and ritonavir. Two weeks later, he presented with abdominal pain. Exam was notable for absence of edema. A patient recovering renal function from this disease after long term dialysis.

Chlorambucil showed acute kidney injury (BUN 25mg/dL, Cr 1.9mg/dL). Serum albumin was 2.1 g/dL and cholesterol was 158 mg/dL. Formal proteinuria of 0.26 g/g. On work up, proteinuria was unremarkable. Viral load and CD4 count showed improvement on HAART. A renal biopsy was performed normal glomeruli with acute tubular necrosis and absence of immune deposits. Electron microscopy showed global podocyte effacement. He was prescribed steroids. Over the next 4 months, he was repeatedly admitted for abdominal pain but never exhibited edema or hypercholesterolemia. He refused to take steroids and was noncompliant with HAART. Proteinuria gradually tapered and she was established onto maintenance dialysis. Remarkably 11 months on the spontaneous remitted: peritoneal equilibration test revealed a residual creatinine clearance of 20mL/min. After ceasing dialysis her creatinine nadired at 1.15mg/dL and protein to creatinine ratio of 0.8g/g. She remained in remission until 7 years later where (now 70 years old) she became nephrotic with a creatinine of 5.94mg/dL. Biopsy reconfirmed FSGS (NOS category) of one tip, one perihilar and one cellular variant, with acute tubular injury, and mild interstitial fibrosis and tubular atrophy (IFTA) (figure 1). She was brought into remission by prednisolone 50mg and cyclosporin 100mg twice daily. 8 months later she re-presented with oligoanuric renal failure. Repeat renal biopsy confirmed FSGS, acute tubular injury and mild IFTA. Immunosuppressant therapy failed therefore was tapered and she was established onto maintenance dialysis. Remarkably 11 months on the spontaneous remitted: peritoneal equilibration test revealed a residual creatinine clearance of 20mL/min. After ceasing dialysis her creatinine nadired at 1.15mg/dL and protein to creatinine ratio of 0.8g/g. She remained in remission until 7 years later where (now 70 years old) she became nephrotic with a creatinine of 5.94mg/dL. Biopsy reconfirmed FSGS (NOS category) of one tip, one perihilar and one cellular variant, with acute tubular injury and mild IFTA. After treatment with plasma exchange her creatinine has improved to 2.29mg/dL.

Discussion: This case of spontaneous remission in prolonged dialysis dependent FSGS prompts physicians to monitor the progress of all their patients with FSGS – Even those on dialysis!

Figure 1: FSGS. Tip lesion (arrow)

PUB615

Case Report: Spontaneous Remission of Dialysis-Dependent Focal Segmental Glomerulosclerosis

Juan Cheng,1 Alan Parrtham,3 Megan N. Turner,3 Westmead Hospital, Westmead, NSW, Australia; 3Gold Coast University Hospital, Gold Coast, QLD, Australia; 4Sullivan and Nicolaides Pathology, Bowen Hills, Queensland, NSW, Australia.

Introduction: It is uncommon for focal segmental glomerulosclerosis (FSGS) to enter spontaneous remission. As far as the authors are aware there are no reports of a patient recovering renal function from this disease after long term dialysis.

Case Description: A 61 year old Caucasian female presented with nephrotic syndrome and acute kidney injury. There was no relevant medical history (including intravenous drug use) or medications. She was hypertensive and 33 pounds above her baseline. Urinalysis demonstrated 100 red blood cells/hpf, a protein to creatinine ratio of 7.5 g/g, albumin 1.8 g/dL. Creatinine increased from 0.68 to 1.45mg/dL. Vasculitic, infective and myeloma screen was normal. Renal biopsy demonstrated tip variant FSGS affecting 3 of 13 biopsied glomeruli, acute tubular injury, and mild interstitial fibrosis and tubular atrophy (IFTA) (figure 1). She was brought into remission by prednisolone 50mg and cyclosporin 100mg twice daily. 8 months later she re-presented with oligoanuric renal failure. Repeat renal biopsy confirmed FSGS, acute tubular injury and mild IFTA. Immunosuppressant therapy failed therefore was tapered and she was established onto maintenance dialysis. Remarkably 11 months on the spontaneous remitted: peritoneal equilibration test revealed a residual creatinine clearance of 20mL/min. After ceasing dialysis her creatinine nadired at 1.15mg/dL and protein to creatinine ratio of 0.8g/g. She remained in remission until 7 years later where (now 70 years old) she became nephrotic with a creatinine of 5.94mg/dL. Biopsy reconfirmed FSGS (NOS category) of one tip, one perihilar and one cellular variant, with acute tubular injury and mild IFTA. After treatment with plasma exchange her creatinine has improved to 2.29mg/dL.

Discussion: This case of spontaneous remission in prolonged dialysis dependent FSGS prompts physicians to monitor the progress of all their patients with FSGS – Even those on dialysis!

Figure 1: FSGS. Tip lesion (arrow)
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

Tumor Lysis Syndrome in a Patient with Chronic Lymphocytic Leukemia

Nwabundo Anusim, Daniel E. Ezekwudo, Ishmael Jaiyesimi. Beaumont Hospital, Royal Oak, MI

Introduction: Tumor lysis syndrome (TLS) occurs as a result of tumor cell death and release of intracellular contents into circulation resulting in multi-organ dysfunction and death. It rarely occurs spontaneously in patients with chronic lymphocytic leukemia (CLL). We present a 75-year-old female with a history of CLL in remission that presents with confusion and diagnosed with spontaneous TLS.

Case Description: A 75 year old Caucasian female with a history of stage I right sided breast cancer and left sided DCIS/p mastectomy and tamoxifen for 5 years, CLL Rai stage IV treated due to symptomatic splenomegaly with bendamustine and rituximab (BR) with excellent hemato logical response. Nine years post treatment with BR, hematological analysis revealed lymphocytosis, progressive anemia, thrombocytopenia and splenomegaly. Subsequently, she presented at an outside facility with acute encephalopathy following a viral prodrome. Laboratory results showed white blood cell count (WBC) of 300 x 10^9/L. She was transferred to our facility for emergent leucapheresis. On presentation, she was confused and oliguric. She had a WBC of 270 x 10^9/L with predominant lymphocytosis 248 x 10^9/L, creatinine 4.65 mg/dl, potassium 6.0 mmol/L, phosphorus 4.9 mg/dl, calcium 7.8 mg/dl, bicarbonate of 7 mmol/L, and uric acid 16.1 mg/dL. Peripheril blood smear revealed smudged cells but no blasts. She was aggressively hydrated, given rasburicase and emergent dialysis. Following dialysis, her mental status and renal function significantly improved. Bone marrow biopsy analysis showed hypercellular marrow with extensive involvement of CLL, CLL genotype showed an unmutated immunoglobulin variable region heavy chain status (IgVH) and cerebrospinal fluid analysis showed a flow cytometry positive for monotypic B-cell population with a CLL phenotype. She follows with her oncologist and was started on Ibrutinib.

Discussion: TLS is an oncologic emergency and requires immediate treatment with aggressive hydration to prevent renal failure, seizures and cardiac arrhythmias resulting from the toxic intracellular material released during cell lysis1. High burden, chemoresistant cases with high proliferative rate or high transitional histology are often associated with TLS. However, TLS is rarely seen in patients with CLL due to its low proliferation and very limited data on TLS in CLL has been reported1. Further investigation into the clinic-pathologic mechanism for TLS in patients with CLL is pertinent.

PUB620

Diagnostic Role of Cystatin C in the Assessment of Kidney Function on PARP Inhibitors

Hao Wang, Abdallah Sassine Gera, Jonathan J. Hogan. Hospital of the University of Pennsylvania, Haddonfield, NJ

Introduction: Novel targeted therapies have expanded the arsenal of treatment options for various malignancies and led to significant improvement in prognosis. However, as new drugs rapidly enter the clinical arena, potential nephro toxic effects are often poorly defined or understood due to the higher increasing rate of drug development. Poly (ADP-ribose) polymerases (PARP) inhibitors are a class of medications that promote tumor cell death and have emerged as a treatment option for patients with solid-organ malignancies; namely, ovarian, breast, and pancreatic cancers. These medications interact with transporters along the renal tubules involved in the secretion process. An increase in serum creatinine has been reported in patients treated with these agents; in fact, in phase II open-label trials of rucaparib, an elevation in creatinine occurred in 92% of patients. However, it remains unclear whether these represent impact on creatinine secretion alone versus acute or enduring decrement to glomerular filtration rate.

Case Description: A 54-year-old man with stage 2 chronic kidney disease from prior cisplatin-toxicity and pancreaticobiliary adenocarcinoma was initiated on rucaparib, a PARP inhibitor. His past medical history was notable for type 2 diabetes on insulin. He did not use nonsteroidal anti-inflammatory drugs, antibiotics-converting enzyme inhibitors, or statins. On admission, his creatinine was 1.4 mg/dl (eGFR of 57 mL/min/1.73 m^2) by the CKD-EPI equation. Following PARP inhibitor therapy, his serum creatinine rose to 2.0 mg/dl (eGFR of 35 mL/min/1.73 m^2). Renal ultrasound showed normal kidney size without evidence of hydronephrosis or stones. Concurrent serum C was 1.4 mg/dl, corresponding to an eGFR of 51 mL/min/1.73 m^2 by the CKD-EPI cystatin C equation.
Discussion: Accurate assessment of kidney function for patients on PARP inhibitors is extremely challenging. Elevations in creatinine can be seen in patients from receiving IV contrast for needed surveillance imaging, can prompt nephrotoxic referral and additional diagnostic testing, and potentially lead to hospital admissions for acute kidney injury. While cystatin C has been slow to gain traction for clinical use, it may have an important role in understanding renal effects of novel drug therapies, especially in the evolving world of onco-nephrology.

PUB621
Who Sux-My Electolytes? A Case of Fanconi Syndrome with Hifosmide Use
Laila Babar,1, 2 Sohlah Zahid,3, Deep Shah,4 Obaid Ashraf,5 Larisa Greenberg,6 Christie Hilton,7 1 Internal Medicine, Allegheny Health Network, Pittsburgh, PA; 2 Allegheny General Hospital, Pittsburgh, PA.

Introduction: Hifosamide is an anti-neoplastic alkylating agent used in to treat various malignancies. It has been linked to severe nephrotoxicity and can lead to Fanconi syndrome. This is a type II proximal renal tubular dysfunction characterized by hypophosphatemia, hypocitratabemia, hypokalemia, glucosuria and amino acidauria. Nephrotoxicity with Hifosamide is common but a complete Fanconi syndrome is rare, especially in adults.

Case Description: 64 year old gentleman with a history of myxoid spindle cell neoplasm was admitted for severe electrolyte abnormalities. He had received 5 cycles of Adriamycin, Hifosamide and Mesna (AIM) along with 4400 cGy radiation and his cumulative Hifosamide dose was 30g/m2. His last treatment was one week prior to presentation. He tolerated his cycles well with no grade 3-4 toxicities. On presentation, his creatinine was elevated at 1.84 from a baseline of 0.90, he had severe hypokalemia of 2.8 mEq/L and did not correct with multiple runs of IV Potassium. His bicarbonate level was 11, phosphate 1.2, magnesium 1.5 and his urinalysis was positive for glucose, ketones and protein. His fractional excretion of phosphate was elevated to 70%. Nephrology was consulted and he was diagnosed with Fanconi syndrome secondary to Hifosamide toxicity. He was kept inpatient and received twice daily electrolyte supplementation and supportive treatment with IV hydration. After 10 days of supportive treatment he did not require further electrolyte supplementation.

Discussion: There is a 1.5-4% chance of developing Fanconi syndrome with Hifosamide use in children however, there have only been isolated case reports in adults. It is usually related to a high cumulative dose of 45-60 g/m2. The exact mechanism of renal injury is unclear but its related to the byproduct Chloracetaldehyde induced wasting of the ATPase in the Na/K cotransporter on the proximal tubule cells causing electrolyte wasting. The mainstay treatment is supportive management with IV hydration and electrolyte supplementation. Early diagnosis and vigilant electrolyte monitoring is essential for a good outcome. Fanconi syndrome can occur days to weeks after treatment and should always be a differential in patients on AIM with electrolyte wasting. It is generally reversible and needs supportive care to ensure the electrolyte imbalance does not cause life threatening arrhythmias.

PUB622
A Unique Case of Clarkson Disease in a Multiple Myeloma Patient
Adedunmola M. Adeboye1, Aimen Liaqat,2, Sema Karargousar,2,1 Daniel Angeli,2,3 1 Saint Barnabas Medical Center, Livingston, NJ; 2 Saint Barnabas Medical Center, West Orange, NJ; 3 Nephrology Associates, Livingston, NJ.

Introduction: The first fatal case of a rare systemic capillary leak syndrome (SCLS) was reported by Clarkson and since then, approximately 100 cases have been reported. It is a rare syndrome that mimics septic shock and is frequently associated with monoclonal gammopathy.

Case Description: A 50-year female with hypothyroidism and chronic kidney disease presented with presyncope, weakness and hypotension. She had a year history of on and off generalized body swelling unresponsive to diuretics and fluid restriction. She also had a prior admission for septic shock. Labs were significant for leukocytosis, CT abdomen did not show any source of infection and her creatinine was 1.3-1.5 mg/dl. On further evaluation, she had proteinuria of 2 g/m2/d without cavitary lesions; hepatitis panel, TB, and HIV were negative; urinalysis showed protein 2+, RBC 182/hpf, WBC 31/hpf and a few A. Nephra titers 1:640, Cr 117, C4 44.8, MPO-ANCA 17.8, PR3-ANCA<3.5. Due to elevated MPO-ANCA levels and Cr 4.7 mg/dl with proteinuria, a kidney biopsy was obtained which surprisingly showed poorly differentiated high grade adenocarcinoma involving almost the entire sample, favoring high grade serous carcinoma of ovarian primary with positive staining for WT-1, P66, PAX-8, ER and P53. The light microscopy sample had one gliomerulus that showed nodular diabetic glomerulosclerosis. Follow up pelvic ultrasound did not reveal any malignant lesions. CT abdomen did not correct with multiple runs of IV Potassium. His bicarbonate level was 11, phosphate 1.2, magnesium 1.5 and his urinalysis was positive for glucose, ketones and protein. His fractional excretion of phosphate was elevated to 70%. Nephrology was consulted and he was diagnosed with Fanconi syndrome secondary to Hifosamide toxicity. He was kept inpatient and received twice daily electrolyte supplementation and supportive treatment with IV hydration. After 10 days of supportive treatment he did not require further electrolyte supplementation.

Discussion: There is a 1.5-4% chance of developing Fanconi syndrome with Hifosamide use in children however, there have only been isolated case reports in adults. It is usually related to a high cumulative dose of 45-60 g/m2. The exact mechanism of renal injury is unclear but its related to the byproduct Chloracetaldehyde induced wasting of the ATPase in the Na/K cotransporter on the proximal tubule cells causing electrolyte wasting. The mainstay treatment is supportive management with IV hydration and electrolyte supplementation. Early diagnosis and vigilant electrolyte monitoring is essential for a good outcome. Fanconi syndrome can occur days to weeks after treatment and should always be a differential in patients on AIM with electrolyte wasting. It is generally reversible and needs supportive care to ensure the electrolyte imbalance does not cause life threatening arrhythmias.

PUB624
Multiple Myeloma in Association with Light Chain Deposition Disease in a 39-Year-Old: A Case Report
Amareh R. Vanga,1 Varun Malhotra,2,3 Alamgir Mirza.1 1 Nephrology, Eastern Virginia Medical School, Norfolk, VA; 2 Nephrology Associates of Tidewater, LTD, Virginia Beach, VA.

Introduction: Multiple myeloma is a cancer of the elderly and most often the suspicion is raised in the older population. Only 2 percent of all cases of multiple myeloma present in patients younger than 40. Here we present a case of light chain deposition disease(LCDD) with features of cast nephropathy which is diagnostic of myeloma kidney in a 39-year-old male. Thus, recognition and knowledge of varied presentations can help in early diagnosis and treatment of the disease.

Case Description: A 39-year-old male with a history of hypertension presents with body aches for the past 2 weeks. He was mildly hypertensive at presentation (BP–152/90 mmHg). He was kept inpatient and received twice daily electrolyte supplementation and supportive treatment with IV hydration. After 10 days of supportive treatment he did not require further electrolyte supplementation.

Discussion: There is a 1.5-4% chance of developing Fanconi syndrome with Hifosamide use in children however, there have only been isolated case reports in adults. It is usually related to a high cumulative dose of 45-60 g/m2. The exact mechanism of renal injury is unclear but its related to the byproduct Chloracetaldehyde induced wasting of the ATPase in the Na/K cotransporter on the proximal tubule cells causing electrolyte wasting. The mainstay treatment is supportive management with IV hydration and electrolyte supplementation. Early diagnosis and vigilant electrolyte monitoring is essential for a good outcome. Fanconi syndrome can occur days to weeks after treatment and should always be a differential in patients on AIM with electrolyte wasting. It is generally reversible and needs supportive care to ensure the electrolyte imbalance does not cause life threatening arrhythmias.

PUB625
Gemcitabine Drug-Induced Thrombotic Microangiopathy: A Clinical Diagnosis
Nihal Bashir, Khuloud A. Al mutawa, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates.

Introduction: Thrombotic Microangiopathy (TMA) is a pathologic abnormalities in the arterioles and capillaries that is characterized by thrombocytopenia or thrombocytosis, membrane destruction, and platelet microparticles. It is mainly caused by tissue injury. Biopsy: 2 mechanisms are involved in D-TMA, immune-mediated, and dose or
Myeloma (MM), affecting approximately 50% on diagnosis. Renal impairment if often associated with MM. Kidney disease is one of the most common complications in Multiple Myeloma (MM), affecting approximately 50% on diagnosis. Renal impairment if often described due to Hypercalcemia, Cast Nephropathy and Amyloidosis. We present an unusual form of kidney injury associated with MM.

**Case Description:** Woman, 71 yo, previously hypertensive, complained of weight loss over the last year. During initial evaluation, the patient presented with: Hemoglobin 5.1 g/dL, Reticulocytes 2.2%, SCR 2.78 mg/dL, BUN 16 mg/dL; Calcium 8.5 mg/dL; no hematuria and no leukocyturia at urinalysis; UPCR 3.76 g/g; SLEP with Gammaglobulin Monoclonal peak of 6.4 g/dL and Albumin 2.5 g/dL; Serum and Urine Immunofluorescent exhibit IgG/Lambda paraproteins; Bone marrow aspirate with 39.2% of clonal plasma cell, confirming MM diagnosis. Kidney biopsy showed an atypical monoclonal plasma cell infiltrate on renal parenchyma, confirmed by CD138 and MUM1 staining with 39.2% of clonal plasma cell, confirming MM diagnosis. Kidney biopsy showed an atypical monoclonal plasma cell infiltrate on renal parenchyma, confirmed by CD138 and MUM1 staining with 39.2% of clonal plasma cell, confirming MM diagnosis.

**Introduction:** Kidney disease is one of the most common complications in Multiple Myeloma (MM), affecting approximately 50% on diagnosis. Renal impairment if often described due to Hypercalcemia, Cast Nephropathy and Amyloidosis. We present an unusual form of kidney injury associated with MM.

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**Discussion:** Cast Nephropathy is the single most common finding among patients with MM and clinical kidney involvement, leading to AKI. We report a patient with an unusual kidney involvement, with atypical monoclonal plasma cell infiltration of the renal parenchyma, which is often reported on advanced disease. Kidney biopsy is mandatory for diagnosis and establishes the degree of activity and chronicity, in order to determine the treatment intensity and prognosis. On behalf of that, we decided to keep the chemotherapy in our patient.

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**PUB626**

**Differential Diagnosis on Kidney Impairment Related to Multiple Myeloma: A Case Report**

**Fabio M. Torres, Pablo A. Vale, Jeison Goy, Rafael A. Souza, Fabio A. Reis, Luiz V. Affonso, Guilherme P. Santa Catharina, Igor Smolentzov, Livia B. Cavalcante, Cristiane B. Dias, Luis Yu, Viktoria Woronik, Leticia Jorge. Nephrology, University of Sao Paulo, S. Brazil.**

**Introduction:** Kidney disease is one of the most common complications in Multiple Myeloma (MM), affecting approximately 50% on diagnosis. Renal impairment if often described due to Hypercalcemia, Cast Nephropathy and Amyloidosis. We present an unusual form of kidney injury associated with MM.

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**Discussion:** Cast Nephropathy is the single most common finding among patients with MM and clinical kidney involvement, leading to AKI. We report a patient with an unusual kidney involvement, with atypical monoclonal plasma cell infiltration of the renal parenchyma, which is often reported on advanced disease. Kidney biopsy is mandatory for diagnosis and establishes the degree of activity and chronicity, in order to determine the treatment intensity and prognosis. On behalf of that, we decided to keep the chemotherapy in our patient.

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**PUB627**

**An Unusual Case of Acquired Fanconi Syndrome with Acute Myelogenous Leukemia**

**Robert C. Hartley, Matthew Gumbleton, Terrence S. Bjordahl, Josephine Abraham. University of Utah, Salt Lake City, UT.**

**Introduction:** Acquired Fanconi syndrome is frequently associated with certain drugs and toxins, multiple myeloma and some autoimmune diseases. However, we present a case with a patient undergoing treatment for acute myelogenous leukaemia (AML) who developed with Fanconi syndrome and imaging consistent with infiltrative disease in the kidneys.

**Case Description:** A 19-year-old woman with AML who was admitted for salvage chemotherapy. She was previously treated with cytarabine and daunorubicin, cladribine and then gemcitabine. The salvage regimen consisted of vinorelbine, topotecan, thiotepa and clofarabine. Urine output ranged from 4-13 liters per day. Chemistry studies were notable for hypernatremia with serum sodium of 153 mmol/L, hypokalemia with potassium of 2.7 mmol/L, non-gap metabolic acidosis with serum bicarbonate of 10 mmol/L. Creatinine phosphokinase was 1.5 mg/dL, hypophosphatemia with serum phosphate of 1.2 mg/dL, hypouricemia with serum uric acid of 1.8 mg/dL, serum glucose of 106 mg/dL and a serum creatinine of 0.6 mg/dL. Urine studies showed glycosuria despite normoglycemia, elevated beta-2-microglobulin, elevated trans-tubular potassium gradient and elevated urine anion gap. Follow up studies showed atypical cells in urine cytology. Contrast enhanced CT-Imaging of the abdomen showed voluminous kidneys with decreased enhancement bilaterally. The patient’s electrolytes and polypuria were treated with aggressive repletion and administration of desmopressin. She underwent bone marrow transplant, but contracted multiple opportunistic infections including mucormycosis sinusitis, fungemia and bacteremia. These progressed to septic shock ultimately leading to her death five weeks after the initial evaluation.

**Discussion:** Fanconi syndrome is classically associated with cisplatin, ifosfamide and plasma cell dyscrasias in hematologic malignancy, but not any of the agents used to treat this patient. Here, however, we present a case with findings consistent with Fanconi syndrome most likely secondary to infiltrative AML in the kidneys, as evidenced by nephropagly and atypical cells on urine cytology. Similar cases have been reported in the pediatric literature associated with acute lymphocytic leukemia which resolved with treatment of the underlying disease.

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**PUB628**

**Nephrotic Syndrome: A Clue to Diagnosing Chronic Graft vs. Host Disease**

**Nirav Parikh,1 Pooja D. Aamarapurkar.2 1Emory University School of Medicine, Atlanta, GA; 2Emory University Renal Division, Atlanta, GA.**

**Introduction:** Nephrotic range proteinuria (NRP) is a result of primary glomerulopathy, or renal manifestation of systemic diseases such as Diabetes Mellitus, Amyloidosis and Lupus Nephritis, to name a few. Complication of hematopoietic cell transplantation (HCT) such as Graft versus Host Disease (GvHD) is a less common yet well-established cause of NRP.

**Case Description:** We present a case of a 63-year-old male with a diagnosis of Myelodysplastic Syndrome. He was initially treated with chemotherapy agent azacitidine without response and eventually underwent an allogeneic stem cell transplant with minimal residual disease. Maintenance immunosuppression was tacrolimus and low dose prednisone with gradually decreasing doses. His medical condition remained stable for about two years until he presented to the hospital with new onset anasarca. He had no other symptoms and serum creatinine level was within normal limits at that time. Further work up at that time was unremarkable. Evaluation of urinary protein excretion revealed greater than 13 grams of protein in 24 hours with a spot urine protein to creatinine ratio that is greater than 8 grams. He was diagnosed with new onset Nephrotic Syndrome and was given intravenous Lasix with good response. A renal biopsy was performed to evaluate the cause of NRP. The renal pathology was reported as Membranous Nephropathy (MN) with features suggestive of a secondary cause. MN was thought to be the renal manifestation of GvHD. The patient was restarted on Tacrolimus 1 mg twice daily and Prednisone dose was increased to 60mg daily. A bone marrow biopsy was not performed. The GvHD was presumed to be renal limited; the patient was continued on tacrolimus 1 mg twice daily with tapering doses of steroids with significant improvement of proteinuria.

**Discussion:** This case highlights an important aspect of recognizing NRP as a manifestation of Renal limited GvHD in order to prevent hematopoietic cell transplant complications. Occasionally NRP may be the only manifestation of GvHD which is a rather systemic process. Adjustment and or increase in the immunosuppressive regimen is necessary to manage such cases and thus can save the transplanted tissue from failure. More studies are needed to further understand this entity.

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**PUB629**

**Long-Term Management of Idiopathic Retroperitoneal Fibrosis**

**Eddy J. De Jesus, Justin Lee Loy, Gajapathiraju Chamathiri, I. D. Weiner. University of Florida, Gainesville, FL.**

**Introduction:** Retroperitoneal fibrosis (RF) is a condition characterized by the presence of fibromuscular and fibroadipose tissue that often encases the ureters or abdominal organs. We present a case of retroperitoneal fibrosis that was treated with various immunosuppressive therapies over seven years with variable response to therapy.
Fanconi syndrome. Early detection and treatment is key to preventing further deterioration of hypokalemia, hypophosphatemia and hyperchloremic acidosis which is consistent with Our patient had glycosuria in the presence of normal blood glucose, aminoaciduria, to deplete intracellular glutathione in the renal tubule, predisposing to cellular damage. It is postulated that chloroacetaldehyde (CAA), a toxic metabolite is thought to be involved in the mechanism of Ifosfamide-induced Fanconi syndrome. It is a rare complication in adults.

Case Description: A 43-year-old male presented with abdominal pain; CT scan findings revealed circumferential soft tissue thickening around the abdominal aorta consistent with findings of RF. Prednisone was initiated, with improvement after 1 month followed by a steroid taper with recurrence of symptoms within 11-months. He was concerned for steroid side effects and opted for Cellcept. After 6 months he decided to be off medications and within a year, initial symptoms returned and restarted on high dose steroids. After tapering he was transitioned to Temozolomide which later was switched to methotrexate and subsequently Imuran; all were discontinued due to GI intolerance. He opted for colchicine and 3 months into regimen he continued with no symptoms and stability of RF in repeat imaging.

Discussion: Management of RF is aimed to halt the progression of the fibrotic process and prevent a recurrence. In idiopathic cases, steroids as induction therapy should be initiated as soon as the diagnosis is made. In those who do not respond to steroid therapy or cannot tolerate the side effects, studies using Cellcept, Temozolomide, Imuran, and Methotrexate have all been used with various degrees of success. For colchicine therapy, a case series involving seven patients were treated with colchicine plus prednisone, and after reaching a clinical response, the steroid dose was tapered, maintaining daily colchicine therapy with no recurrence or treatment failure observed during follow-up.

PUB630 Ifosfamide-Induced Fanconi Syndrome: A Rare Complication in Adults

Muhammad A. Ali, Mary O. Muoneke. Emory University, Atlanta, GA.

Introduction: Fanconi syndrome is a metabolic disorder characterized by severe proximal renal tubule dysfunction. It leads to impaired reabsorption of amino acids, glucose, phosphorus, potassium, urate and bicarbonate. Ifosfamide is used in the treatment of a variety of childhood and adult malignancies. Pathophysiology of its toxicity is unclear, but thought to be due to accumulation of the toxic metabolite chloroacetaldehyde in proximal tubular cells. Only a few cases have been reported in adults. We describe a case of an adult with diffuse large B cell Lymphoma who developed Fanconi Syndrome following Ifosfamide use.

Case Description: A 70-year-old Caucasian female with history of diffuse large B cell lymphoma presented to the ER with complaints of increased fatigue and confusion, which started a day after chemotherapy session with Ifosfamide. Physical exam revealed a confused female with trace pedal edema but otherwise normal exam. BP: 175/93, HR: 84/min, RR: 20/min, Temp: 36.6°C. Imaging studies were normal. Labs revealed Sodium 143, Potassium 2.5, HCO3 16, chloride 119, phosphorus 1.5mg/dl magnesium 1.3 mg/dl, creatinine 1.4, serum glucose109. She had a hyperchloremic metabolic acidosis and acute kidney injury with glycosuria with normal serum glucose. Fanconi’s syndrome was suspected and 24 hour urine amino acid screen came back positive for Aspartic Acid, Threonine, Serine, Glutamic Acid, Glutamine, Glycine, Alanine, Cystine, Methionine and Isoleucine, amongst others A diagnosis of Ifosfamide induced Fanconi syndrome was made and aggressive electrolyte-bicarbonate and fluid repletion was started. Ifosfamide was discontinued and she improved remarkably after two weeks.

Discussion: The mechanism of Ifosfamide induced renal injury is not completely understood. It is postulated that chloroacetaldehyde (CAA), a toxic metabolite is thought to deplete intracellular glutathione in the renal tubule, predisposing to cellular damage. Our patient had glycosuria in the presence of normal blood glucose, aminoacidaemia, hypokalemia, hypophosphatemia and hyperchloremic acidosis which is consistent with Fanconi syndrome. Early detection and treatment is key to preventing further deterioration in renal function and mental status. Although uncommon, Fanconi syndrome can be fatal and should be considered in any patient with any degree of renal impairment on Ifosfamide.

PUB631 Oliguric AKI Following Laparoscopic Ablation of Liver Metastases

Anish Bobba, Andy Chuu, Tingting Li. Washington University in St. Louis, St. Louis, MO.

Introduction: Microwave ablation is a form of thermal ablation used for the treatment of solid liver lesions. With this therapy, the reported incidence of acute kidney injury (AKI) has been as high as 20% with tumor size > 5cm but AKI requiring dialysis is a relatively rare complication. AKI as a result of microwave ablation has gained increasing attention among surgeons in recent years but remains a relatively unknown phenomenon among nephrologists. We present a case of oliguric AKI requiring dialysis following microwave ablation of liver lesions.

Case Description: A 42-year-old male was admitted following laparoscopic microwave ablation of metastatic liver lesions from colon cancer. Ablation was performed on four liver lesions, with the largest measuring 1.5 cm. There was minimal blood loss and patient was hemodynamically stable during the intra-operative and post-operative period. He developed AKI on post-op day 1 with a rise in creatinine (Cr) to 2.51 mg/dL (11 mg/dL prior to ablation) accompanied by oliguria. A careful review of history (medications, IV contrast, etc) and search for potential causes (ANA, ANCA, anti-GBM antibody, complements, CFPK) were unrevealing. Renal ultrasound with dopplers was unremarkable. Urinalysis was positive for 2+ protein, 3+ blood, 1+ glucose. Urine microscopy showed no granular casts or cells. Patient was given intravenous fluids for possible volume depletion but renal function continued to worsen. By day 3, his Cr was 8.1mg/dL and hemodialysis was initiated for oligoanuria and volume overload. Further testing revealed haptoglobin < 10 mg/dL and elevated LDH of 492 units/L. Hemoglobin dropped from 13.9 to 11.3 within the first 3 days post-op. Due to lack of recovery, a kidney biopsy was performed and pathology showed acute tubular injury with evidence of hemoglobin casts in the tubules.

Discussion: This case report highlights the importance of recognizing AKI related to hemolysis as a potential complication following microwave ablation. The liver is a highly vascular organ and carries an inherent risk of hemolysis resulting from exposure to adjacent thermal energy during ablation. Temperatures can reach as high as 100°C. Preventative measures including pre-op hydration, intra-op limits on the duration and applied energy, and close postop monitoring may help in prevention and early identification of AKI related to hemolysis secondary to microwave ablation.

PUB632 Plasma Exchange Therapy as Treatment for Myeloma Kidney

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Introduction: Multiple myeloma (MM) is characterized by a clonal proliferation of malignant plasma cell producing monoclonal proteins, which can lead to organ damage. Renal involvement is present 20-40% of MM. Severe acute kidney injury (AKI) related to intratubular cast formation is a common manifestation. Early reduction of serum free light chain (FLC) is associated with recovery of AKI. Survival of MM is related to kidney function. Plasma exchange therapy has been studied for myeloma kidney, although data is limited and current evidence is non-conclusive. We herein report a case of myeloma kidney with renal recovery after plasma exchange therapy.

Case Description: A 64-year-old female with history of multiple myeloma treated with a cycle of bortezomib and dexamethasone presented to the hospital with AKI. Labs upon presentation were showing a creatinine of 4.8 from baseline creatinine of 1.2. Serum kappa FLC of 7287 with a kappa/lambda ratio of 3259. Vital signs and physical examination were unremarkable. Patient received standard chemotherapy and fluid resuscitation. Given significant kidney dysfunction and severely elevated kappa FLC plasmapheresis was recommended. Patient received 3 sessions of plasma exchange. Before and after kappa FLC were measured. A significant decrease in creatinine and kappa FLC was observed by post-procedure day A, with creatinine of 2.9 and kappa FLC of 2999. Patient was discharged and followed up at clinic.

Discussion: Our case demonstrates that plasma exchange therapy might provide a benefit to patients with severely elevated kappa FLC and significant kidney dysfunction. More clinical trials are needed to further establish the role of plasma exchange in Myeloma Kidney.

PUB633 Retroperitoneal Hematoma Manifesting as Pancreatic Adenocarcinoma in a Renal Allograft

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Introduction: A retroperitoneal mass could represent a hematoma, cyst or tumor. We present an unusual case of pancreatic adenocarcinoma presenting as retroperitoneal cystic mass in a renal transplant recipient.

Case Description: A 47-year-old African-American female with history of End Stage Renal Disease (ESRD) secondary to IgA nephropathy. She received her first renal transplant in 1999 which lasted till 2004. She received her second transplant in 2005. Her post-transplant course was uneventful for about 12 years until she presented with a left
abdominal palpable mass with pain for 2 weeks. CT scan of the abdomen/pelvis revealed a large heterogeneous mass with significant involvement of the 6 cm cystic mass in the lower quadrant without involving the surrounding structures. Upon resection, the mass yielded approximately 1.5 liters of old clotted blood. Sections of the tumor demonstrated cystic and solid areas with complex epithelial architecture including papillary and cribriform patterns and ovarian or ovarian-like stroma suggesting the possibility of an ovarian or gastrointestinal malignancy. PET CT showed increased uptake and thickening to the left psoas muscle at the posterior margin of the atrophed left native kidney. Final pathology of the rim was consistent with adenocarcinoma of unknown primary. The tissue staining was positive for CK 7 and CK 20 making colon primary less likely. CEA and CA-125 were normal. CA 19-9 was elevated, and the immunohistochemistry and gene expression profiling revealed pancreatic adenocarcinoma as the primary tumor. Despite aggressive chemotherapy, subsequent PET scans revealed disease activity in lungs, mediastinal lymph nodes and abdominal mesentery for which she is currently receiving palliative chemotherapy.

**Discussion:** The presentation of an isolated retroperitoneal hematoma initially thought to be a fluid collection in this case, was infact a malignant presentation. One possible hypothesis is that long-standing immunosuppression could have contributed to the tumor formation. After identifying the primary site and the unusual site of metastatic presentation, this case was a diagnostic challenge.

**PUB634**

**Checkpoint Check-Up: Pembrolizumab and Interstitial Nephritis**

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**Introduction:** Over the last few years, the FDA has approved pembrolizumab - one of the checkpoint inhibitors - for the treatment of several cancers. As the field of therapeutic immuno-oncology rapidly expands, enigmatic complications in conjunction with these agents are arising.

**Case Description:** We present a 52-year-old female with history of metastatic melanoma treated with pembrolizumab and no prior kidney disease who had recurrent relapses of acute kidney injury [AKI] due to acute tubulointerstitial nephritis [AIN]. He first presented with AKI six weeks after starting therapy. On admission his creatinine [Cr] was >9 and was thought to be due to excessive concurrent NSAID use. A two-month steroid taper was started and pembrolizumab was held until renal function normalized. Subsequently pembrolizumab was reinstated. He underwent a total 13/17 cycles without difficulty and stayed off NSAIDs. Unfortunately, seven months after restarting therapy he was readmitted with AKI and peak Cr > 9. This was about three weeks after his last pembrolizumab dose. A renal biopsy revealed AIN secondary to pembrolizumab. Patient was discharged on a 20-day taper of prednisone and pembrolizumab was discontinued in consultation with his oncologist. Two weeks later while still on the prednisone taper, the patient was admitted to the ICU for shock and AKI. His AKI was thought to be related to septic shock rather than worsening AKI, and at discharge he was continued on his previous prednisone taper. Unfortunately, he returned within one week with another AKI. It was concluded that his steroids were tapered too rapidly, and he was placed on high dose prednisone and renal function stabilized with plan for a prolonged taper over months. Remarkably, the patient never required dialysis and was not oliguric at any time.

**Discussion:** This case demonstrates the difficulty of establishing a treatment regimen for relapsing AIN with checkpoint inhibitor use. Case series point out a variable incidence of AIN with pembrolizumab use in 5.1% associated with checkpoint inhibitor use. Per reports there were cases with AIN seen even weeks to months after conclusion of checkpoint inhibitor therapy. However, no consensus/guidance about duration of treatment is available to the best of our knowledge. This case highlights the need for prolonged treatment with steroids in case of relapsing AIN with checkpoint inhibitor use.

**PUB635**

**Immune Checkpoint-Inhibitor Induced AKI**

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**Introduction:** Drug-induced acute interstitial nephritis (DI-AIN) is a common cause of AKI, affecting about 20% of patients with unexplained AKI, and leads to CKD and ESRD. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two essential immune checkpoint receptors that play an essential role in negatively regulating T cell activation. Immune checkpoint inhibitors (ICI) are widely being used in the treatment of several malignancies.

**Case Description:** A 70-year-old female with a past medical history of lung adenocarcinoma presented to the hospital with nausea, poor appetite, and lower extremity edema. The patient received a total of four cycles of Pembrolizumab which started three months prior to presentation for stage IV lung adenocarcinoma. She has been using ibuprofen for years. On admission, she was found to have stable vital signs. Physical exam revealed mild leg edema without any lung rales or aristies. Labs revealed SCR 10 mg/dL (baseline 0.7), BUN 55 mg/dL NA 134 mmol/L K 4.3 mmol/L and CO2 22 mmol/L. Urinalysis showed >100 WBC/HPF, >100 RBC/HPF, +++ protein with no casts. UPCR 6.64 g/g. ANCA ab, Anti GBM ab, and SLEP were negative. A renal biopsy revealed moderate inflammation of the interstitium with lymphocytic tubulitis and diffuse tubular injury. Trichrome staining was consistent with moderate interstitial fibrosis and edema.

Pembrolizumab was promptly discontinued on admission. The patient was initiated on IV pulse dose steroids with significant improvement in renal function. SCr improved to 1.9 mg/dL after 3 weeks of steroids. She never required dialysis.

**Discussion:** AKI incidence rate is estimated to be of 2.1% in patients who received PD-1 inhibitor therapy. Acute interstitial nephritis induced by ICPIs is related to severe myelosuppression and continued to improve until his successful discharge after 29 days. This case demonstrates that combination therapy of early CVVH, leucovorin and glucarpidase therapy in the successful treatment of a patient with MTX toxicity.

**Case Description:** The 79 year old patient was diagnosed with stage 4 Non-Hodgkins Lymphoma and was commenced on R-CHOP therapy. He was admitted for IV MTX as an adjunct to his chemotherapy. At this time, his renal function was normal. He proceeded to treatment with IV isonicotinic b cinematic and high-dose leucovorin. During his inpatient stay, he was maintained on a pre renal level. He required transfer to ICU for non invasive ventilatory support due to respiratory sepsis. At 48 hours post infusion his MTX levels were 19.61 umol/L. CVVH was started at a dose of 30 ml/kg/hr, within 52 hours of administration of MTX. The patient did not become oliguric and his peak creatinine was 1.89mg/dl. His MTX levels continued to fall over subsequent days. At hour 58 post infusion, the patient was administered glucarpidase, a recombinant bacterial enzyme which cleaves MTX into two non-cytotoxic metabolites. Of note is that immunosassay does not differentiate between the levels of active MTX and inactive metabolites. Due to this, CVVH was continued until MTX levels were below 1 umol/L. The patient was transferred from ICU after 9 days and was discharged following 29 days of admission with restored renal function.

**Discussion:** Previous cases reports have demonstrated the usage of CVVH in MTX toxicity when absolute indications arise for renal replacement therapy. However, here, CVVH was commenced with the express intent of reducing absolute serum MTX levels. The patient did not develop any haemorrhagic or infective complications of myelosuppression and continued to improve until his successful discharge after 29 days. This case demonstrates that combination therapy of early CVVH with glucarpidase therapy in conjunction with high dose leucovorin can be associated with promising outcomes in terms of therapy of MTX toxicity.

**PUB637**

**Salt-Losing Nephropathy Associated with Use of Foscarnet in a Patient with Lymphoma**

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**Introduction:** Salt losing nephropathy is an uncommon cause of hyponatremia. We report a case associated with the use of foscarnet.

**Case Description:** A 60 year old female with history significant for DLBCL status post Yescarta CD19 CAR-T cell therapy with Flu/Cy lymphodepleting regimen who presented with neurotoxicity related to her therapy. Work up revealed a HHV-6 encephalitis found in both plasma and cerebrospinal fluid. Patient was started on foscarnet for treatment of her HHV-6 encephalitis, however patient developed both hyponatremia and natriuresis. Subsequent investigation demonstrated Hyponatremia due to salt-wasting nephropathy likely induced by foscarnet. Patient was started on salt replacement with both oral and IV sodium chloride to maintain her serum sodium above 130 meq/L. Urinary sodium losses were as high as 15 g/day. Unfortunately, foscarnet was unable to be discontinued as patient had persistent HHV-6 titer on LP three months into treatment and ganciclovir was added. Patient then cleared her HHV-6 a month later, and both medications were stopped. IVF were soon able to be stopped, but she continued to require sodium chloride replacement at time of discharge to maintain a normal serum sodium.

**Discussion:** Foscarnet is a phosphonoformate analog of inorganic pyrophosphate which is used in the treatment of herpes encephalitis, varicella, and CMV. It can cause various electrolyte abnormalities including hypokalemia, hypomagnesia, hypocalcemia, and hypophosphatemia. We present a rare case of foscarnet causing hyponatremia due to salt wasting. The specific mechanism involved in the salt loss is unclear.
PUB638

Pseudonulmonary C4d Deposits in a Hereditary Glomerulopathy Caused by a Novel NC1 Collagen-4-Anti-Alpha-5 Missense Mutation: A ‘New Disease Entity’?
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Introduction: Glomerular C4d deposits in kidney biopsies are incompletely characterized and usually not used for diagnostic decision making. It was not until recently that isolated pseudonulmonary glomerular C4d deposits were identified as markers of structural glomerular capillary wall remodelling. Here we report a case that furthers our understanding of “pseudonulmonary glomerulopathies”: C4d beyond antibody and immune-complex mediated injury.

Case Description: We report a hypertensive, otherwise healthy 60-year-old male with a 5-month history of isolated nephrotic range proteinuria, no hematuria; normal serum creatinine, complement and ANA levels. Work-up showed MUGS (IgG/kappa restricted). A diagnostic renal biopsy to search for ‘MGUS of renal significance’ demonstrated thickened glomerular capillary walls with strong pseudonulmonary complement factor C4d deposits by immunofluorescence microscopy (IF; Fig. A); all other IF studies including stains for COL4A3 were unremarkable with only minor equivocal abnormalities seen for COL4A5. The unusual C4d staining of undetermined significance triggered electron microscopic studies uncovering a hereditary nephropathy with marked GBM remodelling (Fig. B). Genetic testing unveiled a novel “Alport” COL4A5 missense mutation in a C4d positive hereditary nephropathy unexpectedly diagnosed in an older male presenting with isolated proteinuria. We provide further evidence of complement as building blocks in C4d remodelling and pseudonulmonary C4d deposits as morphologic symptoms of architectural GBM disturbance that guided in-depth diagnostic work-up in our patient.

AIF: Global pseudonulmonary C4d staining along capillary walls (B) EM: Marked structural capillary wall remodelling.

PUB639

A Case of IgG4-Related Disease with Tubulointerstitial Nephritis and Glomerular Endocapillary Hypercellularity
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Introduction: IgG4-related disease (IgG4RD) is an uncommon autoimmune disease that affects multiple organ systems. The most commonly affected organs are the pancreas, liver, gall bladder, lachrymal glands, salivary gland, lung, and kidney. Renal involvement of IgG4RD typically presents as IgG4-positive plasma cell-rich tubulo-interstitial nephritis and storiform fibrosis.

Case Description: A 61-year-old man with a history of asymptomatic pancreatic swelling and impaired renal function was referred to our hospital. Laboratory data showed an increased serum creatinine concentration (1.33 mg/dL) and a high serum level of IgG4 (1020 mg/dL). All autoimmune antibodies were negative, and the serum complement levels were within a normal range. Protein urine excretion was 0.69 g/day without microscopic hematuria. Abdominal Magnetic Resonance Imaging revealed enlargement of the pancreas and multiple bilateral renal parenchymal nodules with hypointensity in T2 image. A renal biopsy revealed storiform fibrosis and IgG4-positive plasma cell infiltration of the interstitium, which was consistent with IgG4-related kidney disease. Three out of 13 glomeruli exhibited segmental endocapillary hypercellularity. Of note, marked infiltration of monocytes to the vascular pole was observed, which is likely to be continuous to interstitial lesions. Immunohistochemistry and electron microscopic examination did not show any evidence of immune-mediated glomerular diseases including membranous nephropathy.

Discussion: We herein describe a case of IgG4RD with tubule-interstitial nephritis and focal endocapillary hypercellularity in the glomeruli. Although membranous nephropathy is a common glomerular presentation of IgG4RD, proliferative glomerulonephritis has only rarely been reported previously. To our knowledge, this is the first case of glomerular endocapillary hypercellularity in a patient with IgG4RD.

PUB640

Gastrointestinal and Renal Allograft Involvement by Light Chain Deposition Disease: Report of Two Cases
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Introduction: Light chain deposition disease (LCDD) is a rare entity both in native and transplant kidneys, and concurrent involvement of the kidney allograft and other organs has been rarely described. We report two cases of post-transplant LCDD in which gastrointestinal symptoms preceded a diagnosis of LCDD initially made on kidney allograft biopsy, and subsequently detected on previous gastrointestinal biopsies.

Case Description: The first patient was a 59-year-old female with end-stage renal disease (ESRD) of unknown cause, who presented with chronic diarrhea and acute kidney injury (AKI), 1 year after kidney transplant (KT) from unrelated living kidney donor (LURT). Gastrointestinal (GI) endoscopy, as well as light microscopy of gastrointestinal biopsies were negative and the GI symptoms were ascribed to Mycoplasmal infection (MMF) effect. MMF was discontinued with no benefits. Renal function kept worsening and an allograft kidney biopsy was performed, revealing LCDD, with a subsequent diagnosis of kappa light chain myeloma. The second patient was a 46-year-old male with ESRD of unknown cause, status-post KT from LURT, who presented 4 years post-transplant with chronic vomiting, diarrhea and AKI. Weeks-long recurrent episodes of nausea and vomiting, with non-bloody watery diarrhea, had been occurring for a year prior to admission. GI endoscopy as well as light microscopy of gastrointestinal biopsies were negative and the symptoms were ascribed to MMF effect. MMF was suspended with no benefits. Two subsequent allograft biopsies were diagnostic for LCDD. A work-up for plasma cell dyscrasias identified a clone secreting kappa light chains, consistent with monoclonal gammapathy of renal significance. We retrospectively stained previous GI biopsy specimens for light chains and found that both patients had kappa chain-restricted linear deposition along the basement membranes of gastric glands.

Discussion: These cases highlight (i) the rationale for screening kidney transplant recipients with serum protein electrophoresis for early diagnosis of plasma cell dyscrasias, (ii) the importance of full immunofluorescence staining panels and electron microscopy on allograft kidney biopsies after 6 months from KT, and (iii) the need to screen for extra-renal involvement by LCDD.

PUB641

Medullary Angiitis: Presentation and Diagnostic Challenges
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Introduction: When histopathologic exam of the native kidney is performed, conditions are diagnosed usually by microscopic examination of the renal cortex. Not many disease entities have been known to involve the renal medulla or have a medullary component. We present a very rare case of a subtype of small vessel vasculitis primarily involving the renal medulla that helps us understand the characteristic pathological features under microscopic examination and the challenges in establishing this diagnosis.

Case Description: A 75-year-old male with PMH of CKD Stage 3 with baseline serum creatinine (Scr) of 1.4, history of FSGS 18 years back, not on any medications and no other comorbidities came for evaluation of worsening Scr of 2.23. Labs were significant for creatinine, 2.23 mg/dl, with urinalysis showing hematuria, proteinuria without any RBC casts with urine protein creatinine ratio of 1400 mg/g. P-ANCA was positive but ANA, Anti dsDNA, serum protein electrophoresis, C-ANCA, HIV, Hepatitis B, and C were negative with normal serum complements. The renal US did not show any abnormalities. No history of skin or throat infections in the past. The biopsy was diagnostic of medullary angiitis which is

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
a subtype of small vessel vasculitis. The patient was started on prednisone 40mg per day with a plan to start rituximab infusions. In subsequent follow-ups, patient’s SCr was stable at 2.2.

**Discussion:** Renal medullary angiitis was first described by Watanabe et al in 1983 and is an extremely rare condition with an incidence of 0.19%, which involves vasa recta of the renal medulla. Histopathological exam of the renal medulla has been described as the presence of interstitial hemorrhage with polymorphonuclear leukocyte infiltrate. Diagnosis of this condition is challenging, as most renal biopsies involve only the renal cortex and it can be misdiagnosed as acute interstitial nephritis due to the above microscopic features. Almost 63% of the reported medullary angiitis cases are ANCA positive and among non-ANCA related medullary angiitis, 20% have been reported to be due to IgA nephropathy. In fact, medullary angiitis may be the first systemic manifestation of an ANCA associated vasculitis and hence it should be differentiated from acute interstitial nephritis which has different etiologies.

**PUB642**

Non-Myeloma Hematologic Malignancies in Renal Biopsies: A Single Institution Experience

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**Introduction:** Hematologic malignancies other than myeloma are relatively rare in renal biopsies. We present 5 diverse cases of hematologic malignancies with histologic, immunohistochemical, and immunofluorescent evidence of renal involvement. Consecutive native and transplant renal biopsies from year 2015 to 2018 were reviewed.

**Case Description:** Both lymphoid and myeloid malignancies were noted.

**Discussion:** This case series demonstrates that renal involvement is possible in any hematologic malignancy. Renal biopsy findings may sometimes direct evaluation for an unsuspected hematologic malignancy, possibly allowing for earlier detection and improving patient outcome.

**Key Patient Findings in Renal Biopsy Specimens**

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Sex</th>
<th>Non-renal symptoms</th>
<th>Renal symptoms</th>
<th>Renal function at presentation</th>
<th>Non-hematologic finding in renal</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-75</td>
<td>M</td>
<td>Fatigue, dyspnea, anemia</td>
<td>None</td>
<td>Moderate proteinuria</td>
<td>None</td>
<td>Prednisone, Chlorambucil</td>
<td>1 year</td>
</tr>
</tbody>
</table>

**PUB643**

Lupus Ecephalopathy and 87.5% Glomeruli with the Formation of Crescent in a Childhood-Onset Systemic Lupus Erythematosus: A Case Report

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**Introduction:** Systemic lupus erythematosus (SLE) associating with lupus encephalopathy and lupus nephritis has been reported in previous case reports. The crescent formation could be detected under the microscope at the same time. Here, we present a rare case that 87.5% glomerular crescent formation. Up to now, there have no report about crescent formation much more than this proportion in this type of patient.

**Case Description:** We report a case of a 14-year-old female who presented severe oliguric renal failure and uncoordinated movement. The highest serum creatinine reached 2.9mg/dl. She was diagnosed as lupus encephalopathy and severe diffuse proliferative lupus nephritis. A renal biopsy revealed that 18 of 21 glomeruli had crescent formation (11 cellular crescents, 5 fibrous-cellular crescents and 2 fibrous crescents), accounting for 87.5% of total. There were IgG, IgA, IgM, C3, Clq, both kappa and lambda light chains on Immunofluorescence staining. The patient was immediately treated with glucocorticoid, mycophenolate mofetil, immunoglobulin and plasmapheresis. She had symptomatic improvement and the serum creatinine also dropped to normal levels in 42 days later. No infection occurred during treatment. In addition, follow-up of 3 months after discharge showed stable kidney function and no recurrence of edema, oliguria or other symptoms.

**Discussion:** It’s a rare case of lupus nephritis with 87.5% glomerular crescent formation accompanied by lupus encephalopathy. Such patients have a poor prognosis. However, renal function returned to normal after a series of aggressive treatments. It suggests that aggressive short-term combination therapy is beneficial for children with lupus nephritis with large amounts of glomerular crescent formation.
Coexistence of Triple Viral Infection as a Trigger of Severe Rhabdomyolysis-Associated AKI in an Adolescent

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Introduction: Rhabdomyolysis has many triggers, including trauma, drugs, autoimmune disorders, infection and genetic mutations. Prevalence of viral-induced rhabdomyolysis is 38% in pediatric population. Here we describe a case of acute kidney injury (AKI) from rhabdomyolysis secondary to viral infection.

Case Description: An 18-year-old African American female college student with past medical history of febrile seizures, Kawasaki disease and obesity presented with a one-week history of myalgias, productive cough, abdominal pain and dark urine. She denied sick contacts, recent travel, rash, arthralgias, trauma. Physical examination revealed tachycardia, abdominal and lower extremities tenderness, inability to ambulate. On admission, creatinine (cr) was elevated at 1.56 mg/dl, potassium, 5 mmol/l; CK-200,000 IU/L, AST, 2033 U/L; ALT, 595 U/L. Urinalysis showed amber urine, 3+ blood, 2+ protein, 1-5 RBC and no casts. Drug screen was negative. Viral and bacterial serologies were negative with the exception of PCR-positive Parainfluenza and Epstein Barr virus (EBV), and Coxsackievirus group B antibodies (titers 1:32). Complement levels were normal, pANCA and cANCA <1:20. ANA titer was 1:160 with speckled pattern. On day 3, lower extremities MRI showed diffuse, symmetric muscle edema. Muscle biopsy demonstrated acute myonecrosis. PCR of muscle sample for EBV was negative. Stains for mitochondrial, glycogen, lipid storage myopathies were unremarkable. The patient was managed with intravenous volume resuscitation. On day 4, cr decreased to 1.25 mg/dl and CK decreased to 183,600 IU/L. On day 14, she was discharged home with normal renal function and CK of 617 IU/L.

Discussion: Coexistence of viral infections led to severe rhabdomyolysis in our patient. However, given the reported history of vasculitis, investigation of potential autoimmune etiology was pursued, and subsequently excluded. As a result, steroid therapy was withheld and resolution occurred with intravenous volume resuscitation alone. Clinicians should have a high index of suspicion for rhabdomyolysis in patients who present with muscle pain and weakness and elevated creatine. Further, timely investigation of the etiology of rhabdomyolysis, including viral, autoimmune, and genetic disorders, has implications for management and prognosis of AKI.

Transplant Renal Artery Stenosis in a Child with BK Nephropathy

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Introduction: Transplant renal artery stenosis (TRAS) and BK nephropathy are known complications of renal transplantation, but the association has not been reported.

Case Description: A 2-year-old girl received a kidney transplant from a 20-year-old deceased donor, along with native nephrectomies. She had a delayed graft function due to a renal artery thrombus and required thrombectomy with reanastomosis, heparin and aspirin. Thymoglobulin, tacrolimus and mycophenolate were started. CMV and EBV DNA PCRs were negative but developed BK viremia at 2 months (peak 260,000 copies/mL). Serum creatinine remained stable at a baseline of 0.9 mg/dl. After immunosuppression reduction and leflunomide initiation, her BK load decreased to 1200 copies/mL after 4 months. There were no episodes of rejections, hydropnephrosis or hemorrhia. Blood pressure (BP) was well controlled on low dose amlopidine. 5 months later, she presented with hypertensive emergency, following a respiratory infection. Her BP’s remained refractory to 8 antihypertensive agents and required dialysis for oliguric acute kidney injury. Allograft biopsy showed evidence of BK nephropathy. Immunosuppression was further minimized. Doppler renal sonogram and duplex study of renal artery were both suggestive of TRAS. Angiogram showed severe proximal anastomotic TRAS (> 95% occlusion). Balloon angioplasty with stenting was done with immediate improvement in the blood flow and gradient reduction to 18 from 50 mm Hg. BP’s and renal function normalized. 7 months post-transplant, she remains stable, with no BK viremia and while on 2 antihypertensives.

Discussion: Although ureteral and urethral stenosis is known to occur with BK infection, TRAS is an interesting association. Timely recognition and management of both is important to prevent uncontrolled hypertension and allograft dysfunction.

A Rare Etiology of Bilateral Hydronephrosis in Adolescents

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Introduction: Nonurological etiologies of bilateral hydronephrosis in children include external compression by a tumor, lymph nodes, retroperitoneal fibrosis, blood clots, and fungal ball.

Case Description: A 14 years old male presented to the emergency department with nausea, vomiting, and decreased energy for a month. He was found to have stage III hypertension. Blood workup showed BUN of 58 mg/dl and creatinine of 5.4 mg/dl. Renal ultrasound showed severe bilateral hydronephrosis with cortical thinning (Image 1). CT abdomen showed 11.5 cm retroperitoneal mass encasing the aorta and right common iliac artery with obstruction of the right ureter and a hyperdense mass in the parapelvic left kidney (Image 2). Biopsy of the retroperitoneal and kidney mass was consistent with retroperitoneal fibrosis. It showed sclerotic fibrosis with lymphoplasmacytic, eosinophil, and macrophage infiltrates. Immunohistochemistry showed predominant CD3+ T-cells, CD20+ B-cells, eosinophils, plasmacytes, and S-100+ dendritic cells/macrophages. Fibrosis contained smooth muscle actin+ spindle cells. The number of CD3+ T cells were disproportionally higher than CD20+ B cells which suggests IgG related disease. IgG4:IgG ratio was normal. Work up for other etiologies is still ongoing.

Discussion: The pathogenesis of retroperitoneal fibrosis (RF) can be due to asbestos, smoking, vasculitis, drugs, radiotherapy, neoplastic or infection. Idiopathic RF or Ormond’s disease is a rare disease in all age groups. The first reported pediatric case in literature was in 1962. It is rare, with an incidence of 1.3 per 100,000 population/year with adult predilection. Its presentation is related to the organ involved, most commonly kidneys.
An Unusual Vintage: Wine-Colored Urine in a Postoperative Patient

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Introduction: A variety of drugs and diseases may cause discoloration of urine. Some associations are well-known, but newer medications and novel uses for old medications may induce changes which can be disturbing to patients and providers. Laboratory abnormalities and dialysis machine dysfunction may also be associated as presented in this case of wine-colored urine.

Case Description: A 38-year-old man with a history of chronic kidney disease stage 3 and flank pain was found to have a pheochromocytoma. He presented for left adrenalectomy and nephrectomy, complicated by both intra- and post-operative hypotension requiring pressor support. He received methylene blue (100 mg) and hydroxycobalamin (5 mg, Cyanokit) peri-operatively for vasoplegia. Nephrectomy was called on the 2nd post-operative day for evaluation of deep purple urine. Urine sediment revealed muddy brown casts, 25 RBCs/HPF and scattered WBCs, although creatinine remained near baseline of 2.8 mg/dL. The urine discoloration was due to the combination of methylene blue and high dose hydroxycobalamin. It resolved over the ensuing 14 days.

Discussion: Vasoplegia is an increasingly recognized complication of surgery, characterized by hypotension refractory to pressor support despite a normal cardiac output. There is evidence for the use of 2 agents, methylene blue and hydroxycobalamin, in the treatment of vasoplegia. Methylene blue causes a blue-green urine and is associated with serotonin syndrome in patients on SSRIs. Hydroxycobalamin causes a deep red to purple discoloration of both urine and plasma, and is associated with falsely elevated creatinine, among other lab abnormalities. It can also cause a false blood leak alarm on certain dialysis machines leading to dialysis cessation. Recognizing these effects will be increasingly important for nephrologists caring for patients in the post-operative period as the recognition of vasoplegia and the use of methylene blue and hydroxycobalamin becomes more prevalent.

Cefepime Neurotoxicity: At-Risk Population and Preferred Treatment Modality

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Introduction: Correct assessment of renal function in hospitalized patients is of paramount importance as it influences not only the choice of drug but also the specific route and dose. We present a case of cefepime neurotoxicity caused by incorrect dosing in a patient with unrecognized severe acute renal failure.

Case Description: A 51-year-old woman was admitted to the hospital with abdominal pain and chills. She was febrile to 38.8°C with low normal blood pressure. She had white blood cell count 23000/mm³. Serum creatinine (Scr) 0.62 mg/dL. Vancomycin and piperacillin/tazobactam were begun. A contrast CT scan revealed a complex fluid collection in the lower pelvis which was drained by interventional radiology. Two days after admission, Scr was 1.2 mg/dL with eGFR of 46 ml/min/1.73m². Because of the concern for nephrotoxicity, she was switched to cefepime. On the fourth day of hospitalization, she had progressive decline in mental status. She also had asterixis. Scr was 4.2 mg/dL with blood urea nitrogen 26 mg/dL. Prompting consultation with nephrology. It was noted that she had had a total of 12 grams of cefepime over last 48 hours. The constellation of symptoms suggested cefepime neurotoxicity. Investigation for other causes of her neurologic decline was unrevealing. She was started on continuous venovenous hemodialysis (CVVH) with a replacement fluid (RF) flow rate of 20 ml/kg/hr. Over the ensuing few hours, she became more altered and developed expressive aphasia. For the concern for inadequate clearance, RF flow rate was increased to 30 ml/kg/hr. Improvement in her mental status was observed in the next 12-15 hours. She subsequently regained her baseline mental status and renal function.

Discussion: The estimation of renal function is difficult in hospitalized patients as they are not always in a steady state. Despite that, eGFR estimation through Scr is still relied heavily upon. This patient had an anephric rate of rise in Scr, and cefepime grossly overestimated her true renal function and led to prescription of an excessive cefepime dose and subsequent toxicity. This case illustrates the importance of correct dosing based on active assessment of renal function. It also underlines the pitfalls of using a laboratory eGFR in hospitalized patients. Cefepime is best cleared using conventional hemodialysis but requires RF flow rate of at least 30 ml/kg/hr with CVVH for adequate clearance.

Recurrence of Fibrinogen Alpha Amyloidosis in Transplant Kidney

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Introduction: Fibrinogen Alpha chain amyloidosis is an autosomal dominant disease associated with mutations in the fibrinogen Alpha chain (FGA) gene. Patients typically present with kidney impairment and progress to end-stage renal disease over a median time of 4.6 years. Variant fibrinogen is produced in the liver and solitary renal allograft fails in 1-7 years with recurrent amyloidosis. In the largest series to date recurrence was noted in 4/8 kidney transplants (50%). We present a case of recurrence of amyloidosis in transplant allograft in less than 2 years post-transplant.

Case Description: 55 year old man with history of ESRD secondary to fibrinogen-alpha amyloidosis had DDKTx on 3/16/17. Creatinine post-transplant settled in the 1.0-1.3mg/dl range. His post-transplant course was complicated with bilateral DVTs and PE. He developed proteinuria to 2.8 gm/gm on spot urine protein/Cr and a 24 hr urine collection 74g of protein. His serum Kappa/lambda free light chain ratio was also elevated, which was suspicious for recurrent renal amyloidosis. He had a renal biopsy on 11/14/17 that demonstrated FSGS (likely due to hyperfiltration injury) and did not demonstrate amyloidosis. He was started on losartan and a repeat 24 hour urine collection showed 22mg/24hr of proteinuria. He underwent a second renal biopsy for a rise in his creatinine in January 2019, which was positive for Congo red staining suggestive of disease recurrence. To confirm diagnosis mass spectrometry was done and it showed peptide profile consistent with fibrinogen alpha type amyloid deposition (Glu 520, His, Val, Gly, Glu, Asp). This patient had a variant fibrinogen with one less aminodicresine.

Discussion: Recurrence appears to be common in fibrinogen-alpha amyloidosis who receives a kidney transplant alone. In largest series, recurrence was noted in 4/8 successful kidney allograft. 3 were lost as direct result of recurrence (median 6 yrs). By comparison this patient’s homogeneous liver/kidney transplantation and no recurrence have been found in 6 surviving patients. Even if reports are scarce, a fibrinogen-alpha amyloidosis recurrence could be a factor of poor prognosis and graft loss. As fibrinogen production is

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The supplement was discontinued, and tacrolimus levels decreased. However, he restated the treatment for symptomatic relief and tacrolimus level was 17.2 ng/mL. While on the supplement, his tacrolimus dosage was decreased to 0.5 mg daily to achieve tacrolimus levels of 5.8 to 9.9 ng/mL. During evaluation for hepatitis C treatment, his glucosamine and chondroitin formulation was found to have Boswellia serrata extract. It was reduced, and his tacrolimus level was reduced to 3.2 ng/mL. His subsequent tacrolimus levels stabilized on a total of 2.5 mg of tacrolimus a day, in 2 divided dosages, without Boswellia and his transaminases normalized.

**Discussion:** Common OTC preparations can cause severe morbidity and mortality in specific patient populations. Boswellia containing compounds may be effective in relieving joint pain but can have critical drug interactions. We report the first case of Boswellia induced tacrolimus toxicity in a renal transplant patient.

**PUB653**

**Early BK Virus-Associated Nephropathy: A Double-Edged Sword and Unbeatable Barrier for Renal Allograft Survival**

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**Introduction:** The prevalence of BK virus-associated nephropathy (BKVAN) in kidney transplant (KTx) recipients is estimated to be 1 to 10%. We report a case of young woman with the first KTx complicated by an early onset BKVAN contributing to renal allograft loss.

**Case Description:** A 30-year-old Hispanic woman with ESRD due to reflux nephropathy underwent a 2-A-B-DR mismatched deceased donor renal transplantation with anti-thymocyte globulin induction. She had an immediate allograft function and was discharged on post-KTx. Baseline serum creatinine (SCr) was 0.8 – 1.1 mg/dL. Three months post-KTx, she developed new-onset BK viremia with a serum BK virus titer of 32,889 copies/ml. A 12-hour tacrolimus level ranged between 5.1 and 7.5 mg/L. Even after lowering mycophenolate sodium (MPS) to 360 mg twice daily, BK titer increased to 315,000 copies/ml at 8 months post-KTx. MPS was discontinued and leflunomide was started. Within 4 weeks, BK virus titers progressively increased to 2 million copies/ml by 11 months post-KTx. SCr was elevated to 2.4 mg/dL. A transplant renal biopsy revealed tubulointerstitial inflammation and diffuse SV40 immunostain positivity consistent with BKVAN without evidence of acute cellular (ACR) or antibody-mediated rejections (ABMR). Even after receiving IVIG, serum BK titers continued rapidly rising up to 15 million copies/ml at 13 months post-KTx with a worsening SCr of 3.5 mg/dL. All immunosuppressive medications were discontinued and serum BK titers decreased to 2,370 copies/ml, although renal allograft function progressively worsened. Repeat transplant renal biopsy showed evidence of ABMR and 1b ACR with moderate IFTA and negative SV4. There was no additional escalation of immunosuppressive medication and hemodialysis was initiated at 16 months post-KTx.

**Discussion:** Early occurrence of highly elevated level of BKVAN in a young woman is very difficult to treat in kidney transplant patients. Immunosuppression post-KTx can lead to BKVAN which is common cause of allograft dysfunction contributing to renal allograft loss. Both, over-immunosuppression and de-escalation should be avoided, to mitigate the risk for BKVAN, and enhance the risk for rejection respectively. Initial over-immunosuppression led to BKVAN and subsequent de-escalation led to acute rejection and ultimately allograft loss in this patient.

**PUB654**

**Graft Simple Cyst Infection in Late Transplantation**

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**Introduction:** Describe of a simple Cyst (SC)(Bosniak I) infection in a renal allograft is unprecedented in literature

**Case Description:** KM, 34-year-old female, presented end stage renal disease due to diabetes related nephropathy.14 months prior to the presentation she received a preemptive living donor kidney transplantation. Before implant, a 7cm Bosniak I cyst in kidney graft was marsupialized. Patient presented to the emergency department with pain in the right iliac fossa, without fever or urinary symptoms. Beta HCG was negative, computed tomography (CT) showed small non-obstructive calculi in calix calyx and the patient was discharged. Within 6 days, the cyst progressively increased to 2.0 cm. Patient was referred to the nephrology service. Laboratory revealed leukocytosis with left upper shift and an acute kidney injury KDIGO 1. Graft Doppler ultrasound showed no vascular or perfusion changes, but heterogeneity and debris in the SC. With the mentioned findings, it was thought that the previously SC was infected. Ciprofloxacin with adjunct caffeine was started, however patient presented only partial clinical response with sustained leukocytosis. On the third day we performed a percutaneous CT-guided drainage of the SC with 170ml of purulent secretion. A drainage catheter was planted and maintained for 7 days and antibiotics we’re re changed. Patient renal function and infectious parameters come back to normal.

**Discussion:** SC prevalence increases with age, occurring in up to 28-43% of kidney donor candidates. Despite the high occurrence, SC related complications are rarely reported. When facing a renal cysts infection, the antibiotic choice should take into consideration the cyst penetration profile (eg. Quinolone). Beta-lactamase association for synergism is controversial. SC infections requiring drainage are rare in native kidneys. The management was based on native kidney SC infections and ADPKD cyst infection reports.
Kaposi Sarcoma of the Tonsils in a Renal Transplant Patient Treated with Resection and Sirolimus


Introduction: Kaposi sarcoma (KS) is a locally aggressive vascular tumor which is strongly associated with human herpesvirus infection (HHV-8; also known as Kaposi sarcoma-associated herpesvirus or KSHV). KS is most often seen in patients with HIV infection, but can occur in patients who are on immunosuppressive therapy, particularly transplant recipients, with an incidence at least 9 fold greater than the general population. While skin and the oropharynx are the typical sites for KS accounting for 60% of cases, only 2% of these are confined to the mouth or oropharynx. Presentations involving the tonsils specifically are rare.

Case Description: We describe a case of tonsillar KS occurring in a kidney transplant patient. He presented 16 months post-transplant with dysphagia, odynophagia, and tonsils specifically are rare.

Discussion: Reduction of immunosuppression is an important part of the treatment of KS, but alone can be insufficient for inducing remission in the majority of cases as well as placing patients at increased risk for rejection and graft failure. Other immunosuppressants, notably sirolimus, have been shown to improve outcomes. Extensive or refractory cases may still require chemotherapy. Clinicians should be aware of dysphagia and tonsillar enlargement as a rare presentation of KS in post-transplant patients, particularly during the first 2 years when most cases occur. Our patient was maintained on low dose tacrolimus and sirolimus, and he continues to have good graft function and stable disease 5 months post diagnosis.

Thrombotic Microangiopathy in a Liver Transplant Patient on Tacrolimus

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Introduction: Thrombotic microangiopathy (TMA) is a rare adverse reaction of calcineurin inhibitors. TMA is fatal in solid organ transplant patients, with a reported incidence of 0.5-3% and mortality of about 75%. We report the case of a 19-year-old woman with Tacrolimus (Tac) induced TMA treated with eculizumab (EZZB).

Case Description: A 19-year-old female with autoimmune hepatitis status post Orthotopic Liver Transplant on Tacrolimus (Tac), Chronic Kidney Disease Stage III presented with diarrhea. Initial Labs: creatinine 12 mg/dl, platelet count 30,000/cumm, hemoglobin 5.2 g/dl, elevated LDH 635 IU/L, haptoglobin (HP) < 30 mg/dl, many schistocytes on peripheral smear. ADAMTS-13 activity: 55%, Stool PCR: Negative for Shiga Toxin and E.Coli. Clinically, typical TTP was ruled out. HUS was diagnosed, supported by subsequent kidney biopsy finding of TMA. As Tac can cause TMA, it was switched to sirolimus. Treatment with EZZB was instituted [900 mg IV weekly x four weeks, then 1200mg IV biweekly from doses 5 to 7]. By the 5th EZZB dose, renal function improved (creatinine down to 2.3 mg/dl), LDH decreased to 338 IU/L, although hemoglobin remained 30 g/dL. With ongoing hemolysis (elevated LDH and low HP), a 2nd renal biopsy was done following the 6th EZZB dose, which showed FSGS. Due to persistent proteinuria and ongoing TMA, sirolimus was discontinued. After the 7th EZZB dose, Cr level improved (68 to 128 IU/L). C4 was normal, LDH improved to 250 IU/L. Results of anti-complement H autoantibodies and aluHs genetic panel including C5 polymorphisms which is associated with poor response to EZZB were negative; but, heterozygous variant (c.3287G>A, p. Arg1096His) in exon 25 of the ADAMTS13 gene was positive. The patient’s renal function stabilized to creatinine of 2.1 mg/dl. In anticipation of discharge, outpatient EZZB treatment was arranged; unfortunately, she developed cardiac arrest and passed away.

Discussion: The case highlights that EZZB may improve Tac induced TMA without plasmapheresis. Per biopsy, patient’s AKI was a combination of ATN and TMA, so it is unclear the extent EZZB contributed to renal function improvement. Despite the finding of a heterozygous variant, the normal-ADAMTS 13 activity and data from the clinvar database clarified that the variant is benign and common in the population. Thus, it is likely that this is a case of tac-induced TMA that responded to EZZB treatment.
microangiopathy. Clinical symptoms can be asymptomatic to life threatening organ dysfunction. Diagnosis is through positive polymerase chain reaction and confirmed by a bone marrow biopsy showing decreased erythropoiesis and giant pro-erythroblasts with nuclear viral inclusions. The recommended treatment is with intravenous immunoglobulins (IVIG) with or without reducing immunosuppression. The dose and duration of IVIG is much debated. Due to the severity of anemia, viral load should be frequently assessed pre and post-transplant till resolution is achieved. In conclusion PIA is a rare but serious complication and a higher index of suspicion is advised when a transplant patient presents with severe and refractory anemia.

**PUB659**

De Novo Collapsing FSGS Secondary to Cytomegalovirus Infection in a Deceased Donor Kidney Transplantation Recipient

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Introduction: This case describes the case of a kidney transplant recipient, who developed collapsing FSGS in the setting of CMV infection two weeks after the standard CMV prophylaxis therapy was discontinued.

Case Description: A 59 year-old African American man with a history of deceased donor kidney transplant due to ESRD secondary to hypertension presented to the ER with an acute febrile illness seven months following his transplant surgery. Symptoms included two weeks of diarrhea, anorexia, fever, cough and decreased urine output. Transplant history: CYPRA 90%; Immediate graft function; CMV status D+/R. For induction received Velcade, Thymoglobulin and Simulject. Prophylaxis included nystatin and Bactrim. Valgancyclovir for six months post-operation. Maintenance immunosuppression consisted of tacrolimus, mycophenolate and prednisone. In the ER he was found hemodynamically stable, ill-appearing, benign cardipulmonary and abdominal exams and no edema. Initial lab remarkable for leukopenia, thrombocytopenia, acute kidney injury, nephrotic range proteinuria. Renal allograft ultrasound was normal. Initial management included IV fluids and empirical antibiotics. Flexible sigmoidoscopy performed which was negative for gross lesions. CMV PCR results positive for 895,000 viral copies. Immediately started on Ganciclovir and MMF dose was reduced. Due to worsening renal function the patient underwent kidney allograft biopsy which revealed: Collapsing FSGS. Stain for CMV was positive. The viral load downtrended in the first week of induction therapy. Patient made a symptomatic recovery and his hematocrit improved.

Discussion: This case describes a kidney transplant recipient who developed CMV infection despite completing the appropriate prophylaxis and developed secondary FSGS of the allograft as a result. This case is notable for nature of the renal allograft injury and the fact that he recovered allograft function through treatment of his CMV infection.

**PUB660**

Central Diabetes Insipidus Unmasked After Kidney Transplant: A Case Report

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Introduction: Patients who undergo pruritic surgery are prone to develop Central Diabetes Insipidus (CDI) post-operatively on top of other hormonal deficiencies. CDI is characterized by decrease in release of antidiuretic hormone (ADH) and present clinically with polyuria, nocturia and polydipsia. In patients with End Stage Renal Disease (ESRD) and on maintenance dialysis, CDI may be masked and then unmasked after transplantation. To the best of our knowledge, there have only been 4 published studies with regards unmasking of CDI post-kidney transplantation.

Case Description: We report a case of a 62 year old male with history of resection of a pituitary macroadenoma and ESRD secondary to Diabetic Nephropathy on maintenance dialysis, admitted for living non-related kidney transplantation. Pre-transplantation, he was on desmopressin for CDI but when he developed ESRD, CDI was masked and desmopressin was discontinued. His kidney transplant went uneventful. Post-transplantation, he developed polyuria, increasing serum sodium levels, borderline high serum osmolality and low urine osmolality. In lieu of transtaging plasma ADH levels, fluid restriction was done which resulted to increase sodium levels. A diagnosis of CDI was made. He was started on oral desmopressin with noted improvement of symptoms. He was eventually discharged improved. On succeeding outpatient consults, patient’s daily urine output exceeded to 4L/day and his dose of desmopressin was increased to 100mcg twice daily. Thereafter, he remained clinically stable with average daily urine output of 3L/day, normal sodium levels and good renal allograft function.

Discussion: Successful kidney transplantation leads to unmasking of pre-existing CDI which missed may lead to rapid dehydration and hypernatremia. Frequent monitoring is necessary for early detection and management of CDI. Furthermore, CDI is not a contraindication for transplantation as long as patient is closely monitored for adequate titration of fluids and prompt management with desmopressin.

**PUB661**

More Than Meets the Eye: Acute Cellular and Antibody-Mediated Renal Allograft Rejection Associated with Donor-Specific Antibodies (DSA) Angiotensin II Type 1 Receptor (AT1R) Antibodies

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Introduction: Kidney transplant is associated with improved survival in end stage renal disease (ESRD) patients and although 1 year allograft survival rates continue to improve, long term allograft survival remains low. Immune-mediated graft loss remains a challenge and non-HLA antibodies increasingly are recognized as contributing to allograft dysfunction. We present a case of a deceased donor renal transplant (DDRT) patient who presented with acute kidney injury from mixed cellular and antibody mediated rejection.

Case Description: An 18 year old woman with ESRD from neurogenic bladder received a 2A282DR HLA mismatch DDRT, low immunologic risk without DSA, with basiliximab induction and maintenance immunosuppression with mycophenolate mofetil, tacrolimus and prednisone. She had a history of spina bifida and repaired meningo-myelocle necesitating self-catherization, with unfortunately increased urinary tract infections. At age 12, she had bladder augmentation with small bowel and ureteral re-implantation, with continued intermittent self-catherization. Post-transplant course was complicated by recurrent, multidrug-resistant UTIs, leading to reduction in maintenance immunosuppression and nonadherence to medications by the patient. On post-op month 5, she was noted to have an acute kidney injury with Cr increase from 1 mg/dL to 4.47 mg/dL. A renal biopsy was obtained which showed acute T cell mediated rejection and C4d negative antibody mediated rejection. DSA was positive and non-HLA testing was pursued which was negative for endothelial cell and MAC antibodies but positive for AT1R. Treatment with ATG, plasma exchange, IVIG, steroids and Rituximab was given. Patient was started on Losartan for AT1R antibody. Her Cr improved to baseline and she remains with stable allograft function.

Discussion: In addition to the common factors that contribute to allograft injury such as infection and non-adherence, non-HLA antibodies are becoming increasingly more relevant in renal allograft dysfunction, contributing to graft loss. AT1R antibodies are usually associated with ABMR histopathology and lead to cytokine release. They further enhance vascular inflammation and allograft dysfunction. They should always be considered when rejection is diagnosed in the absence of HLA antibodies.

**PUB662**

Undiagnosed Anti-GBM Antibodies Causing Rapid Loss of a Kidney Transplant

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Introduction: Many patients have renal dysfunction attributed to co-morbid conditions. Depending on the clinical scenario, a serologic workup or renal biopsy for definitive diagnosis may not be deemed necessary. However, definitive diagnosis may be crucial for the success of a subsequent kidney transplant. Here we present a case of a young man with unknown etiology of his native kidney disease who received a kidney transplant that failed rapidly due to the presence of undiagnosed circulating anti-GBM antibodies.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.
Case Description: This is a 33yo CM with HTN and tobacco use who presented with 3 weeks of vomiting, diarrhea, and weight loss. He was anemic with a creatinine of 25 mg/dL and was started on chronic dialysis. Two years later, he underwent a living unrelated kidney transplant. He received alemtuzumab, solumedrol, tacrolimus, and mycophenolate mofetil. Surgery was uncomplicated but after 12hrs his urinary output started to decline and was normal. DSA was negative. UA had 100 mg/dl protein, 30 WBC, 921 RBC. Urine PCR was 1/g. Renal biopsy was performed which showed 17/25 glomeruli with active lesions – 13 with cellular crescents and 4 with fibrinoid necrosis. Immunofluorescence showed diffuse, global, linear capillary loop staining for IgG and C3. Anti-BGM level was 213 AU/mL. He was treated with steroids, plasmapheresis, and cyclophosphamide without response and required re-initiation of dialysis. His course was further complicated by septic shock due to Bacteroides fragilis bacteremia to which he ultimately succumbed 6 weeks post-transplant. Serum virea was collected 1 week prior to transplant and subsequently tested positive with the presence of anti-BG antibodies, specifically 3,5 collagen IV antibodies.

Discussion: In this case, the rapid and unexpected failure of a newly transplanted kidney was caused by circulating anti-BG antibodies. Their presence was unsuspected due to the lack of definitive diagnosis for his native kidney disease and absence of common clinical features of anti-BG antibody disease. anti-BG antibody disease at the time of transplant. Presumably, the patient suffered from anti-BG disease causing failure of his native kidneys. This compelling case suggests that in a young male with undiagnosed etiology of kidney failure, a test for the presence of anti-BG antibodies should be considered before transplantation.

PUB664

Great Threat from a Benign Drug: Vitamin C Causing Severe AKI in a Renal Transplant Patient

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Introduction: Ascorbic acid (AA) is an essential and relatively harmless vitamin if taken in doses less than 2g/day. Despite the lack of randomized controlled trials validating its efficacy, the use of high doses of Vitamin C has been increasing in the intensive care unit (ICU) setting as part of septic shock treatment. AA metabolizes to oxalate and once excreted by the kidneys can deposit in the tubules leading to oxalate nephropathy. In this report, we highlight a case of allograft nephropathy related to oxalate deposition in the setting of high dose vitamin C use to treat septic shock.

Case Description: 70-year-old female, with history of end stage renal disease due to autosomal dominant polycystic kidney disease, underwent deceased donor kidney transplantation 21 years ago on mycophenolate, tacrolimus, and prednisone. Neutrotoxoplasmosis After Kidney-Pancreas Transplantation

Neurotoxoplasmosis After Kidney-Pancreas Transplantation

Javier Catarina,1,2 Catarina Renal Transplant Patient

Publication-Only

PUB665

Is Cidofovir an Option for Refractory BK Nephropathy?

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Introduction: BK human polyomavirus typically seroprevalent in humans however BK appears to affect immunocompromised patients and cause clinical disease. In Kidney transplant patients, degree of immunosuppression is associated with BK viremia and nephropathy (BKVN) and has a prevalence of approximately 5 % in post kidney transplant patients. We present the case of a patient who underwent deceased donor renal transplant and developed BK viremia within a month of receiving her transplant. BK viremia was associated with stage 3 AKI. BKVN is associated with BK viremia and nephropathy (BKVN) and has a prevalence of approximately 5 % in post kidney transplant patients. We present the case of a patient who underwent deceased donor renal transplant and developed BK viremia within a month of receiving her transplant. BK viremia was associated with stage 3 AKI.

Case Description: 42 year old female with past medical history including end stage renal disease due to diabetic nephropathy who underwent deceased donor renal transplant and patient had immediate graft function. Maintenance immunosuppression including Tacrolimus, Mycophenolate and Prednisone. She developed BK viremia with in first month after transplant; subsequently mycophenolate was discontinued, and she was started on Leflunomide and IVIG infusion. She received total of eight doses of IVIG. Due to worsening creatinine, patient underwent transplant graft biopsy #1 which showed stage A BK nephropathy with polyoma viral load (PVL) 1-10%. Second renal biopsy four months later showed stage B BK nephropathy with a PVL > 3 % and SV 40 positive in cortex > 10%. Patient was started on Cidofovir intravenous infusion 0.5 mg/kg every 2 weeks in addition to renal replacement therapy. Cidofovir infusion 500 ml. The patient’s BK viremia started to trend down after initiation of cidofovir (figure 1).

Discussion: BK virus affects immunocompromised renal transplant patients. Transplant graft biopsy will give the definite diagnosis of BKVN with positive for SV40. BKVN thought to be secondary to over immunosuppression. The initial treatment for BK viremia includes lowering immunosuppression followed by IVIG as well as Leflunomide. In patients who are refractory to initial treatment, cidofovir can be a treatment option.

PUB666

Neurotoxoplasmosis After Kidney-Pancreas Transplantation

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Introduction: Toxoplasmosis is a potentially life-threatening infection that is strongly associated with immunosuppression, such as after solid organ transplantation. Although most cases occur during induction of immunosuppression, reactivation or de novo infection may occur in those with a remote history of solid organ transplantation. We report a case of cerebral toxoplasmosis that mimicked malignancy.

Case Description: A 71-year-old male with end-stage kidney disease status post kidney-pancreas transplantation 21 years ago on mycophenolate mofetil, tacrolimus, and prednisone presented with three weeks of left sided weakness. Vital signs were stable and examination was unremarkable. CT head for 4/5 strength of the left upper and lower extremities. A right parieto-temporal mass lesion with surrounding edema concerning for malignancy was found on MRI. Chest, abdomen, and pelvis PET/CT scan showed no FDG-positive lesions. Five days later, his mental status acutely worsened. Repeat MRI showed an acute right temporal lobe infarction with transcortical hemorrhage, requiring urgent mass resection. Histo-pathologic examination showed necrosis with toxoplasma tachyzoites and cystozoites. Immunohistochemistry stains for HSV, VZV, SV-40, CMV, as well as Gram, AFB and Gomori trichrome stains, were negative. HIV serology was negative. Toxoplasma IgG was positive, and IgM was indeterminate. Immunosuppression was discontinued and pyrimethamine-sulfadiazine was initiated. He was discharged to an acute rehabilitation facility after 2 weeks.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only

Underline represents presenting author.

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presentation of AT1R mediated graft dysfunction associated with pre-existing DSA highlighted the potential for multiple mechanisms for graft injury and develop screening protocols post-transplant.

**Case Description:** A 56 year old African American female with end-stage renal disease due to lupus nephritis received a standard criteria deceased donor kidney transplant. She had prolonged diabetes and obesity and was debridged due to pre-existing class II DSA with low mean fluorescent intensity (MFI) (900-1600). On post-op day 1 she started 5 sessions of plasma exchange (PE) followed by GammaGard intravenous immunoglobulins. Graft function was immediate, but on day 15, acute kidney injury (AKI) with GFR of 27 mL/min/1.73m2 developed. (23.6 mg/dL to 7.7 mg/dL). Allograft biopsy lacked features of cellular or humoral rejection, was C4d negative and showed only severe ischemic tubular injury (ATN). Given DSA with low stable MFI, and absence of any ischemic event to explain ATN, ATIR titer was measured. Pre-PP titer was 1:40. HLA-DR typing revealed high titer initial PP. With continued PP and titer (<16 units/ml) her creatinine improved to 1.1 mg/dL.

**Discussion:** Our patient had persistent low level class II DSAs in a range not expected to cause severe graft dysfunction and severe AKI. Furthermore, her biopsy had no evidence of humoral or cellular rejection. Only severe ischemic ATN was observed without an obvious cause. As described in preclinical, we propose ATIR may impair signals leading to endothelial cell dysfunction and sustained vasoconstriction leading to poor perfusion and ischemia. We argue that ATIR can present without significant inflammation and can function as an agonistic antibody that may be internalized once ligated to membrane bound receptor, thereby avoiding severe complement mediated inflammation and damage.

**PUB667**

**Pulmonary Necrotic Rhodococcus equi Infection in a Kidney Pancreas Transplant Recipient: A Rare Case Treated Without Surgical Intervention**

**Khawaja O. Omar, Tim E. Taber, Muhammad S. Yaqub, Oluwafisayo O. Adebiyi, Asif A. Sharafuddin. Indiana University School of Medicine, Indianapolis, IN.**

**Introduction:** Rhodococcus equi has emerged as a serious pathogen in solid organ transplant recipients. Primary pulmonary involvement is the most common manifestation. However, this opportunistic pathogen is often not considered in the differential diagnosis of pneumonia in transplant recipients. Approximately less than 30 cases in renal transplants and only 2 in pancreas transplants have been reported with up to 20-25% mortality.

**Case Description:** 57-year-old white male who had received his 3rd renal transplant 2 years and 1st pancreas transplant 12 years earlier. At the time of presentation, he was on tacrolimus, mycophenolate mofetil, prednisone and basiliximab for immunosuppression. He presented with a 2 month history of a cough and weight loss. He had been prescribed azithromycin, doxycycline, and ciprofloxacin by his local providers with no improvement. Chest x-ray showed necrotic 5cm cavitary right middle lobe lung lesion. On evaluation for pneumonia in transplant recipients. Approximately less than 30 cases in renal transplants and only 2 in pancreas transplants have been reported with up to 20-25% mortality. He was then given minocycline after 6 months, while the azithromycin prophylaxis was continued. He was switched to vancomycin, meropenem for 6 weeks and his symptoms improved. He was switched to tacrolimus, mycophenolate mofetil, prednisone and basiliximab for immunosuppression. He was then given minocycline after 6 months, while the azithromycin prophylaxis was continued. He was also given voriconazole for his aspergillosis for 12 months. Repeat chest imaging near total improvement in the cavitary lesion and his symptoms resolved over the next 6-9 months. Although surgery was considered an option, due the pericardial location of the abscess, this was elected and he was managed with antibiotics. He developed severe pain to palpation on bilateral thighs and crepitus in the groin region, tracking to the left medial thigh. He was taken back to OR for debridement, and 70% of the skin flap was debrided with an omental of purulent material. He developed new areas of blistering, erythema and worsening crepitus in the groin, thigh, and hip for which he underwent bedside debridement. Despite aggressive resuscitation, the patient died on the third day of hospitalization.

**Discussion:** Several reports have emphasized importance of Gram-negative rods in NF. To our knowledge, only 3 cases of E. coli associated NF in kidney transplant recipients. It is important to note that monomicrobial ESBL producing E. coli infection can lead to necrotizing NF, and appropriate antibiotic selection on initial presentation is critical.

**PUB669**

**Zebra Bodies in a Kidney Transplant Recipient**

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**Introduction:** Fabry disease is an X-linked genetic disorder due to deficiency of lysosomal enzyme α-galactosidase A characterized by glycosphingolipids accumulations within body cells and development of concentric lamellar bodies or zebra bodies. It is associated with renal and extra-renal manifestations including angioarteriomas, hypohidrosis, hearing loss, corneal opacity, neurological and cardiac involvement.

**Case Description:** A 63 year old white male with a 10 year history of hypertension and end stage renal disease secondary to hypertension presented with a 2-week history of lower extremity edema. Clinical findings was remarkable for 2+ pedal edema, and laboratories with slightly elevated serum creatinine, 2.3 mg/dL, a spot urine protein to creatinine ratio of 7.6 g/g creatinine and tacrolimus level of 4.7 ng/ml. The serum α-galactosidase A level was normal; BK virus PCR and donor specific anti-HLA antibodies were negative. Medications consisted of micophenolate mofetil, tacrolimus, prednisone, sertraline, nifedipine and vitamin D3. One month post-transplant, he had one episode of biopsy proven rejection without complications. The biopsy of the transplanted kidney revealed focal mild to moderate interstitial fibrosis/tubular atrophy, glomeruli with lobulation of tufts, large endothelial cells with foamy cytoplasm, glomerular capillary endothelial cells and mesangial cells containing lamellar and dense cytoplasmic inclusions or myelin bodies, and cholesterol clefts related thickening of glomerular basement membrane. No rejection or viral cytopathic effects, immune complex deposits or fibrils were identified. The stain for poliovirus and the C4d were negative. In addition to chronic transplant glomerulopathy, the diagnosis of glomerular phospholipidosis was entertained.

**Discussion:** Renal phospholipidosis post-kidney transplant is rarely known. The diagnosis is based on clinical signs and symptoms, confirmed by low enzyme activity in peripheral blood or in leukocytes, or by genetic mutation analysis. Recurrence in allograft post-kidney transplant from non-Fabry Disease donors is rare, therefore awareness among transplant providers of drug induced renal phospholipidosis is important as it can result in post-transplant renal dysfunction and proteinuria.

**PUB670**

**Darling’s Disease Presenting with Hypercalcemia in a Kidney Transplant Recipient**

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**Introduction:** Histoplasmosis is an infection caused by a fungus called Histoplasma. The fungus lives in the environment, particularly in soil. Spread occurs mainly by aerosolization of spores. Most people that are exposed to Histoplasma do not display symptoms. Those who do typically have fever, cough, and fatigue. Most infections resolve spontaneously without treatment. Infection may be severe in people that are immunosuppressed.

**Case Description:** A 61-year-old man with previous ESRD due to hypertension, second kidney transplant recipient, history of left transplant nephrectomy due to left renal transplant rejection with complaints of fever, worsening fatigue, and unintentional weight loss of 11 lbs (in the last 2 months) a year after his second kidney transplant. He was admitted to the hospital with suspected pneumonia as worsening bilateral reticular nodular opacities were present on chest radiographs. CT scan of the chest showed bilateral small bilateral edema along with bilateral consolidation of the right upper lobe with mild mediastinal adenopathy. Empiric cefepime and azithromycin was started for coverage of atypical pneumonia. Bronchoscopy with broncho alveolar lavage (BAL) was done by Pulmonary service and serological workup was sent. (1,3)-Beta-D-Glucan and Histoplasma capsulatum and Human Urine Antigen were positive. Serum calcium was high normal on admission but peaked at 12.5 mg/dL. Vitamin D 25-OH was 56 ng/mL and Vitamin D 1,25-OH was markedly elevated at 104 ng/mL suggesting exogenous production. Pulmonary histoplasmosis was diagnosed. Mycophenolate was discontinued. Bacterial infection was covered with piperacillin/tazobactam and Ciprofloxacin. The peritransplant fluid and blood was sent for BAL washings fungal culture after 3 weeks. Vitamin D 1,25-OH levels and Histoplasma Galactomannan Urine Antigen concentration has decreased on 1 month follow up.
Discussion: This is a classic case of pulmonary histoplasmosis in an immunocompromised patient, in Texas, where Histoplasma is only mildly endemic. The proposed mechanism for hypercalcemia in patients with granulomatous disease (e.g. Histoplasmosis) is increased 1-alpha-hydroxylation production by alveolar macrophages.

PUB671
Metabolism Matters: An Interesting Case on Immediate Tacrolimus Metabolism in a Renal Transplant Recipient on Ritonavir-Boosted Antiretroviral Therapy
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Introduction: Access to solid organ transplantation in the setting of human immunodeficiency virus (HIV) infection has been increasing. HIV positive solid organ transplant recipients are at increased risk of acute rejection – partly because of drug interactions. Multiple studies report serious interactions between tacrolimus and ritonavir-boosted HIV-1 protease inhibitors (PIs). The conventional approach is to reduce the tacrolimus dose to around ten percent of the standard dose and anticipate a ritonavir ‘washout’ period of up to ten days. Local experience managing liver transplant recipients with HCV at this centre have led to the conclusion that the interaction period is much shorter. Therefore we advocate less aggressive tacrolimus dose reductions in view of the even higher risks of early rejection if tacrolimus levels are low.

Case Description: We present an interesting case of a patient undergoing haemodialysis who was matched to a deceased brain dead donor through the national organ sharing scheme in the United Kingdom. The patient was on antiretroviral therapy with ritonavir and their HIV viral load had been undetectable for several years. The HIV specialist team recommended a change to a non-tacrolimus interacting regimen at the time of transplantation. The last dose of ritonavir was taken 40 hours before the first administration of tacrolimus. Induction was with basiliximab and maintenance therapy was with tacrolimus (Adopta), mycophenolate mofetil and prednisolone. Whole body tacrolimus concentrations were measured at the time of first administration (standard single 0.05 mg/kg dose) and at 30, 60, 120, 240, 360, 480 and 720 minutes. Please see the attached graph image below

Discussion: Although there is concern about concomitant use of ritonavir and tacrolimus, this case suggests minimal interaction only 40 hours after the last dose, with appropriate tacrolimus concentrations and an exposure to tacrolimus (area under the curve of 91.2 ng/mL) comparable to patients receiving tacrolimus not on ritonavir. We conclude that if a patient on antiretroviral therapy is taken off a ritonavir-boosted protease inhibitor regimen when starting or taking tacrolimus therapy, the standard dosing should be considered at the time of the change along with close therapeutic drug monitoring.

PUB672
PTH-Independent Severe Hypercalcemia Secondary to Pneumocystis jiroveci Pneumonia in a Renal Transplant Recipient: A Case Report
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Introduction: Hypercalcemia following renal transplant is a common finding due to pre-existing hyperparathyroidism. Pneumocystis jiroveci Pneumonia (PJP) is an opportunistic infection in solid organ transplant with rare incidence in renal transplant recipients. We report a case of hypercalcemia due to PJP following a change in immunosuppression.

Case Description: 55 year old male, who is a non-sensitized recipient of a second DDKT 34 years ago. He now has CKD stage 3 of the allograft with no prior history of rejection. He presented with a 3 week history of dry cough, hypoxia, lethargy, progressive weakness, 10 pound weight loss associated with diarrhea. He was previously on maintenance immunosuppression with cyclosporine and azathioprine. 6 months prior to presentation, azathioprine was changed to mycophenolate in order to accommodate allopurinol for gout treatment and prevention. He was found to be positive for influenza, clostridium difficile and low grade CMV viremia (2000 IU/ml). Chest x-ray showed multiple bilateral infiltrates. Labs showed calcium of 16mg/dl, ionized calcium of 1.83, PTH of 30pg/ml (baseline 110pg/ml), PTHPr <2pmol/L, calcitriol of 66pg/ml and 25-OH vitamin D of 35ng/ml. He underwent bronchoscopy, BAL was positive for PJP and he was started on IV Bactrim and steroids. He was initially given IV fluids and calcitriol for the hypercalcemia. Kidney function levels did not improve. After a week of initiation of IV Bactrim, his ionized calcium decreased to 1.2.

Discussion: The prevalence of hypercalcemia ranges from 8.5 to 71% in renal transplant patients, it is most likely secondary to hyperparathyroidism. Case reports have shown the association of PJP pneumonia and hypercalcemia. Hypercalcemia in PJP is thought due to PTH-independent extra-renal production of 1,25 di-hydroxy vitamin D by activated alveolar macrophages. Previous case series have reported that risk factors associated with PJP pneumonia in solid organ transplant recipients are mycophenolate use, CMV (10% to 40%) and age >75 years. We believe that switching to mycophenolate led to over immunosuppression which resulted in him developing opportunistic infections, particularly PJP pneumonia. PJP pneumonia is a rare cause of hypercalcemia and should be considered in immunocompromised patients presenting with pneumonia.

PUB673
Arterial Thrombosis from Vascular Clamp Injury: Magnetic Resonance Angiography for Evaluation
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Introduction: The most common vascular complications after kidney transplant are renal artery and renal vein thrombosis. Imaging studies with contrast are often avoided immediately after transplant because of concern of nephrotoxicity with iodinated contrast and risk of nephrogenic systemic fibrosis with gadolinium. We present a case of thrombosis of external iliac artery due to vascular clamp injury diagnosed using non-contrast magnetic resonance angiography (MRA).

Case Description: A 68 year old female with end-stage renal disease presumed due to diabetes and hypertension underwent deceased donor kidney transplant after 8 years of dialysis. Operative course was uneventful. Donor kidney biopsy showed severe vasculopathic changes with concentric fibrointimal hyperplasia. Post-operative course was complicated by delayed graft function and renal ultrasound (US) revealed decreased flow of the main renal artery and vein with resistive index of 0.88-1.0. Repeat US on post-operative day (POD) 2 revealed parvus tardus waveforms in both main renal arteries and minimal arterial perfusion of the transplanted kidney. Non-contrast MRA was obtained, which showed the loss of signal in the proximal right external iliac artery just above the arterial anastomosis, concerning for vascular clamp injury versus thrombosis. Right common iliac arteriogram subsequently showed filling defect in the proximal right external iliac artery at the origin of the upper renal artery transplant anastomosis and retrograde filling of lower renal artery. Attempt at suction thrombectomy was unsuccessful and exploration of aortofemoral graft revealed intramural hematomas in external iliac artery proximal to anastomosis. The patient underwent right external iliac local endarterectomy and reanastomosis of donor renal artery to native external iliac artery. Repeat US on POD 4 revealed improved perfusion of the transplanted kidney. Allograft function improved and the patient came off dialysis on POD 8.

Discussion: Vascular clamp injury is a rare complication after kidney transplantation. Due to impaired renal function, non-contrast diagnostic imaging with contrast is usually avoided. In the case described above, non-contrast imaging study was used to arrive at the diagnosis of clamp injury induced thrombus. Non-contrast MRA can be helpful early post-transplant to identify vascular complications when contrast study is not an ideal choice because of impaired kidney function.

PUB674
Proliferative Glomerulonephritis with Monoclonal Immune Deposit in a Transplanted Kidney
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Introduction: Proliferative glomerulonephritis is known recur or develop de-novo in the transplanted kidney, and can lead to graft failure. MPGN is a diagnosis of exclusion, and various other diagnoses based on etiology can lead to this pathologic lesion. One cause is immune deposition disease, for which the differential includes SLE, cryoglobulinemic, infection-related, C3 GN, or monoclonal immune deposition disease (MIDD). We present a case of MIDD with proliferative glomerulonephritis in a transplant, with discordant kappa free light chains and plasma cell mechanism vs lambda glomerular deposition on biopsy.

Case Description: 58 yr female with history of ESRD from nephrotic syndrome of unclear etiology, multiple myeloma, and DM type 2. She received chemotherapy for myeloma in 2012 with good response. Kidney biopsy in 2012 after initiating hemodialysis, but before myeloma treatment, showed no evidence of paraprotein deposition. The patient was monitored for smoldering myeloma with serial bone marrow exams. She was cleared for transplant and received deceased-donor kidney March 2018. Stable serum Cr 1.0-1.5 and spot urine protcreat <0.5, until she presented Nov 2018 with acute onset hematuria, edema, AKI and nephrotic range proteinuria. No other systemic signs or symptoms of myeloma. Serum kappa free light chains elevated with elevated kappa/lambda ratio. Renal biopsy showed acute proliferative glomerulonephritis with lambda predominant IgG immune deposition. Pulse-dose steroids were given, and she was initiated on CyBorD chemotherapy for myeloma. The patient had rapid improvement in renal function to baseline and resolution of proteinuria.

Discussion: We present a rare case of proliferative glomerulitis with monoclonal IgG immune deposits in a transplanted kidney. This syndrome has been characterized as monoclonal gammapathy of renal significance, or “MGRS”. The case is notable for discrepancy between lambda light chain deposition on renal biopsy and kappa restricted plasma cells in bone marrow, as well as serum free light chains. In this patient, there was rapid recovery of transplant kidney function following treatment for myeloma.
**PUB675**

Atypical Case of Calcium Phosphate Deposits in Renal Allograft
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Introduction: Calcium phosphate crystals have been observed in renal allografts within the first six months of transplantation in patients with hyperparathyroidism prior to transplant. Calcium phosphate deposits correlate significantly to mineral metabolism abnormalities. We report a case of persistent renal allograft dysfunction secondary to calcium phosphate crystals with no evidence of hyperparathyroidism or other known risk factors.

Case Description: A 38 y.o male PMH of ESRD secondary to Diabetes Mellitus underwent a simultaneous kidney pancreas transplant. Post-transplant allograft biopsies were done at 15,18,21 months for persistent renal function impairment. All biopsies were noted to have heavy calcium phosphate deposits in the renal tubules and persistent severe acute tubular injury. Post-transplant serum calcium ranged between 9.1-9.6 mg/dl, phosphorus 2.7-3.4 mg/l which were similar to pretransplant levels, calcium excretion ratio showed no hypercalciuria, serum PTH was decreased from a pretransplant value of 587 to 156 pg/ml. Despite normal calcium and phosphorous levels, along with decreasing PTH, heavy calcium phosphate deposits persisted in the allograft. Serum creatinine has remained in the range of 1.8-2.2 mg/dl suggesting calcium phosphate deposits as underlying etiology. Immunosuppression regimen included mycophenolate mofetil, extended release tacrolimus(envarsus) and sulfamethoxazole trimethoprim as prophylaxis.

Discussion: Calcium phosphate deposits in the renal allograft have been typically noted with persistent hyperparathyroidism post-transplant. However, in our patient this was observed with normal calcium phosphate product and in setting of decreasing PTH levels. The mechanism of calcium phosphate deposits in this setting is unclear suggesting possible drug induced due to new drugs as extended release tacrolimus(envarsus).

**PUB677**

Persistently Elevated Human Chorionic Gonadotropin in a Non-Pregnant Premenopausal Patient with ESRD
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Introduction: b-hCG has clinical uses in detection of pregnancy, abnormalities in pregnancy, and monitoring trophoblastic diseases and malignancies. Elevated post-menoopause physiologic hCG levels and decreased renal clearance are thought to play a prognostic role in chronic kidney disease, however elevated hCG levels have also been reported in premenopausal women with established ESRD. This age group is especially important due to possibility of pregnancy. Here report a case of persistently elevated b-hCG over several menstrual cycles in a premenopausal woman with ESRD.

Case Description: A 27 year-old woman with ESRD on hemodialysis was hospitalized several times for recurrent abdominal pain in a 50 day period and found to have intermediate range (5 – 15 IU/mL) hCG levels at each of her visits. The patient has a complex medical history including congenital absence of one kidney, past renal transplant, heart failure with reduced ejection fraction and hypertension. The cause of her abdominal pain was never diagnosed but believed to be secondary to either gastritis or hepatic congestion from her congestive heart failure. Her hCG levels showed no obvious associations with timing of hemodialysis sessions or menstrual cycle, or creatinine levels.

Discussion: Very few cases of elevated b-hCG in a non-pregnant premenopausal female with ESRD. Our case had several unique and new findings, including consistently lower hCG levels not meeting the positive threshold but in the intermediate range. Our case also covers the longest timespan of elevated hCG measurements for ESRD patients and only report throughout several menstrual cycles, suggesting that hCG is chronically elevated. The patients multiple organ disease have unclear significance at this time but may contribute information about characteristics of patients with elevated hCG. Her age and lack of hCG correlation with creatinine levels suggests another mechanism for elevated hCG apart from increased postmenopausal levels and decreased renal clearance.

This case provides further evidence that special consideration should be given to patients with elevated b-hCG levels who have chronic kidney disease, including women of reproductive age.

**PUB678**

Unilateral Renal Fibromuscular Dysplasia Presenting as Macroscopic Hematuria in an Normotensive Elderly Female
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Introduction: Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory, hyperplastic disorder that affects medium and small arteries. It occurs predominantly in young females and usually involves the renal and carotid arteries. Classically, renal FMD presents as early onset or difficult to control hypertension.

Case Description: Our patient is a 77-year-old Caucasian female with normal renal function and no history of hypertension who presents to an outpatient nephrology clinic with a several month history of painless gross hematuria. Prior urologic evaluation inclusive of computed tomography (CT) of the abdomen/pelvis showed no masses, no hydronephrosis, a right (R) kidney measuring measuring 6.5cm, a left (L) kidney measuring 9.7cm, multiple renal cysts and apparently patent renal arteries and veins. Cystoscopy suggested bleeding from the R ureteral orifice. Subsequent uroscopy revealed inflammatory changes of several R renal calyces and a clot in the R ureteral orifice. Biopsies were obtained and negative for neoplasia. In our clinic, her blood pressure was normal and physical exam benign. Urinalysis noted gross hematuria with many monomorphic red blood cells observed on urine microscopy. Renal ultrasound substantiated the CT findings of a R smaller than L kidney without findings to support renal artery stenosis. Ultimately, a magnetic resonance angiogram of the renal arteries showed hemodynamically significant stenosis in the R renal artery. Bilateral renal angiogram following which elucidated an irregularity involving a R renal artery branch consistent with FMD that was successfully balloon angioplastied resulting in resolution of her hematuria both grossly and microscopically which has continued for several months following the procedure.

Discussion: Despite renal FMD typically presenting with hypertension in the young, our elderly patient presented with normal blood pressure and unilateral hematuria. Hematuria is a common medical problem and several renal vascular pathologies have been associated with hematuria, including renal FMD, which causes microscopic hematuria in about 50% of cases. Conventional contrast angiography remains the gold standard in confirming this rare diagnosis. Percutaneous renal artery recanalization is currently considered the optimal treatment option with good outcomes in the majority of cases, including our own.
PUB679

Dysnatremia from Vasopressinase in Pregnancy: A Case Series
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Introduction: Sodium homeostasis in pregnancy dramatically differs from that of a non-pregnant state. Vasopressinase is a hormone secreted by trophoblasts. Here, we report cases of hyper/hyponatremia in gestation and discuss the pathophysiology role of vasopressinase.

Case Description: Case 1 (hypernatremia): 28-year-old woman (G3P2, 37 week) with no known past medical history presented with one week of abdominal pain, vomiting, excessive thirst and polyuria for 2 weeks. BP 148/100mmHg. Laboratory data was significant for: AST 739U/L, ALT 1387U/L, bilirubin 3.0mg/dL, Cr 1.77mg/dL, Na 144mmol/L, K 4.5mmol/L, plasma Osm 307mOsm/kgH2O, albumin 2.4g/dL, urine protein 1.6g/gCr. She underwent emergent C-section. Perioperative course was notable for persistent polyuria with urine output of 200-600cc/hr with urine osmolality (Uosm) 113mOsm/kgH2O. Diagnosed with gestational diabetes insipidus (DI), She was started on dDAVP 10 mcg intranasally and her Na stabilized ~139mmol/L with Uosm 300mEq/L. Case 2 (hyponatremia): 40-year-old woman (G1P0, 27 week) with no past medical history presented with abdominal pain, vaginal bleeding, hypertension and leg edema. She developed hypertension around 22-weeks and mild abnormality in liver function tests since 24-weeks. Vital signs were notable for HR 75, BP 158/102. Laboratory data significant for Na 118mmol/L, K 4.3mmol/L, Cr 0.51mg/dL, urine protein 0.39g/gCr, Psom 240mOsm/kgH2O, UoSm 500mOsm/kgH2O, UNa+2mEq/L. Urine output remained 20-560cc/hr. Diagnosed with SIADH and initiated 3% NaCl infusion perioperatively. She underwent C-section due to fetal distress. Postoperatively her Na remained low ~120 mmol/L. Eventually Na corrected to ~139 mmol/L with fluid restriction.

Discussion: These cases highlight the role of vasopressinase in pregnancy. Gestational DI is rare (2-4 in 100,000 pregnancies), and is felt to be due to impaired degradation of vasopressinase. It is degraded in the liver and is associated with HELLP syndrome. Vasopressinase cleaves AVP but not the synthetic version, dDAVP. Increased vasopressinase levels last up to 6-weeks post-partum. In contrast, there have been only several case series of gestational SIADH. This is thought to be related to preeclampsia-associated SIADH with defective placenta producing insufficient vasopressinase. This results in higher ADH levels, causing hyponatremia.

PUB680

Emphysematous Pyelonephritis: An Ultrasound Look-Alike of Staghorn Calculus

Introduction: Emphysematous pyelonephritis (EPN) is a gas producing, necrotizing infection involving the renal parenchyma and surrounding tissue that is associated with high mortality and morbidity. On a sonogram, it appears as multiple hyperechoic foci with posterior acoustic shadowing mimicking a staghorn calculus. With growing interest in point of care ultrasonography (POCUS) among nephrologists, it is important to be aware of and consider this condition in the differential diagnosis of nephrolithiasis, especially in diabetic patients.

Case Description: A 22-year-old woman with a history of uncontrolled type II diabetes mellitus and hypertension presented with fever and left flank pain for three days. She denied any history of nephrolithiasis. Laboratory data was significant for a serum creatinine of 12. Urine microscopy showed >50 WBC/hpf, 10 RBC/hpf, and numerous bacteria. She was diagnosed with EPN and treated with intravenous antibiotic therapy and showed improvement of renal function and normalization of platelet levels.

Discussion: These cases highlight the role of vasopressinase in pregnancy. Gestational DI is rare (2-4 in 100,000 pregnancies), and is felt to be due to impaired degradation of vasopressinase. It is degraded in the liver and is associated with HELLP syndrome. Vasopressinase cleaves AVP but not the synthetic version, dDAVP. Increased vasopressinase levels last up to 6-weeks post-partum. In contrast, there have been only several case series of gestational SIADH. This is thought to be related to preeclampsia-associated SIADH with defective placenta producing insufficient vasopressinase. This results in higher ADH levels, causing hyponatremia.

PUB681

Pregnancy-Associated Atypical Hemolytic-Uremic Syndrome
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Introduction: Pregnancy-associated atypical hemolytic-uremic syndrome (p-aHUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Triggered by pregnancy, uninhibited activation of the alternative pathway of the complement cascade induces endothelial host cell damage and results in a thrombotic microangiopathy.

Case Description: A 20 year old African American female with history of sickle cell disease was admitted for severe preeclampasia and was treated in the postpartum period at our facility for severe thrombocytopenia and acute kidney injury. The patient was treated for suspected pregnancy induced HUS with plasmapheresis and IV steroids with improvement of renal function and normalization of platelet levels.

Discussion: Pregnancy-associated atypical hemolytic-uremic syndrome (p-aHUS) is a rare condition. The pathogenesis and presentation of p-aHUS remain ill-defined. Diagnosis of p-aHUS is challenging, as it can mimic various diseases found during pregnancy and the postpartum period. Correct diagnosis and timely management are crucial to improve outcomes. Comprehensive genetic and molecular study of the alternative complement pathway are recommended to confirm the diagnosis and to identify patient at risk for aHUS in subsequent pregnancies.

PUB682

Improvement in Cervical Radiculopathy by Erenumab During the Preventive Treatment of Migraine in a Patient with CKD
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Introduction: Pain control of chronic kidney disease (CKD) patient can be challenging especially in those with multiple comorbidities. We present the incidental finding of improvement in cervical radiculopathy in a CKD patient receiving erenumab for the preventive treatment of migraine.

Case Description: A 75-year-old lady with HTN, DM2, CKD, CHF, peripheral vascular disease, osteoarthritis, osteoporosis and migraine presented with a sharp, intermittent, shooting neck pain, which was 7/10 in intensity, radiating to both arms, aggravated by movement of the neck, without a motor deficit. She was taking pantoprazole, sacubitril/valsartan, metoprolol, clonidine, aspirin, linagliptin, pravastrain, alirocumab, gabapentin, pentoxifylline, calciort, erythropoietin, sevelamer and pain medications including narcotics. Physical exam revealed severe paresthesia from neck to arms, significant neck spasms, loss of cervical lordosis and reduced deep tendon reflexes. MRI of the cervical spine revealed mild nerve root impingement. Appropriate pain medications with gabapentin, non-narcotic and narcotic medications were used without success. The pain progressively worsened within 3 weeks, the intensity being 9/10. Surgery was considered high-risk due to multiple comorbidities. Meanwhile, erenumab was initiated for the preventive treatment of migraine. Neuropathic neck pain intensity concomitantly decreased from 10/10 to 3/10 within a week of erenumab treatment without administering any pain medications, resulting in improvement in her quality of life.

Discussion: Erenumab, a human immunoglobulin G2 (IgG2) monoclonal antibody and a calcitonin gene-related peptide (CGRP) receptor antagonist, has been indicated for the preventive treatment of migraine in adults. CGRP mediates the trigeminovascular pain transmission from intracranial blood vessels to the central nervous system, as well as the vasodilatory component of neurogenic inflammation. Improvement in her cervical radiculopathy during preventive treatment of migraine may be due to inhibition of CGRP, a major mediator of neurogenic inflammation and vasodilation. This incidental finding may suggest additional use of CGRP-inhibitor for the treatment of radiculopathy. Therefore, further researches are necessary to prove this hypothesis.
Severe Arteriosclerosis in a Young Patient

Houssam Mhanna. Nephrology, University of Michigan, Ann Arbor, MI.

Introduction: Progressive renal failure and HTN in a young patient warrants thorough investigation in an attempt to identify treatable causes.

Case Description: 32 y/o F with HTN and primary hyperPTH s/p partial parathyroidectomy. Had episodes of “Panick attacks” with evidence of episodic and then persistent HTN. PE was normal. Her serum Cr in January 2015 was 1.05 mg/dL, gradually increased over 2 years to 2 mg/dL. UPCR 0.38. No hematuria. urine sediment was unremarkable. CBC normal. Immunological serologies and Secondary HTN w/u were unrevealing. Renal biopsy: severe arteriolosclerosis with glomerular obsolescence (19/42) and commensurate tubular atrophy and interstitial fibrosis; no evidence of glomerulonephritis. The larger arterioles had moderate fibrous intimal thickening which narrows the vascular lumen, and many small arterioles have completely obliterated vascular lumens. No arthritis or thrombosis is identified. Schistocytes in the walls of small arterioles were seen, indicating arteriolar TMA.

Discussion: This is a case of progressive renal failure and HTN in a young previously healthy patient. The findings in the arterioles in a woman of this age were striking according to expert renal pathologists and likely are the cause of the glomerular obsolescence and tubular atrophy and interstitial fibrosis. However, the etiology of her vascular disease is less clear. HTN is a possible cause of the renal failure. On the other hand, pt may have a primary renal disease that is not completely understood caused HTN. Arteriolar TMA was a pathological diagnosis.
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epithelial........FR-PO120, FR-PO349, FR-PO598,
FR-PO980, FR-PO1002, SA-PO074,
SA-PO078, SA-PO456, SA-PO476,
SA-PO745, SA-PO752
epithelial sodium channel................. TH-OR006,
FR-PO600, SA-PO318, SA-PO328
epithelial sodium transport............... FR-PO589,
SA-PO102, SA-PO305

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epoetin..........TH-PO169, SA-PO218, SA-PO220,
SA-PO254, SA-PO257
erythropoietin................ TH-OR026, TH-OR028,
TH-OR030, FR-PO311, FR-PO560,
FR-PO1165, SA-OR009, SA-OR036,
SA-OR060, SA-PO069, SA-PO219,
SA-PO231, SA-PO241, SA-PO249,
SA-PO251, SA-PO252, SA-PO253,
SA-PO254, SA-PO777, SA-PO1017,
SA-PO1018, SA-PO1019, SA-PO1033
ESRD (end-stage renal disease)....... TH-OR027,
TH-OR028, TH-OR033, TH-OR097,
TH-OR107, TH-OR111, TH-OR138,
TH-PO075, TH-PO166, TH-PO174,
TH-PO193, TH-PO198, TH-PO218,
TH-PO229, TH-PO249, TH-PO252,
TH-PO264, TH-PO265, TH-PO268,
TH-PO269, TH-PO270, TH-PO277,
TH-PO278, TH-PO281, TH-PO287,
TH-PO288, TH-PO417, TH-PO437,
TH-PO444, TH-PO453, TH-PO570,
TH-PO585, TH-PO589, TH-PO595,
TH-PO610, TH-PO623, TH-PO643,
TH-PO644, TH-PO646, TH-PO649,
TH-PO673, TH-PO701, TH-PO710,
TH-PO714, TH-PO719, TH-PO722,
TH-PO728, TH-PO781, TH-PO782,
TH-PO806, TH-PO824, TH-PO853,
TH-PO863, TH-PO926, TH-PO934,
TH-PO991, TH-PO1019, TH-PO1022,
TH-PO1094, TH-PO1116, TH-PO1117,
TH-PO1132, TH-PO1142, FR-OR017,
FR-OR036, FR-OR060, FR-OR109,
FR-OR110, FR-PO131, FR-PO139,
FR-PO150, FR-PO156, FR-PO174,
FR-PO260, FR-PO264, FR-PO268,
FR-PO276, FR-PO326, FR-PO399,
FR-PO404, FR-PO405, FR-PO407,
FR-PO408, FR-PO412, FR-PO422,
FR-PO428, FR-PO429, FR-PO440,
FR-PO447, FR-PO460, FR-PO468,
FR-PO477, FR-PO483, FR-PO519,
FR-PO520, FR-PO521, FR-PO527,
FR-PO550, FR-PO551, FR-PO566,
FR-PO575, FR-PO651, FR-PO764,
FR-PO808, FR-PO891, FR-PO911,
FR-PO990, FR-PO1025, FR-PO1041,
SA-OR037, SA-OR038, SA-OR039,
SA-OR058, SA-OR059, SA-OR061,
SA-OR065, SA-OR080, SA-PO001,
SA-PO182, SA-PO206, SA-PO220,
SA-PO256, SA-PO257, SA-PO285,
SA-PO310, SA-PO536, SA-PO542,
SA-PO547, SA-PO643, SA-PO652,
SA-PO654, SA-PO662, SA-PO669,
SA-PO721, SA-PO722, SA-PO753,
SA-PO754, SA-PO774, SA-PO809,
SA-PO812, SA-PO823, SA-PO886,
SA-PO899, SA-PO902, SA-PO963,
SA-PO973, SA-PO975, SA-PO976,
SA-PO977, SA-PO979, SA-PO980,
SA-PO981, SA-PO985, SA-PO986,
SA-PO991, SA-PO992, SA-PO996,
SA-PO998, SA-PO1001, SA-PO1003,
SA-PO1006, SA-PO1011, SA-PO1016,
SA-PO1018, SA-PO1023, SA-PO1024,
SA-PO1025, SA-PO1028, SA-PO1039,
SA-PO1043, SA-PO1046, SA-PO1047,
SA-PO1050, SA-PO1051, SA-PO1052,
SA-PO1060, SA-PO1064, SA-PO1069,
SA-PO1072, SA-PO1074, SA-PO1075,
SA-PO1084, SA-PO1087, SA-PO1094,


ethnic minority .............. TH-PO26, TH-PO27, TH-PO54, TH-PO72, TH-PO73, TH-PO78, TH-PO86, TH-PO90, TH-PO91, TH-PO114, TH-PO115, FR-OR039, FR-PO259, FR-PO271, FR-PO310, FR-PO397, FR-PO1063, FR-PO1193, SA-OR060, SA-PO542, SA-PO860, SA-PO867, SA-PO893, SA-PO1048, SA-PO1049, SA-PO1064, PUB404, PUB498

extracellular matrix ........ TH-OR036, TH-OR082, TH-OR083, TH-PO189, TH-PO405, TH-PO503, TH-PO504, TH-PO546, TH-PO570, TH-PO78, TH-PO898, TH-PO946, FR-PO222, FR-PO944, FR-PO1125, SA-PO307, SA-PO111, SA-PO398, SA-PO497, SA-PO581, SA-PO730, SA-PO786, PUB145, PUB435

Fabry disease .............. TH-PO798, FR-PO974, SA-PO360, SA-PO415, SA-PO416, SA-PO421, SA-PO422, SA-PO423, SA-PO424, SA-PO425, SA-PO1119, PUB216, PUB544, PUB669

factor ................................ TH-PO735, FR-PO93, SA-PO288, PUB142

failure .............. TH-OR092, TH-PO1110, FR-PO500, FR-PO512, FR-PO535, FR-PO573, FR-PO1155, FR-PO1193, SA-OR105

familial nephropathy .............. TH-PO1002, TH-PO1066, FR-PO809, FR-PO811, SA-PO676, PUB542

family history .............. TH-PO1037, FR-PO807, FR-PO808, FR-PO1071, PUB214

fibroblast .............. TH-PO503, TH-PO219, TH-PO468, TH-PO475, TH-PO480, TH-PO505, TH-PO519, TH-PO774, FR-PO161, FR-PO348, FR-PO356, FR-PO375, FR-PO411, FR-PO826, SA-PO121, SA-PO729, SA-PO760, PUB054, PUB434

fibronectin .............. FR-PO801, FR-PO802, SA-PO135

fibrosis (continued) ........ FR-OR112, FR-OR115, FR-PO999, FR-PO219, FR-PO237, FR-PO313, FR-PO349, FR-PO356, FR-PO369, FR-PO373, FR-PO375, FR-PO376, FR-PO386, FR-PO396, FR-PO731, FR-PO766, FR-PO885, FR-PO971, FR-PO972, FR-PO980, FR-PO984, SA-OR033, SA-OR039, SA-OR069, SA-OR070, SA-OR076, SA-OR105, SA-PO502, SA-PO77, SA-PO112, SA-PO113, SA-PO117, SA-PO120, SA-PO123, SA-PO128, SA-PO129, SA-PO132, SA-PO315, SA-PO429, SA-PO452, SA-PO456, FR-PO459, SA-PO463, SA-PO529, SA-PO537, SA-PO565, SA-PO566, SA-PO569, SA-PO571, SA-PO574, SA-PO575, SA-PO583, SA-PO625, SA-PO731, SA-PO740, SA-PO743, SA-PO766, SA-PO775, SA-PO938, SA-PO941, SA-PO942, SA-PO945, SA-PO946, SA-PO950, PUB044, PUB149, PUB427, PUB429, PUB433, PUB434, PUB438, PUB484, PUB549, PUB646

gastrointestinal complications .............. TH-PO242, TH-PO756, FR-OR128, FR-PO116, FR-PO118, FR-PO114, FR-PO1063, SA-OR103, SA-PO700, SA-PO820, SA-PO964, SA-PO1091, PUB029, PUB034, PUB586, PUB598


gastrointestinal medications .............. TH-OR050, TH-OR165, FR-PO856, FR-PO891, SA-PO273, SA-PO882, SA-PO899, PUB322, PUB386, PUB512

gender difference .............. TH-PO395, TH-PO717, TH-PO718, TH-PO721, TH-PO722, TH-PO723, TH-PO749, TH-PO1015, TH-PO1046, TH-PO1119, TH-PO1169, FR-PO211, FR-PO263, FR-PO595, FR-PO977, SA-PO27, SA-PO106, SA-PO316, SA-PO405, SA-PO425, SA-PO855, SA-PO1045, PUB182, PUB319, PUB362, PUB381, PUB678

gene expression .............. TH-OR001, TH-OR020, TH-OR079, TH-PO818, TH-PO376, TH-PO380, TH-PO522, TH-PO799, TH-PO869, TH-PO875, TH-PO889, TH-PO926, TH-PO1080, TH-PO1097, TH-PO1109, FR-OR123, FR-PO88, FR-PO1113, FR-PO116, FR-PO119, FR-PO120, FR-PO354, FR-PO355, FR-PO368, FR-PO740, FR-PO770, FR-PO830, FR-PO36, FR-PO918, FR-PO931, FR-PO946, FR-PO954, FR-PO955, FR-PO963, FR-PO968, SA-OR030, SA-OR049, SA-PO084, SA-PO355, SA-PO408, SA-PO409, SA-PO565, SA-PO580, SA-PO613, SA-PO782, SA-PO1117, PUB467, PUB682

gene therapy .............. FR-OR066, FR-OR083, FR-PO997, FR-PO715, FR-PO1116, SA-OR29, SA-OR057, SA-PO430, SA-PO466, PUB068

gene transcription .............. TH-OR049, TH-PO481, TH-PO582, TH-PO873, TH-PO906, TH-PO297, FR-PO977, SA-PO68, SA-PO710, SA-PO858, SA-PO415, SA-PO416, SA-PO590

genetic renal disease ......... TH-PO162, TH-PO275, TH-PO768, TH-PO795, TH-PO796,
macrophages, lymphocytes, malfolding proteins

microlumination ...

mineral metabolism ...

mortality ...

molecular genetics ...

molecular biology ...

MPGN (membranoproliferative glomerulonephritis) ...

mRNA ...

multiple myeloma ...

muscle-derived cells ...
nephrectomy

myeloma

nephrin

nephrogenic diabetes insipidus

nephrogenic systemic fibrosis

nephrotic syndrome

obstructive uropathy

organ transplant
pancreas transplantation.............. SA-PO1098, PUB664, PUB667
parathyroid hormone............. TH-OR048, TH-PO328, TH-PO532, TH-PO537, TH-PO556, TH-PO568, TH-PO580, TH-PO583, TH-PO636, FR-PO128, FR-PO130, FR-PO132, FR-PO135, FR-PO138, FR-PO139, FR-PO142, FR-PO143, FR-PO164, FR-PO177, FR-PO441, SA-PO265, SA-PO282, SA-PO304, SA-PO306, SA-PO354, SA-PO792
pathology............ TH-PO027, TH-PO430, TH-PO567, TH-PO798, TH-PO978, TH-PO1018, TH-PO1027, TH-PO1066, TH-PO1075, FR-OR097, FR-OR098, FR-OR100, FR-OR117, FR-PO684, FR-PO689, FR-PO714, FR-PO821, FR-PO860, FR-PO901, FR-PO912, FR-PO956, FR-PO974, FR-PO989, FR-PO994, SA-OR023, SA-PO405, SA-PO140, SA-PO192, SA-PO353, SA-PO536, SA-PO544, SA-PO563, SA-PO655, SA-PO658, SA-PO693, SA-PO696, SA-PO703, SA-PO706, SA-PO713, SA-PO726, SA-PO1118, SA-PO1167, PUB027, PUB070, PUB240, PUB255, PUB310, PUB583
patient satisfaction.............. TH-PO233, TH-PO274, TH-PO279, TH-PO309, TH-PO1150, TH-PO1162, FR-OR108, FR-PO225, FR-PO240, FR-PO292, FR-PO295, FR-PO351, FR-PO1043, SA-OR059, SA-PO013, SA-PO032, SA-PO035, SA-PO890, SA-PO1071, PUB161
patient self-assessment................ TH-PO208, TH-PO243, TH-PO244, TH-PO259, TH-PO260, TH-PO277, TH-PO313, TH-PO354, TH-PO599, TH-PO650, TH-PO672, TH-PO1000, TH-PO1153, FR-OR08, FR-PO335, FR-PO526, FR-PO1177, SA-PO846, SA-PO851, SA-PO865, SA-PO884, SA-PO889, SA-PO894, SA-PO1094, SA-PO159, PUB117, PUB370
pediatric intensive care medicine........ TH-PO652, TH-PO996, TH-PO115, TH-PO776, TH-PO777, TH-PO788, FR-PO1081, FR-PO1087, SA-OR017
pediatric kidney transplantation........... TH-OR122, TH-PO696, TH-PO772, TH-PO775, TH-PO1113, TH-PO1151, TH-PO1152, TH-PO1153, TH-PO1154, FR-PO1195, SA-PO1146, PUB309, PUB645
pediatric nephrology...... TH-OR118, TH-OR121, TH-OR126, TH-PO052, TH-PO096, TH-PO163, TH-PO605, TH-PO695, TH-PO750, TH-PO753, TH-PO762, TH-PO767, TH-PO768, TH-PO771, TH-PO773, TH-PO780, TH-PO785, TH-PO786, TH-PO866, TH-PO1038, FR-OR067, FR-PO012, FR-PO300, FR-PO301, FR-PO302, FR-PO303, FR-PO307, FR-PO606, FR-PO756, FR-PO816, FR-PO1070, FR-PO1073, FR-PO1076, FR-PO1078, FR-PO1081, FR-PO1086, FR-PO1094, FR-PO1095, FR-PO1097, SA-PO152, SA-PO203, SA-PO345, SA-PO376, SA-PO384, SA-PO400, SA-PO412, SA-PO675, SA-PO687,
pediatric nephrology (continued)............ SA-PO684, SA-PO720, PUB222, PUB311, PUB312, PUB313, PUB314, PUB589

pharmacokinetics........... TH-PO085, TH-PO120, TH-PO355, TH-PO356, TH-PO357, TH-PO358, TH-PO362, TH-PO368, TH-PO369, TH-PO761, FR-PO497, FR-PO718, SA-PO159, SA-PO391, PUB316
phosphate binders............. TH-PO242, TH-PO499, TH-PO553, TH-PO581, FR-OR031, FR-OR033, FR-OR036, FR-OR134, FR-OR147, FR-OR148, FR-OR149, FR-OR150, FR-OR151, FR-OR169, FR-PO441, SA-PO245, SA-PO793, SA-PO1011, SA-PO1030, SA-PO1031, PUB064, PUB188
phosphate uptake............. TH-OR043, TH-PO536, TH-PO538, TH-PO541, TH-PO545, FR-OR034, FR-OR144, FR-PO154, FR-PO157, FR-PO170, FR-PO607, FR-PO643, FR-PO677, FR-PO683, FR-PO693, PUB060, PUB524
platelets............. TH-PO129, TH-PO742, FR-PO495, FR-PO943, FR-PO1040
potassium (K) channels

primary glomerulonephritis

progression
terminology

proteinuria (continued)

quality of life (continued)

RAGE (receptor for AGES)

reactive oxygen species

renal artery stenosis

renal autoregulation

renal carcinoma

renal cell carcinoma

proliferation

polycystic kidney disease

primary glomerulonephritis

potassium (K) channels

progression of renal failure

proteinuria
FR-OR131 - Retracted by ASN on May 20, 2021

Pooled Efficacy and Cardiovascular (CV) Analyses of Roxadustat in the Treatment of Anemia in CKD Patients on and Not on Dialysis

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Background: Roxadustat is an oral hypoxia–inducible factor prolyl hydroxylase inhibitor that regulates erythropoiesis & iron metabolism. Integrated Phase 3 analyses examine efficacy & safety of roxadustat in CKD patients (pts).

Methods: Phase 3 studies comparing roxadustat to placebo (pbo), in pts with Stage 3-5 non-dialysis-dependent (NDD) & dialysis-dependent (DD) patients were pooled. Death, MI, & stroke (MACE), & heart failure or unstable angina requiring hospitalization (MACE+ FH) were adjudicated. Efficacy analyses assessed HB & rescue therapy (transfusion, IV iron & ESA). CV endpoints included MACE & MACE+ FH.

Results: In NDD, 4270 pts were randomized (2386 roxadustat/1884 pbo). The primary endpoint (mean Hb CFB; Wks 28-52) was +1.85(94/9)g/dL in the roxadustat group vs pbo (+0.0109) (p<0.001) with lower risk of rescue therapy (HR 0.75%, CI 0.23, 1.16, reduction p<0.001) in roxadustat. Using ITT long-term follow-up, the HR for time to MACE was 1.08(95% CI 1.4, 1.24) for roxadustat vs pbo, & 1.04(95% CI 0.91, 1.18) for MACE+ FH. In the subgroup eGFR<10 (n=3431), MACE HR (95% CI)=99(84,1.16) & MACE+ FH=98 (85.14, for roxadustat vs pbo. In DD, 3917 patients were randomized (1960 roxadustat/1957 epoetin alfa). The primary endpoint (mean Hb CFB; Wks 28-52) was 1.21 in roxadustat vs 0.95 in pbo in EPO (difference 0.26g/dL;95%CI 0.20, 0.33) in pooled analysis; roxadustat was noninferior & superior to EPO (p<0.001). The roxadustat group received fewer transfusions, 9.5 v. 12.8%; HR(95% CI)= 0.72 (0.67, 0.99). Compared to roxadustat, HR for MACE, FR= HR(95% CI)=0.77 (0.72, 0.83), & for MACE+ FH= 0.77 (0.72, 0.82) in DD pts. Of 1526 incident pts (dialysis <4 months), HRs for MACE & MACE+ FH= 0.70 (95% CI, 0.51, 0.97) (p=0.03) & 0.66 (95% CI, 0.50, 0.89) (p=0.05).

Conclusions: These integrated Phase 3 analyses provide evidence for roxadustat superiority in anemia correction with transfusion reduction & acceptable CV safety profile.

Funding: Commercial Support - FibroGen Inc. AstraZeneca plc

FR-OR132

Effect of Angiotensin-Nephrilysin Inhibition on Renal Outcomes in Heart Failure with Preserved Ejection Fraction

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Background: Chronic Kidney Disease (CKD) confers an increased risk of cardiovascular (CV) and renal events in patients with heart failure and preserved left ventricular ejection fraction (HFpEF). We assessed the long-term renal effects of angiotensin/nephrilysin inhibition, a prespecified secondary outcome, in patients with HFpEF enrolled in the PARAGON-HF trial.

Methods: In this randomized, double-blind, parallel group, active controlled, event-driven trial, we assigned 4,822 patients with chronic HFpEF to receive sacubitril/valsartan or valsartan. Key exclusion criteria included a baseline eGFR <30ml/min/1.73m2. The prespecified renal outcome, a key secondary endpoint, was the time to first occurrence of worsening renal function, defined as a ≥40% reduction in eGFR relative to baseline, attainment of an eGFR <30mL/min, or death, or renal disease. We also evaluated the effect of treatment on the change in eGFR during follow up, and the influence of eGFR on the efficacy of sacubitril/valsartan for reducing the primary composite outcome.

Results: The mean age was 73.8±7 years; 52% were female. At baseline, mean (± SD) eGFR was 63±19 mL/min/1.73m2; 2,341 participants (49%) had CKD (eGFR <60 mL/min/1.73m2) and 43% had diabetes. At study closure, the composite renal outcome had occurred in significantly fewer patients in the sacubitril/valsartan group compared with the valsartan group (HR 0.50, 95% CI 0.33, 0.77, p=0.002), and the renal composite outcome with CKD (HR 0.72, 95%CI 0.59-0.86) and without CKD (HR 0.76, 95%CI(0.63, 0.92) - results to be shown at ASN. The composite renal endpoint was observed in 28 (1.2%) patients in the DAPA group vs 39 (1.6%) in the pbo arm (HR 0.71, 95% CI 0.44, 1.16). Renal serious adverse events and investigator reported acute kidney injury were significantly less common in the DAPA group. Additional results, including eGFR over-time, will be shown at the ASN annual meeting.

Conclusions: In this trial including HFpEF patients with and without T2D, DAPA reduced the composite of a worsening heart failure event or cardiovascular death, both in patients with CKD and in those without CKD. The absolute benefit in patients with CKD was substantial.

Funding: Commercial Support - AstraZeneca

FR-OR134

Efficacy and Safety of Difelikefalin in Patients Undergoing Hemodialysis with Pruritus: Results from a Phase 3 Randomized, Controlled Study (KALM-1)

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Background: There is an unmet need for effective treatments for pruritus associated with chronic kidney disease (CKD-d or uremic pruritus), a debilitating condition present in patients undergoing hemodialysis (HD). Difelikefalin (DFK, CR845) is a novel, peripherally restricted kappa opioid receptor (KOR)-specific agonist in development for treatment of pruritus. Here we report on the first Phase 3 study of DFK in HD patients with CKD-d.

Methods: Patients with moderate-to-severe CKD-d undergoing HD (N=377) were randomized 1:1 to receive an IV bolus of DFK 0.5 mg/kg (N=189) or placebo (PBO) (N=188), thrice weekly post dialysis, over 12 weeks. The primary endpoint was the proportion of patients achieving ≥2-point improvement from baseline (BL) to Week 12 in total pruritus score applied during the entire dialysis session. The primary endpoint was defined as a ≥40% reduction in the mean of 24-hr daily Worst Itching Intensity Numerical Rating Scale (NI-RS) scores. Secondary endpoints included the change in itch-related QoL measured by 5-D Icht and Skindex-10 questionnaires and the proportion of patients achieving ≥4-point WNI-RS score improvement from BL to Week 12. Safety was assessed based on vital signs, clinical laboratory results, ECG, and adverse event (AE) reporting.

Results: The primary and all secondary efficacy endpoints were met. BL mean NI-RS scores were 7.1 and 7.3 in DFK and PBO groups. Percentages of patients with ≥3-point improvement and ≥4-point improvement in mean NI-RS scores at Week 12 were 51% vs 28% (p<0.001; odds ratio (OR) 2.7) and 39% vs 18% (p<0.001, OR 2.9) for DFK vs PBO. Separation from PBO in WNI-RS score change from baseline was observed at Week 1. All QoL measures were significantly improved vs PBO (p<0.001). Serious AE incidence was similar for DFK vs PBO; most common treatment emergent AEs were diarrhea (9.5% vs 3.7%), dizziness (6.9% vs 1.1%), and vomiting (5.3% vs 3.2%).

Conclusions: This study demonstrated that DFK significantly reduced itch intensity in HD patients. Patients treated with DFK were about 3 times (based on OR) more likely to have a clinically meaningful reduction in itch intensity vs PBO and had significant improvements in itch-related QoL measures overall and well tolerated across the study profile. DFK could represent an important advance for treatment of pruritus in HD patients.

Funding: Commercial Support - Cara Therapeutics, Inc.
FR-OR135
Mycophenolate Mofetil vs. Azathioprine in Kidney Transplant Recipients on Steroid-Free, Low-Dose Cyclosporine Immunosuppression: The ATHENA Trial
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Background: Registration trials with old sandimmune formulation of cyclosporine (CsA) suggested that Mycophenolate Mofetil (MMF) prevents acute cellular rejection (ACR) more effectively than Azathioprine (AZA), but multiple trials with standard-dose of more stable microemulsion formulation of CsA (Neoral) did not confirm this.

Methods: The ATHENA trial (NCT00494741) was a randomized, prospective, multicenter trial comparing The Effect on chronic allograft Nephropathy prevention of mycophenolate mofetil versus Azathioprine as the sole immunosuppressant for kidney transplant recipients. All patients were induced with low-dose Thymo + basiliximab. Those with stable graft function, no previous ACRs and no infilrates at 1-y surveillance biopsy underwent CsA tapering to half of the initial dose. Primary endpoint was cumulative incidence of chronic allograft nephropathy (CAN) at 3 yrs.

Results: We included 233 patients (119 on MMF; 114 on AZA). At 3 yrs, 38 patients on MMF (31.9%) vs 37 on AZA (32.4%) developed ACR (Figure); 22 on MMF (18.5%) vs 24 on AZA (21.1%) had biopsy-proven ACR (p=0.72); 11 on MMF (9.2%) and 10 on AZA (8.7%) had sub-clinical (sCreat increase <10% during previous 3 mo) ACR vs 24 on AZA (21.1%) had biopsy-proven ACR (p=0.72); 11 on MMF (9.2%) and 10 on AZA (8.7%) had sub-clinical (sCreat increase <10% during previous 3 mo) ACR vs 24 on AZA (21.1%) had biopsy-proven ACR (p=0.72); 11 on MMF (9.2%) and 10 on AZA (8.7%) had sub-clinical (sCreat increase <10% during previous 3 mo) ACR vs 24 on AZA (21.1%) had biopsy-proven ACR (p=0.72). Post-tapering eGFR was stable.

Conclusions: In kidney transplant recipients on low-dose CsA and no steroids, AZA and MMF are associated with similar incidence of CAN, of clinical or subclinical ACR, and graft survival and function. AZA represents a valuable, less expansive, alternative to MMF also on low-dose maintenance immunosuppression.

Funding: Government Support - Non-U.S.

FR-OR136
A Phase 2 Randomized, Controlled Study of Obinutuzumab with Mycophenolate Mofetil or Corticosteroids in Proliferative Lupus Nephritis
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Background: Type I anti-CD20 antibodies such as rituximab fail to achieve complete B-cell depletion in lupus nephritis (LN). NOBILITY tested whether enhanced B-cell depletion with the type II anti-CD20, obinutuzumab (OBI), could improve responses in LN compared to placebo (PBO). (NCT02550652)

Methods: Patients with active Class III/IV LN (n=125) received standard-of-care mycophenolate and steroids and were randomized to OBI or PBO and followed for 104 weeks. The primary endpoint (PE) was complete renal response (CRR) at week 52.

Results: Baseline mean urine protein:creatinine ratio (UPCR) and serum creatinine were UPCR=0.84 mg/dL, OBI was associated with increased renal responses vs. PBO at weeks 52 and 76 (Table). 80% of OBI pts and 0% of PBO pts had CD19+ count <0.441 cells/µL at week 52. Significant improvements in anti-dsDNA, C3, and C4 were observed with OBI vs. PBO. Through week 76, severe adverse events (OBI 24% vs. PBO 29%) and serious infections (6% vs. 18%) were not increased with OBI. Numerous infusion-related reactions were more common with OBI (16% vs. 10%). There were 5 deaths (1 OBI, 4 PBO).

Conclusions: NOBILITY met its primary and secondary efficacy EPIs. OBI was superior to PBO for the achievement of renal response at 12 and 18 months in proliferative LN patients treated with mycophenolate and steroids. There were no unexpected safety findings.

Funding: Commercial Support - F. Hoffmann-La Roche

Kaplan-Meier of CAN incidence in the two study arms.
FR-OR138

Effects of Vitamin D and Omega-3 Fatty Acid Supplementation on Kidney Function and Damage in Type 2 Diabetes

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Background: Vitamin D and omega-3 fatty acid supplements are readily available and safe interventions that may help prevent the development and progression of diabetic kidney disease. Preclinical and observational studies suggest that vitamin D suppresses the renin-angiotensin system, reduces renal inflammation and fibrosis, and exerts direct pro-survival effects on podocytes, while omega-3 fatty acids have potentially beneficial anti-inflammatory, antithrombotic, and vascular properties.

Methods: We performed a randomized clinical trial of 1,312 adults with type 2 diabetes to test whether supplementation with vitamin D, or omega-3 fatty acids for five years prevents the development or progression of CKD. The study was completed as an ancillary study to the VITamin D and Omega-3 Trial (VITAL). In a 2-by-2 factorial design, participants were randomly assigned to vitamin D3 (2000 IU daily) or placebo and to omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid, 1 g daily) or placebo. The primary outcome of the ancillary study was the rate of CKD progression, defined by RIFLE criteria, within first 3 days of surgery. (Trial registration:NCT01652872) with 377 subjects randomized to the TD and 379 to the FD treatment for up to 2 years. The primary endpoint was the percentage of subjects transfused. Transfusions, per protocol, were performed as deemed necessary by the treating physician and were prospectively adjudicated.

Results: There were no significant differences in patients’ pre & intra-operative data or to participants who were highly adherent to study medications. No significant difference was observed in secondary outcomes, including change in eGFR after 2 years of treatment, a composite outcome of loss of eGFR ≥40% from baseline or kidney failure (NEJM, 2019). There was no significant difference in the incidence of blood transfusions, atrial fibrillation, infections, cerebrovascular events, median ICU and in-hospital stays between the two groups. One patient in the control group died prior to hospital discharge. The number needed to treat (NNT) with the TD group to prevent AKI was 9 patients

Conclusions: In patients at-risk for AKI, undergoing cardiac surgery with the CPB, the RenalGuard® system significantly reduced the incidence of AKI and can be used safely & reproducibly. Larger studies will be required to assess the cost benefit of this device

Funding: Other NIH Support - National Institute of Health Research UK, West Midlands CRN, Commercial Support - RenalGuard plc

TH-PO1184

Results of the START-CKD Trial (Strategies Using Darbepoetin Alfa to Avoid Transfusions in CKD)

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Background: Exposure to high doses of an erythropoiesis stimulating agent (ESA), high cumulative dose, wide Hb excursions, and rapid hemoglobin (Hb) rises may contribute to cardiovascular adverse events with ESA use. Thus, there is a desire to define an ESA dosing strategy that minimizes red blood cell transfusion and limits dose. The START-CKD trial evaluated such a dosing strategy using darbepoetin in anemic subjects with stage 3-5 CKD using a fixed dosing (FD) strategy of 0.45 μg/kg Q4 wks or a Hb-based titration dose (TD) algorithm (per US prescribing information (USPI)).

Methods: This was a US phase 3, multicenter, randomized, double-blind, parallel group study (N=756; ClinicalTrials.gov, NCT01652872) with 377 subjects randomized to the TD and 379 to the FD treatment for up to 2 years. The primary endpoint was the percentage of subjects transfused. Transfusions, per protocol, were performed as deemed necessary by the treating physician and were prospectively adjudicated.

Results: Mean age of the subjects, baseline Hb and eGFR: 69 yrs., 9.0 g/dL and 22 ml/min/1.73m², respectively and were balanced between arms. The % of subjects transfused was 24.1% vs 24.4% in the FD and TD groups, respectively, with similar time to first transfusion (HR 1.01, Figure A). Average Hb achieved was greater in the TD group compared to the FD group, 9.7 vs 9.4 g/dL respectively (Figure B). Average cumulative dose of darbepoetin per 4 wks was less in the FD group, 30.8 μg vs 50.7 μg/g.

Conclusions: In this study, minimizing RBC transfusion can be achieved using a low fixed-dose of darbepoetin with lower cumulative dose than use of Hb-based dose titration approach.

Funding: Commercial Support - Amgen, Inc.

Figure A. Kaplan-Meier Plot of Time to First RBC Transfusion

Figure B. Hemoglobin Concentration at Each Study Visit (Mean +/- SE)
TH-PO1185

Phase 3 Study to Compare the Efficacy and Safety of Enarodust (JTZ-951), an Oral HIF-PH Inhibitor, with Darbeopetin Alfa in Anemic Patients with CKD Not Requiring Dialysis

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1Showa University School of Medicine, Tokyo, Japan; 2Pharmaceutical Division, Japan Tobacco Inc., Tokyo, Japan.

Background: This phase 3 study was conducted to verify the efficacy (non-inferiority to darbeopetin alfa (DA)) and safety of enarodust in Japanese anemic patients with CKD not requiring dialysis in randomized, open-label, parallel-arm comparison manner for 24 weeks.

Methods: Patients were respectively randomized in 1:1 ratio to receive either enarodust orally once daily or DA subcutaneously every 2 or 4 weeks. The doses were adjusted every 4 weeks to maintain Hb levels within a target range (10-12 g/dL). The primary endpoint was difference in mean Hb level between arms during the evaluation period defined as Week 20-24 (non-inferiority margin: -0.75 g/dL). Other assessments included proportion of patients whose Hb level was within the target range, iron-related parameters, renal function-related parameters, and NT-pro BNP.

Results: 216 patients were randomized to receive either enarodust (n=107) or DA (n=109). The mean Hb level of each arm during the evaluation period was 10.96 g/dL (95% CI: 10.84, 11.07) with enarodust arm and 10.87 g/dL (95% CI: 10.75, 10.99) with DA arm. The difference between arms in the mean Hb level was 0.09 g/dL (95% CI: -0.07, 0.26), confirming the non-inferiority to DA. Proportions of patients whose Hb level was within the target range during the evaluation period were 78.2% in enarodust arm and 90.7% in DA arm. Increase of TIBC and decrease of hepcidin were observed through Week 4 in enarodust arm, respectively. No apparent difference between arms in the incidence of AEs or adverse drug reactions or in the incidence of other safety parameters was observed. There were no negative effects of enarodust on NT-pro BNP or renal function-related parameters.

Conclusions: Enarodust, administered orally, was as effective as DA, administered subcutaneously, in maintaining Hb levels in Japanese anemic patients with CKD not requiring dialysis. No new safety concerns were identified when compared with DA.

Funding: Commercial Support - Japan Tobacco Inc.

TH-PO1186

Phase 3 Study to Compare the Efficacy and Safety of Enarodust (JTZ-951), an Oral HIF-PH Inhibitor, with Darbeopetin Alfa in Anemic Patients Receiving Maintenance Hemodialysis

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1Showa University School of Medicine, Tokyo, Japan; 2Pharmaceutical Division, Japan Tobacco Inc., Tokyo, Japan.

Background: This phase 3 study was conducted to verify the efficacy (non-inferiority to darbeopetin alfa (DA)) and safety of enarodust in Japanese anemic patients with CKD receiving maintenance hemodialysis in randomized, double-blind, parallel-arm comparison manner for 24 weeks.

Methods: Patients, who have been receiving a stable dose of ESAs and have protocol specified Hb criteria (Hb level of 9.5-12.0 g/dL or <12.0 g/dL, were randomized in 1:1 ratio to receive either enarodust orally once daily or DA intravenously every week after switching from ESAs. The doses were adjusted every 4 weeks to maintain Hb levels within a target range (10-12 g/dL). Intravenous iron preparations were prohibited during the screening period and the initial treatment period (Week 0-4). The primary endpoint was difference in mean Hb level between arms during the evaluation period defined as Week 20-24 (non-inferiority margin: -1.0 g/dL). Other assessments included proportion of patients whose Hb level was within the target range and iron-related parameters.

Results: 173 patients were randomized to receive either enarodust (n=87) or DA (n=86). The mean Hb level of each arm during the evaluation period was 10.73 g/dL (95% CI: 10.56, 10.91) with enarodust arm and 10.85 g/dL (95% CI: 10.72, 10.98) with DA arm. The difference between arms in the mean Hb level was -0.12 g/dL (95% CI: -0.33, 0.10), confirming the non-inferiority to DA. Proportions of patients whose Hb level was within the target range during the evaluation period were 78.2% (95% CI: 76.4, 80.8) in enarodust arm and 88.8% (95% CI: 79.7, 94.7) in DA arm. Increase of TIBC and decrease of hepcidin were observed in enarodust arm, respectively. No apparent difference between arms in the incidence of AEs or adverse drug reactions or in the incidence of other safety parameters was observed. There were no negative effects of enarodust on NT-pro BNP or renal function-related parameters.

Conclusions: Enarodust was proved to be non-inferior to DA in the treatment of anemia in Japanese CKD patients receiving maintenance hemodialysis, and was generally well-tolerated.

Funding: Commercial Support - Japan Tobacco Inc.
TH-PO1189
Efficacy of phytonadione in calciphibaxis

TH-PO1190
Effect of Etelcalcetide in Patients on Hemodialysis with Secondary Hyperparathyroidism: The DUET Trial
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Background: Etelcalcetide is a second-generation calcimimetic agent approved for treatment of Secondary Hyperparathyroidism (SHPT). The DUET trial (NCT040180108) was designed to clarify the efficacy of etelcalcetide, and to identify sensitive markers for vascular calcification.

Methods: The DUET study was a 12-week multicenter, open-label, randomized (1:1:1) parallel-group study in SHPT patients undergoing maintenance hemodialysis. Patients were randomly assigned to etelcalcetide + oral calcium preparation (Group E+Ca), or control groups (Group C). The primary end point was to compare the proportion of patients with a 50% reduction from baseline in intact parathyroid hormone (iPTH) levels and iPTH levels at the end of week 12. Secondary outcomes included aortic calcification (AC), estimated glomerular filtration rate (eGFR), serum and urine markers of bone and mineral metabolism.

Results: 278 participants from Australia, Malaysia and New Zealand were randomly assigned to lanthanum carbonate (n=138) or placebo (n=140) (mean age 63.1 ± 7.3 years, 63.9% male, 33% stage 3b CKD, 67% stage 4 CKD, mean eGFR 26.6 ± 3.8 ml/min/1.73 m², 45% diabetes, 32.1% CV disease). Mean serum phosphate was 1.25 ± 0.20 mmol/L, mean PWV 10.8 ± 3.3 mm/s and 81.3% had AC at baseline (median [IQR] 1.55 [1.31, 1.74] mm/cm). PWV at 12 weeks, change in PWV did not differ significantly between the groups (diff [95%CI] 0.07 [-0.2, 1.6], P = 0.13). Change in AC score was also not significantly different (+154 [-334, 641] HU, P = 0.53) and there were no differences in serum phosphate, c-terminal and intact FGF23, and 24-h urinary phosphate excretion between the groups. Non-low adverse events were reported in 63 (46%) and 66 (47%) participants on lanthanum and placebo respectively.

Conclusions: In stage 3b/4 CKD patients, treatment with the phosphate-lowering agent lanthanum carbonate over 96 weeks did not result in any difference in change in arterial stiffness or aortic vascular calcification.

Funding: Commercial Support - Shire Pharmaceuticals, Government Support - Non-U.S.

TH-PO1191
A Precision Medicine Approach to Treatment of Osteoporosis in CKD-5D
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Background: This prospective stage II proof-of-concept randomized controlled study uses different treatments for osteoporosis in low vs. non-low bone turnover (Low TO vs. Non-low TO) CKD-5D patients.

Methods: In 36 dialysis clinics across Kentucky, 96 CKD-5D patients with established Low TO and Non-low TO osteoporosis were enrolled. Low TO was determined by serum measurements of PTH, PTH ratio, and TRAP-5b below race-specific normal ranges histologically validated by our laboratory. In Low TO patients, teriparatide combined with cinacalcet was given to stimulate bone formation. In Non-low TO patients, alendronate was administered to reduce bone resorption. The primary endpoint was 1-year change in bone mineral density (BMD) measured by QCT.

Results: Patient status is shown in the Table. In Low TO patients, change in Total Hip BMD demonstrated a positive effect of treatment (Treatment: 12.6 mg/cm² [SE 5.8] ± 8; Control: -14.1 [SE 7.7] ± 8; P = 0.076). The mortality rate was 17% (10/60) in Low TO patients with no deaths in Low TO patients (Figure, p = 0.003). Only two Non-low TO control patients survived to complete the study, thus group comparisons are not yet feasible; Non-low TO treated patients had bone loss of only 4.0 mg/cm². In Low TO patients identified through blood tests, teriparatide has a positive effect on reversing bone loss in CKD-5D.

Conclusions: This study demonstrates better survival in Low TO vs. Non-low TO CKD-5D osteoporotics; supporting the precision medicine approach.

Funding: NIDDK Support

Underline represents presenting author/disclosure.

B5
**TH-PO1192**

A Randomized Crossover Trial of Ultrafiltration (UF)-Profiled Hemodialysis (HD) for UF Rate-Related Harm

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**Background:** Rapid UF is associated with adverse outcomes among HD patients. UF profiling, the practice of varying UF rates to maximize fluid removal during periods of greatest hydration and oncopressure, may reduce UF rate-related complications.

**Methods:** In this 4-phase, blinded crossover trial, participants (UF rates >10 mL/h/kg in ≥ 20% of screening treatments) were assigned in random order to receive HD with conventional UF vs. UF-profiled HD; each 3-wk treatment period was followed by a 1-wk washout period. Participants crossed into each treatment arm twice (2 phases/arm). Each patient was their own control. The primary outcomes were intradialytic hypotension (IDH, nadir systolic BP <90mmHg), rise in serum troponin T from pre- to post-HD (≥10%), and change in left ventricular global longitudinal strain (GLS) from baseline to peak intra-HD stress (%). Secondary outcomes included intra-HD symptoms and blood volume monitor-measured plasma refill (hematocrit fall by ≥0.5%), a volume status measure.

**Results:** On average, the 34 randomized patients (mean age 56y, 24% female, mean HD vintage 6.3y) had UF rates > 10 mL/h/kg in 56% treatments during the 4-wk screening period. All but 2 patients completed the 15-wk study (long hospitalization, transplant). With UF-profiled HD, patients had significantly lower odds of light-headedness and plasma refill (i.e. less post-HD hypervolemia) compared to HD with conventional UF. There was no significant difference in IDH. There was a non-significant trend toward a lower odds of troponin T rise with UF-profiled HD.

**Conclusions:** UF-profiled HD did not reduce the odds of IDH or troponin T rise but did reduce the odds of light-headedness and post-HD plasma refill.

**Funding:** NIDDK Support

**Selected outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio (95% confidence interval)</th>
<th>UF-profiled HD vs. conventional HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin T (≥0.05)</td>
<td>0.85 (0.31-2.28)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular GLS (%)</td>
<td>-0.13 (0.21-0.15)</td>
<td></td>
</tr>
<tr>
<td>Light-headedness</td>
<td>0.48 (0.28-0.85)</td>
<td></td>
</tr>
<tr>
<td>Plasma refill</td>
<td>0.65 (0.40-1.08)</td>
<td></td>
</tr>
</tbody>
</table>

* Difference of outcomes between the UF-profiled intervention arm and the conventional UF control arm were assessed with likelihood ratio tests using various generalized linear mixed models depending on outcome type.

**Funding:** Commercial Support - Medtronic

**Estimated marginal mean changes in dp-ucMGP levels from baseline (95% CI).**

**TH-PO1194**

Effects of Exercise Training on Psychosocial Health and Cognition in Elderly Hemodialysis Patients


**Background:** The impact of exercise training on health-related quality of life (HRQOL) and cognition in chronic kidney disease has not been fully explored. We aimed to determine the effects of 12-weeks of home-based exercise training on psychosocial health and cognition outcomes among elderly maintenance hemodialysis (MHD) patients.

**Methods:** Fifty-six patients (66 ± 7 years; exercise [Ex]; n=28, usual care [UC]: n=28) with end-stage renal disease on MHD (mean years of MHD: 4±5; mean K/V=2.1) were studied using the SF-36 v2, Kidney Disease and Quality of Life (KDQOL) and a battery of cognitive function tests as part of a randomized trial. Ex subjects underwent a home-based aerobic and resistance training program for 12 weeks. Eight components of the SF-36 v2 (bodily pain, general health, mental health, physical functioning, role physical, role emotional, social functioning, vitality) and 5 components of the KDQOL (burden of kidney disease, symptoms, effects, physical component score [PCS], and mental component score [MCS]) were assessed. Tests of cognitive function assessing general cognition, executive function, memory and verbal learning were obtained.

**Results:** Ex patients improved peak VO2 by 11% (p=0.01), while no differences were observed among UC. A 20-point increase in general health was observed among Ex (p=0.04), and trends were observed for increases in physical functioning and role emotional (p=0.08). No other HRQOL measures differed between Ex and UC patients. KDQOL symptoms improved in Ex (p=0.05). PCS increased slightly from 38±12 to 45±10 (p=0.12) in Ex. KDQOL measures were unchanged in UC. There were no significant changes in cognition within or between groups.

**Conclusions:** Home-based exercise training promotes health-related quality of life and some symptom metrics but did not affect cognition.

**Funding:** Veterans Affairs Support

**Underline represents presenting author/disclosure.**
Methods: 12 prevalent HD patients were randomly allocated to receive 4 hours either SHD (dialysate temperature 37°C) or CHD (programmed cooling using BTM device). All other HD prescription and operating conditions remained constant. Participants were exposed to initial modality for two weeks undergoing serial multiparametric MRI (Phillips 3T Ingenia) of the heart and brain prec, during (30min and 180min) and 30min post HD. Cognitive function was assessed pre and post HD. Participants then crossed over to the other modality and the study protocol repeated.

Results: Median age of participants was 59.5yrs (IQR 25), 3 had diabetes and diabetes vintage was 18.5months (IQR 25). Participants were significantly cooled during CHD (-0.40°C±0.31°C to SHD 0.28±0.24°C, P<0.02). Ultrafiltration rate was 7.5±2.6ml/kg/hr in CHD vs 6.9±2.7ml/kg/hr in SHD (P<0.3). BF velocities fell in carotid (-19.2%, P<0.001) and basilar arteries (-16.3%, P<0.004) during HD and reached nadir in the 4th hour, as did cardiac index and stroke volume index (-29.2% and -32.2%, respectively). Reductions in BF and fluid volumes were maximized with CHD. Changes in cerebral BF and cardiac function were not different between CHD and SHD. Reduction in carotid BF was associated with higher ultrafiltration volumes (R2=0.43, P=0.005) and slower completion of trial making: part B (R2=0.33; P=0.03).

Pre-HD myocardial T2 and left ventricular mass were lower after two weeks of CHD as compared to SHD (128±14±138±18, P=0.03; 128±1±137±12, P=0.003).

Conclusions: HD and fluid volume reduction adversely affects cardiac function, carotid and basilar artery BF, with acute changes similar during SHD and CHD. However, lower myocardial T2 and left ventricular mass may indicate reduced myocardial tissue oedema with CHD.

Funding: Commercial Support - Fresenius Medical Care

TH-PO1198

Effect of Allopurinol on the Progression of CKD: The CKD-FIX Study

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Background: Hyperuricemia is a common finding in chronic kidney disease (CKD) and associated with increased risk of progression of CKD. The effect of urate-lowering therapy on CKD progression remains uncertain. We therefore assessed whether allopurinol attenuates the decline of estimated glomerular filtration rate (eGFR) over 2 years in people with high CKD-progression risk.

Methods: In this double-blind randomized controlled trial, adults with CKD stage 3 or 4, urinary albumin-to-creatinine ratio (UACR) ≥30 mg/mmol or decrease in eGFR ≥0.33 ml/min/1.73 m² in the preceding ≥12 months, and no history of gout, were randomized to allopurinol (100-300 mg once daily) or placebo. The primary outcome was change in eGFR (ml/min/1.73 m²) up to 104 weeks. The key secondary endpoints were 40% reduction in GFR, progression to end-stage kidney disease (ESKD), blood pressure, albuminuria, and adverse events.

Results: 369 participants were randomised to the allopurinol group (n=185) or placebo group (n=184). Six withdrew before the baseline visit (3 in each group).

The rate of eGFR decline did not differ significantly between the allopurinol (-3.33 ml/min/1.73 m²/yr, 95% CI -4.11 to -2.55) and placebo (-3.23 ml/min/1.73 m²/yr, 95% CI -3.98 to -2.47) groups (difference -0.10 ml/min/1.73 m²/yr, 95% CI -1.18 to 0.97, P=0.85). 63 (35%) and 51 (28%) participants in the allopurinol and placebo groups experienced a secondary composite endpoint of 40% eGFR decline, ESKD, or death from any cause (RR 1.23, 95% CI 1.00 to 1.67). There were no significant differences in changes in UACR (P=0.25), and systolic blood pressure (P=0.30) between the two groups. Serum urate was significantly lower in the allopurinol group (mean difference -0.16 mmol/L, 95% CI -0.17 to -0.15, P<0.001). Serious adverse events were reported in 84 (46%) and 79 (44%) participants in the allopurinol and placebo groups, respectively (P=0.63).

Conclusions: In CKD patients with elevated CKD-progression risk, urate-lowering treatment with allopurinol did not result in slower eGFR decline than placebo. These results do not support the use of urate-lowering therapy to slow CKD progression.

Funding: NIDDK Support, Government Support - Non-U.S.
A Phase 3 Randomized Controlled Trial on the Effect of Losartan vs. Add-On Aliskiren in CKD
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Background: The potential long-term safety and efficacy of aliskiren in non-diabetic CKD is unknown.

Methods: Non-diabetic CKD stages 3-4 patients were randomized to receive aliskiren added on to losartan (maximal tolerated dose) or losartan alone. The primary outcome was the slope of eGFR at 3 years, along with other secondary endpoints. Composite renal outcomes of doubling of baseline serum creatinine (sCr) or a 40% reduction in eGFR or incident end-stage renal disease (ESRD) or death was analysed as post-hoc analysis.

Results: After follow-up of 144 weeks in 76 subjects (Table 1), there was no difference in the slope of eGFR (Fig 1). 6 patients receiving aliskiren and 7 control patients reached the renal composite endpoint (16.2% vs. 17.9%, P = 0.84). Cardiovascular events rate was 10.8% vs. 2.6%, P = 0.217. Hyperkalemia rate was 18.9% vs. 5.1% (Fig 2).

Conclusions: Compared to losartan alone, add-on aliskiren conferred no further renoprotective benefit but increased hyperkalemia risks in non-diabetic CKD patients.

Baseline demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (y)</th>
<th>Aliskiren Group (n=38)</th>
<th>Losartan Group (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>55.1±11.3</td>
<td>55.6±11.3</td>
<td>55.1±11.2</td>
</tr>
</tbody>
</table>

Fig 1. Slope of eGFR. Adjusted mean of eGFR (95 CI) by mixed model adjusted for baseline, treatment, trial visit, interaction between trial visit and baseline. P (χ² test)=0.52 for intergroup difference.

Fig 2. Cumulative incidence of hyperkalemia with 95% CI. Adjusted HR=7.71

Safety and Efficiency of Nephroprotective Therapy with Ramipril in Children
Oliver Gross, GPN-study group and EARLY PRO-TECT Alport investigators University Medicine Goettingen, Goettingen, Germany.

Background: Children with Alport syndrome (AS) develop renal failure early in life. The safety and efficacy of preemptive nephroprotective therapy is uncertain.

Methods: In an investigator-initiated, double-blinded, randomized, placebo-controlled trial, we treated pediatric patients with Ramipril. Pretreated children and patients whose parents refused randomization versus placebo were treated open label. Prospective data from the US-Alport registry (NCT00622544) were added to substantiate our results in a Bayesian evidence synthesis analysis. The primary endpoints were safety: adverse drug reactions before disease progression and efficacy: time to progression.

Results: Sixty-six oligosymptomatic children with (yet) normal renal function entered the up to 6-year treatment phase with a total of 216.4 patient-years on Ramipril. Most important, Ramipril was safe (hazard ratio 1.06, 95% CI 0.83-1.21). Efficacy analyses, though not significant, cumulated evidence in favor of Ramipril: in the randomized arm, Ramipril decreased the risk of disease progression by >40% (0.51; 95% CI 0.23-1.22), diminished the slope of albuminuria progression and the loss of glomerular filtration rate. Only 27.3% (3/11) of Ramipril-treated, but 55.6% (5/9) of placebo-treated children progressed. Efficacy was confirmed by comparison of untreated children from the US with participants treated open label, in whom Ramipril again reduced disease progression by >40% (0.53; 95% CI 0.23-1.24).

Conclusions: Early initiation of Ramipril therapy in children with AS is safe and can be expected to slow renal failure by many years. A phase 4 study is ongoing to definitively prove the value of preemptive therapy in this CKD. Thus, screening programs for glomerular hematuria in children and young adults should include genetic testing for AS-gene variants. (Funded by the German Federal Ministry of Education and Research; EARLY PRO-TECT Alport ClinicalTrials.gov number, NCT01485978).

Funding: Government Support - Non-U.S.

Double-Blind, Randomized Phase 3 Study Comparing Esaxerenone with Placebo in Type 2 Diabetes Patients with Microalbuminuria (ESAX-DN Study)
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Background: The progression of kidney disease in type 2 diabetes mellitus (T2DM) is not always adequately controlled by renin-angiotensin system inhibitors. In preclinical studies, Esaxerenone (ESAX), a non-steroidal mineralocorticoid receptor blocker, showed kidney protective effects; it may be effective for diabetic kidney disease. Here, the efficacy and safety of ESAX were evaluated in comparison with placebo in 455 Japanese patients with type 2 diabetes mellitus with microalbuminuria.

Methods: ESAX-DN Study was a multicenter, randomized, double-blind, placebo-controlled, phase 3 study. Hypertensive T2DM patients treated with ACEI or ARB with microalbuminuria (UACR ≥45 to <300 mg/g Cr in at least two measurements) and an estimated glomerular filtration rate ≥30 mL/min/1.73 m² were eligible. Patients were randomized to ESAX (1.25mg to 2.5mg) or placebo groups for 52 weeks with a follow-up of 4 weeks. The primary endpoint was the proportion of patients of UACR remission, defined as a reversal of UACR to normoalbuminuria (<30 mg/g Cr) and a decrease in UACR by ≥30% from baseline at the end of treatment. Secondary endpoints were the change in UACR from baseline, comparison of the transition rate to overt albuminuria at the end of treatment, and safety assessed in terms of adverse events (AEs).

Results: ESAX significantly reduced UACR (-58.3%) compared with placebo (8.5%) (61.6% reduction relative to placebo, P=0.0001), showed a significantly higher UACR remission rate (22.1% vs. 4.0%) and a significantly lower transition rate to overt albuminuria (1.4% vs. 7.5%) compared with placebo (P=0.0001, P=0.0016). Incidence of

Underline represents presenting author/disclosure.
Canagliflozin (CANA) Slows Declines in Kidney Function in People with Baseline (BL) eGFR <30 mL/min/1.73 m²

Background: The CREDENCE trial demonstrated that the SGLT2 inhibitor CANA significantly reduced kidney failure and cardiovascular (CV) events in participants with type 2 diabetes and chronic kidney disease. During the study, participants continued treatment until initiation of dialysis or kidney transplantation. The predefined sTNFR1 cutpoint of 4.3 ng/mL for CANA was based on the kidney function trajectory of CANA in the subgroup of participants with BL eGFR <30 mL/min/1.73 m² were evaluated.

Methods: While eligibility, in part, required a screening eGFR of 30-90 mL/min/1.73 m², all participants received the study medication regardless of BL eGFR. CANA treatment was started in a randomized fashion with microalbuminuria receiving ACEi or ARB. Although the serum potassium increase was higher with CANA than placebo, all participants recovered to treatment after week 12 and were clinically acceptable.

Results: Among a subgroup of participants with BL eGFR <30 mL/min/1.73 m², CANA reduced the rate of eGFR decline and slowed progression to ESKD. The renal and CV outcome comparisons were consistent with results in the overall study population.

Funding: Commercial Support - Gilead Sciences, Inc

Impact of Canagliflozin (CANA) on eGFR Slope in People with Optimized Glucose Control: Randomized Analyses from CREDENCE

Background: CANA appears to slow renal function loss in those with optimized glucose control and chronic kidney disease. During the study, participants continued treatment until initiation of dialysis or kidney transplantation. The predefined sTNFR1 cutpoint of 4.3 ng/mL for CANA was based on the kidney function trajectory of CANA in the subgroup of participants with BL eGFR <30 mL/min/1.73 m² were evaluated.

Methods: While eligibility, in part, required a screening eGFR of 30-90 mL/min/1.73 m², all participants received the study medication regardless of BL eGFR. CANA treatment was started in a randomized fashion with microalbuminuria receiving ACEi or ARB. Although the serum potassium increase was higher with CANA than placebo, all participants recovered to treatment after week 12 and were clinically acceptable.

Results: Among a subgroup of participants with BL eGFR <30 mL/min/1.73 m², CANA reduced the rate of eGFR decline and slowed progression to ESKD. The renal and CV outcome comparisons were consistent with results in the overall study population.

Funding: Commercial Support - Gilead Sciences, Inc

Soluble Tumor Necrosis Factor Receptor 1 (sTNFR1) Is Prognostic for ESRD over 48 Weeks in a Randomized Clinical Trial in Moderate to Advanced Diabetic Kidney Disease (DKD)

Background: Serum sTNFR1 associates with progression to ESRD in natural history studies of DKD. A predefined sTNFR1 cutoff has been proposed as a potential patient selection criterion for clinical trials. We conducted a pre-planned retrospective analysis of the prognostic power of sTNFR1 over 48 weeks (48W) in a Phase 2 trial of selensertib (SEL) in patients with DKD at high risk of progression based on estimated glomerular filtration rate (eGFR) and albuminuria.

Methods: The Phase 2 SEL trial comprised 333 patients randomized 1:1:1 to receive SEL (2, 6, or 18 mg) or matching placebo for 48W. Serum sTNFR1 and UACR cut-points previously described in Joslin type 1 DKD (T1DKD n=279) and T2DKD (n=221) cohorts (Yamashita et al, Kidney Int 2017;92:258) were applied to evaluate risk of the composite endpoint: ESRD, 40% decrease in eGFR, or nonrenal death. Cox proportional hazards models compared event rates by sTNFR1. Results were evaluated in propensity score matched patients by age, sex and race.

Results: The proportion of the Phase 2 SEL trial patients categorized as high risk based on sTNFR1 >4.3 ng/mL was higher than the Joslin cohorts combined (60% vs 33%, p<0.001 as was the high risk subgroups with UACR >1900mg/g and sTNFR1 >2.9-4.3 ng/mL (8% vs 6%, p<0.01. In the SEL trial, we observed 32 events, 0.58% vs 1.5% event rates at 15% vs 1% in patients above or below sTNFR1 4.3 ng/mL, respectively (p=0.002). Comparable event rates were observed in the subgroup of matched SEL trial and Joslin T2DKD patients (n=121 pairs, 21% vs 4% and 21% vs 8%, respectively). Further, each standard deviation increase of sTNFR1 was associated with a higher risk of the composite endpoint in the full SEL trial (HR 1.64, 95% CI 1.12-2.41) and full Joslin T2DKD cohort (HR 1.76, 95% CI 1.31-2.38).

Conclusions: We validated a predefined cutoff of serum sTNFR1 associated with a higher event rate in a DKD trial population already selected for high risk based on eGFR and albuminuria criteria. sTNFR1 may improve the efficiency of DKD trial design as a patient stratification or selection biomarker.

Funding: Commercial Support - Gilead Sciences, Inc

Late-Breaking Clinical Trials Posters

Poster/Thursday
Figure. Acute and chronic changes in eGFR in CREDENCE participants with HbA1c<7% and ≤5%.2

*Compensatory symmetry was used with identical results from an autoregressive structure.

**TH-PO1205**

Prevention of CKD with Dapagliflozin: Analysis of the DECLARE-TIMI 58 Trial

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**Background:** Patients with early stage kidney disease incur low rates of hard renal endpoints, limiting the ability to demonstrate drug efficacy in this population. Consequently, the regulatory agencies including Federal Drug Administration and European Medicines Agency now consider eGFR based endpoints as acceptable surrogates. In the DECLARE-TIMI-58 study, dapagliflozin showed robust reduction in cardiovascular and renal specific composite outcomes in the overall population.

**Methods:** 17,160 patients with type 2 diabetes were randomly assigned to dapagliflozin or placebo and followed for a median of 4.2 years. The baseline eGFR was 85.3 ml/min/1.73m² and only 7% of patients had an eGFR <60 mL/min/1.73m². We analyzed eGFR slopes from randomization to end of treatment with dapagliflozin vs. placebo.

**Results:** Dapagliflozin attenuated the eGFR decline overall in the trial and in subgroups based on eGFR, UACR, use of ACEI/ARB and diuretics (table). Fewer patients experienced an eGFR decline of 30%, 40% or 50% to eGFR<60 with dapagliflozin vs. placebo, HR (95% CI): 0.68 (0.58, 0.79); 0.54 (0.43, 0.67); 0.57 (0.40, 0.81) respectively, all p<0.002.

**Conclusions:** Dapagliflozin slowed the progression of renal disease across all subgroups of patients with type 2 diabetes, even in patients with normal kidney function and in patients with normo-albuminuria, highlighting its potential for primary prevention of chronic kidney disease.

**Funding:** Commercial Support - AstraZeneca

Mean eGFR slopes per year from randomization to EOT by treatment arm

**TH-PO1206**

Randomized Controlled Trial of Tacrolimus vs. Prednisolone Monotherapy for Adults with De Novo Minimal Change Disease

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**Background:** Standard treatment of de novo nephrotic syndrome secondary to Minimal Change Disease with high dose corticosteroids is associated with the risk of adverse side effects. However there is a paucity of Clinical Trials to guide the use of steroid free alternative regimens in this rare disease in adults. This multicentre prospective, open-label, randomised controlled trial (EudraCT 2009-014292-52, ClinicalTrials.gov NCT00982072) involving 6 nephrology units across the UK investigated whether tacrolimus monotherapy without corticosteroids would be effective for the treatment of de novo minimal change disease. We hypothesised nephrotic syndrome remission rates would be non-inferior for tacrolimus monotherapy compared to corticosteroids.

**Methods:** Adult patients with first presentation of minimal change disease and nephrotic syndrome were randomised to oral tacrolimus at 0.05mg/kg twice daily, or prednisolone at 1mg/kg daily up to 60mg daily. 50 patients completed the trial.

**Results:** There were no significant differences between the tacrolimus and prednisolone treated cohorts in the proportion of patients in complete remission at 8 weeks (primary outcome: 21 of 25 (84%) for prednisolone and 17 of 25 (68%) for tacrolimus (p=0.32), at 16 weeks (23 of 25 (92%) for prednisolone and 19 of 25 (76%) for tacrolimus (p=0.25), or at 26 weeks (23 of 25 (92%) for prednisolone and 22 of 25 (88%) for tacrolimus (p=0.99)). Likewise there was no difference in total remission (complete or partial) at 4 weeks (20 of 25 patients (80%) in the prednisolone and 19 of 25 patients (76%) in the tacrolimus cohort (p=0.99), or at the subsequent time points. There was no significant difference in relapse rates (17 of 23 (74%) for prednisolone and 16 of 22 (70%) for tacrolimus (p=0.66)), in the time from complete remission to relapse, or in time from baseline to relapse.

**Conclusions:** Tacrolimus monotherapy treatment for adults with newly presenting minimal change disease was non-inferior to oral prednisolone in achieving remission from nephrotic syndrome. This is the 1st multicentre randomised controlled trial demonstrating an effective alternative for patients wishing to avoid steroid therapy. This heralds a new era in the management of adults with minimal change disease.

**TH-PO1207**

A Phase 2 Open-Label Trial Evaluating the Efficacy and Safety of Daratumumab in Treatment of Patients with Proliferative Glomerulonephritis with Monoclonal Immune Deposits (PGNMID)


**Background:** PGNMID is the result of the direct deposition of monoclonal proteins in the kidney and the ensuing inflammation. There are no proven therapies available. Rituximab or combination of cyclophosphamide, bortezomib & dexamethasone have been used with variable success.

**Methods:** In this trial we evaluated the safety & efficacy of daratumumab (an anti-CD38 plasma therapy). The primary safety end point was incidence of major infections, grade 3 or 4 pancytopenias. The primary efficacy end point was rate of complete remission (CR) (proteinuria <500 mg & <10% drop in eGFR) or partial remission (PR) (50% reduction in proteinuria & <30% drop in eGFR). Patients were treated with daratumumab IV at a dose of 16mg/kg once weekly for 8 weeks followed by once every other week for an additional 8 doses.

**Results:** Total of 9 patients were recruited. The mean age was 53.6±20.3 years. There were 5 males. Two withdrew from the study. At the end of treatment (6 m) the median 24hr urinary protein (UP) declined from 6.0g (IQ 4.4-8.2) to 0.64g (5.3-0.0), p=0.003 with a corresponding rise in serum albumin from 2.9±0.63 to 3.7±0.48 g/dL (p=0.03). Serum creatinine showed improvement from 1.52 ± 0.52 to 1.39 ± 0.47 mg/dL (p=0.1). At 6m, of the 7 patients, 1 achieved CR and 4 achieved PR. In 5 patients who had 12m data available, median 24hr UP at 6m was 3.0g (IQ 0.5-4.3) which decreased significantly from baseline, p=0.01. Median 24hr UP at 12 m was lower at 1.29 (IQ 0.3-4.0), p=0.01. Mean serum creatinine at 12m was 1.15 ± 0.32 and unchanged from 6m (1.18±0.35, p=0.1). Four of the 5 achieved PR at 12 m. There were two serious adverse events. One was acute glaucoma which occurred 45 min into 1 st infusion (patient was withdrawn). Another was eye chemosis/headache after receiving one infusion. Patient withdrew, but 2 m after, the 24hr UP showed no proteinuria (baseline of 2.3 g/24hr). The most common side effects were infusion-related reactions. There were no major infections or pancytopenias.

**Conclusions:** In this trial, daratumumab was shown to be effective in reducing proteinuria dramatically in patients with PGNMID along with stabilization of renal function. The effect is sustained at 12 m. In conclusion daratumumab is a promising therapy for treatment of patient with PGNMID.

**Funding:** Commercial Support - Janssen Pharmaceutica Research Foundation
Intensive Supportive Care Plus Immunosuppression in IgA Nephropathy: Long-Term Renal Outcomes

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Background: Our randomized, controlled STOP-IgAN trial in patients with IgA nephropathy (IgAN) and substantial proteinuria failed to detect a benefit of immunosuppression added on top of supportive care on the decline in estimated glomerular filtration rate (eGFR) over 3 years. We now evaluated long-term renal outcomes after observational follow-up.

Methods: We obtained information on serum creatinine, proteinuria, end-stage renal disease (ESRD) and death as censored by 03/31/2018. The primary endpoint was the time to first occurrence of a composite of all-cause death, ESRD or eGFR decline by ≥40% compared to baseline, i.e. randomization in the STOP-IgAN trial.

Results: Long-term data were available for 149 STOP-IgAN participants (i.e. 92% of the patients originally randomized). Median follow-up after randomization was 7.4 years (IQR 5.7-9.3 years). The primary endpoint was reached in 36 patients (50.0%) originally randomized to supportive care and 35 patients (45.5%) of those receiving additional immunosuppression (HR 1.20; 95%CI 0.75 to 1.92; p=0.45). ESRD occurred in 17 patients (23.6%) in the supportive care arm and in 20 patients with additional immunosuppression (26.0%). An eGFR loss ≥40% occurred at the same rate in both arms and annual eGFR loss also did not differ significantly. Two patients in the supportive care arm and three in the arm with additional immunosuppression died during follow-up.

Conclusions: Over a follow-up of up to 10 years, we failed to detect differences in key clinical outcomes in IgAN patients randomized to receive added immunosuppression on top of supportive care versus supportive care alone (ClinicalTrials.gov number, NCT03488368).

Primary endpoint analysis. Kaplan-Meier curves showing survival without occurrence of the primary endpoint in the STOP-IgAN cohort.

The Gut-Kidney Axis in Man: GLP-1’s Natriuretic Action Is Abolished by the GLP-1 Receptor Antagonist Exendin 9-39

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Background: We have recently demonstrated that extracellular fluid volume expansion in healthy participants uncovered a natriuretic action of GLP-1 probably via a tubular mechanism secondary to suppression of angiotensin II (ANG II). In the current study, we designed an additional study day to investigate whether GLP-1’s natriuretic effect is mediated via activation and signaling of the GLP-1 receptor.

Methods: Under basal sodium intake for 4 days before each study day, 6 healthy male participants were recruited from our recent study (1) and examined during a 3-hour infusion of GLP-1 (1.5 pmol/kg/min) together with a 3.5-hour infusion of the GLP-1 receptor antagonist, exendin 9-39 (Ex 9-39) (900 pmol/kg/min), initiated 30 minutes before start of GLP-1 infusion. Timed urine collections were conducted throughout the experiments. Renal plasma flow (RPF), glomerular filtration rate (GFR), and uptake and release of hormones and ions were measured via Fick’s principle after catheterization of a renal vein.

Results: During co-infusion of GLP-1 and Ex 9-39, urinary sodium and osmolar excretions remained at baseline levels compared to a mean 2-fold natriuretic effect during GLP-1 infusion alone. Arterial plasma ANG II levels were unaffected during co-infusion of GLP-1 and Ex 9-39, whereas ANG II decreased significantly during GLP-1 alone. Arterial plasma renin levels decreased similarly on the two study days, and arterial aldosterone levels remained unchanged on both days. RPF and GFR remained unchanged on both days.

Conclusions: GLP-1’s natriuretic action is abolished by the GLP-1 receptor antagonist Ex 9-39, probably via the antagonized GLP-1-mediated ANG II suppression.

TH-PO1211

Lack of Concordance Between Changes in the Serum Creatinine and Measured GFR in Patients with Acute Decompensated Heart Failure

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Background: The impact of serum creatinine-based episodes of acute kidney injury (AKI) on outcomes in patients with acute decompensated chronic heart failure (ADHF) is currently unknown. Unfortunately, creatinine and estimated GFR (eGFR) may not accurately reflect renal function under non-equilibrium conditions and might be affected by shifts in volume distributions in the context of decongestive therapy. In this study we measured plasma volume (PV) and GFR (mGFR) in patients undergoing treatment for ADHF and correlated them with creatinine dynamics and AKI based on KDIGO.

Methods: In a prospective cohort study in 50 hospitalized subjects with ADHF, PV and GFR were measured using a two-component intravenous visible fluorescent injectate (VFI) at two time points 48h apart during the course of treatment. Serum concentrations of a high molecular weight dextran component of VFI were measured 15, 60 and 180min after a single injection to quantify PV using the indicator-dilution principle. At the same time, concentrations of a low molecular weight dextran were measured to determine mGFR based on PV-normalized plasma pharmacokinetics. Linear correlation and Bland-Altman plots were used to compare changes in eGFR (CKD-EPI) and mGFR and to correlate changes in mGFR and eGFR. 38 patients had complete serial data regarding GFR dynamics during 48h of treatment.

Results: While eGFR and mGFR correlated well at the time of study inclusion (r=0.829, p<0.01), changes of eGFR and mGFR during 48h of ADHF treatment correlated poorly (r=0.3, p=0.08). 7 patients (18%) showed a decrease of mGFR by >25% during 48h of treatment, but only one of these patients showed a corresponding decrease of eGFR by >25%. Conversely, ten patients (26%) had a >0.3mg/dl increase of creatinine within the 48h of treatment indicating a diagnosis of AKI by KDIGO, but only three of these patients (30%) had a decrease of mGFR by >25%.

Conclusions: In patients hospitalized for ADHF undergoing recompensation, changes of measured GFR displayed a remarkable disconnect from estimated GFR predictions. Serum creatinine-based KDIGO AKI criteria frequently provided GFR-independent false-positive signals, indicating a need for improved diagnostics to identify worsening GFR in these patients.

Funding: Commercial Support - FAST Biomédical

TH-PO1212

Water Intake and Blood Pressure in Children: Results from the SPA Project

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Background: Sodium (Na) intake (I) is involved in the development of hypertension (HTP) and obesity. NaI is important in the treatment of HTP, but also the increase in renal Na excretion (E) might be a potential preventive and/or therapeutic opportunity. The SPA Project studied blood pressure (BP) in relation to water (H2O) and NaI with the working hypothesis that an increased H2O I can improve renal Na handling.

Methods: 339 healthy, non-overweight children (162 girls, 167 boys), 5.7 years old (IQR: 3.1–8.6) were characterized for: BP (using standardized multiple office BP measurement), Na and H2O I (by means of urinary Na and creatinine from 4 samples taken in 4 days). After categorizing subjects as low/high Na I and low/high water I (based on median value), BP was compared.

Results: Among children with higher Na I, those producing >800mL urine/24H showed a significantly (p<0.001) lower BP (both systolic and diastolic) compared to those who drank less (fig.). This difference was not observed among children with lower Na I.

Conclusions: Our findings support the hypothesis that an increased H2O I, reduces BP perhaps by increasing Na renal E. We speculate that this simple, highly acceptable, inexpensive and harmless measure might have a role in preventing and minimizing the epidemics of HTP and related morbidities.

Funding: Private Foundation Support

TH-PO1213

ANG-3777 Improves Outcomes in Patients with Delayed Graft Function: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial with 12-Month Follow-Up

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Background: Delayed graft function (DGF) is associated with lower graft survival & higher mortality. ANG-3777 is a hepatocyte growth factor mimetic shown in animal models to enhance tissue repair & function in damaged organs.

Methods: Kidney transplant patients producing <50cc urine/H over 8 consecutive hours post-transplant, or with CRR <30% at 24h, were randomized to ANG-3777 (2mg/kg IV QD x 3D; N=19) or Placebo (PBO, N=9). Primary endpoint: median time to a1200cc urine/24H.

Results: Study arms were generally balanced, though history of CVD was higher in PBO (ANG-3777=79%; PBO=100%). Kidney/Donor characteristics were similar: Donation after brain death (ANG-3777=68.4%; PBO=77.8%); time from procurement to transplant (ANG-3777=23.7±9.2; PBO=23.7±10.3); DGF incidence (ANG-3777=73.6%; PBO=66.6%). Figure 1: ANG-3777 was more likely to achieve a1200cc urine/24H (ANG-3777=79%, median 5 days; PBO=44%, median 14 days). Figure 2: ANG-3777 had higher eGFR at Days 14, 28, 168, 365. Number of dialysis sessions was equivalent (ANG-3777=1.9 Days±1.3; PBO=1.8 Days±1.5), but ANG-3777 had shorter duration of dialysis (4.1±5.5 vs 6.0±8.4 Days) & transplant hospitalization (7.6±2.3 vs 11.4±9.7 Days). PBO had 2 graft failures vs 0 in ANG-3777 (Log Rank χ²=4.6, p=0.03). Treatment Emergent Serious Adverse Events (TSEAEs) were similar (ANG-3777=42.1%; PBO=44.4%); TSEAEs/subject was higher in PBO (ANG-3777=2.0; PBO=4.3). No TSEAEs were drug related.

Conclusions: ANG-3777 showed better short & long-term graft function, and similar safety to PBO.

Funding: Commercial Support - Angion Biomedica Corp.
TH-PO1214

Durable Donor Hematopoietic Stem Cell (HSC) Chimerism Is Associated with Protection from Native Renal Autoimmune Disease Recurrence in Recipients of Combined Stem Cell/Kidney Transplants

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Background: Recurrence of autoimmune disease (AD) that caused ESRD has been observed in standard of care (SOC) renal transplants (KTx). Since 2009 we have conducted a Phase 2 trial of combined stem cell/living donor kidney transplantation in mismatched related and unrelated subjects with the goal of establishing durable donor chimerism. Our phase 2 is now closed and we have analyzed disease-recurrence in durably chimeric vs. transiently chimeric subjects.

Methods: We hypothesized that durable chimerism will protect against native AD recurrence. Our protocol is based on tolerogenic CD8+/TCR- facilitating cells (FC) and 200 cGy TBI-based nonmyeloablative conditioning with fludarabine (30mg/m2/dose, days -5,-4,-3), cyclophosphamide (50mg/kg/dose, day-3 and+3), 200 cGy TBI (day-1) followed by a living donor KTx (day0). A G-CSF mobilized apheresis product was collected from the donor >=2 weeks pre-KTx, processed to remove graft-versus-host disease-producing cells yet retain HSC and FC (FCRx), and cryopreserved until infusion on day+1 post-KTx. 36 subjects are more than 1 year post-KTx (12-105 months). Subjects ranged in age from 18-65 years and were from 6/6 HLA matched related to 0/6 matched unrelated: 16 unrelated and 20 related donors. MMF and tacrolimus immunosuppression (IS) was weaned and discontinued at 1 year post-KTx if chimerism, normal renal function and normal KTx biopsy were noted.

Results: 12 subjects had AD as the cause of ESRD (6 IgAN, 2 FSGS, 2 Membranous GN, 2 Alport’s). 7 had durable chimerism, allowing full withdrawal of IS; none had disease recurrence, including 2 with FSGS. 3 subjects had transient chimerism. In that cohort, Membranous GN recurred in 1 subject. 2 had no donor chimerism; 1 IgAN recurrence which resolved with corticosteroids. There were no graft losses or patient deaths in these 12 subjects. Renal function (eGFR) has been excellent (eGFR range 56-102 ml/min). In conclusion, durable chimerism using the FCR001 approach protects against recurrent AD.

Conclusions: The FCR001 approach may be particularly suited for patients at high risk for disease recurrence post-KTx, such as FSGS.

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